Determination of relationship and frequency of sensorineural hearing loss in previously diagnosed diabetes mellitus and/or hypertensive adults using qualitative semi-structured interviews

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Abstract

Background: Sensorineural hearing loss (SNHL) is most common form of hearing loss, (90% of hearing loss cases). It was observed that diabetes and hypertension both can cause SNHL through diabetic microangiography and hypertensive retinopathy in ear respectively. Considering prevalence of diabetes and hypertension in India, particularly in state of Maharashtra and their association with sensorineural hearing loss, it was decided to evaluate relationship and frequency of SNHL in adult population of Mumbai metropolitan region.

Methodology: The aim of study was to investigate relationship and frequency of SNHL due to previously diagnosed diabetes mellitus and/or hypertension in adult population of Mumbai metropolitan region. In present study, protocol was designed for semi-structured qualitative interviews of physicians to determine relationship and prevalence of SNHL. In total 25 respondents were replied to semi-structured interviews.

Results: Semi-structured interviews of physicians and audiologists revealed that there exists close association with duration and control of diabetes and/or hypertension. In semi-structured interviews it was found that out of all SNHL patients, there were 71.43% cases of diabetes; 39.29% cases of hypertension; and 53.57% of both diabetes and hypertension. Severity of hearing loss due to diabetes and/or hypertension was found to be moderate with more prevalence in age group of 50-60 years.

Conclusion: It was found that sensorineural hearing loss occurs due to diabetes and/or hypertension. Better control of these conditions at early stage might prevent causation or progression of sensorineural hearing loss. There is need to create awareness amongst public about hearing loss and utility of hearing aids.

Keywords: Sensorineural hearing loss, diabetes, hypertension, semi-structured interviews.

Introduction

Sensorineural hearing loss is most common form of hearing impairment amongst human population. It is accounted to be 90% of all hearing disorders (Latoche, Neely & Noben-Trauth, 2011). SNHL, sometimes referred as “nerve deafness” which results due to dysfunction in inner ear i.e. cochlea or cranial nerve VIII (auditory nerve) or due to any dysfunction in central nervous system processing (Bhattacharyya, & Thaj 2010). As per updated report of WHO in 2013, prevalence of hearing loss increases as per age with maximum incidence above age of 65.

This is estimated to be 50% in South Asia and 18% in high income region (Duthey 2013, Shield 2006). Report from Shield (2006) states that 1 in 7 people in UK or around 9 million people are suffering from hearing impairment. Statistics in India suggests that one in twelve persons have hearing loss (Project Deaf India, 2013).

Recent studies have shown that diabetes and hypertension have close relationship to cause sensorineural hearing loss. Since 1961, studies are underway to investigate relationship of diabetes and hearing loss. Microvascular complications occur in ear
due to diabetes leading to thickening of basement membrane of capillaries of inner ear. Diabetes causes diabetic microangiopathy leading to thickening of vascular membranes and vascular endothelium of ear. Reduced flow due to narrowing of vasculature leads to degeneration of VIII cranial nerve (Makishima & Tanaka 1971, Taylor & Irwin 1978, Costa 1967, Smith, Raynor, Prazma, Buenting & Pillsbury 1995). In study by Makishima et al. (1971), it was found that in diabetic individuals, demyelination of auditory nerve occurs due to degeneration of myelin sheath. Apart from this; alterations in axon, atrophy in spinal ganglion leading to cellular loss in cochlear basal and middle turns and loss of nerve fibres in spiral lamina occurs. These collectively lead to sensorineural hearing loss. The cross sectional clinical trial conducted by Diniz and Guida (2009) wherein worse audiometric thresholds were seen amongst diabetes mellitus patients. Increased levels of serum creatinine due to poor control of blood sugar level in diabetic individuals causes diabetic microangiopathy leading to sensorineural hearing loss (Kakarlapudi, Sayer & Staecker 2003). Age at onset and duration of diabetes is also associated with SNHL (Mozaffari, Tajik, Ariaei, Ali-Ehayaii & Behnam 2010). Study by Nishio et al. (2012) suggests that polymorphism of complement factor H (CFHY402H) in diabetic individual make them more susceptible to sudden sensorineural hearing loss.

As per criteria set by NICE guideline, elevated blood pressure in arteries above 140 (systolic) and 90 (diastolic) mm Hg is regarded as hypertension (NICE Clinical Guideline 127). High blood pressure was also found to be associated with SNHL (Mondell & Lopes 2009, Marchiori, Filbo & Mastuo 2006). In 1982, McCormick et al. (1982) investigated relationship of hypertension in rats with reduced cochlear potentials. Findings indicated that hypertension is important risk factor in age related hearing loss. Another study by Sui et al (2003) also reported similar findings in Wistar rats. Report from US National Health and Nutrition Examination Survey from 1999 to 2002 suggest that cardiovascular risk factors (hypertension, smoking, and diabetes) are responsible for hearing loss (Agrawal, Platz, & Niparko 2009).

Hypertension may lead to structural changes in blood supply of inner ear or may cause inner ear haemorrhage leading to sudden or progressive hearing loss. Underlying pathological mechanisms might be increased blood viscosity, reduction in capillary blood flow, reduction in oxygen transport and hypoxia, changes in ionic cell potentials. These cumulatively lead to hypertensive retinopathy (i.e. damage in end organ blood vessels). This in turn results in problems in hearing capacity (Marchiori, Filbo & Mastuo 2006, Tan, Rahmat, Prepageran, Fauzi, Noran & Raman 2009). Other two studies by Esparza et al (2007) and Wallhagen et al (1997) also indicate relationship of hypertension and sensorineural hearing loss.

Most of times, hypertension is associated with diabetes. Findings from Screening India’s Twin Epidemic (SITE) study suggest that one in five of Indian adults and one in three in state of Maharashtra suffer from both diabetes and hypertension (Joshi, Vadvale, Dalal & Das 2011, Viswanathan, Seedat & Pradeepa 2013). In UK, 3 people out of 10 who have type 1 diabetes and 8 people out of 10 with type 2 diabetes have hypertension (Patient.co.uk).

Individual studies to determine association of SNHL with diabetes or hypertension were done earlier. However, only one case control study from Brazil was conducted in order to determine association of both diabetes and hypertension. However, this study examines only idiopathic sudden SNHL and no other forms of SNHL were considered (Nagaoka, Anjos, Takata, Chaim, Barros & Penido 2010). No study has been conducted considering these conditions and their association with bilateral, progressive or irreversible SNHL. Considering high prevalence of diabetes and hypertension and hearing loss in India, it becomes essential to perform this study to determine association or relationship and frequency of SNHL which occurs due to diabetes and/or hypertension.
Methodology

To get detailed insight on one disorder, (i.e. sensorineural hearing loss); study was designed to explore three different perspectives wherein opinion of physicians and audiologists; adult child or family member; and common public can be evaluated.

Semi-structured interviews or qualitative interviews provide detailed information about the topic. As it basically focuses on opinions, results or responses of interviewees might be controversial. However, aim of study remains to stimulate reflection and exploration of information about the disease condition (Davies 2007). Purpose of choosing semi-structured interviews is their value in picking up unique findings of physicians that they have acquired over years of experience as well as some common experiences. These things cannot be explored from conventional questionnaire based surveys. Before preparation of protocol for semi-structured interviews, pre-pilot or exploratory study and pilot study were carried out.

Pre-pilot study

Pre-pilot study serves as thought clarifying stage for qualitative research (Davies 2007). This involved conversation with one female audiologist with 22 years experience. This conversation serves as essential step in design of questionnaire for protocol of semi-structured interviews.

Preparation of draft of protocol for semi-structured interviews

After pre-pilot study, relevant literature search was done and draft protocol of semi-structured interview was written. Most questions were open ended in order to get more information from physicians and audiologists. Probes were provided so as to obtain detailed view of physicians and audiologists. Protocol contained outline such as introduction, ground rules, brief information, and 24 open ended questions. This protocol was then subjected to pilot study.

Pilot study

Draft of protocol of semi-structured interviews was sent to Dr. Prof. Phil Warner, Cranfield University, UK and discussed with one MD; two MBBS; one MS (ENT) and one audiologist.

Finalisation of protocol for semi-structured interviews

Changes suggested by all of them were made and protocol was finalised.

Study design

This was qualitative research using semi-structured interviews of physicians and audiologists.

Study setting: Study was carried out in private clinics, hospitals, Govt. hospitals of Mumbai metropolitan region.

Study population and sample size: Study involved semi-structured interviews of physicians and audiologists with following qualifications.

Physicians
• MBBS (Bachelor of medicine and bachelor of surgery)
• MD (Doctor of medicine) (Medicine) (Diabetologist and Cardiologists)
• MS (ENT) (Master of surgery in Ear, Nose and Throat)
• Audiologists
• BSc /M Sc AST (Bachelor of Science in Audiology and Speech Therapy)

Exclusion criteria: Physicians practising alternative systems of medicine such as Ayurveda, Siddha, Unanai, Naturopathy, Yoga, Acupuncture, Acupressure, physiotherapy and Homeopathy were excluded from study.
Potential participants were identified by using local healthcare professionals’ directory (Arogyadeep 2013). They were contacted by using telephone or face to face contacts and appointments were fixed based on mutually agreed suitable time. Participants were informed about study conduction and confidentiality.

**Sample size:** Total number of participants targeted was calculated from pilot study. Number of professionals targeted was 49.

**Study duration:** Study was carried out from 08 October 2013 to 01 December 2013.

**Recording of semi-structured interviews:** Responses of semi-structured interviews of physicians and audiologists were recorded using Sony Walkman NWZ-B163F. All participants were informed prior to recording the interview.

**Record keeping and confidentiality:** All participants were informed that all records will be kept in electronic mp3 file format on Lenovo B490 laptop in secure folder. Destruction of notes and audio tapes will be done after 5 years of completion of this study.

**Ethical considerations:** As this is non interventional study of physicians no ethical approval was obtained.

**Data collection and analysis**

While taking interview, written notes were taken so as to identify key points in interview. Recording of interview audio tapes were heard and transcribed into notes. This data was categorised so as to convert it into quantitative data and this data was represented graphically in form of bar graphs. Wherever applicable, percentage analysis was done. Data analysis and representation was done using Microsoft Excel 2007.

**Results**

Study was designed in order to study three different perspectives such as physicians, family member or adult children and awareness amongst public. Recordings of semi-structured qualitative interviews were transcribed. Along with this, data from study note book was referred.

**Respondent’s pattern**

In total, 49 physicians and audiologists were approached for semi-structured qualitative interviews. It was found that professionals declined to respond as many of them were not aware about method of semi-structured interviews; they had lack of time; or they were not comfortable with recording of interview session. Out of 49 professionals approached, only 25 physicians and audiologists responded to the invitation. Therefore, response rate observed was 51.02 percent. Physicians approached were qualified (MBBS, MD (medicine), MS (ENT), audiologists) and were having different experience in their profession (0 to 50 years). In total, 9 MBBS, 5 MD (medicine), 6 MS (ENT), 5 audiologists gave their response. More experienced professionals have accurate diagnosis and can provide better treatment. Audiologists look after maximum cases (35) of SNHL per month than other physicians MS (ENT) (28), MD (medicine) (16), MBBS (7).

**Investigation of Frequencies of conditions**

**Percentage of patients that have both diabetes and SNHL:** Questionnaire was focused to determine of percentage of patients of SNHL which have diabetes. This may be estimate of co-existence of these conditions. While interviews, different physicians and audiologists told different figures about co-existence of diabetes with SNHL. Therefore, mean values were determined as per qualifications of professionals and percentages were determined. Out of total percentage of patients of SNHL per month, Figure 1 represents percentage of patients with diabetes and SNHL. Figure 1 showed
that MS (ENT) specialists have large number of patients (71.43%) of diabetes and SNHL.

Figure 1: Percentage of patients with diabetes which have sensorineural hearing loss

**Percentage of patients of hypertension which have sensorineural hearing loss:** Physicians were asked to estimate number of patients of hypertension out of total number of SNHL patients. Therefore, each response was collected and mean value was determined as per their qualifications and percentage was calculated. Figure 2 shows number of patients of hypertension which have SNHL. Figure 2 suggests that there is small difference in number of patients with hypertension and SNHL in every professional (percentage ranges from 34.29 to 42.86%).

Figure 2: Percentage of patients with hypertension which have sensorineural hearing loss
Percentage of patients with both diabetes and hypertension along with SNHL: Diabetes and hypertension alone can cause SNHL. In state of Maharashtra, statistics of SITE study suggests that one in three suffer from both diseases. Therefore, it becomes essential to determine percentage of patients which have both diseases along with SNHL. Figure 3 shows that number of patients with both above conditions out of total percentage of SNHL patients per month. It suggests that ENT specialists observe around 53.57% of cases and MBBS (General practitioners) observe 42.86% of cases which is more than MD (Medicine) (31.25%). The reason behind second rank of MBBS practitioners is that they are referred as family physicians by most of population who manages treatment of both diabetes and hypertension.

![Figure 3: Percentage of patients with both diabetes and hypertension with SNHL patient factors](image)

Questions were asked during interview to evaluate duration of occurrence (in time period) of SNHL, age of patients, gender, job description, family history of patient etc.

Physicians gave different responses ranging from 7 years to 10 years for occurrence of SNHL. Mean values as per qualifications of physicians were calculated. This indicates that MBBS, MD (Medicine) and Audiologists suggest duration of occurrence of SNHL as 8 years whereas MS (ENT) suggest it to be 9 years. 52% of physicians said that patients in age group 50-60, SNHL is observed mostly. This is further supported by following two responses:

A female audiologist with 25 years experience stated following:
“Generally SNHL is observed in age of 55 to 60 years and above. However, it has been observed from case histories, that when patient has diabetes particularly, this age group is around 50 to 60 or sometimes less than 50 also. This can be also true in case of hypertension”

According to male MBBS physician 35 years of experience, “I think if patient is diagnosed with both diabetes and hypertension, chances of hearing loss increase. This might lower age of occurrence of sensorineural hearing loss. Hence, probably age of SNHL in both cases may be 50-60.”

Around 56% of physicians said, there was no difference in gender to cause SNHL. However, 40% of physicians said that males were more prone to have SNHL.

Female audiologist with 22 years experience added the fact, “Although males are more prone to have SNHL, prevalence in females is also higher. But in India, many females are housewives or homemakers. They neglect fact of hearing loss and even working women do not agree to wear hearing aid due to
issue of aesthetics. So there lies lot of social stigma when prevalence is compared in males and females.”

A mixed opinion was received when physicians and audiologists were asked about relation of job description and SNHL. Forty four percent of physicians and audiologists said that factory workers are more prone whereas same percentage of physicians and audiologists said that there is no relation or discrimination due to job description or working style of patient.

However, female audiologist with 25 years of experience whose clinic is near to railway station area said,

“As my clinic is near to railway station, I see many cases of hearing loss. Particularly workers in railway factory or workshop that have diabetes and hypertension are more prone to have SNHL at age of 50-60.”

Male MS (ENT) surgeon with 7 years of experience said,

“Factory workers are more prone to have SNHL. However, this depends on location of clinic. As my clinic is situated near to industrial area, I get more number of patients who are factory workers. But this may not be the case of every physician or audiologist.”

Physician’s recommendations about hearing loss

MBBS physicians, Audiologists and MD (Medicine) refer to MS (ENT) specialist for detailed examination of sensorineural hearing loss (SNHL). About 76% physicians observed cases having SNHL in both ears and about 84% physicians said patient have family history about close relationship with causation of SNHL. Physicians were asked whether they recommend audiometric tests for patients of diabetes and/or hypertension. Results showed that half of respondents said they recommend and half said they do not recommend audiometric tests to patients. About 48% physicians recommend conduction of audiometric tests after 7-10 years duration of both diabetes and hypertension. Other physicians mostly MBBS and MD (Medicine) did not answer this question. In patients with diabetes and/or hypertension, frequency of audiometric tests is once in year, recommended by 68% respondents while remaining have not answered this question. Non respondents were majorly MBBS and MD (Medicine) physicians. While performing audiometric tests, all MS (ENT) and audiologists ask their patients about presence of hypertension and/or diabetes. Different computerised tests such as automated otoacoustic emissions (AOAE) test and automated auditory brainstem response (AABR) are available, but in India, pure tone audiometry and impedance test were used. Pure tone audiology was used by 72% of respondents and both pure tone and impedance tests were used by 28% of respondents.

Inner ear pathology analysis were recommended by only 20% professionals only if advised by ENT surgeon. Seventy two percent of physicians and audiologists do not refer the patient to have inner ear pathology analysis.

Hearing related conditions

Degree or severity of condition is important aspect for initiation of treatment or therapy. According to 76% of respondents, moderate sensorineural hearing loss occurs due to diabetes and/or hypertension. Some physicians suggest use of hearing aid for SNHL. Hearing aids are of different types such as behind the ear (BTE), in the canal (ITC), in the ear (ITE), receiver in canal (RIC), completely in canal (CIC), etc. Even they are available in digital and analog modes. Many respondents have different opinions regarding hearing aids. 60% physicians recommend BTE type of hearing aid while remaining refer other types almost with equal proportion. Some of the prominent ones are given below.

One female audiologist with 22 years of experience said,
“Generally when hearing loss is detected, I provide detailed information about different types and utility of hearing aids. However, choice of hearing aid depends totally on economical condition of patient. Many times, working women feel awkward while wearing behind the ear type, so they prefer to choose completely in canal type. However, this again depends on severity of sensorineural hearing loss.”

One male ENT surgeon with 15 years of experience added,

“Of course pocket of patient i.e. economical condition matters while choice of hearing aid. But in severe cases we don’t advice them to have completely in canal type of hearing aid. This creates problematic situation when patient wishes that his/her hearing aid should not be noticed by people but we cannot provide him that type considering his/her severity of sensorineural hearing loss.”

One male audiologist with 18 years of experience said,

“Choice of hearing aid is totally dependent on patient. But in India, patients prefer behind the ear (BTE) type due to its low cost. But younger population with 40-50 age groups prefer completely in canal (CIC) type of invisible kind of hearing aids. In very old people with dexterity problems of age above 60, I refer them pocket model or behind the ear. But in total in India, very few patients buy digital hearing aid due to its high cost and need of programming.”

Tinnitus is presence of hissing, roaring, ringing or whooshing sound in one or both ears of patient. Tinnitus is most commonly associated with sensorineural hearing loss.

Regarding the relation of tinnitus and SNHL, one male ENT surgeon with 29 years of experience said,

“In SNHL due to diabetes and/or hypertension, nerve and/or hair cell damage of inner ear occurs. In 80% of such cases subjective tinnitus occurs. This form of tinnitus makes patient difficult to concentrate and sometimes anxious. Therefore, this can be treated by using antidepressant or anti-anxiety drugs or simply using stress management or music therapy.”

Out of all respondents, 68% reported occurrence of tinnitus due to both diabetes and hypertension whereas, 16% reported occurrence due to diabetes only.

In literature, it was seen that there is a close relation between vertigo and SNHL. Vertigo is form of dizziness that occurs due to dysfunction of vestibular system. All respondents agreed this fact that in SNHL due to both diseases diabetes and/or hypertension chances of vertigo increase.

Diabetes, SNHL, hypertension

Question was asked to professionals regarding preference for treatment whether drug treatment or hearing aid or combination of these two. Respondents showed mixed opinion regarding this. Fifty two percent prefer drug therapy and 40 % refer to hearing aid only and 8% refer to both of these.

However, one male ENT surgeon with 7 years of experience added,

“Although allopathic drugs are available for treatment, I prefer to use herbal remedies such as Gingko biloba, Ginseng, etc. along with methylcobalamin. In case of severe or profound sensorineural hearing loss I advice patient to have cochlear implant. But this totally depends on economical condition of patient.”

Literature have shown, hypertension causes sensorineural hearing loss in patients. Forty percent of respondents said that 160 systolic and 110 diastolic mmHg levels of blood pressure can cause sensorineural hearing loss. Graphically different levels are represented in Figure 4.
Figure 4: Blood pressure levels to cause SNHL

Duration of hypertension in patients to cause SNHL was asked to physicians and audiologists. Interestingly, half of the professionals (52%) did not answer question whereas 24% professionals said it to be 8 years. Figure 5 shows results.

Figure 5: Duration of hypertension to cause SNHL

One male ENT surgeon with 30 years of experience said, "Along with duration of diabetes and/or hypertension, management of these conditions is essential. As SNHL gets worse over the years if underlying cause is untreated"

Question was asked about if there is any impact of antihypertensive drugs on causation of SNHL. All physicians and professionals did not have knowledge about effect of antihypertensive drugs to cause hearing loss.

Like hypertension, diabetes is also one of the cause for SNHL. Different responses were obtained when professional were asked about blood glucose levels that can
cause SNHL. These responses were categorised into groups and mean levels were considered. 32% of physicians think that glucose levels of 200/350 (fasting/postprandial) can cause SNHL. This is represented in figure 6.

![Blood glucose levels to cause SNHL](image)

Figure 6: Blood glucose levels to cause SNHL

Duration of diabetes is also important to cause SNHL. Results indicate that diabetes from around 8 years duration can lead to SNHL. Results are shown graphically in figure 7.

![Duration of diabetes (in years) to cause SNHL](image)

Figure 7: Duration of diabetes (in years) to cause SNHL

Insulin or oral hypoglycaemic drugs are prescribed for diabetes. Professionals were asked that whether taking insulin reduces sensorineural hearing loss as compared to taking oral hypoglycaemic drugs. Thirty six percent physicians answered that insulin reduces SNHL whereas 64% do not know about any kind of such relationship.
Obesity and high body mass index (BMI) are well known causes of diabetes. Hence, physicians were asked about relationship of obesity and high BMI with SNHL. 88% of physicians and audiologists responded that there exists relationship of obesity and high with SNHL. Only twelve percent physicians think that there exists no relation between these factors.

Question was asked about relationship of high levels of lipids with causation of SNHL. Results showed that 52% physicians think that high levels of triglycerides and 20% of physicians think that high levels of LDL cause SNHL.

Discussion

Both diabetes and hypertension are one of prevalent disorders in world and have their effect on other systems of body. Present study was to investigate relationship and frequency of sensorineural hearing loss (SNHL) due to previously diagnosed diabetes mellitus and/or hypertension in adult population of Mumbai metropolitan region.

Patient factors

Although response rate of 51.02% seems very low, possible reasons behind this might be recording of interview using Sony Walkman NW Z-B163F, non-familiarity with methodology of semi-structured interview or fear of opinions due to recording, etc. The reason explained by one of MD (Medicine) as we generally do not look after cases of hearing loss. However, during entire conduction of study, co-operation of audiologists and MS (ENT) physicians was encouraging. Many of them said there is need to conduct such bridging studies as people and even physicians take hearing loss conditions very lightly. Studies have revealed that more experience provide expertise to physicians in particular area. Experience of physicians is also important as it has capacity to provide right answers through their clinical judgement (Akl, Khairy, Abdel-Aal, Deghedi & Amer 2006, Kim, Park H. G., Park E. C., & Park K. 2011). During this study responses were obtained from physicians of experience 7 years to 43 years.

Particularly, audiologists and ENT surgeons look after large number of cases due to their expertise in hearing conditions. However, MBBS (being family physicians or general practitioners) and MD (Medicine) (Diabetologist/Cardiologist) look after less number of cases comparatively. Out of these diagnosed cases of SNHL by ENT surgeon, cases of diabetes were 71.43%; cases of hypertension 39.29% and both conditions 53.57%. This highlights higher prevalence of diabetes and hypertension in India. Studies by Friedman et al (1975) and Kakarlapudi et al. (2003) suggest that incidence of hearing loss in diabetic patients is around 30 percent to 95 percent. Findings of current study were in similar range. High frequencies of diabetes and hypertension in Indian population were earlier suggested by SITE study (Mozaffari, Tajik, Ariaei, Ali-Ehayaii & Behnam 2010). According to many studies which have highlighted relationship of age and sensorineural hearing loss (Friedman, Schulman & weiss 1975, Kakarlapudi, Sawyer & Staehler 2003) occurrence of hearing loss increases after age 65. Similarly, report by Shield states that in UK, prevalence of hearing loss increases particularly in age groups 61-70 and 71-80 (Shield 2006).In present study, high frequencies of SNHL were found in age group of 50-60 (52%). However, frequencies in age group 60-70 were 8%. This seems contradictory with earlier studies. However, it must be noted that earlier studies (Shield 2006, Gates, Cooper & Kannel 1990) were done in US, Europe and UK and no data from India was available. Therefore, there is necessity to conduct large studies to evaluate prevalence of hearing loss in India. Another reason might be high occurrence of diabetes and hypertension in Indian population ((Mozaffari, Tajik, Ariaei, Ali-Ehayaii & Behnam 2010) which might pose to early age of hearing loss in Indian population.
In the UK, men were more prone to have hearing loss in age above 40. However, prevalence in women was less. In India, study by Rajendran et al. (2011) suggests that there is no gender difference in causation of sensorineural hearing loss. Findings of present study indicate that 56% of physicians said there is no discrimination of gender and 40% said hearing loss was more prevalent in men. There was mixed opinion (44% both opinions saying no discrimination among all job descriptions and for factory workers) amongst physicians regarding working style or job descriptions of patients who had SNHL. However, studies indicate that workers which are working in industrial environment or noisy places were more prone to have SNHL.

**Physician’s recommendations for hearing loss**

Semi-structured interviews of physicians suggest that sensorineural hearing loss occurs in both ears i.e. bilateral (76%). Results of clinical trial done in 120 patients in India suggest that SNHL was bilateral in most patients (Rajendran, Anandhalakshmi & Rao 2011) whereas study in South Korea showed that SNHL was unilateral. Pure tone audiometry was most preferred (72%) by physicians and audiologists. Along with this tympanometry or impedance test was also referred by 28% physicians. These tests help in providing estimation of degree of hearing loss.

Considering close association of diabetes and blood pressure with SNHL, it is necessary to recommend patients of these conditions to have audiometric test at least once a year. Around 52% of physicians and audiologists were aware of this fact and recommended audiometric tests. However, there are no such studies which signify importance of audiometric tests in diabetes and/or hypertension. There are no studies conducted in order to determine duration of diabetes and/or hypertension for conduction of audiometric tests. However, many physicians answered it could be 7 to 10 years. Majority of physicians (68%) recommended that audiometric test should be conducted once a year so as to ensure normal hearing of patient of diabetes and/or hypertension.

Family and medical history of conditions play crucial role in diagnosis of disease conditions. Findings of McMahan CM et al (2008) suggests strong relationship between maternal history and hearing loss. Particularly in case of diabetics, maternal family history plays significant role in causation of deafness in North Americans. Results of current study showed close relationship of family history with sensorineural hearing loss as per 84% of physicians. In case medical history of disease, results of present study suggested that all ENT surgeons and audiologists ask patients about history of diabetes and/or hypertension while conduction of audiometric tests.

Inner ear pathology is useful in determining underlying cause of sensorineural hearing loss as it is used to investigate structural and pathological changes in inner ear. Based on this, line of treatment can be initiated. This study showed that referral for inner ear pathology was advised by only 20% of physicians.

**Hearing related conditions**

Semi-structured interviews suggested drug therapy as first choice option for sensorineural hearing loss and hearing aid as second preferred choice. Drug therapy includes use of steroids, vasodilators, diuretics and use of low salt diets with controlled intake of sugar (Patient.co.uk, Nagaoka, Anjos, Takata, Chaim, Barros & Penido 2010). Therefore, findings of study were in accordance with recommendations of “Action on Hearing Loss, UK” (Patient.co.uk).

The choice of hearing aid depends totally on economical condition of patient as well as degree of severity of hearing loss. Completely in canal (CIC) type or in the canal (ITC) type of hearing aids were of no use if hearing impairment is profound. The age of patient is also another contributing factor for this. If age of patient is
greater than 60 and patient has dexterity problems; then audiologists generally refer pocket model or behind the ear (BTE) type of hearing aid. Results of our study indicated that behind the ear type of hearing aid was mostly preferred by patients (60% respondents). Govt. of India has National Program for Prevention and Control of Deafness (NPPCD) wherein hearing aids are provided and amount is reimbursed by governmental authority (Ministry of health and family welfare, Govt. of India). Particularly government provides reimbursement of 7000 INR for analogue BTE and 20,000 INR for digital BTE (Ministry of health and family welfare, Govt. of India). However, according to opinion of physicians, very few patients were aware of this scheme and avail this facility. Therefore, there is need to promote this program effectively by government. Even this program should be promoted in private clinics and hospitals so that every person with hearing impairment will get benefitted. Whenever, hearing impairment is profound, hearing aids are of no use. In such circumstances cochlear implants or bone conduction implants are necessary. Indian NPPCD program does not covers these implant procedures. However, there is need to devise such policy for implant procedures. In UK, these procedures are covered under NHS (Patient.co.uk).

Occurrence of tinnitus in SNHL patients suffering from diabetes and hypertension was 68% and in SNHL patients with diabetes was 16%. Even physicians suggest that there are 80% cases of subjective type of tinnitus. This fact also highlighted earlier indicating presence of unilateral and bilateral tinnitus. The presence of tinnitus could be attributed to damage to hair cells of cochlea leading partial loss of inhibitory functions of associated neurons causing firing of them even when no sound is present. Opinion of one male ENT surgeon with 29 years of experience was found to be similar as that of mechanism mentioned above.

Dysfunction in vestibular system results in vertigo. All respondents said that there exists close association of vertigo and SNHL. This statement is in accordance with different studies. Persistent high frequency sensorineural hearing loss due to dysfunction in basal turn of cochlea and vestibule leads to vertigo. Study have showed this fact in clinical trial in 67 patients. Occlusive arterial disease of inner ear caused due to hypertension leads to vertigo. Therefore findings of current study indicate relation of vertigo with SNHL along with presence or hypertension and diabetes.

**Diabetes SNHL, Hypertension**

*Duration of hypertension:* Report from US National Health and Nutrition Examination Survey from 1999 to 2002 suggest that cardiovascular risk factors (hypertension, smoking, and diabetes) are responsible for hearing loss (Mozaffari, Tajik, Ariaei, Ali-Ehayaii & Behnam 2010). Results of present study indicated that hypertension from 7 to 9 years (i.e. 4, 24 and 20% of respondents) could lead to SNHL.

*Range of blood pressure and underlying mechanism for SNHL:* Whenever range of blood pressure was concerned, 40% respondents said that 160/110 mmHg (systolic and diastolic) blood pressure was responsible to cause SNHL. The reason behind causation of SNHL due to hypertension is attributed to structural changes in blood supply of inner ear or inner ear haemorrhage leading to sudden or progressive hearing loss. Underlying pathological mechanisms might be increased blood viscosity, reduction in capillary blood flow, reduction in oxygen transport, hypoxia, and changes in ionic cell potentials. These cumulatively lead to hypertensive retinopathy (i.e. damage in end organ blood vessels). This in turn results in problems in hearing capacity (Kakarlapudi, Sayer & Staecker 2003, Marchiori, Filbo & Mastuo 2006). However, there is need of further investigation about duration of hypertension and its relation to severity of SNHL.
Results of study indicate that all physicians did not have knowledge about effect of antihypertensive drugs on hearing loss. However, literature suggests that diuretics were more prone to cause tinnitus and hearing loss as compared to angiotensin II receptor blockers.

**Insulin versus hypoglycaemic agents and its effect on SNHL:** This was much debated amongst scientific community that taking insulin for control of glycaemia would reduce diabetes and in turn SNHL. Thirty six percent of respondents of semistructured interview suggested that insulin reduces causation and progression of SNHL and 64% were unaware of any such kind of relationship. However, single blinded randomised controlled study by Celik et al. (1996) showed that neither insulin treatment nor oral hypoglycemics have effect on hearing thresholds. However, this study involved only 28 participants. Therefore, there is need to conduct randomised controlled trial involving more number of subjects of various ethnicities.

**Blood glucose levels:** Around 32% of physicians said that glucose levels of fasting 200 mg/dl and postprandial 350 mg/dl can cause SNHL. Similar results were obtained earlier by Rajendran et al (2011) which showed that 73.3% of diabetic individuals have SNHL with levels of glucose fasting 181 mg/dl and postprandial 286 mg/dl.

**Duration of diabetes:** Results of semi-structured interviews indicated that duration of diabetes from around 8 years could lead to SNHL. Similarly, in case control study, it was observed that diabetes was present since 5 to 15 years (2 cases of 5-10 years, 3 cases of 10-15 years). These results seem somewhat contrasting to results of earlier studies. Study by Rajendran et al. (2011) stated that duration of diabetes above or below 10 years including control of glycaemia of above or below 8 years had no effect on incidence of SNHL. It was also observed that increase in duration of diabetes up to 15 years, incidence of SNHL increased (Celik, Yalcin, Celebi, & Ozturk 1996). One study indicated higher incidence of hearing loss in females whereas other indicated higher incidence in males. In present study physicians opined that males were more prone to SNHL than females. There is need for further investigation using randomised controlled clinical trial. Relationship of obesity, high BMI with hypertension and diabetes is well known. Physicians in present study also said same fact. 88% of physicians opined that obesity and high BMI could cause diabetes and hypertension which in turn could lead to SNHL. Report by Shield (2006) state that obesity and high BMI were related to SNHL.

Results showed that 52% of physicians think high triglycerides and 20% physicians think high low density lipoprotein (LDL) levels were responsible factor for causation of SNHL. Results of this study were in accordance with earlier studies. The underlying mechanism behind causation of SNHL due to higher lipid levels was causation of spasm of spiralismodiolic artery and vestibulocochlear artery due to lipids (Oreskovsi, Shejbal, Bicanic & Kekic 2010, Swaminathan, Sambandam & Bhashkaran 2011).

**Conclusions**

Sensorineural hearing loss is most commonly observed form of hearing loss which occurs due to damage to inner ear or nerve pathways (particularly in vestibulocochlear nerve or cranial nerve VIII) or problems in central processing of brain. Diabetes and hypertension accounts for major healthcare problem in India. Literature search revealed that both diabetes and hypertension play important role in causation of sensorineural hearing loss. Therefore, there was need to evaluate relationship and frequency of diabetes and/or hypertension with sensorineural hearing loss.

Findings of study revealed that there exists close association of diabetes and/or hypertension with sensorineural hearing loss. It was found that out of all SNHL patients, there were 71.43% cases of diabetes; 39.29% cases of hypertension; and 53.57% of both diabetes and hypertension. SNHL was found to be more prevalent in
age group 50-60 years with moderate degree. It was found that medical and family history of diabetes and/or hypertension plays important role in causation of SNHL. Behind the ear (BTE) type of hearing aid was most used in patients of SNHL. High LDL, BMI, blood pressure and glucose levels are risk factors for causation of SNHL. Tinnitus and vertigo also have close relationship with causation of SNHL.

There is need to conduct large scale multicentric randomised controlled clinical trial to investigate and confirm association of diabetes and/or hypertension with sensorineural hearing loss. Apart from this, awareness amongst public regarding hearing loss, usefulness of hearing aid, control of diabetes and/or hypertension is essential.

References


Literature review of Triple-negative breast cancer metastasis to lungs and its management through Chemotherapy

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Abstract

The present study is a review of literature that covers an aspect of role of BRCA1 gene mutation in breast cancer metastasis, risk of recurrence influenced by stage at initial presentation, the underlying biology of the tumor, time of relapse after diagnosis of the primary tumor, reasons for metastasis, various biological markers discovered up till date, discussion of several mathematical models, with a focus on how they have been used to predict the initiation time of metastatic growth, and standard choice of treatment best suited for triple negative breast cancer metastasis.

Breast cancer starts as a local disease, but it could metastasize to the lymph nodes and distant organs. As by definition, Metastatic breast cancer, also known as Advanced or Stage IV breast cancer, is the stage in breast cancer progression in which malignant cells from the primary tumor successfully create new tumors in distant organs. According to the Research studies, women who have BRCA1 mutations are at higher risk for triple negative breast cancer. The prognosis of women with triple negative breast cancers (ER-negative, PR-negative and HER2-neu –negative) is poor as compared to women with other subtypes of breast cancer. TNBC relapses more frequently than hormone receptor-positive subtypes and is often associated with poor outcomes.

Patients and oncologists always have a dilemma on how to cope with this aggressive disease. For patients, the diagnosis of breast cancer is fearsome; so when they know additionally that they suffer from TNBC—a subtype with poor outcomes—this situation is often more stressful. TNBC patients have a unique pattern of relapse, which occurs mostly in the first 3 years following diagnosis. Although metastatic breast cancer is not curable, meaningful improvements in survival have been seen, coincident with the introduction of newer systemic therapies.

Keywords: TNBC (Triple Negative Breast Cancer), Metastasis, tumor, ER-negative, PR-negative, HER2-neu negative, BRCA1 mutations, Overall Survival, Lungs, Mathematical Models, Recurrence, Chemokines, Chemotherapy.

Introduction

The aim of this review study is to assess the rate, pattern and time of recurrence in patients with TNBC and to evaluate factors influencing recurrence and overall survival in this group of patients. The preferential site of metastasis varies by breast cancer subtype, with TNBC preferring visceral organs, for example, the lungs (Pogoda et al., 2013). A major goal of this study is to identify the genes that drive metastasis in patients with TNBC and determine their mechanism of action (Pogoda et al., 2013). The goals of the study are to:

(i) Identify the transcriptional changes that drive breast cancer metastasis to the lungs (Pogoda et al., 2013).
(ii) Functionally characterize how these changes contribute to breast cancer metastasis (Pogoda et al., 2013).
(iii) Validate the findings in human breast cancer samples (Pogoda et al., 2013).
(iv) Clinical and Preclinical Evidences to support the study.
This review would highlight focus on molecular features, risk/epidemiological factors, patterns of metastatic spread, prognostic implications, novel “targets”, and emerging therapeutic strategies for this clinically challenging and aggressive entity. Tumor metastasis is a multistage process during which malignant cells spread from the primary tumor to distant organs (Talmadge & Fidler, 2010). A person who has a BRCA1 mutation is called as BRCA1 carrier and BRCA1 carriers have a 55 to 65% chance of developing breast cancer by the age of 70 (Deng, 2006).

Triple negative is an unsatisfactory category in the following 3 ways:
1. It is not a biologically homogeneous subgroup (Pestalozzi, 2009).
2. It does not help to select a particular treatment (Pestalozzi, 2009).
3. Overall prognosis is poor (Pestalozzi, 2009).

Pathogenesis of metastasis

The term “Metastasis” was coined in 1829 by Jean Claude Recaimer (Talmadge & Fidler, 2010). The pathogenesis of metastasis involves a series of steps, dependent on both the intrinsic properties of the tumor cells and the host response (Talmadge & Fidler, 2010). The spread of cancer or metastasis entails various biological processes.

1. The Cancer cells invade nearby healthy cells. When the healthy cell is taken over, it too could replicate more abnormal cells (Talmadge & Fidler, 2010).
2. Cancer cells penetrate into the circulatory or lymph system. Cancer cells travel through the walls of nearby lymph vessels or blood vessels (Talmadge & Fidler, 2010).
3. Migration through circulation. Cancer cells are carried by the lymph system and the bloodstream to other parts of the body (Talmadge & Fidler, 2010).
4. Cancer cells lodge in capillaries. Cancer cells stop moving as they are lodged in capillaries at a distant location and divide and migrate into the surrounding tissue (Talmadge & Fidler, 2010).

Below given is the illustration of pathogenesis of Metastasis as hypothesized by different authors:

<table>
<thead>
<tr>
<th>Author/ Study</th>
<th>Hypothesis/Theory</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stephen Paget</td>
<td>Identification of the role of host-tumor cell interactions. Remarks: High incidence of metastasis to the liver, ovary due to discrepancy between the blood supply and frequency of metastasis to specific organs (Talmadge &amp; Fidler, 2010).</td>
</tr>
<tr>
<td>Virchow Theory</td>
<td>Metastasis could be explained simply by the arrest of tumor-cell emboli in the vasculature (Talmadge &amp; Fidler, 2010).</td>
</tr>
<tr>
<td>Paget Observation</td>
<td>Remote organs cannot be altogether passive or indifferent regarding embolism (Talmadge &amp; Fidler, 2010).</td>
</tr>
<tr>
<td>Ewing</td>
<td>Mechanical forces and circulatory patterns between the primary tumor and the secondary site accounted for organ specificity (Talmadge &amp; Fidler, 2010).</td>
</tr>
</tbody>
</table>
Fidler & coworkers Although tumor cells traffic through the vasculature of all the organs, metastases selectivity develops in congenital organs (Talmadge & Fidler, 2010).


Biology of Metastasis

<table>
<thead>
<tr>
<th>YEAR</th>
<th>Theory</th>
</tr>
</thead>
<tbody>
<tr>
<td>1991</td>
<td>Relationship between Metastasis and Angiogenesis in breast cancer (Talmadge &amp; Fidler, 2010).</td>
</tr>
<tr>
<td>1994</td>
<td>Removal of malignant primary tumor in mice spurs growth of remote tumors, or Metastases (Talmadge &amp; Fidler, 2010).</td>
</tr>
<tr>
<td>1997</td>
<td>Visualization of tumor cell invasion and metastases using GFP expression (Talmadge &amp; Fidler, 2010).</td>
</tr>
<tr>
<td>2000</td>
<td>Gene expression pattern diversity in breast cancer tissue (Talmadge &amp; Fidler, 2010).</td>
</tr>
<tr>
<td>2001</td>
<td>Role of cancer stem cells in Metastasis (Talmadge &amp; Fidler, 2010).</td>
</tr>
<tr>
<td>2002</td>
<td>EMT could explain metastatic progression (Talmadge &amp; Fidler, 2010).</td>
</tr>
<tr>
<td>2002</td>
<td>Heterogeneity of single disseminated tumor cells in minimal residual cancer (Talmadge &amp; Fidler, 2010).</td>
</tr>
<tr>
<td>2002</td>
<td>Metastatic potential determined early in tumorigenesis; metastatic molecular signature in primary tumor (Talmadge &amp; Fidler, 2010).</td>
</tr>
<tr>
<td>2002</td>
<td>Gene-expression profile of primary breast cancer associated with metastasis and poor outcome (Talmadge &amp; Fidler, 2010).</td>
</tr>
<tr>
<td>2003</td>
<td>Breast cancer metastasis ability resides in a few breast cancer stem cells by highly resistant to chemotherapy (Talmadge &amp; Fidler, 2010).</td>
</tr>
<tr>
<td>2006</td>
<td>Role of genetic susceptibility for metastasis (Talmadge &amp; Fidler, 2010).</td>
</tr>
<tr>
<td>2007</td>
<td>First metastasis-promoting micro-RNA (Talmadge &amp; Fidler, 2010).</td>
</tr>
<tr>
<td>2008</td>
<td>Micro-RNA expression patterns can predict metastatic risk (Talmadge &amp; Fidler, 2010).</td>
</tr>
<tr>
<td>2008</td>
<td>Micro-RNAs can suppress metastases (Talmadge &amp; Fidler, 2010).</td>
</tr>
</tbody>
</table>


Classification of breast cancer metastasis

1. Local Recurrence: It is the breast area where the cancer was originally diagnosed (As cited in...
2. Regional Recurrence: Spread of the cancer cell to the lymph nodes in the armpit or collarbone area where the cancer was originally diagnosed (As cited in http://www.breastcancer.org/symptoms/types/recur_metast/where_recur/metastatic).

3. Metastatic or Distant Recurrence: Spread of cancer to another part of the body such as lungs, bones, or brain (As cited in http://www.breastcancer.org/symptoms/types/recur_metast/where_recur/metastatic).

4. Symptoms of Metastatic Recurrence: According to the American Society of Clinical Oncology (ANCO) guidelines on breast cancer follow-up and management, symptoms of breast cancer recurrence include presence of new breast lumps, pain in the bone, chest or abdomen, dyspnea and constant headaches (Scully et al., 2012). Various other symptoms included, Constant back, bone or joint pain, Difficulty with urinating, Numbness or weakness anywhere in the body, Constant dry cough, Difficulty breathing, Shortness of breath, Chest pain, Loss of appetite, Abdominal bloating, pain or tenderness, Constant nausea, vomiting or weight loss, Jaundice, Severe headaches, Vision problems (blurry vision, double vision, loss of vision), Seizures, Loss of balance (unsteadiness), Confusion, Difficulty with speech, Memory problems, Changes in Pleural effusion (As cited in http://www.breastcancer.org/symptoms/types/recur_metast/where_recur/metastatic).

Pathological features of Tumor with TNBC BRCA1 mutations: Various pathological features included, High grade cancers, High mitotic index, Lymphocytic infiltrate, “Pushing” tumor margins with smooth edges, High proliferation rate, Nuclear Pleomorphism, Ductal and metaplastic histology, p53 mutations (Anders et al., 2009) & (Hedenfalk et al., 2001). Moreover, TNBC tumors often present as interval cancers with weak relationship between tumor size and node status (Dent et al., 2007).

Immunophenotypic characteristics of Tumor with TNBC BRCA1 mutations: It includes the properties such as Estrogen receptor negative, HER 2 negative, P-cadherin negative, P63 negative, C-kit positive, Vimentin positive, Cytokeratin positive (Anders et al., 2009) & (Hedenfalk et al., 2001).

1. Epidemiology of Triple-negative breast cancer: The incidence of breast cancer is increasing almost everywhere throughout the world (Boyle, 2012). Only a decade ago, breast cancer was considered a relatively ‘simple’ disease in many respects, with focus essentially on quantifying whether a tumor was, or was not, dependent on estrogen, a situation which had lasted for a century (Boyle, 2012). A quiet revolution has occurred, and breast cancer is now characterized by its molecular and clinical heterogeneity (Boyle, 2012). Perou et al. were the first to describe the various molecular sub-types or molecular profiles of breast cancers (As cited in http://www.breastcancer.org/symptoms/types/recur_metast/where_recur/metastatic).

5. They described four sub-types based on cDNA micro-arrays, including a basal-like sub-type of breast cancer, and noted that most triple-negative tumors clustered in the basal-like sub-type (As cited in http://www.breastcancer.org/symptoms/types/recur_metast/where_recur/metastatic).
Of the global breast cancer burden, it has been estimated that ~170,000 are TNBC and are often, but not always, basal-like breast cancer; another study has estimated that ~75% are basal-like (Boyle, 2012).

Studies have shown that breast cancers in women with germ line BRCA1 mutations are more likely to be triple negative and high grade (Ismail-Khan & Bui, 2010). Gene expression studies have confirmed this phenomenon and BRCA1-associated breast cancer appear to cluster in the basal-like subtype (Ismail-Khan & Bui, 2010). The highest risk of relapse in TNBC patients is between the first and third year after primary treatment (Pogoda et al., 2013). In cases of recurrence, the survival is shorter than in non-TNBC patients (Pogoda et al., 2013). The global cancer control, GLOBOCAN series summarized cancer incidence and mortality in 182 countries (Anderson et al., 2013). The data indicated that breast cancer was the most frequent cancer in women, the second most frequent cancer overall and the leading cause of all cancer death in women (Anderson et al., 2013). A treatment approach that stratifies subtypes and receptor status will allow for an optimal and unique therapeutic advantage (Anderson et al., 2013). The tumor classification depends on the size and extent of tumor in the breast (Anderson et al., 2013).

**Cancer Susceptibility Gene: BRCA1**: It is mapped to a region on chromosome 17q through linkage studies (Marcus et al., 1996). If the tumors are “negative” then there are few or none receptors. TNBC is very unique as it is very aggressive and tends to grow faster (Marcus et al., 1996). It could be treated but it might recur early and spread to other parts of the body due to lack of targeted treatments (Marcus et al., 1996). Metastasis can be viewed as an evolutionary process, culminating in the prevalence of rare tumor cells that overcame stringent physiological barriers as they separated from their original environment and developmental fate (Nguyen et al., 2007). This phenomenon brings into focus long-standing questions about the stage at which cancer cells acquire metastatic abilities, the relationship of metastatic cells to their tumor of origin, the basis for metastatic tissue tropism, the nature of metastasis predisposition factors and, importantly, the identity of genes that mediate these processes fate (Nguyen et al., 2007).

**Breast Cancer Subtypes**: Breast cancer can be divided into subtypes based upon a common phenotype or genotype that co-relates with a consistent response to certain treatments (Anderson et al., 2013). The most common phenotype, hormone receptor positive breast cancer, is characterized by expression of either or both the estrogen receptor (ER) and Progesterone receptor (PR) (Anderson et al., 2013). The normal breast cancer subtype is poorly characterized and appears to possess an intrinsic subtype similar to fibroadenomas and normal breast samples (Anderson et al., 2013). Basal breast tumors are almost entirely estrogen-, progesterone-, and HER2-negative, making the triple-negative phenotype a sensitive and practical surrogate marker for basal breast cancer (Kennecke et al., 2010). The 4 molecular subgroups of breast cancer vary importantly with respect to clinical features, natural history, and outcomes (Kennecke et al., 2010). In particular, the basal or triple-negative phenotype appears to have a more aggressive course than other breast cancers, with shorter disease-free survival and overall survival (OS) times (Kennecke et al., 2010).

**Evidence**: The fact that the majority of BRCA1-associated breast cancers are also triple-negative and basal-like leads researchers to wonder about the extent to which the BRCA1 pathway contributes to the behavior of “sporadic” basal-like breast cancers (Ismail-Khan & Bui, 2010). It has been shown that basal-like breast carcinomas frequently harbor defects in DNA double-strand break repair through homologous recombination such as BRCA1 dysfunction (Ismail-Khan & Bui, 2010).
INSTRINSIC SUBTYPE MODEL

Luminal A
- mostly corresponds to the hormone receptor positive phenotype
- Represents 50-60% of all breast cancers
- characterized by an absence of HER2 expression
- low histological grade & expression of ER, PR & Cytokeratin

Luminal B
- expresses an EGFR & HER 2 molecular profile
- constitutes to between 10-20% of all breast cancers
- more aggressive phenotype, worse prognosis
- high histological grade & high proliferative index

HER 2-
Characterized by 15-20% of primary breast cancer
Clinically co-related with a poor prognosis

Basal -
- Represents 10-20% of all breast cancer
- tend to be infiltrating ductal carcinomas with a high mitotic index, tumor necrosis and expanding margins
- Basic expression of genes of high molecular weight, cytokeratins CK5 & CK17, P cadherin and caveolin 1 & 2

Normal
- 5-10% of all breast cancers
- poorly characterized appears to possess an intrinsic subtype similar to fibroadenomas and normal breast samples

Claudin-low
- low expression of genes
- correlated with the formation of tight junctions and intercellular adhesions

Figure 1: Breast cancer subtypes
Molecular Biology of Breast Metastasis: Mathematical Models

These models are used to predict the initiation time of Metastatic growth (Clare et al., 2000).

Table 3: Mathematical models representing molecular biology of breast metastasis.

<table>
<thead>
<tr>
<th>Mathematical Model</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Gompertz Model</td>
<td>Mainstay for models of solid tumors, including breast cancer for a considerable period of time. This model is a modification of exponential growth, with the addition of a decreasing growth rate over time. This decelerated growth causes the cancer to asymptotically approach a limiting size, referred to as its carrying capacity. This limited growth is attributed to several factors, including hypoxia and the lack of nutrients (Clare et al., 2000).</td>
</tr>
<tr>
<td>2. Speer et al. Model</td>
<td>Observation of the subclinical duration of growth given by the original Gompertz growth equation, using a range of parameter values which is too short, i.e., approx. 4 months (Clare et al., 2000).</td>
</tr>
<tr>
<td>3. Spratt et al. Model</td>
<td>Indicated that, although the original Gompertz model can give a good approximation to clinical tumor growth over the short term, the growth rate of the cancer is more likely to be stochastic over the full history of the cancer. This allows for various growth patterns, including dormancy (Clare et al., 2000).</td>
</tr>
<tr>
<td>4. Spratt et al. Model</td>
<td>Determined from the mammogram data that the median doubling time is 260 days for breast tumors at detectable levels. In fact, he considered one of the slower growing breast cancers that they observed, with a doubling time of 7051 days (Clare et al., 2000).</td>
</tr>
<tr>
<td>5. Koscielnny et al. Model</td>
<td>Concluded that the metastatic doubling time is 2.2 times faster than that of the primary. The number of cells needed for metastatic initiation is greater than a single cell. The growth duration of metastasis is approx. 3.8 years (Clare et al., 2000).</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>6.</td>
<td>Retsky &amp; coworkers, Denicheli et al., Swartzendruber et al.</td>
</tr>
<tr>
<td>7.</td>
<td>Norton &amp; Simon Model</td>
</tr>
<tr>
<td>8.</td>
<td>Goldie – Coldman Model</td>
</tr>
</tbody>
</table>


According to Gompertzian kinetics, as the tumor becomes smaller, its growth fraction increases and it regrows at a faster rate. (Clare et al., 2000). At some point the rate of cell kill might equal the rate of cell repopulation, and the cell population would approach asymptotic limit (Clare et al., 2000). If the asymptotic limit after chemotherapy is always greater than one cell, a cure will never be effected (Clare et al., 2000). However, if it is less than one cell, a cure could reasonably be expected (Clare et al., 2000).

Thus, it could be concluded from the above demonstrated mathematical models that the metastatic growth rate is proportional to the size of the tumor from which it was derived (Clare et al., 2000). Secondly, the probability of metastasis is related to the primary tumor doubling time (Clare et al., 2000).

**Effects of surgery on Metastasis:** According to Retsky et al., the distribution included a sharp peak of relapse at 18 months and another broad peak at 60 months after surgery (Clare et al., 2000). They attributed the bimodal distribution to the effects of surgery on promoting metastatic growth (Clare et al., 2000). The higher rates of relapse among patients with triple-negative breast cancer appeared attributable to residual disease at the time of surgery, highlighting a need for either more effective neoadjuvant therapies or defined adjuvant, residual disease protocols (Anders & Carey, 2009). Metastasis is unpredictable in onset and it exponentially increases the clinical impact to the host (Talmadge & Fidler, 2010).

**Evidence 1:** The cell line MDA-MB-231 was derived from the pleural effusion of a breast cancer patient suffering from widespread metastasis years after removal of her primary tumor (Andy et al., 2005). Individual MDA-MB-231 cells grown and tested as single-cell-derived progenies (SCPs) had distinct metastatic abilities and tissue tropisms despite having similar expression levels of genes constituting a validated Rosetta-type poor prognosis signature (Andy et al., 2005). These different
metastatic behaviors, including different tropisms to bone and lungs, were associated with discrete variation in overall gene expression patterns (Andy et al., 2005).

**Recurrence**: TNBC has a characteristic pattern of recurrence. During the 6 years of observation, the metastatic disease occurred in one-third of all TNBC patients (including these 9 patients initially with stage IV disease): 15 % in the brain, 14 % in the lungs, 11 % in the bones, 8 % in the liver, and 14 % patients had locoregional relapse (Rakha et al., 2008). The most common site of the first recurrence was lungs (Rakha et al., 2008). The highest risk of recurrence was during the first 3 years after primary treatment, and then, during the next 2 years of observation, it did not change significantly (Rakha et al., 2008). Dent et al. reported that in their study the risk of recurrence rose sharply from the date of diagnosis, peaked at 1–3 year interval and then dropped quickly (Anders & Carey, 2009). Liedtke et al reported that patients with triple-negative breast cancer have higher rates of recurrence in visceral organs and soft tissue, with lower rates of bone disease, compared with hormone-sensitive counterparts (Anders & Carey, 2009). Similar results were reported among 344 lymph node–negative primary breast tumors subject to molecular classification (Anders & Carey, 2009). Lung relapse was most abundantly seen among patients with breast tumors classified as basal-like breast tumors (Anders & Carey, 2009).

Factors influencing recurrence were tumor size and systemic adjuvant chemotherapy, while factors influencing overall survival were tumor size, nodal status, adjuvant/neoadjuvant treatment, and metastases (Pogoda et al., 2013). The tumor size was responsible for recurrence despite lack of involvement of lymph nodes (Pogoda et al., 2013).

<table>
<thead>
<tr>
<th>Site of metastases</th>
<th>After 1 year (%)</th>
<th>After 2 years (%)</th>
<th>After 3 years (%)</th>
<th>After 5 years (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brain</td>
<td>4.3</td>
<td>12</td>
<td>16</td>
<td>17.6</td>
</tr>
<tr>
<td>Lungs</td>
<td>3.8</td>
<td>10.7</td>
<td>15.1</td>
<td>15.7</td>
</tr>
<tr>
<td>Liver</td>
<td>4.2</td>
<td>6.5</td>
<td>9.1</td>
<td>9.1</td>
</tr>
<tr>
<td>Bones</td>
<td>4.3</td>
<td>6.7</td>
<td>8.1</td>
<td>9.4</td>
</tr>
<tr>
<td>Local recurrence</td>
<td>3.9</td>
<td>13.3</td>
<td>13.9</td>
<td>14.6</td>
</tr>
</tbody>
</table>

*Source*: Triple-Negative Breast Cancer and PTEN (Phosphate and Tensin Homologue) loss are predictors of BRCA1 Germline Mutations in women with Early-onset and familial Breast Cancer, but not in women with isolated late-onset breast cancer, (2012) (Phuah et al., 2012).
Figure 2: Most common metastasis sites of breast cancer at autopsy
Below is the illustration of Breast cancer metastasis prognostic markers:

<table>
<thead>
<tr>
<th>Marker</th>
<th>Use in clinic</th>
<th>Metastatic determinants</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tumor Size</td>
<td>Established</td>
<td>Tumors under 2 cm in diameter have a low risk of metastasis; Tumors of 2-5 cm have a high risk of metastasis; Tumors over 5 cm have a very high risk of metastasis</td>
<td>Independent Prognosis marker</td>
</tr>
<tr>
<td>Axillary lymph-node status</td>
<td>Established</td>
<td>If there are no lymph-node metastases, the risk of metastasis is low, if lymph-node metastases are present, the risk of metastasis is high; the presence of over 4 lymph-node metastases is associated with very high metastasis risk</td>
<td>Related to tumor size</td>
</tr>
<tr>
<td>Histological grade</td>
<td>Established</td>
<td>Grade 1 tumors have a low risk of metastasis, Grade 2 tumors have an intermediate risk of metastasis,</td>
<td>Related to tumor size</td>
</tr>
</tbody>
</table>
### Table: \( \text{Grade 3 tumors have a high risk of metastasis.} \)

<table>
<thead>
<tr>
<th>Angioinvasion</th>
<th>Established in patients with lymph-node-negative tumors</th>
<th>The presence of tumor emboli in over 3 blood vessels is associated with metastasis</th>
<th>In patients with lymph-node-negative tumors</th>
</tr>
</thead>
<tbody>
<tr>
<td>uPA/PAI1 protein level</td>
<td>Newly established marker</td>
<td>High protein levels of uPA and PAI1 are associated with high metastasis risk</td>
<td>Independent Prognosis marker</td>
</tr>
<tr>
<td>Steroid-receptor expression</td>
<td>Established for adjuvant therapy decision</td>
<td>Low steroid-receptor levels are associated with metastasis</td>
<td>Short term predictor of metastasis risk (5 years); related to histological grade</td>
</tr>
<tr>
<td>Gene-Expression Profiling</td>
<td>Currently being tested</td>
<td>A 'good signature' of 70 genes is associated with low metastasis risk; A 'poor signature' of 70 genes is associated with high metastasis risk</td>
<td>Tested in patients with lymph-node-negative tumors</td>
</tr>
</tbody>
</table>


**Role of Chemokines in the process of Metastasis to lungs:** Breast cancer tissue highly expresses the chemokine receptor, chemokine (L-X-C motif) receptor 4 (CXCR4) while its ligand, chemokine (C-X-C motif) ligand 12 (CXCL 12) is predominantly expressed in lymph nodes, lung, liver and bone marrow (Scully et al., 2012). Organs with higher expression of CXCL 12 are associated with being common sites of metastatic breast cancer (Scully et al., 2012). Muller et al. demonstrated that the CXCR4-CXC12 interaction and the cadherin family encouraged breast cancer metastasis (Scully et al., 2012). Down-regulation of E-cadherin and up-regulation of N-cadherin was shown to be a determinant in the outgrowth of metastatic breast cancer cells (Scully et al., 2012).

**Evidence 1:** There is compelling evidence that the stromal cells aid migration of tumor cells (Scully et al., 2012). The majorities of stromal cells within breast cancer are fibroblasts and are usually referred to as carcinoma associated fibroblasts (CAFs) (Scully et al., 2012). Immunodeficient nude mice when injected with both human CAFs & MCF7-ras human breast cancer cell lines, exhibited enhanced breast tumor growth and angiogenesis when compared to mice injected with normal human fibroblasts (Scully et al., 2012).

In a similar manner, tumor–stroma interactions, occurring via soluble growth factors, cytokines and chemokines, remodeling of the extracellular matrix, or direct cell–cell adhesion, are critical for tumor growth, migration, and metastasis (Fantozzi & Christofori, 2006). Alteration of the expression or function of adhesion molecules responsible for the adhesion of breast cancer cells to themselves, to stromal cells, or to tumor matrix, including integrin family members, immunoglobulin-domain cell adhesion molecules (such as L1 and NCAM), cadherin family members, or other cell surface receptors (such as CD44), contributes predominantly to late stage tumor...
progression and metastatic dissemination of cancer cells (Fantozzi & Christofori, 2006). The cross-talk and interactions between tumor cells and the surrounding stroma, the extracellular matrix (ECM), and infiltrating cells of the immune system are constantly modulating tumor development (Fantozzi & Christofori, 2006). The formation of new blood vessels (angiogenesis) is crucial for the growth and persistence of primary solid tumors and their metastases, and it has been assumed that angiogenesis is also required for metastatic dissemination, because an increase in vascular density will allow easier access of tumor cells to the circulation (Fantozzi & Christofori, 2006). Induction of angiogenesis precedes the formation of malignant tumors, and increased vascularization seems to correlate with the invasive properties of tumors and thus with the malignant tumor phenotype (Fantozzi & Christofori, 2006). Pulmonary involvement is common for TNBC metastasis patients’ because of the circulation of entire cardiac output through the lung capillary network (Gluz et al., 2009). Most commonly, lung metastatic lesions initiate at the level of small pulmonary arterioles, where they must either burst through or otherwise breach both the tight endothelial junctions of lung blood vessels and the underlying basement membrane (Gupta & Massagué, 2006). Once in the lung parenchyma, metastatic cells might survive and grow in this unique microenvironment, which contains highly organized extracellular matrix and specialized cell types for the purpose of respiration (Gupta & Massagué, 2006).

Through the research, a molecular switch has been discovered according to which the TNBC cells mature as amoeba-like protrusions which then escape from a primary tumor to metastasize throughout the body (Weill Cornell Medical College, 2013, January 14). Thus, the role of miRNA was examined in the spread of TNBC, which accounts for 15% to 25% of all the breast tumors (Weill Cornell Medical College, 2013, January 14). Secondly, the process of focal adhesion signaling cascade was found to be important modulator for organ-specific relapse (Smid et al., 2008).

**Evidence 2**: In breast cancer, the TGFβ and NF-κB pathways had been implicated in lung metastasis (Gupta & Massagué, 2006). During in vivo lung metastasis of breast-cancer cells a gene-expression signature was identified that was highly enriched in mediators of pulmonary metastasis (Gupta & Massagué, 2006). This diverse set of genes encoded for secreted factors (including epiregulin, CXCL1, and SPARC), cell-surface receptors (e.g., VCAM1 and IL13Rα2), extracellular proteases (e.g., MMP1 and MMP2), and intracellular effectors (e.g., Id1 and COX2), which cooperated to promote lung metastasis (Gupta & Massagué, 2006). Significantly, these genes were further validated in a cohort of primary breast tumors, where expression of these genes correlated with lung metastatic relapse in the corresponding patients (Gupta & Massagué, 2006).

**Evidence 3**: For the lung relapse patients, Focal adhesions cascade played an important role (Smid et al., 2008). Focal adhesions are specific types of large protein complexes through which the cytoskeleton of a cell connects to and communicates with the extracellular matrix (Smid et al., 2008). Of the focal adhesion genes that were annotated by KEGG, many are up-regulated in the luminal A subtype and down-regulated in tumors from patients who had a lung relapse (Smid et al., 2008). Because very few patients in the luminal A subtype had relapses to the lung, it seemed that the involved focal adhesion molecules impede a lung relapse (Smid et al., 2008).

**Evidence 4**: In both laboratory cells and in animal studies, Vivek Mittal, PhD, of well Cornell Medical College along with his colleagues identified the function of miR-708 which is located on cell membrane of endoplasmic reticulum, in order to suppress the protein neuronatin (Weill Cornell Medical College, 2013, January 14). According to this research, neuronatin controls the level of calcium in and out of the organelle (Weill Cornell Medical College, 2013, January 14). It is calcium that provided legs to the cancer cells escape a primary tumor (Weill Cornell Medical
So, miR-708 acted as a suppressor of metastasis by keeping neuronatin in check (Weill Cornell Medical College, 2013, January 14). If miR-708 is itself suppressed, there was an increase in production of neuronatin proteins, which then allowed more calcium to leave the endoplasmic reticulum and activated a cascade of genes that turn on migratory pathways leading to metastasis (Weill Cornell Medical College, 2013, January 14). Moreover, it was found that delivering synthetic miR-708, carried by bubbles of fat, blocked metastatic outgrowth of TNBC in the lungs of mice (Weill Cornell Medical College, 2013, January 14).

Evidence 5: The intravenous injection of radiolabeled B16 melanoma cells revealed that by 24 hours after injection into the circulation, 0.1% or less of the cells were still viable, and less than 0.01% of tumor cells within the circulation survived to produce experimental lung metastases (Talmadge & Fidler, 2010).

Evidence 6: Wnt signaling:

Wnt family members were the first proto-oncogenes to be discovered by an MMTV-mediated insertion–activation mechanism (Fantozzi & Christofori, 2006). Transgenic expression of Wnt-1 in the mammary gland of transgenic mice resulted in mammary adenocarcinomas with metastasis to lymph nodes and lungs (Fantozzi & Christofori, 2006).

Evidence 7: To identify genes that mediated lung metastasis testing was done on parental MDA-MB-231 cells and the 1834 sub-line (an in vivo isolate with no enhancement in bone metastatic behavior) by injection into the tail vein of immunodeficient mice (Andy et al., 2005). Metastatic activity was assayed by bioluminescence imaging (BLI) of luciferase-transduced cells as well as gross examination of the lungs at necropsy (Andy et al., 2005). The 1834 cells exhibited limited but significant lung metastatic activity compared with the parental population (Andy et al., 2005). When 1834-derived lung lesions were expanded in culture and reinoculated into mice, these cells (denoted LM1 subpopulations) showed increased lung metastatic activity (Andy et al., 2005).

To test this, a cohort of 82 breast cancer patients was used in a univariate Cox proportional hazards model to relate the expression level of each lung metastasis signature gene with clinical outcome (Andy et al., 2005). Twelve of the 54 genes are significantly associated with lung-metastasis-free survival, including MMP1, CXCL1 and PTGS2 (Andy et al., 2005). A cross-validated multivariate analysis using a linear combination of each of the 54 genes weighted by the univariate results distinguished between patients with a high risk and those with a low risk for developing lung metastasis (10-year lung-metastasis-free survival of 56% versus 89%, P = 0.0018) (Andy et al., 2005). When a similar multivariate analysis was performed by weighting each gene by a t-statistic derived from a comparison of its expression between the LM2 cell lines with that of the parental MDA-MB-231 cells, the 54 genes again distinguished patients at high risk for developing lung metastasis (62% versus 88%, P = 0.01) (Andy et al., 2005). These results indicate that a clinically relevant subgroup of patients might express certain combinations of lung metastasis signature genes (Andy et al., 2005). To identify patterns of gene expression associated with aggressive lung metastatic behavior, a transcriptomic microarray analysis of the highly and weakly lung-metastatic cell populations was performed (Andy et al., 2005). The gene list obtained from a class comparison between parental and LM2 populations was filtered to exclude genes that were expressed at low levels in a majority of samples and to ensure a threefold or higher change in expression level between the two groups (Andy et al., 2005). A total of 95 unique genes (113 probe sets) met these criteria: 48 were overexpressed and 47 under expressed in cell populations most metastatic to the lungs (Andy et al., 2005).

Evidence 8: A subset of biologically interesting genes overexpressed in the 54 gene list was selected for functional validation (Andy et al., 2005). These genes
included those encoding the epidermal-growth-factor family member epiregulin (EREG), which is a broad-specificity ligand for the HER/ErbB family of receptors, the chemokine GRO1/CXCL1, the matrix metalloproteinases MMP1 (collagenase 1) and MMP2 (gelatinase A), the cell adhesion molecule SPARC, the interleukin-13 decoy receptor IL13Rα2 and the cell adhesion receptor VCAM1 (Andy et al., 2005). These genes encoded secretory or receptor proteins, indicating possible roles in the tumor cell microenvironment (Andy et al., 2005). In addition to these genes, we included the transcriptional inhibitor of cell differentiation and senescence ID1 (Andy et al., 2005). To determine whether these genes have a causal function in lung metastasis, they were overexpressed by retroviral infection in the parental population either individually, in groups of three, or in groups of six (Andy et al., 2005). Only cells overexpressing ID1 alone were modestly more active at forming lung metastases than cells infected with vector controls. Combinations of these genes invariably led to more aggressive metastatic activity (Andy et al., 2005).

Detection of Breast Cancer Metastasis

1. Biopsies of affected organs (Scully et al., 2012).
2. Radiological evaluations (Scully et al., 2012).
3. Imaging methods and serum tumor markers (Scully et al., 2012).
4. Bone Scintigraphy (Scully et al., 2012).
5. Liver echography (Scully et al., 2012).
6. Chest X-ray (Scully et al., 2012).

Evidence 1: Nicolini et al. emphasized that the inclusion of serum tumor markers is an important factor in the post-operative monitoring of breast cancer patients (Scully et al., 2012).

Evidence 2: Another suggestion is to have intense post-operative follow up which include consultations every 4-6 months, physical examination and evaluation of serum carcinoembryonic antigen (CEA), tissue polypeptide antigen (TPA) and breast cancer associated Ag 115, D8/DF3 (CA15.3), at each visit (Scully et al., 2012).

Evidence 3: Circulating Tumor cells are the tumor cells originating from primary sites or metastases that circulate in patients’ blood stream (Scully et al., 2012). Circulating tumor cells are recognized as playing important roles in the metastasis of carcinomas and their analysis enables the prediction of metastatic relapse and progression (Scully et al., 2012).

Management of TNBC metastasis through novel “Targeted” therapeutic agents

Clinical and pathological risk factors, such as age, tumor size and steroid receptor status, are commonly used to assess the likelihood of metastasis development (Chuang et al., 2007). A better understanding of patterns of metastatic spread might influence adjuvant therapy and surveillance decisions and determine which investigations and therapies are appropriate once distant disease has been diagnosed (Kennecke et al., 2010).

Factors influencing Chemotherapy Choice: There are many agents including single agent or a combination regimen available for treating TNBC, yet there is no sequence of treatment that could be ideally applied to all the patients suffering (Schott et al., 2015). However, below given is the illustration of the principles that can guide the choice of therapy in the first- or later-line setting (Schott et al., 2015).

1. Tumor burden — Tumor burden (the extent of disease detected on imaging or clinical exam and/or the presence of tumor-related symptoms) can impact on whether single-agent chemotherapy or a combination regimen is to be administered (Schott et al., 2015).
2. The patient with a limited tumor burden or minimal cancer-related symptoms, preference is given to the sequential use of single-agent chemotherapy, which is less toxic ultimately resulting in better overall survival (Schott et al., 2015).

3. Patients with a large tumor burden in symptomatic disease due to location of specific metastatic lesions e.g., dyspnea due to diffuse lung metastasis), preference is given to the use of a combination regimen to obtain a higher response rate (Schott et al., 2015).

I. Combination Regimen containing anthracycline drugs: doxorubicin (Adriamycin) and epirubicin (Pharmorubicin) (Scully et al., 2012).

II. Combination Regimen containing taxane: paclitaxel (Taxol) and docetaxel (Taxotere) (Scully et al., 2012).

III. Single agent Chemotherapy drug, i.e., platinum based drugs widely used for treating triple negative and basal-like tumors: cisplatin (Platinol AQ and carboplatin (Paraplatin, Paraplatin AQ) (Scully et al., 2012).

IV. Single agent Chemotherapy drug, i.e., Eribulin: eribulin mesylate (Halaven) - improved overall survival (OS) of patients with triple-negative and HER2-negative metastatic breast cancer (Inman, 2014).

Table 6. Therapeutic strategies, confirmed and in development, for triple-negative breast cancer

<table>
<thead>
<tr>
<th>Therapeutic Strategy or Target</th>
<th>Status of Development</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anthracycline-/taxane-based chemotherapy</td>
<td>Proven efficacy, phase II/III clinical trials</td>
</tr>
<tr>
<td>Platinum agents</td>
<td>Active agents, phase II clinical trials</td>
</tr>
<tr>
<td>EGFR inhibition</td>
<td>Modest activity, phase II clinical trials</td>
</tr>
<tr>
<td>Antiangiogenesis</td>
<td>Efficacy in subset analysis, phase III trials</td>
</tr>
<tr>
<td>PARP1 inhibition</td>
<td>Safety illustrated, efficacy results anticipated, phase I/II trials</td>
</tr>
<tr>
<td>Src inhibition</td>
<td>Modest activity, phase II trials</td>
</tr>
<tr>
<td>HDAC inhibition</td>
<td>Activity in preclinical studies, early clinical development</td>
</tr>
<tr>
<td>MEK inhibition</td>
<td>Activity in preclinical studies</td>
</tr>
</tbody>
</table>


Survival outcomes for patients with metastatic triple-negative breast cancer: According to NCCN guidelines, treatment of Triple negative breast cancer is based both on tumor size and cellular characteristics (Ismail-Khan & Bui, 2010). Oncologists tend to treat patients with triple negative breast cancer with more aggressive chemotherapy, both in the neoadjuvant and the adjuvant setting (Ismail-Khan & Bui, 2010). Progression-free survival is estimated to be four months at best in TNBC for first line therapy, even with Avastin-based therapy (Ismail-Khan & Bui, 2010).

Evidence 1: Miller et al demonstrated a significant improvement in progression-free survival (11.8 vs 5.9 months, HR = 0.60, P <.001) when adding bevacizumab to paclitaxel chemotherapy compared with single-agent paclitaxel alone in first-line
treatment of metastatic disease (Ismail-Khan & Bui, 2010). Examining the TNBC subset of patients in this study confirmed the same improvement (HR = 0.53, 95% confidence interval = 0.40–0.70) (Ismail-Khan & Bui, 2010). Thus, it could be concluded that Avastin combination for first line therapy could be considered while treating patients with metastatic triple negative breast cancer (Ismail-Khan & Bui, 2010).

**Evidence 2:** As presented in the plenary session of the American Society of Clinical Oncology (ASCO) meeting in 2009, the results of a randomized phase II study with BSI-201 (a PARP Inhibitor) showed benefit in patients with TNBC who had two or fewer previous lines of chemotherapy (Ismail-Khan & Bui, 2010). When BSI-201 was combined with gemcitabine and carboplatin, the clinical benefit rate improved to 62 percent when compared to the gemcitabine and carboplatin alone arm at 21 percent (p<0.002) [21]. (Clinical benefit rate is defined as complete response plus partial response plus stable disease lasting six months or more) (Ismail-Khan & Bui, 2010). In addition, the overall response rate was notably improved in the BSI-201 arm at 48 percent compared to the control arm at 16 percent (Ismail-Khan & Bui, 2010). Progression-free survival was improved to 6.9 months in the BSI-201 arm of the study versus 3.3 months in the gemcitabine and carboplatin alone arm (Ismail-Khan & Bui, 2010).

**Evidence 3:** Mammography showed that primary breast tumors have an average doubling time of 157 days, varying from 44 to more than 1800 days during exponential growth (Talmadge & Fidler, 2010). Thus, the growth of a tumor from initiation to a size of 1 cm required an average of 12 years (Talmadge & Fidler, 2010). This finding is significant because a 1-cm tumor has $10^9$ cells and has undergone at least 30 doublings from tumor initiation to diagnosis (Talmadge & Fidler, 2010). On the basis of these parameters and the observations that a tumor burden of approximately 1,000 cm$^3$ was considered lethal, the time from diagnosis to mortality represents 10 doubling times from a 1-cm tumor and shorter time frame (Talmadge & Fidler, 2010). Therefore, three quarters of a tumor’s life history had occurred prior to diagnosis, and metastasis could occur prior to diagnosis (Talmadge & Fidler, 2010).

<table>
<thead>
<tr>
<th>Site of metastases</th>
<th>No. of patients</th>
<th>Median (months)</th>
<th>95% CI (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brain</td>
<td>34</td>
<td>6.3</td>
<td>4.9–7.7</td>
</tr>
<tr>
<td>Lungs</td>
<td>33</td>
<td>9.8</td>
<td>1.7–17.8</td>
</tr>
<tr>
<td>Local recurrence</td>
<td>31</td>
<td>9</td>
<td>7.5–10.6</td>
</tr>
<tr>
<td>Bones</td>
<td>26</td>
<td>5.5</td>
<td>2.7–8.4</td>
</tr>
<tr>
<td>Liver</td>
<td>19</td>
<td>3.5</td>
<td>0–7.7</td>
</tr>
</tbody>
</table>


**Discussion**

Once a diagnosis of a primary cancer is established, the urgent question is whether it is localized or metastasized (Talmadge & Fidler, 2010). Prognostic and predictive factors are well established in early-stage breast cancer, but less is known about which metastatic sites would be affected. As described above, triple-negative breast cancer is highly responsive to primary anthracycline and anthracycline/taxane chemotherapy;
however, a high risk of relapse remains if the tumor is not eradicated. Both preclinical and clinical studies indicated that tumors with BRCA1 dysfunction, the majority of which are triple negative, harbor deficient double-stranded DNA break repair mechanisms and are sensitive to DNA-damaging chemotherapeutic agents, such as platinum agents (i.e., cisplatin and carboplatin). The association between BRCA1 dysfunction and triple-negative breast cancer has led to several neoadjuvant/adjuvant and metastatic studies evaluating platinum agents in the setting of triple-negative breast cancer (Anders & Carey, 2009). The ability to determine the initiation time of metastatic growth would enable to determine the likelihood of a patient having metastatic recurrence (Clare et al., 2000). As predicted, the initiation time relies significantly on the model of the cancer’s natural history (Clare et al., 2000).

3 main growth stages of metastasis:

- Dormant single metastatic cell (Clare et al., 2000).
- Avascular stage modeled by Gompertzian growth, with a limiting size of approx. $10^5$ cells (Clare et al., 2000).
  The size is limited by the fact that the cells must be nourished by diffusion of nutrients from the existing vasculature (Clare et al., 2000).
- Vascular stage also modeled by Gompertzian growth with a limiting size of approx. $10^{12}$ cells (Clare et al., 2000).
  The transition between these three phases is considered as stochastic (Clare et al., 2000).

Although the specific adjuvant regimens that might be most effective for TNBC are still being determined, third-generation chemotherapy regimens using dose dense or metronomic polychemotherapy are among the most effective tools presently available (Ismail-Khan & Bui, 2010). The role of specific chemotherapy agents in the treatment of TNBC remains incompletely defined and warrants careful review to ensure that the most effective therapy is delivered while minimizing unnecessary toxicity (Ismail-Khan & Bui, 2010). Platinum agents have seen renewed interest in TNBC based on a growing body of preclinical and clinical data suggesting encouraging activity (Ismail-Khan & Bui, 2010). Taxanes and anthracyclines are active in TNBC and remain important agents but have not shown specific benefit over non-TNBC (Ismail-Khan & Bui, 2010). There was a rapid rise in risk of recurrence following diagnosis (Dent et al., 2007).

Moreover, it is been observed that there is a peak rise of recurrence at 1-3 years of interval (Dent et al., 2007). Distal recurrence rarely preceded by local recurrence (Dent et al., 2007). Local recurrence was not found to be predictive of distal recurrence (Dent et al., 2007). Also, there was an increased mortality rate in the first 5 years (Dent et al., 2007). Majority of deaths occurred in first 5 years due to Rapid progression to distant recurrence (Dent et al., 2007).

**Conclusion**

Metastasis is frequently a final and fatal step in the progression of solid malignancies. Metastatic spread of cancer cells is the main cause of death of breast cancer patients, and elucidation of the molecular mechanisms underlying this process is a major focus in cancer research. As in many other metastatic cancer types, specific molecular changes occurring within both the tumor cells and the tumor microenvironment contribute to the detachment of tumor cells from the primary tumor mass, invasion into the tumor stroma, intravasation into nearby blood vessels or lymphatics, survival in the bloodstream, extravasation into and colonization of the target organ and, finally, metastatic outgrowth.

Advanced modeling approaches, technological ingenuity, and an emphasis on clinical validation have all contributed to a rapid rate of recent progress. It could be envisioned metastasis as one possible outcome from the somatic evolution of
cancerous cells that have lost control over the integrity of their genome. As these tumors go on to spew cells and soluble factors into the circulation, the entire body becomes an evolutionary playing field. Until the primary tumor is diagnosed and surgically removed, one might even imagine a period of dynamic interplay between cells in the primary mass and those that have already undergone dissemination.

One of the reported aspects is that the aggressiveness of a tumor, i.e., the ability to metastasize, is driven by a distinct set of genes, different from those involved in the capacity to home, survive, and proliferate in a particular organ. This might tie in with the self-seeding theory and the seed and soil theory of Paget. The latter theory proposes that specific organs are in some way predisposed targets for secondary growth. This may reflect the necessity for the primary tumor to express a certain genetic module to invade specific organs. The self-seeding theory offers the view that dislodged cancer cells may either reenter the primary tumor bed or otherwise colonize a distant organ, the latter cell possibly needing additional (genetic) properties. Metastatic cells are genetically unstable with diverse karyotypes, growth rates, cell-surface properties, antigenicities, immunogenicities, marker enzymes, and sensitivity to various therapeutic agents resulting in biological heterogeneity (Talmadge & Fidler, 2010). Review of the history of pioneering observations and discussions of current controversies should increase understanding of the complex and multifactorial interactions between the host and selected tumor cells that contribute to fatal metastasis and should lead to the design of successful therapy. Yet the process of tumor metastasis remains controversial. The present study reveals how aggressive primary tumorigenic function could be mechanistically coupled to greater lung metastatic potential. The ongoing challenge is to identify new prognostic markers that are more directly related to disease and that can more accurately predict the risk of metastasis in individual patients (Chuang et al., 2007).

Research is underway to find out:

a. Which chemotherapy drugs work best for triple negative tumors or basal-like tumors (Scully et al., 2012).
b. Whether there are different treatments needed for triple negative tumors and basal-like tumors (Scully et al., 2012).
c. Whether chemotherapy given with less time between treatments (dose dense) is more effective (Scully et al., 2012).

Limitations

1. To identify low risk and high-risk groups.
2. To pinpoint those patients who are most likely to benefit from systemic adjuvant treatment retrospectively.
3. To identify the potential marker to be tested in large patient cohorts with a long follow-up period.
4. Financial burden to test all new tumor markers.

References


Analysis of correlation of CYR61 and MTHFR Gene Polymorphism in Legg-Calve-Perthes disease

Abstract

Background: Legg-Calve-Perthes disease (LCPD) is one of the most common causes of paediatric femoral head osteonecrosis. Besides the other known etiological aspects, till now genetic aspect has not been studied extensively. The present study was aimed to find the association of genetic polymorphism of CYR61 and MTHFR gene with the LCPD.

Materials and Methods: Single Nucleotide Polymorphisms (SNPs) analysis of the CYR61 and MTHFR genes in 41 LCPD patients and 110 healthy controls were genotyped in this hospital-based study by polymerase chain reaction and restriction fragment length polymorphism (PCR-RFLP).

Results: The frequency of CYR61 gene homozygous mutant GG polymorphism was not significant in LCPD patients when compared with controls. MTHFRC677T homozygous mutant TT polymorphism was significant in LCPD patients as compared to controls.

Conclusions: The present study showed a significant association of T allele of MTHFR C677T polymorphism with LCPD and may be regarded as a risk factor to develop the LCPD in North Indian patients.

Keywords: Perthes disease, CYR61, MTHFR, Etiology of Perthes disease, Risk factors of Perthes disease

Introduction

Legg-Calve-Perthes disease (LCPD) is the clinical manifestation of vascular compromise of femoral capital epiphysis having unknown etiology, primarily affecting children between 4-12 years of age. This most often happens when the lateral epiphyseal vessels the primary source vascular supply of the femoral capital epiphyseal region are involved[1]. The annual incidence of LCPD in children below 15 yrs of age ranges from 0.2 to 19.1 per 100 000 [2]. LCPD has usually an asymmetric presentation with only 15% of cases having bilateral involvement. Incidence of LCPD is 3-4 times more in boys than girls and is mainly occurs in children exposed to maternal smoking during pregnancy, low birth weight neonates, low socioeconomic groups, and children of white ethnicity [2-5]. The affected children are relatively short stature and have delayed osseous growth [6]. Exact pathogenetic mechanism of LCPD is still unknown and it may probably cause a multifactorial etiology which still remains a question [7].

Most of the cases of LCPD not require any specific treatment as most of them are self-limiting and resolving in nature [8]. Moreover, among many children primary complaint is a painless limp {but all cases with limp (painful/painless) in children of this age group are not LCPD} [9]. Further, according to literature, only half of the cases of LCPD are diagnosed in their advanced stages, despite having complained of pain or a limping gait. Thus it is not surprise that a huge number of LCPD patients in their initial stages are missed due to which the actual incidence revealed in literature is probably just a tip of an iceberg.

The cysteine-rich protein 61 (CYR61) regulated by 1 alpha, 25-dihydroxyvitamin D(3) (1,25-(OH)(2)D(3)), belongs to the growing CCN (CYR61/CTGF/NOV) family of immediate
early genes, which modulate angiogenesis process, cell growth as well as cell proliferation and differentiation. The CYR61 gene acts as a growth factor in fetal human osteoblasts, identified as an extracellular matrix-associated protein that modulates basic fibroblast growth factor signalling, angiogenesis, and binds to integrin alpha(v)beta(3). CYR61 is secreted in primary osteoblasts and suggests that CYR61 gene might function as an extracellular signalling molecule in human bone [10].

Folate is a methyl donor during DNA methylation, as it provides substrate for MTHFR to convert 5, 10 MTHF to 5-MTHF and subsequently metabolise it to methionine [11]. MTHFR is involved in DNA methylation and the availability of uridylates and thymidylates for DNA synthesis and repair [12]. In humans, under such circumstances, allele T of C677T associated with greater enzyme sensitivity to reduce availability of 5-MTHF, would maintain the required supply of 5, 10-MTHFR for nucleotide synthesis. Previously, it has been reported that MTHFR gene polymorphism genotype was involved in LCPD [13].

Till date despite having detailed characterization of clinical and radiological features of LCPD, its etiology still remains essentially unknown [14,15]. Although, it may be thought that both environmental and genetic factors have a role to play in development as well as its progression of LCPD [16]. It has been also been shown in experimental models that disrupted blood supply and infarction of the femoral head cause changes similar is seen in MRI/HPE of head femur of LCPD patients [17].

Previous studies have reported that apoptosis of osteoblasts and osteoclasts is a strictly regulated process and plays vital role in physiological bone turnover and in the development of pathological conditions in skeleton [18], but none of the studies have questioned this mechanism as an etiopathogenesis in LCPD patients so far. Alter inosteogenesis/bone remodelling is the one of the most important factor in the pathophysiology of LCPD, which leads to development of severe deformity in the affected hip [19].

CYR61 gene has a major contribution role in the process of osteogenesis as well as angiogenesis, which are the major factors that involved in the pathogenesis of LCPD. As it is well known that MTHFR polymorphism genotype associated with LCPD [13]. So we planned this study to find the association if any, of genetic polymorphism of CYR61 and MTHFR gene with the LCPD.

The role of this single nucleotide polymorphism (SNP) involving CYR61 gene in LCPD, if proved, may open new horizons for innovations in this field with an addition to our armamentarium to deal with complications associated with LCPD, and to diagnose LCPD in initial stage which might reveal exact burden of this disease and standardize and improved treatment protocols.

**Materials and methods**

In this case-control study, we enrolled 41 cases of LCPD and 110 healthy controls. The study was carried out in the Department of Orthopaedic Surgery and Department of Biochemistry, King George’s Medical University, Lucknow. The Institutional Review Board and Ethics Committee approved this study and it was carried out during January 2012 to July 2015. Before enrolment, each parent/guardian’s written informed consent was obtained in response to a fully written and verbal explanation of the nature of study.

All the patients with age between 4-14 years with clinic-radiologically proven LCPD of either sex reporting within first year of onset of symptoms were enrolled as cases. However, patient with age less than 4 or more than 14 years, having known or symptomatic cardiovascular disease, active or chronic infection or malignancy, history of drug consumption e.g: anticancer, steroid, cases of known congenital dysplasias or sickle cell anaemia, history of direct injury of the hip, immune-compromised patients as well as known case of chronic disease like kidney malfunction, liver disorders, hypothyroidism etc. were excluded from case enrolment.

The diagnosis of LCPD in cases was established according to standard clinical criteria: onset of groin pain, disturbed stance on the affected leg and waddling gait, limitation of hip
joint movements, especially abduction and internal rotation and absence of clinical signs suggesting trauma or infection. The radiographic signs considered for establishing diagnosis of LCPD include condensation or fragmentation of the epiphyseal ossification center with or without loss of femoral head sphericity.

**Isolation of genomic DNA**

Whole venous blood (2ml) was collected in 0.5M EDTA vial and stored -80°C from all cases. Genomic DNA extraction for molecular genetic studies was performed using the commercially available extraction kit (Bangalore Genei, India) and was stored at -80°C. The DNA concentration was measured with a Nanodrop ND-100 Spectrophotometer (Thermo Fisher Scientific Inc., Wilmington, DE).

**Analysis of the CYR61and MTHFR gene polymorphism**

The CYR61 and MTHFR gene polymorphism was analysed by the polymerase chain reaction (PCR) followed by restriction fragment length polymorphism (RFLP). Genomic DNA was amplified by (PCR Thermocycler (Applied Biosystems, Germany) using following PCR conditions: 95°C for 5 minutes, 39 cycles at 95°C for 40 seconds, 50°C (CYR61 gene) for 50 seconds and (MTHFR gene) 56°C for 40 seconds, 72°C for 50 seconds, and finally 72°C for 10 minutes. The primers used for amplification of the CYR61 gene polymorphisms were as follows: forward primer 5′-CTTGCCCTCTACCTTCGCTGTTAA-3′ and reverse primer 5′-GTCGTTTTTGTGGTGTATGCGA-3′ [20] and MTHFR gene polymorphism are as follows: forward primer 5′-TGA AGG AGA AGG TGT CTG CGG GA-3′ and reverse primer 5′-AGG ACGGTGCAGTGAGATG-3′ [21]. Amplification was performed with 25 µl PCR reaction mixture containing 100 ng template DNA, 10 pmol of each primer and 2X PCR master mixes (Fermentas, Germany). Amplification success of samples was monitored by 2% agarose gel electrophoresis. Thereafter the PCR products were subjected to digestion by KspAI enzyme (Fermentas, Germany) for CYR61 gene polymorphism and Hinf1 enzyme (NEB, UK)) for MTHFR gene polymorphism. The enzymatic mixture contained 0.8 µL restriction enzyme 2 µL 10X buffer, 10 µL PCR products and 7 µL distilled water and incubated overnight at 37°C for digestion. The digested product was run on 3% agarose gel, electrophoresis at 70 volts for 1 hour. In cases with CYR61 gene polymorphism, an undigested 104 bp band showed wild-type TT genotype, while two bands of 80 and 24 bp confirmed mutant GG genotype and three bands of 104, 80 and 24 bp were detected in the heterozygous TG genotype [20] (Figure 1). Whereas in MTHFR gene polymorphism, an undigested 198bp band showed wild type CC genotype, while two bands of 175 and 23bp confirmed mutant TT genotype and three bands of 198, 175 and 23bp were detected in a heterozygous CT genotype [21] (Figure 2).

**Statistical analysis**

The significance of this study was evaluated by Chi-square test. Odds ratio (OR) was calculated as an estimate of relative risk of having disease according to the relative frequency of different genotypes among the cases as well as the controls. The association between the polymorphisms and fracture non-union was estimated by odds ratios (ORs) and their 95% confidence intervals (CIs), which were calculated by unconditional logistic regression. P-value was considered significant at <0.05. The value was expressed in mean ± SD (Standard Deviation).

**Results**

In our study we included 41 cases with LCPD out of which 29 were males and 12 were females. The calculated mean age of cases was 10.5± 4.94 years and that of 110 controls was 11.5 ± 4.21 years. All demographic characteristics of cases and controls were summarized in Table 1. All the cases and controls were successfully genotyped by PCR- RFLP. The results of the molecular analysis are showed in Table 2. The average CYR61 gene genotype
frequencies of TT, TG and GG were calculated to be 36.6%, 51.2%, 12.2% in cases and 32.7%, 55.5%, 11.8% in controls respectively. The MTHFR gene genotype frequencies of CC, CT and TT were calculated to be 58.5%, 34.2%, 7.3% in cases and 30.0%, 51.0%, 19.0% in controls respectively. In comparisons to controls, the CYR61 gene polymorphisms of genotype homozygous GG, heterozygous TG and TG+GG were not significant in cases. We also observed that the frequency of CYR61 gene polymorphism of mutant allele G in cases was not significant in comparison to controls (Table 2). Similarly in MTHFR gene polymorphism, T allele frequency in cases was significant in comparison to controls (p = 0.0022). We examined, significant TT homozygous (p = 0.0202), heterozygous genotype (p = 0.0120) and a slight rise of CT+TT genotypes (p = 0.0025) in cases as compared to the controls.

**Discussion**

Legg-Calve-Perthes disease (LCPD) is a self-limiting disease of children mainly characterized by interrupted blood supply to the capital femoral epiphysis that may further leads to necrosis of the epiphysis [22]. LCPD is the juvenile form of ischemic osteonecrosis of the femoral head that mainly affects the children between 2-12, causing the femoral head deformity and premature osteoarthritis [23]. The study was done by comparing the genotypes of cases with healthy controls of matched age, gender, haemoglobin and other characteristic risk. The present observational study was designed to examine the impact of CYR61 and MTHFR genes polymorphisms on LCPD.

The analysis of data obtained revealed that MTHFR gene T allele is significantly associated with the development of LCPD (OR = 2.49, 95% CI = 1.40- 4.40, p = 0.0022). However, the CYR61 gene polymorphism of genotype is not associated with cases as compared to controls. Similar observation has been reported in study by Sanja et al., (2015), who concluded that MTHFR gene polymorphism of genotype is associated with LCPD [13].

In our study, C677T variant in the MTHFR gene polymorphism was associated with LCPD. It is interesting to note that the frequency of T allele of the MTHFR gene was rather high in our patient than the controls, pointing to the population specificity of frequency of this allele. This allele frequency in our population was similar with other Caucasian subjects [24], while the studies from Asia reported much lower frequency of these allele in their populations [25-27].

In conclusion, we provide the first evidence supporting the genetic effect of a MTHFR gene polymorphism as a potential risk factor in cases with LCPD in north Indian population. The involvement of a high MTHFR T allele frequency observed in cases with LCPD in our subset of population (North Indian), it opens new horizons for further workup in this direction for prospective investigators, as the genetic pattern may affect the bone physiology and consequently lead to LCPD. The exact etiology for LCPD still remains a mystery, and so as a result we are still unable to determine the specific risk factors which are responsible for its occurrence and therefore we lack proper screening test at genetic level to predict the same. In our study we have found genetic association of a particular gene and identified allele with LCPD. As the sample size in our study is not large enough, so we insist further studies with large sample size to establish the statistical significance of this association which will further validate our conclusion. This can help in opening new horizons in the diagnosis as well as management of LCPD and will definitely help us to know the exact burden of this disease.

**Conflict of interest**

The authors have no conflict of interests in this article.

**Acknowledgements**

This study was supported by Department of Orthopedics Surgery with collaboration with Department of Biochemistry, King George’s Medical University, Lucknow, Uttar Pradesh, India.
References


Table 1: Demographic details of cases and controls.

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Cases (n=41)</th>
<th>Controls (n=110)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>10.5 ± 4.94</td>
<td>11.5 ± 4.21</td>
<td>0.2254</td>
</tr>
<tr>
<td>Male</td>
<td>70.7% (n=29)</td>
<td>55.5% (n=61)</td>
<td>0.0820</td>
</tr>
<tr>
<td>Female</td>
<td>29.3% (n=12)</td>
<td>44.5% (n=49)</td>
<td>0.0931</td>
</tr>
<tr>
<td>Haemoglobin (Hb)</td>
<td>12.25 ± 3.25</td>
<td>13.15 ± 3.10</td>
<td>0.0616</td>
</tr>
<tr>
<td>Lower limb (Right)</td>
<td>23 (56.1%)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Lower limb (Left)</td>
<td>13 (31.7%)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Bilateral lower limbs</td>
<td>05 (12.2%)</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

Table 2: Frequencies of alleles and genotypes of CYR61 and MTHFR genes polymorphism in cases and controls.

<table>
<thead>
<tr>
<th>Polymorphism</th>
<th>CYR61 (T→G)</th>
<th>Polymorphism</th>
<th>MTHFR (C→T)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Cases (n=41)</td>
<td>Controls (n=110)</td>
<td>P-value</td>
</tr>
<tr>
<td>TT</td>
<td>15 (36.6%)</td>
<td>36 (32.7%)</td>
<td>-</td>
</tr>
<tr>
<td>TG</td>
<td>21 (51.2%)</td>
<td>61 (55.5%)</td>
<td>0.0780</td>
</tr>
<tr>
<td>GG</td>
<td>05 (12.2%)</td>
<td>13 (11.8%)</td>
<td>0.0895</td>
</tr>
<tr>
<td>TG + GG</td>
<td>26 (63.4%)</td>
<td>74 (11.8%)</td>
<td>0.0800</td>
</tr>
<tr>
<td>T allele</td>
<td>51 (62.2%)</td>
<td>133 (60.5%)</td>
<td>-</td>
</tr>
<tr>
<td>G allele</td>
<td>31 (37.8%)</td>
<td>87 (39.5%)</td>
<td>0.0886</td>
</tr>
</tbody>
</table>

* = Significant value.
**Figure 1.** 3% Agarose gel analysis of CYR61 (T→G) polymorphism. Lane 1 50 bp Ladder, Lane 2, 6 TT genotype 104bp, Lane 3, 4 TG genotype 104, 80, 24 bp, Lane 5 GG genotype 80, 24 bp.

**Figure 2.** 3% Agarose gel electrophoresis analysis of MTHFR C677T polymorphism. Lane 2, 5, 7, 8 CC genotype (198 bp), Lane 3, 4 CT genotype (198, 175, 23 bp), Lane 6 TT genotype (175, 23 bp) and Lane 1 Ladder 100bp
Integration of various Quality Management Systems in Clinical Trials: A Perspective

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Abstract

Background: In clinical trials, turnaround time, data accuracy and quality are critical for developing safe and new medicine for patients. The cost of a one-day delay in a drug being brought to the market can be in millions. It is essential; therefore, that all stakeholders in clinical trials take steps forward to improve efficiency, accuracy and quality of the clinical research overall. Doing so requires that organizations look beyond symptoms to uncover the true causes of errors in quality and delays. Additionally, new processes must be implemented in such a way as to become part of institutional culture, ensuring the consistent, on-going success of future efforts.

Purpose/Aim: To integrate, study and develop a stable, robust and reproducible Quality Management System (QMS) using combined quality management techniques such as Six Sigma, ISO and Lean together in clinical research.

Methods: Group of Students and working professionals will be asked to assess these three techniques individually and combined using pre-defined, developed and validated paper questionnaires. Different studies will be conducted over the period of 6-18 months and data will be collected. These studies will have an objective of testing each of three techniques on established processes to see if these can be used for process improvements. Result of these studies and quality matrix will be looked at to see how Six Sigma, ISO and Lean work independently and in combination of each other at the same time. Validated questionnaires will be used to obtain the results. Any survey tool developed will be piloted before using in the main phase of the study. Model needs will vary according to level of accessibility and sub-techniques, and this will need to be considered when selecting the sample for detailed study. Standard statistical packages will be used for examination. Standard qualitative and qualitative data analysis software package will be used to interpret the data generated form the review, questionnaire and interviews.

Conclusions: It is expected from proposed studies that combined use of ISO, Lean and Six Sigma techniques can improve quality of processes, data and produce robust Quality Management System.

These three techniques are different but complement each other. It is anticipated that a combination of these techniques will be of a great magnitude and beneficial to clinical research.

Keywords: Integration, ISO, Lean, Six Sigma, Quality Management System, Clinical Research

Introduction

Analysis of data available on clinicaltrials.gov – a service of the U.S. National Institutes of Health, shows that there was an approximate 28 fold increase in the total number of clinical trials registered in 2013 (159,318 studies) compared to year 2000 (5635 studies). Following figure 1 shows rapid growth in the registered clinical trials over last 13 years. With increased number of
clinical trials; key parameters of clinical research such as cost of conducting trials and patient safety had increased pressure on quality and for improved QMS.

Figure 1. Number of registered clinical studies over last 13 years on clintrials.gov

In current scenario of clinical trials with increase in regulatory demands, globalization, outsourcing and complexity of clinical trials have raised the bar of achieving global quality within clinical research. There is a growing effort to have established quality systems in place during the planning and execution stages of clinical trials. These quality systems require thorough planning, development and implementation of standards during each step. The quality of the clinical research is judged by regulatory inspections of investigator sites, sponsors and contract research organizations. A systematic approach will produce a more reliable and useful end product with high-quality data without compromising the protection of human subjects’ rights and welfare.3

**Quality Management Systems in Clinical Research** can be described as the authority to provide a solution for the challenges in development of the medicinal product or process while assuring safety for human subjects and patients.

Within current clinical scenario, there are different models of QMS in use. Organizations are trying to develop internal systems based on their processes and advancement; however this has raised many challenges with increase in demand for quality. There are number of activities that QA is involved as a part of clinical research team at current situation. QA is involved to provide input from setting up a clinical trial to post trial activities until that investigational product is launched in the market. Organizations are trying to implement established quality systems such as ISO, Six Sigma et.al but facing difficulties due to lack of their use in clinical research before. Implementing robust QMS always has some challenges. Manpower or additional resources is key hurdle for most of the organizations as this is directly linked to additional budget - costing more money to organization. Too many defined processes and procedures hinder deliverables. Advanced new technologies, electronic data capture and intense data review also contribute in
defining and developing user required QMS. Where special and adaptive clinical study designs, modern statistics and stimulation experiments are improving standard of clinical research; increasingly tight regulatory requirements and recent risk based approach are demanding accurate and robust QMS. (Cynthia F, et.al, 2010)

To fulfill the requirements and improve the quality with no additional challenges and cost; we propose following perspective of the Quality Management System to be used in clinical research.

**The proposed perspective of Quality management System** aims the use of combined techniques such as Six Sigma, ISO and Lean together to establish stable, high standard and precise Quality Management System within clinical research.

Following figure 2 shows a hypothetical model using three techniques in proposed perspective of quality management system.

![Figure 2. Integration of six sigma, ISO and lean](image)

As shown in figure 2, probably the best thing to learn that these three approaches are not exclusive. If you're interested in Six Sigma, that doesn't prevent you from looking into Lean. If you're pursuing ISO certification, that doesn't mean you must avoid Six Sigma. All three approaches offer advantages, and they complement each other. Importantly there is no need to invest additional man power, money and technology for each of three techniques with this approach as they mutually benefit to each other. Within current highly competitive and regulated clinical research industry, it will be added advantage to apply this approach in Quality Management System. Table 1 below shows the comparison of these three techniques on core aspects to describe that they are mutually beneficial to each other. There are similarities in the application of these techniques which makes integration achievable and sustainable.
Table 1 Comparison of six sigma, ISO and lean principles

<table>
<thead>
<tr>
<th></th>
<th>Six Sigma</th>
<th>ISO</th>
<th>Lean</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Goal</strong></td>
<td>Improve process capability and eliminate/minimize variation</td>
<td>Help organizations ensure that they meet the needs of customers and other stakeholders while meeting statutory and regulatory requirements</td>
<td>Understand process flow and eliminate waste</td>
</tr>
<tr>
<td><strong>Application</strong></td>
<td>Any business process</td>
<td>Any business process</td>
<td>Primarily high volume processes</td>
</tr>
<tr>
<td><strong>Project Selection</strong></td>
<td>Gap analysis or business process mapping</td>
<td>QMS</td>
<td>Locally driven as needed</td>
</tr>
<tr>
<td><strong>Infrastructure</strong></td>
<td>Dedicate resource e.g. Quality Assurance</td>
<td>Dedicated resource e.g. Quality Assurance</td>
<td>Minimum resource e.g. Quality Assurance</td>
</tr>
<tr>
<td><strong>Training Required</strong></td>
<td>Learning by doing or classroom</td>
<td>Learning by doing or classroom</td>
<td>Learning by doing or classroom</td>
</tr>
</tbody>
</table>

**Our research model** will use questionnaires which combine three techniques to obtain mainly qualitative responses from users, complemented by interviews and focus groups. The initial target is to gather current subjective and quantitative data on the quality systems of the clinical research. Accessibility of models will be also tested and quality management systems’ matrix will be looked at to assess the impact of each of the individual models. Any survey tool developed will be piloted before using in the main phases of the processes. The drive of pilot is to assess if developed tool/questionnaire serves the purpose of the experiment before using it on large scale. Model needs will vary according to level of accessibility and sub-techniques, and this will be considered when selecting the sample for detailed study.

**In conclusion**, if integrated, Six Sigma, ISO and Lean proponents claim that its benefits may include significant process cycle-time reduction resulting reducing the cost. In 2006, Elliott Liu demonstrated that 70% cycle-time can be reduced using six sigma technique alone in Case Report Form data entry process. With less waste of materials and efforts, better understanding of customer requirements, it is anticipated that customer satisfaction will be improved by more reliable processes, services and products. This could be the highlight of the proposed integration.

These three models have ability to work together and come up with robust QMS to produce accurate and scientifically proven clinical results with improved quality.

Six Sigma, ISO and Lean also have direct impact on society by improving the quality of clinical research and delivering high quality medicines to society – the end users. When there will be stable and improved quality management system in the clinical research; it will provide high quality of research results and precise scientific value of trials. It will have positive impact on the patients taking part in clinical trials improving patient safety, well-being and data integrity. This combine system of three techniques will eventually improve quality of life and better medicine for patients.

**Declaration of conflicting interests**

'The Author(s) declare(s) that there is no conflict of interest'.

(4)
Reference

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Assessment of some haematological parameters among pre-treatment, 2 months, 4 months and 6 months treatment in pulmonary tuberculosis infected individuals in anambra state university teaching hospital, awka. anambra state, nigeria

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Abstract

This present study was designed to assess the level of some hematological parameters among pretreatment pulmonary tuberculosis infected patients, treatment in 2 months, 4 months, 6 months pulmonary tuberculosis infection and control, non-infected subjects in Anambra State University Teaching Hospital, Awka. Anambra State, Nigeria. A total of 220 pulmonary tuberculosis (PTB) infected subjects aged 18 – 60 were recruited for the study. Hundred (100) subjects were in their pretreatment stage (group B), and 40 each in their 2 months (group C), 4 months (group D) and 6 months (group E) treatment stages. Eighty (80) non PTB subjects served as control. Blood samples collected from the subjects were used for the determination of Haemoglobin concentration (g/dl), packed cell volume (l/l), Mean cell haemoglobin concentration (g/dl), Erythrocyte sedimentation rate (mm/hr), platelet count (x10^9/l), total white blood count (x10^9/l), absolute neutrophil count (x10^9/l), absolute lymphocyte count (x10^9/l) and absolute monocyte count (x10^9/l) using standard laboratory methods for analysis as described by Dacie and Lewis[1]. Tuberculosis diagnosis was carried out using Ziehl Neel sen technique. The result showed that the mean ±SD Haemoglobin concentration and packed cell volume were significantly lower in pretreatment PTB subjects than the Post treatment subjects (P<0.05 in each case). The mean ±SD mean cell haemoglobin concentration showed no significant difference among the groups. The mean ±SD ESR in pretreatment subjects was significantly higher than the control and post treatment subjects. The mean (±SD) platelet count (x10^9/l), TWBC (x10^9/l) and ANC (x10^9/l) were significantly higher while the ALC (x10^9/l) was significantly lower respectively in pretreatment PTB patients compared with the control subjects and post treatment PTB subjects (P <0 .05 in each case). The mean (±SD) AMC (x10^9/l) showed no significant difference when compared among the groups (P<0.05).

The result of the present study shows that haemoglobin and packed cell volume in pulmonary tuberculosis patients were reduced while Erythrocyte is increased. Thus indicating anemia of chronic disease. It also showed that platelet count, total white blood count and absolute neutrophil count are increased while absolute lymphocyte count is decreased in pulmonary tuberculosis infection.

Keywords: Pulmonary tuberculosis, Haematological Parameters.
Acronyms

AIDS: Acquired Immune Deficiency Syndrome  
AFB: Acid Fast Bacilli  
DOTS: Directly Observed Short Course Therapy  
ESR: Erythrocyte Sedimentation Rate  
HIV: Human Immunodeficiency Virus  
WHO: World Health Organization  
MDR-TB: Multidrug resistance tuberculosis  
MTB: Mycobacterium tuberculosis  
TB: Tuberculosis  
PTB: Pulmonary Tuberculosis  
PCV: Packed cell volume  
WBC: White blood cell

Background

Tuberculosis is a chronic infectious bacterial disease caused by Mycobacterium tuberculosis (MTB) complex which commonly affects the lungs but can affect any other parts of the body. Mycobacterium tuberculosis is an obligate, acid fast, slender, slow growing, and rod like bacteria. The commonest source of infection is an untreated pulmonary tuberculosis patient who is sputum smear positive.

Pulmonary tuberculosis (PTB) is a common disease in developing countries and efforts have been made to diagnose patients presenting hematological picture.[1] Pulmonary tuberculosis spread through the air when people who have an active Mycobacterium tuberculosis infection cough, sneeze of spit.[2,3] It can also be got through eating meat infected with tuberculosis and drinking unpasteurized milk.

Pulmonary tuberculosis infection is common in Nigeria at an incidence rate of 297 per 100,000 population.[4] Tuberculosis accounts for 1.8 million deaths and is the world’s greatest infections killer of man and the leading cause of death among people with HIV/AIDS.[5] Other contributing factors are poverty, crowded living conditions in some homes, schools, prison, drug abuse, health workers, treatment failures, and insufficient funding for tuberculosis control programs.[6] The emergence of multiple drug resistant strains (MDR-TB) have also contributed to this new epidemic with from 2000 to 2004, 20% of tuberculosis cases being resistant to standard treatment.[4] Haematological abnormalities have been associated with tuberculosis.[7]

Few studies have been reported on the effects of pulmonary tuberculosis on hematological parameters especially in Nigerian literature. Significant abnormal hematological findings such as anemia, high Erythrocyte sedimentation rate, leukocytosis, and neutrophilia have been reported in patients with pulmonary tuberculosis.[8] Studies have reported high prevalence of anemia in patients with pulmonary tuberculosis. The precise mechanism of anemia in PTB patients is not clearly known, however, anemia due to inflammation as well as that of iron deficiency has been implicated. Factors such as decrease in red cell survival and reduced erythropoietin response by the bone marrow erythroid cells are also known to cause anemia. The possibility of poor nutrition has also been suggested to be the cause of anaemia in PTB patients. Haemoglobin concentration and pack cell volume were significantly lower in females than males, probably due to heavy menstrual period. Drug resistance TB is an emerging public health problem in Nigeria. The national MDR-TB survey data recorded 2.9% among the new cases and 14.3 among the retreatment cases. WHO estimated MDR-TB rate of 3.0% among new smear positive cases and 10.1% among re-treatment cases. (WHO Report 2013).
Studies have also documented an increase in platelet counts, Erythrocyte sedimentation rate (ESR), anaemia and Lymphopenia in pulmonary tuberculosis patients.\[8\]

The objectives of this research is therefore to explore avenues to aid in the improved understanding of the disease entity which will enhance the diagnosis and treatment of PTB infected persons by determining the effects of pulmonary tuberculosis on some haematological parameters.

**Methods**

A total of two hundred and twenty pulmonary tuberculosis infected patients aged 18 – 60 years were recruited for the study from the DOTS center of General Hospital, Awka. Based on sputum smear for AFB positive by Ziehl Neelsen’s stain. One hundred (100) were in their pre-treatment stage, and 40 each in their 2 months treatment stage, 4 months treatment stage and 6 months treatment stage respectively.

The TB positive subjects were identified based on sputum smear for AFB positive by Ziehl Neelsen stain technique which relies on the principle that M. tuberculosis is acid fast and stains red due to mycolic acids (fatty acids) in the cell wall which form a complex with carbol fucsin (an arylmethane dye) and cannot be removed by the acid in the decolorizing reagent.\[9\]

Three millimeters (3.0mls) of blood was collected from all the participants for the analysis of the parameters. Hemoglobin concentration, packed cell volume and Erythrocyte sedimentation rate were performed using method described by Dacie and Lewis. Hemoglobin concentration were assayed by the cyanmethaemoglobin method which relies on the principle that when blood is diluted in Drabkin’s fluid it lyses the red cells and converts hemoglobin to cyanmethaemoglobin. The absorbance of this solution is read in a colorimeter at a wavelength of 540nm.

Packed cell volume were assayed by the microhaematocrit method which relies on the principle that when ant coagulated blood in a glass capillary tube of specific length, bore size and wall thickness is centrifuged in a microhaematocrit centrifuge at a high speed of 1200rpm a constant packing of the red cells is obtained. The height of the column of red cells is taken as the packed cell volume.

Erythrocyte sedimentation rate was performed using the Westergreen method which is based on the principle that when citrated blood is left undisturbed in a vertically positioned westergreen pipette. The red cells aggregate, stack together to form rouleaux which sediment through the plasma. The Erythrocyte sedimentation rate indicated by the length of the column of clear plasma above the red cells is measured in mm.

Mean cell hemoglobin concentration (MCHC), the concentration of hemoglobin in g/dl of packed red cells was estimated from hemoglobin concentration (g/dl) and packed cell volume (l/l) as described by Cheesbrough as follows:-Hb (g/dl) divided by PCV (l/l).

Blood cells count (platelet count, total white cell count, white blood cell differential count) was performed using method described by Dacie and Lewis.\[1\]

Platelet count was estimated based on the principle that when whole blood is diluted in a filtered solution of ammonium oxalate reagent the red cells are lysed leaving platelets which are counted microscopically using an improved Neaubauer ruled counting chamber and the number of platelet per liter of blood calculated.

Total white cell count was estimated based on the principle that when whole blood is diluted in Turk’s solution, the red cells are lysed leaving the white cells to be counted. The white cells are microscopically counted using an improved Neaubauer ruled counting chamber and the number of WBC per liter of blood calculated.

White blood cell differential count was performed on a Leishman stained thin blood film made from a drop of blood sample using x100 objective of the microscope. The differential cell count was done by the longitudinal method using the mechanical differential white cell counter. The
percentage of each cell type was expressed as a decimal fraction and the absolute number of each white cell type obtained by multiplying it with the total white cell count.

**Statistical method**

Results generated in this study were tabulated using Excel with statistical analysis done using SPSS package. The variables were expressed in mean and standard deviation. The student’s t-test and ANOVA were used. A P-value of less than 0.05 (P< 0.05) was considered statistically significant.

**Results and discussion**

This present study was designed to assess the level of some hematological parameters among pre-treatment pulmonary tuberculosis infected patients, treatment in 2 months, 4 months, 6 months pulmonary tuberculosis infection and control, non-infected subjects at Anambra State University Teaching Hospital, Awka in Anambra State, Nigeria. A total of 220 pulmonary tuberculosis (PTB) infected subjects aged 18 – 60 were recruited for the study. Hundred (100) subjects were in their pre-treatment stage (group B), and 40 each in their 2 months (group C), 4 months (group D) and 6 months (group E) treatment stages. Eighty (80) non PTB subjects served as control. Blood samples collected from the subjects were used for the determination of Hemoglobin concentration (g/dl), packed cell volume (l/l), Mean cell hemoglobin concentration (g/dl), Erythrocyte sedimentation rate (mm/hr), platelet count (x10^9/l), total white blood count (x10^9/l), absolute neutrophil count (x10^9/l), absolute lymphocyte count (x10^9/l) and absolute monocyte count (x10^9/l) using standard laboratory methods for analysis as described by Dacie and Lewis[10]. Tuberculosis diagnosis was carried out using Ziehl Neelsen technique.

The result of the present study shows that hemoglobin and packed cell volume in pulmonary tuberculosis patients were reduced while Erythrocyte is increased. Thus indicating anemia of chronic disease. It also showed that platelet count, total white blood count and absolute neutrophil count are increased while absolute lymphocyte count is decreased in pulmonary tuberculosis infection.

The mean ±SD hemoglobin concentration g/dl and packed cell volume (l/l) were significantly lower in pre-treatment subjects compared with control and post treatment subjects (P<0.05 in each case). However, the mean ±SD mean cell hemoglobin concentration (g/dl) was not significantly different (P > 0.05) compared among the groups (Table 1)

The mean ±SD platelet count (x10^9/l), total white blood count (x10^9/l) and absolute neutrophils count (x10^9/l) were significantly higher in pre-treatment subjects compared with control and post treatment subjects (p <0 .05 in each case). The mean ±SD absolute lymphocytes count (x10^9/l) were significantly lower in pretreatment subjects compared with control and post treatment subjects (p <0 .05 in each case). However the mean ±SD absolute monocytes count was not significantly different (P >0 .05) compared among the groups (Table 2)

Sex differentiation was observed in control subjects with respect to hemoglobin concentration, packed cell volume and platelet count (Table 3)

Significant drop of hemoglobin concentration and pack cell volume was observed in pre-treatment PTB patients. This is an indication that PTB patients are susceptible to anemia. Studies have reported high prevalence of anemia in patients with pulmonary tuberculosis [2,3]. The precise mechanism of anemia in PTB patients is not clearly known , however, anemia due to inflammation as well as that of iron deficiency has been implicated [11,12]. Factors such as decrease in red cell survival and reduced erythropoietin response by the bone marrow erythroid cells are also known to cause anemia. The possibility of poor nutrition has also been suggested to be the cause of anemia in PTB patients [10]. Hemoglobin concentration and pack cell volume were significantly lower in females than males, probably due to heavy menstrual period.
In the current study, a significant increase in Erythrocyte sedimentation rate was observed. This could be attributed to the chronicity of PTB infection. The findings are fully supported by earlier reports specifying higher ESR values for PTB patients [1,7]. The study concludes that PTB infection predisposes to anemia of chronic disease and raised Erythrocyte sedimentation rate.

Platelet counts were found higher in pretreatment PTB patients as compared with control and post treatment subjects. The findings are in agreement with the earlier reports [1]. The cause for the observed thrombocytosis in PTB cases might be attributed to an immune phenomenon due to production of platelets antibodies and to reactive myeloid hyperplasia [11]. Thrombocytosis was significantly higher in the females than in males, reason not known, but increase production following blood loss due to menstrual flow have been suggested.

Our findings also show significantly increased levels of total white blood count before treatment as compared to the control and post-treatment subjects indicating leucocytosis in Nigeria patients suffering from PTB. Neutrophil composition in PTB patients was found higher as compared to the normal healthy Nigerians and post treatment PTB subjects. Lymphocyte composition in PTB patients was found lower as compared to the normal healthy Nigerians and post treatment PTB subjects. The findings are in agreement with the earlier reports [7].

**Recommendation**

The present study showed that there was no significant difference in absolute monocyte count in pretreatment, post treatment and controls subjects. Therefore we recommend that pre-treatment baseline level in these parameters are obtained prior to treatment of PTB patients in order to monitor the progress of treatment.

**Tables and figures**

**Table 1**: Mean ± SD Hematological parameters among control subjects (group A), pre-treatment PTB patients (group B) and pulmonary tuberculosis patients in their 2-month (group C), 4-month (group D) and 6-month (group E) treatment.

<table>
<thead>
<tr>
<th>Groups</th>
<th>HB (g/dl)</th>
<th>PCV(l/l)</th>
<th>MCHC(g/dl)</th>
<th>ESR(mm/hr)</th>
</tr>
</thead>
<tbody>
<tr>
<td>A – Control(n = 80)</td>
<td>13.53±1.29</td>
<td>0.40± 0.04</td>
<td>33.34± 3.43</td>
<td>5.95± 3.0</td>
</tr>
<tr>
<td>B– Pre-treatment(n = 100)</td>
<td>9.71±1.14</td>
<td>0.29±0.37</td>
<td>33.81±0.88</td>
<td>94.05±16.10</td>
</tr>
<tr>
<td>C–2-month treatment(n= 40)</td>
<td>13.50±0.92</td>
<td>0.40± 0.03</td>
<td>33.54± 0.57</td>
<td>9.33± 2.11</td>
</tr>
<tr>
<td>D–4-month treatment(n=40)</td>
<td>13.41±0.85</td>
<td>0.40± 0.28</td>
<td>33.62± 0.40</td>
<td>7.20± 2.52</td>
</tr>
<tr>
<td>E–6-month treatment(n=40)</td>
<td>13.21±0.88</td>
<td>0.39± 0.28</td>
<td>33.63± 0.46</td>
<td>6.95± 2.41</td>
</tr>
<tr>
<td>F(p)value</td>
<td>195.04(0.00)</td>
<td>174.88(0.00)</td>
<td>0.71(0.58)</td>
<td>1.38(0.00)</td>
</tr>
</tbody>
</table>

| A vs B p value          | 0.00        | 0.00       | 0.76       | 0.00       |
| A vs C p value          | 1.00        | 0.10       | 0.99       | 0.00       |
| A vs D p value          | 0.97        | 0.98       | 0.95       | 0.13       |
| A vs E p value          | 0.48        | 0.58       | 0.94       | 0.29       |
| B vs C p value          | 0.00        | 0.00       | 0.22       | 0.00       |
| B vs D p value          | 0.00        | 0.00       | 0.45       | 0.00       |
| B vs E p value          | 0.00        | 0.00       | 0.55       | 0.00       |
| C vs D p value          | 0.99        | 0.10       | 0.95       | 0.00       |
| C vs E p value          | 0.59        | 0.69       | 0.93       | 0.00       |
| D vs E p value          | 0.84        | 0.87       | 1.00       | 0.99       |

**Key** = (p<0.05)
Table 2: Mean ± SD Blood cells count among control, non-pulmonary tuberculosis subjects (group A), pretreatment pulmonary tuberculosis patients (group B) and pulmonary tuberculosis patients in their 2-month (group C), 4-month (group D), and 6-month (group E) treatment.

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>A – Control(n = 80)</td>
<td>219.71 ± 62.16</td>
<td>4.74 ± 0.73</td>
<td>5.16 ± 23.31</td>
<td>2.10 ± 0.38</td>
<td>± 0.05</td>
</tr>
<tr>
<td>B–Pretreatment(n=100)</td>
<td>372.85 ± 114.25</td>
<td>11.51 ± 8.87</td>
<td>7.94 ± 1.89</td>
<td>1.57 ± 0.76</td>
<td>± 0.08</td>
</tr>
<tr>
<td>C–2-month treatment(n=40)</td>
<td>260.25 ± 57.97</td>
<td>6.19 ± 4.06</td>
<td>4.06 ± 0.88</td>
<td>3.03 ± 0.74</td>
<td>± 0.05</td>
</tr>
<tr>
<td>D–4-month treatment(n=40)</td>
<td>228.90 ± 37.25</td>
<td>4.91 ± 3.72</td>
<td>3.72 ± 0.74</td>
<td>2.16 ± 0.67</td>
<td>± 0.04</td>
</tr>
<tr>
<td>E–6-month treatment(n=40)</td>
<td>245.52 ± 42.41</td>
<td>4.64 ± 3.68</td>
<td>3.68 ± 0.67</td>
<td>2.97 ± 0.56</td>
<td>± 0.04</td>
</tr>
<tr>
<td>F(p)value</td>
<td>10.40 ± (0.00)</td>
<td>26.05 ± (0.00)</td>
<td>118.35 ± (0.00)</td>
<td>1.78 ± (0.13)</td>
<td></td>
</tr>
</tbody>
</table>

A vs B p value 0.01 0.00 0.00 0.00 0.92
A vs C p value 1.00 0.88 0.99 0.38 0.43
A vs D p value 0.82 0.76 0.88 0.93 0.63
A vs E p value 0.99 0.94 0.88 0.32 0.65
B vs C p value 0.00 0.00 0.00 0.00 0.20
B vs D p value 0.00 0.00 0.00 0.00 0.32
B vs E p value 0.00 0.00 0.00 0.00 0.33
C vs D p value 0.07 0.49 0.34 0.49 0.99
C vs E p value 0.80 0.51 0.28 0.56 1.00
D vs E p value 0.24 0.42 1.00 0.11 1.00

Key = (p<0.05)

Table 3: Mean ± SD HB (g/dl), PCV(l/l), MCHC (g/dl), and ESR (mm/hr), Platelet Count (x10^9/L), total white blood count-TWBC (x10^9/L), absolute neutrophil count – ANC (x10^9/L), absolute lymphocyte count – ALC (x10^9/L), absolute monocyte count – AMC (x10^9/L), compared between male and female control subjects.

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Male (n = 44)</th>
<th>Female (n = 36)</th>
<th>F(p)value</th>
</tr>
</thead>
<tbody>
<tr>
<td>HB (g/dl)</td>
<td>14.24 ± 1.23</td>
<td>12.67 ± 0.69</td>
<td>10.67 (0.002)</td>
</tr>
<tr>
<td>PCV (l/l)</td>
<td>0.431 ± 0.04</td>
<td>0.37 ± 0.2</td>
<td>8.47 (0.003)</td>
</tr>
<tr>
<td>MCHC (g/dl)</td>
<td>33.53 ± 0.04</td>
<td>33.11 ± 5.09</td>
<td>2.86 (0.095)</td>
</tr>
<tr>
<td>ESR (mm/hr)</td>
<td>6.45 ± 3.12</td>
<td>5.33 ± 2.84</td>
<td>0.33 (0.56)</td>
</tr>
<tr>
<td>Platelet Count(x10^9/L)</td>
<td>225.95 ± 60.88</td>
<td>305.44 ± 389.15</td>
<td>5.85 (0.018)</td>
</tr>
<tr>
<td>TWBC (x10^9/L)</td>
<td>4.74 ± 0.67</td>
<td>4.74 ± 0.80</td>
<td>0.45 (0.504)</td>
</tr>
<tr>
<td>Abs.Neut.Count(x 10^9/l)</td>
<td>2.53 ± 0.52</td>
<td>4.38 ± 34.74</td>
<td>4.85 (0.31)</td>
</tr>
<tr>
<td>Abs.Lym.Count(x 10^9/l)</td>
<td>2.11 ± 0.38</td>
<td>2.10 ± 0.39</td>
<td>0.04 (0.841)</td>
</tr>
<tr>
<td>Abs. Mon.Count(x10^9/l)</td>
<td>0.037 ± 0.05</td>
<td>0.038 ± 0.04</td>
<td>1.67 (0.199)</td>
</tr>
</tbody>
</table>

Key=( P < 0.05)

References


Awareness, Knowledge and Perception of Safe Surgery Checklist and its Implementation in Jos University Teaching Hospital, Plateau State, Nigeria

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Abstract

Surgery-related complications and mortality have remained unbearably high, particularly in developing countries. Consequently the WHO, developed a Safe Surgery checklist (SSC) to improve the safety of surgeries and reduce mismanagement in surgery. This study was designed to assess the knowledge, attitude and perception of theatre staff about the SSC.

A cross sectional study involving theatre staff of Jos University Teaching Hospital, Nigeria was employed. Information on socio-demographic characteristics, Knowledge and awareness of the SSC, Perception towards safety culture and team work, Willingness and attitude of participants to use the SSC and Challenges affecting the implementation of the SSC in JUTH operating theatres were collected, using a semi-structured questionnaire.

A total of 68 theatre staff participated in the study. Majority 63 (92.5%) had heard about the safe surgery checklist. About 47.0% mentioned they did not usually have enough time for safety preparation, (72.1%) noted that there was not enough resources put in place to ensure safety. Majority (92.7%), indicated that they wanted the checklist to be used for all surgical procedures and also improve communication and collaboration between operating room staff. Only 13.3% agreed that the checklist is easy to use. More than half (54.4%) felt that the checklist may not bring any extra value to existing safety procedures already in place. Lack of commitment from the Management (16.2%), Lack of interest of health worker (14.7%), Shortage/lack of manpower (20.6%), Lack of team spirit (23.5%) and Inadequate supply of consumable instruments and other equipment/facilities (22.0) were pointed out by the participants as challenges that can affect the implementation of the safe surgery checklist.

Keywords: surgery, safe surgery checklist, theatre, knowledge, perception

Introduction

Surgery is an integral area of medical care, and sometimes the only option to saving a patient’s life, reducing pain or managing a disability. According to the World Health Organisation (WHO), about 234 million operations are carried out each year worldwide (WHO, 2009). Among these, medical mistakes and surgical errors in the operating rooms have continued to occur, resulting in 3-16% known complications and 0.4 – 0.8% known death which is approximately 7 million disabling complications and 1 million deaths. After major surgery, the reported crude mortality rate is usually 0.5-5%; complications after inpatient surgeries occur in about a quarter of patients; in economically advanced countries, and almost 50% of all adverse events in hospitalized patients are related to surgery; at least half of the cases in which surgery led to harm are considered preventable while mortality from general anaesthesia can be as high as 60% in Africa (WHO, 2009).

Surgical crises can be very risky and life threatening if immediate attention is not received. In order to reduce these, the WHO, developed a safety checklist with the intention of improving the safety of surgeries, reducing deaths and medical mismanagement in surgery. The practice of
using checklists in surgery, was borrowed from high-risk industries such as aviation where checklists have been tested in simulated settings and shown to improve performance during unpredictable crisis events. It is on this note that the Safe surgery saves lives initiative was formed by the World Alliance for Patient Safety. It is part of the World Health Organization’s efforts to cut down the number of surgery related deaths across the world, its aim is to reinforce accepted safety practices and ensure enhanced communication and teamwork between surgical team workers. The initiative encompasses a set of safety checks focusing on surgical site infection prevention, Safe anesthesia, Safe surgical teams and Measurement of surgical services (WHO, 2008). Contribution from anesthesiologists, nurses, surgeons, patient safety experts, patients, and other professionals were used in the development of this tool. Its use has been demonstrated in a pilot study and also in some other countries that has adapted the intervention. Reports from the study and other participatory countries have associated ‘Safe surgery’ with significant decrease in complication and death rates in different hospital settings, thereby improving the compliance to basic standards of care (IHI, 2015, Harvardgazzette, 2009, Haynes et al.,2009; de Vries EN et al., 2010, van Klei et al., 2012, Neily et al., 2010) and is rapidly becoming a standard of care.(Birkmeyer et al., 2010) When doctors, nurses and surgical staff follow a written safety checklist, they miss a critical clinical step nearly at only 25%, according to a study supported by the Agency for Healthcare Research and Quality (AHRQ), in the United States of America.

In Nigeria, the surgical experience is not any better, Chukuezi and Nwosu, 2010 in Southeastern Nigeria, reported an overall death per admission crude mortality rate of 9.14% in a five year review of the mortality pattern in surgical wards of a federal medical center. In a previous survey study in, over 53% of survey participants reported high proportions of medical errors in their hospital facilities (Ente, et al., 2010).It has also been reported that many surgical units have little guidance or structure for fostering effective team work, thus, to minimize risk to surgical patient is still far. Also the majority of the patient safety and quality improvement efforts have been made at the global level while such improvement or monitoring programs are actually lacking in local facility levels. The need remains to find out basically what surgical team members know about the checklist, their attitude and perception towards its usage. This is what has necessitated this study; it aims to understand the awareness, knowledge and perception of safe surgery practice among surgical care practitioners.

**Problem statement**

In the developing regions of the world, including Nigeria, there is scanty evidence of local initiatives put in place in health facilities to ensure patient care is efficient, suitable, and safe (WHO, 2011). According to Carpenter et al., patient safety and quality of care information from the region is still —infrequent and limited in scope;(Carpenter, et al., 2010). Understanding the depth and breadth of the WHO safety checklist within the health care-delivery system in Africa, may be the first step to establishing sufficient urgency for change and reduction of surgical errors. The utilization of checklists is rapidly becoming a standard of surgical care, however, the impact of using them during a surgical crisis has not been thoroughly investigated (Arriaga et al., 2013).

**Significance of study**

The absence of data on surgery in WHO health metrics has undeniably led to the failure to recognize the many episodes of surgery at a global level and also its role to preventable disability and death (Weiser et al., 2008). This work will provide evidence-based information about the implementation and usage of this promising strategy in Nigeria. The data obtained will inform the stakeholders, health practitioners, about priority areas to focus so as to effect an improvement and reduce incidences of patient harm. It is anticipated that this study would generate data that is
needed to rigorously describe the knowledge, attitude and perception of surgical health workers about the checklist and also highlight priority areas that would need more attention during adaptation, modification and implementation of the surgical checklist in JUTH and by extension, other Nigerian hospitals.

**Specific objectives**

1. To assess the general knowledge of the participants about the safe surgery checklist
2. To assess the perception of the participants towards safety culture and team work as it influences the use of the safe surgery checklist
3. To ascertain the attitude and willingness of the participants to use the safe surgery checklist
4. To explore possible challenges that may come up in the implementation of the safe surgery checklist in the study hospital
5. To identify areas for change in the roles of the hospital administration towards implementation of the safe surgery checklist

**Methodology**

**Study Site**

Jos University Teaching Hospital: Jos University Teaching Hospital, Jos is located in Jos North LGA, Jos, Plateau state. It has 632 beds for inpatients. It offers various clinical services including surgery. There are 11 operating Rooms including the satellite centres in Gindiri and Zamko. Surgery is performed in nine disciplines including General surgery and Obstetrics and Gynaecology.

**Study Population**

All Operating Theatre Users of Jos University Teaching Hospital, Jos. These comprises of Surgeons, Residents, Perioperative Nurses, Anaesthesiologist and Nurse Anaesthetist currently using the theatre. All theatre users who gave their written informed consent were be recruited in to the study.

**Study design**

It is a descriptive, cross-sectional study which involved the use of a pre-tested questionnaire targeted at theatre users.

**Study period**

1 month (May, 2015)

**Sample size determination**

All theatre users who were available during the period of recruitment were given the questionnaire however only 68 completed the questionnaires.

**Sampling method**

All professionals using the theatres in Jos University Teaching Hospital, Jos.

**Inclusion criteria**

All theatre Users of Jos University Teaching Hospital, Jos who gave written and informed consent.

**Exclusion criteria**

All theatre Users of Jos University Teaching Hospital, Jos who refused consent, or was ill or absent during the period of recruitment
Instrument

Pre-tested self-administered questionnaire comprising of both open-ended and closed-ended questions divided into 5 sections was used to obtain information from the participants. The questionnaire was designed in English language. Pre-test of the questionnaires was carried out using 5 perioperative nurse tutors who are also theatre users from other public hospitals. Secondly an observation checklist was used to obtain information on surgical vital statistics and equipment.

Statement of Confidentiality of Data Collected from the Subjects

All information obtained from this study has been kept confidential and will not be linked to the participants in anyway. They were not assigned any identification numbers neither nor identified by their names.

Data Collection Techniques

Data was obtained using pre-tested, structured questionnaires.

Data analysis

SPSS version 16.0 was used for data analysis. Descriptive statistics has been used to summarize the data while Chi square was used to test association between categorical variables, all analysis were done at a 5% level of significance (p < 0.05) with 95% confidence interval.

Limitation

There may be low response rate and some missing data considering the disadvantage of self-administered questionnaire.

Ethical consideration

Ethical approval was obtained from the Jos University Teaching Hospital, Jos research ethical review committee.

Informed consent was also obtained from the proposed participants before they participated in the study as participation was entirely voluntary. The participants were told that they could withdraw at anytime in the study and that their wishes would be respected.

Confidentiality was maintained as participants were not identified by their names or the premise where they work. The study exposes the participants to no risk or harm. The proposal was not translated into any local language because the study population is proficient in English language.

Results

Characteristics of the study population

A total of 68 questionnaires were filled and returned, out of 100 that were shared. The mean age of the study population was 40.1 ± 7.34. There were 26 (38.2%) females and 42 (61.2%) males. About 29.9% of the respondents were peri-operative nurses, 28.4% were resident doctors, 19.4% were nurse anesthetists, 17.9% were surgeon and 4.5% were anesthesiologists. When asked about work experience, a little more than half (58.8%) had been working for about 15 years while about 38.5% had worked 16 years and above.

They were also asked about the number of surgical procedures performed each year, many (68.6%) indicated that they perform about 600 surgeries annually. About one-third (31.7%) of the respondents had at least one additional educational qualification.
Knowledge and awareness of the safe surgery checklist among the respondents

Majority 63 (92.5%) said they had heard about the safe surgery checklist before, among these, 15 (22.0%) indicated that they heard about it from literature on the internet, 23 (34.0%) and 4 (6.0%) heard from colleagues and books respectively. Other places mentioned are shown in the table below. More than half (55.0%) also indicated that they had seen the Safe surgery checklist before, when asked where, various options were noted; these are illustrated in Table 1 below. Their knowledge about SSC was assessed using 10 questions which cut across the content, utilization, implementation and application of the SSC. Correctly answered questions were marked and scored on a 10-point scale. This was further graded into good and poor knowledge. Poor knowledge was for correct responses between 1 - 4, while good knowledge was given to anyone who correctly answered between 5 – 10 questions. Generally, majority (75.0%) had good knowledge while a lesser quartile (25.0%) had poor knowledge. This information is presented in the table below.

Table 1. Knowledge and awareness of the safe surgery checklist among the respondents

<table>
<thead>
<tr>
<th>Variable</th>
<th>Frequency (percentage)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Have you heard of the SSC before?</td>
<td>63 (92.5)</td>
</tr>
<tr>
<td>Yes</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>5 (7.5)</td>
</tr>
<tr>
<td>If Yes, where did you hear about SSC? *</td>
<td></td>
</tr>
<tr>
<td>Literature on the internet</td>
<td>11 (17.4)</td>
</tr>
<tr>
<td>From colleagues</td>
<td>21 (33.3)</td>
</tr>
<tr>
<td>Publicity at the hospital</td>
<td>5 (7.9)</td>
</tr>
<tr>
<td>Training course</td>
<td>17 (27.0)</td>
</tr>
<tr>
<td>From books</td>
<td>3 (4.8)</td>
</tr>
<tr>
<td>Cannot say/No response</td>
<td>13 (20.6)</td>
</tr>
<tr>
<td>Have you ever seen the SSC?</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>38 (55.9)</td>
</tr>
<tr>
<td>No</td>
<td>25 (36.8)</td>
</tr>
<tr>
<td>No response</td>
<td>5 (7.4)</td>
</tr>
<tr>
<td>If Yes, where did you see the SSC? * (n=38)</td>
<td></td>
</tr>
<tr>
<td>Abroad</td>
<td>2 (5.3)</td>
</tr>
<tr>
<td>Another teaching hospital</td>
<td>9 (23.7)</td>
</tr>
<tr>
<td>Academic presentations in JUTH</td>
<td>6 (15.8)</td>
</tr>
<tr>
<td>Online/Internet/Books</td>
<td>10 (26.3)</td>
</tr>
<tr>
<td>A private hospital</td>
<td>1 (2.6)</td>
</tr>
<tr>
<td>No response</td>
<td>10 (26.3)</td>
</tr>
<tr>
<td>Knowledge of respondents on the SSC (n=68)</td>
<td></td>
</tr>
<tr>
<td>Poor (≤4)</td>
<td>17 (25.0)</td>
</tr>
<tr>
<td>Good (≥5)</td>
<td>51 (75.0)</td>
</tr>
<tr>
<td>Mean knowledge score</td>
<td>5.1 ± 1.40</td>
</tr>
</tbody>
</table>

Note: Multiple response included*

Perception of the participants towards safety culture and team work as it influences the use of the safe surgery checklist in their surgical procedures

A greater number (76.5%), (94.1%) and (86.8) indicated that there was widespread adherence to rules and clinical guidelines in their Operating room, Patient safety is the responsibility of all operating room staff and Patient safety is a high priority in their operating rooms. About 57.3% of the participants mentioned that they did not know their staff members by first and last name. About 47.0% did not agree that they had enough time for safety preparation in their operating...
room. Also more than half (58.8%) of the respondents disagreed with the fact that there was generally a good team spirit among their staff. When asked if there was enough resources put in place to ensure safety (e.g. staff, utilization of information systems, machines and equipments), majority (72.1%) were of the contrary opinion; a similar response was observed when respondents were asked if everyone’s opinion was usually heard to, or listened to, many 68.0% indicated that this was not the case. About 55.8% and 60.3% negated the fact that their physicians and nurses work together as a well co-ordinated team; and that disagreement is expressed in a constructive manner in their theatre. A large number (76.4%) affirmed that as staff they were encouraged to report any safety concerns we encounter, a little below half (47.0%) disagreed with the fact that surgical team members were usually eager to help one another.

Table 2. Perception of the participants towards safety culture and team work as it influences the use of the safe surgery checklist in their surgical procedures

<table>
<thead>
<tr>
<th>Opinion</th>
<th>Strongly agree n(%)</th>
<th>Agree n(%)</th>
<th>Disagree n(%)</th>
<th>Strongly disagree n(%)</th>
<th>NR n(%)</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>There is widespread adherence to rules and clinical guidelines in our Operating room</td>
<td>25 (36.8)</td>
<td>27 (39.7)</td>
<td>14 (20.6)</td>
<td>1 (1.5)</td>
<td>1 (1.5)</td>
<td>68</td>
</tr>
<tr>
<td>Patient safety is the responsibility of all operating room staff</td>
<td>47 (69.1)</td>
<td>17 (25.0)</td>
<td>2 (2.9)</td>
<td>1 (1.5)</td>
<td>1 (1.5)</td>
<td>68</td>
</tr>
<tr>
<td>Patient safety is a high priority in our operating rooms</td>
<td>38 (55.9)</td>
<td>21 (30.9)</td>
<td>7 (10.3)</td>
<td>1 (1.5)</td>
<td>1 (1.5)</td>
<td>68</td>
</tr>
<tr>
<td>In our unit, we all know our staff members by first and last name</td>
<td>9 (13.2)</td>
<td>18 (26.5)</td>
<td>29 (42.6)</td>
<td>10 (14.7)</td>
<td>2 (2.9)</td>
<td>68</td>
</tr>
<tr>
<td>There is enough time for safety preparation in our operating room</td>
<td>8 (11.8)</td>
<td>27 (39.7)</td>
<td>29 (42.6)</td>
<td>3 (4.4)</td>
<td>1 (1.5)</td>
<td>68</td>
</tr>
</tbody>
</table>

Information on the willingness and attitude of participants towards the use of the SSC was also sourced for, a large number (92.7%), indicated that they wanted the checklist to be used for all their surgical procedures. Many (83.2%), (72.0%) and (83.9%) disagreed with the fact that the checklist seems like an unnecessary tick box, that they can operate efficiently without having to use the checklist and the list might waste time and can make our operating theatres less efficient.

Almost all (91.1%) and (94.2%) said using the checklist will make them have more confidence and also improve their communication and collaboration between operating room staff. About one-fifth (20.5%) thought the checklist may not be very important as it has its own handicaps. Only 13.3% agreed that the checklist is easy to use, about 85.3% agreed that it is important to use the checklist in every case. More than half (54.4%) felt that the checklist may not bring any extra value to existing safety procedures already in place in the theatre before its implementation.

Participants were asked whether they would like the checklist to be used during their own surgery, about (86.9%) said they would want the list to be used. They were also asked who among the operating room staff is more suitable in taking charge of the checklist; many (66.7%) indicated that the Nurses would be more suitable in taking charge of the checklist; some others (25.0%) were of the opinion that Surgeons would be more suitable while a few others (18.3%) thought that the Anaesthesia would be more suitable. Table 3 summarizes the willingness and attitude of the participants to use the SSC.
Table 3. Willingness and attitude of participants to use the SSC

<table>
<thead>
<tr>
<th></th>
<th>Strongly Disagree n(%)</th>
<th>Disagree n(%)</th>
<th>Strongly Agree n(%)</th>
<th>Agree n(%)</th>
<th>NR n(%)</th>
<th>TOTAL</th>
</tr>
</thead>
<tbody>
<tr>
<td>I want the checklist to be used for all our surgical procedures</td>
<td>2 (2.9)</td>
<td>2 (2.9)</td>
<td>41 (60.3)</td>
<td>22 (32.4)</td>
<td>1 (1.5)</td>
<td>68</td>
</tr>
<tr>
<td>The checklist seems like an unnecessary tick-box</td>
<td>34 (50.0)</td>
<td>22 (32.4)</td>
<td>4 (5.9)</td>
<td>7 (10.3)</td>
<td>1 (1.5)</td>
<td>68</td>
</tr>
<tr>
<td>We can operate efficiently without having to use this checklist</td>
<td>19 (27.9)</td>
<td>30 (44.1)</td>
<td>2 (2.9)</td>
<td>15 (22.1)</td>
<td>2 (2.9)</td>
<td>68</td>
</tr>
<tr>
<td>The Checklist might waste time and can make our operating theatres less efficient</td>
<td>22 (32.4)</td>
<td>35 (51.5)</td>
<td>6 (8.8)</td>
<td>3 (4.4)</td>
<td>2 (2.9)</td>
<td>68</td>
</tr>
<tr>
<td>Using the checklist will make us have more confidence</td>
<td>1 (1.5)</td>
<td>3 (4.4)</td>
<td>36 (52.9)</td>
<td>26 (38.2)</td>
<td>2 (2.9)</td>
<td>68</td>
</tr>
<tr>
<td>The checklist will improve communication and collaboration between staff in the operating room</td>
<td>3 (4.4)</td>
<td>39 (57.4)</td>
<td>25 (36.8)</td>
<td>1 (1.5)</td>
<td>68</td>
<td></td>
</tr>
<tr>
<td>The checklist may not be very important as it has its own handicaps</td>
<td>16 (23.5)</td>
<td>37 (54.4)</td>
<td>2 (2.9)</td>
<td>12 (17.6)</td>
<td>1 (1.5)</td>
<td>68</td>
</tr>
<tr>
<td>The checklist is easy to use</td>
<td>1 (1.5)</td>
<td>8 (11.8)</td>
<td>17 (25.0)</td>
<td>40 (68.8)</td>
<td>2 (2.9)</td>
<td>68</td>
</tr>
<tr>
<td>It is important to use the checklist in every case</td>
<td>1 (1.5)</td>
<td>8 (11.8)</td>
<td>24 (35.3)</td>
<td>34 (50.0)</td>
<td>1 (1.5)</td>
<td>68</td>
</tr>
<tr>
<td>Surgical Safety Checklist causes irritation between staff members</td>
<td>11 (16.2)</td>
<td>37 (54.4)</td>
<td>4 (5.9)</td>
<td>15 (22.1)</td>
<td>1 (1.5)</td>
<td>68</td>
</tr>
<tr>
<td>Surgical Safety Checklist contains ambiguous statements</td>
<td>13 (19.1)</td>
<td>38 (55.9)</td>
<td>2 (2.9)</td>
<td>13 (19.1)</td>
<td>2 (2.9)</td>
<td>68</td>
</tr>
<tr>
<td>Implementing the Safety surgery checklist is a good decision</td>
<td>2 (2.9)</td>
<td>3 (4.4)</td>
<td>32 (47.1)</td>
<td>25 (36.8)</td>
<td>6 (8.8)</td>
<td>68</td>
</tr>
<tr>
<td>The checklist may not bring any extra value to existing safety procedures already in place in the theatre before its implementation</td>
<td>-</td>
<td>28 (41.2)</td>
<td>31 (45.6)</td>
<td>6 (8.8)</td>
<td>3 (4.4)</td>
<td>68</td>
</tr>
</tbody>
</table>

If I were having an operation I would want the checklist to be used (n = 61)
Among the operating room staff, who do you think would be more suitable in taking charge of the checklist? (n =60)

- Surgeon: 15 (25.0)
- Nurse: 40 (66.7)
- Anaesthesia: 11 (18.3)

Any other staff, you think would be more suitable in taking charge of the checklist? (n =5)
- A dedicated theatre staff for the purpose: 2 (40.0)
- All operating team members: 1 (20.0)
- Anybody available at the given time: 1 (20.0)
- Porters: 1 (20.0)

Possible challenges/advice/suggestion towards the implementation of the safe surgery checklist in JUTH operating theatres

Lack of commitment from the Management (16.2%), Lack of interest/will/attitude of health worker (14.7%), Shortage/lack of manpower (20.6%), Lack of team spirit (23.5%) and Inadequate supply of consumable instruments and other equipment/facilities (22.0) were the pointed out by the participants as possible challenges that can affect the implementation of the safe surgery checklist in their operating theatres. Table 4 shows the other issues that were indicated and their frequency among the participants.

Table 4: Possible challenges/advice/suggestion towards the implementation of the safe surgery checklist in JUTH operating theatres

<table>
<thead>
<tr>
<th>Kindly indicate any challenges you think might affect the implementation of the checklist in JUTH * (n =68)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Administrative bottleneck/bureaucracy</td>
<td>8 (11.8)</td>
</tr>
<tr>
<td>Lack of awareness or knowledge</td>
<td>8 (11.8)</td>
</tr>
<tr>
<td>Commitment of staff to duty</td>
<td>1 (1.5)</td>
</tr>
<tr>
<td>Co-operation among staff</td>
<td>8 (11.8)</td>
</tr>
<tr>
<td>Inadequate supply of consumable instruments/other equipment/facilities</td>
<td>15 (22.0)</td>
</tr>
<tr>
<td>Inadequate time to carry out the checklist</td>
<td>3 (4.4)</td>
</tr>
<tr>
<td>Lack of commitment from the Management</td>
<td>11 (16.2)</td>
</tr>
<tr>
<td>Lack of incentive among theatre workers</td>
<td>1 (1.5)</td>
</tr>
<tr>
<td>Lack of interest/will/attitude of health worker</td>
<td>14 (20.6)</td>
</tr>
<tr>
<td>Shortage/lack of manpower</td>
<td>16 (23.5)</td>
</tr>
<tr>
<td>Lack of team spirit</td>
<td>10 (14.7)</td>
</tr>
<tr>
<td>Corruption</td>
<td>1 (1.5)</td>
</tr>
<tr>
<td>Lack of good communication</td>
<td>1 (1.5)</td>
</tr>
</tbody>
</table>

Note: Multiple response included*
Attitude towards role of hospital administration and management in implementation and use of the checklist

From Table 5, Participants’ attitude towards the role of hospital administration and management in implementation and use of the checklist was also assessed. About (44.1%), indicated that having the Administrative Heads (e.g CMD, CMAC, ADNS), Clinical staff (73.5%) and giving a mandatory date/time to commence the use of the checklist by management (54.4%) would enhance the implementation of the safe surgery checklist in this hospital to a large extent.

In the same vein, many of the participants, also believed that the support of the CMD (64.7%), CMAC (63.2%), Head of Departments and Consultants in Surgery (70.6%), Anesthesiology (76.5%), Nursing (76.5%) and Operating Theatre Manager (77.9%) would also enhance the implementation of the safe surgery checklist in this hospital to a large extent.

Table 5. Attitude towards role of hospital administration and management in implementation and use of the checklist

<table>
<thead>
<tr>
<th>In your opinion, to what extent will the following enhance the implementation of the safe surgery checklist in this hospital?</th>
<th>Very great extent n(%)</th>
<th>To Some extent n(%)</th>
<th>Little extent n(%)</th>
<th>Very little extent n(%)</th>
<th>NR n(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Having the Administrative Heads (e.g CMD, CMAC, ADNS) as leaders of the implementation team</td>
<td>30 (44.1)</td>
<td>14 (20.6)</td>
<td>11 (16.2)</td>
<td>7 (10.3)</td>
<td>6 (8.8)</td>
</tr>
<tr>
<td>Having the Clinical staff (those engaged in day to day running of the theatre) as leaders of the implementation team</td>
<td>50 (73.5)</td>
<td>8 (11.8)</td>
<td>3 (4.4)</td>
<td>-</td>
<td>7 (10.3)</td>
</tr>
<tr>
<td>Giving a mandatory date/time to commence the use of the checklist by management</td>
<td>37 (54.4)</td>
<td>14 (20.6)</td>
<td>8 (11.8)</td>
<td>1 (1.5)</td>
<td>8 (11.8)</td>
</tr>
</tbody>
</table>

Support of the following:

<table>
<thead>
<tr>
<th>Support of the following:</th>
<th>Chief Medical Director</th>
<th>Chairman Medical Advisory Committee</th>
<th>Head of Department and Consultants in Surgery Department</th>
<th>Head of Department and Consultants in Anesthesiology Department</th>
<th>The Head Nursing Department</th>
<th>Operating Theatre Manager</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>44 (64.7)</td>
<td>9 (13.2)</td>
<td>2 (2.9)</td>
<td>2 (2.9)</td>
<td>10 (14.7)</td>
<td>52 (76.5)</td>
</tr>
<tr>
<td></td>
<td>43 (63.2)</td>
<td>14 (20.6)</td>
<td>-</td>
<td>-</td>
<td>11 (16.2)</td>
<td>48 (70.6)</td>
</tr>
<tr>
<td></td>
<td>52 (76.5)</td>
<td>5 (7.4)</td>
<td>1 (1.5)</td>
<td>-</td>
<td>10 (14.7)</td>
<td>52 (76.5)</td>
</tr>
<tr>
<td></td>
<td>53 (77.9)</td>
<td>6 (8.8)</td>
<td>-</td>
<td>-</td>
<td>9 (13.2)</td>
<td></td>
</tr>
</tbody>
</table>

Discussion

Knowledge and awareness of the safe surgery checklist among the respondents

From this study, participants had high awareness of the SSC among the respondents; this awareness is similar to that in previous study in the Guatemala (Hurtado et al., 2012) and UK (Watts et al., 2010). The internet was the most mentioned source of information, this could be explained by the recent upsurge in information technology and social networking, and it also
points to the fact that the theatre staff has good knowledge-seeking behaviour, this should be encouraged. Although their knowledge score was also impressive and in line with prior findings, however there is still the need to further educate the operating room staff about the objectives and components of the SSC, some (39.7%) could not mention at least one objective of the SSC, many (95.6%) could not correctly mention the three phases of the SSC in the order they are to be followed and only 32.4% could identify the three fundamental issues in the SSC. This was similar to the findings from the Guatemala study. This underscores the need for proper training and education of the surgical team members on the full knowledge of the SSC.

Perception of the participants towards safety culture and team work as it influences the use of the safe surgery checklist in their surgical procedures

The widespread adherence to clinical guidelines observed in this study is indicative of the fact that the hospital would be receptive to current guidelines; it shows the readiness of the staff to embrace new principles including the SSC in clinical practice if available. This is in line with similar studies’ findings (Abdel-Galil et al., 2010, Gueguen, 2011, Patterson et al., 2009)

There is also the need to improve upon safety principles in the surgical unit of this hospital generally, the contrary opinion among the respondents about having enough resources put in place to ensure safety is of great concern; they also indicate that people’s opinion is not usually listened to similar perception was observed, this indicates that the SSC and its components is not being applied or rather not in use, in this hospital since almost all these areas is included and should be considered if the SSC was actually in use. There was also a recommendable attitude towards the safety of patients among the staff, which also shows that the participants have a good disposition about the interest of their clients.

However there remains the need for improvement in terms of team work, since more than half of the respondents did not know their staff members by first and last names, about the same proportion indicated that they did not have a good team spirit among them and that their physicians and nurses work together as a well co-ordinated team; many even disagreed about eagerness to help one another among the surgical team. All these show the level of interaction and social understanding among the theatre staff and reflects some level of dichotomy, there should be better friendliness and associations among the staff, this will go a long way to bridge the gap that usually exists between the different professional categories and fosters co-operation which in turn improves service delivery.

Some studies by Cullatiet al., 2013 and Pickering et al., 2013, also supported the finding in this study that there is not enough time for safety preparation in their operating room.

Willingness and attitude of participants to use the SSC

This study shows that almost all the surgical team members of JUTH are willing and have a positive attitude towards the use of the SSC, they believed the SSC would improve the clinical outcomes in their surgery practice and majority (86.9%) said they would want the SSC to be used for their own surgery; however the indifferent disposition expressed by more than half of the respondents as to whether the checklist may bring any extra value to existing safety procedures already in place in the theatre before its implementation needs to be further assessed, one of the reasons might be that the full benefits and components of the SSC in terms of Safety is not yet fully understood by the participants. Similar result was observed in Switzerland (Fourcade et al., 2012) but contrary to findings from another similar study (Cullati et al., 2014). It is also obvious that majority were of the opinion that Nurses would be more suitable in taking charge of the checklist than any other operating room staff, although on-fourth though the surgeons were more suitable.
Possible challenges/advice/suggestion towards the implementation of the safe surgery checklist in JUTH operating theatres

Lack of team spirit or dichotomy among the surgical staff was a major challenge identified, this has been a major bottle-neck in Nigeria. Recently, conflicts and disagreements among Doctors, and other health professionals have seriously affected medical service and health care delivery negatively. There have been strikes and slowdowns which have led to shutting down government hospitals for long periods and which unarguably has led to deaths which could have been prevented and meltdown of the health sector services. It is not surprising then, that majority of the participants in this study has pointed out this issue as being a serious challenge that might also affect the implementation of the safe surgery checklist in JUTH operating theatres since in the surgical units we also have Doctors and other health professionals working together in a team.

Secondly, inadequate supply of consumable instruments and other equipment/facilities and Shortage or lack of manpower were indicated as the next major challenges, without the structures, instruments and staff, cutting-edge strategies like the SSC would be difficult to implement; these findings are in line with prior results from a previous study (Thomassen, et al. 2011). Lack of commitment from the Administration or Management unit, the management has always been known to greatly influence the implementation of new policies and strategies in an establishment, the hospitals is not to be left out in this case. The leadership of any establishment plays a major role in adoption of new ideas, this is in line with the results in a previous studies (Kariyoi et al., 2013, Vats et al, 2010 and Edmondson, 2003). Also if the administration or management of this hospital considers the SSC as priority, it is easier to obtain funds to train the surgical staff and purchase instruments or other equipment that must be in place to ensure the kick-off of the use of the SSC.

Attitude towards role of hospital administration and management in implementation and use of the checklist

In terms of management and administration, majority thought that having the Clinical staff (those engaged in day to day running of the theatre) as leaders of the implementation team would go a long way enhancing the implementation of the SSC in the study center, this is in comparison to having the administrative heads or proposing a mandatory policy by the hospital management. This is indicative that although the administrative or management unit of a hospital has an influence on the implementation of new strategies or policies in a health care establishment, it is however very important to ensure the partnership and involvement of the staff or professionals who will actually be the ones to make use of the strategy, in this case the SSC checklist. Thus the need to involve all those engaged in the day to day running of the theatre from the planning to the implementation stage of the use of the SSC, cannot be over-emphasized if this strategy is to be well accepted and properly infused into surgical practice.

This could also be the same reason why most of the participants thought the operating theatre manager and the Head of Department, Nursing were thought to be more influential towards the implementation of the safe surgery checklist in this hospital. Other reasons should be further looked in to; as earlier mentioned previous studies have highlighted similar issues ((Kariyoi et al., 2013, Vats et al, 2010 and Edmondson, 2003).

Conclusion

There is a high awareness and good knowledge of the SSC among the surgical team members of JUTH, however complete knowledge about the components and application is not fully known. In conclusion the Efforts should aim to more awareness and complete knowledge on why and how the checklist should be used. Patient safety was perceived to be of high priority
however team work should be improved upon. Generally the surgical staff were willing and have a positive attitude towards the implementation of the strategy if all other influencing factors are put in place. Challenges highlighted should be looked into and internally solutions should be sought to reduce or totally eradicate these problems, otherwise the implementation of new strategies like the SSC would remain unachievable.

Finally the role of administration in the planning and implementation of the SSC cannot be over-emphasized, there should be a collaboration of all unit heads particularly the nursing unit and operating management for a successful implementation. There is also need for training and frequent re-training of all the surgical team members, this will foster a good understanding and implementation of the SSC.

References

Factors affecting the use of contraception by postnatal mothers at komfo anokye teaching hospital, kumasi, ghana

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\textsuperscript{3}Department of Nursing Science, Kwame Nkrumah University of Science and Technology, Kumasi.
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Email:- emmanwaguy42@yahoo.com

Abstract
This is a cross-sectional descriptive study which sought to identify the factors that affects the use of contraception among postnatal mothers in Komfo Anokye Teaching Hospital (KATH), Kumasi, Ghana. Purposive and convenience sampling methods were used to select the directorates and health workers respectively. Self-structured and validated questionnaires were administered to 200 postnatal mothers at KATH. Data collected was processed and analysed with Statistical Package for Social Sciences and Microsoft Excel. Results obtained showed that mothers’ education and marital status are the main factors affecting the use of family planning. Education exposes the mothers to information on methods of birth control and increases understanding on various aspects of contraceptives such as mechanism of action, method specific instructions and side effects. The years spent in school also delay start of childbearing and enable the women to make informed decisions in matters affecting their reproductive health at a mature age. Marriage exposes mothers to sexual intercourse in the postpartum period and increases the risk of conception. Consequently, the married mothers have a higher intention to use postpartum family planning than their unmarried counterparts. This means that their needs for post-partum family planning (PPFP) should be addressed to ensure their intentions translate into actual use, which will reduce the unmet need for PPFP in KATH.

Keywords: Factors, Contraception, Postnatal mothers.

Introduction
Concerted efforts have been made by the Ghana government through the Ministry of Health and the development partners to meet the contraceptive need of postpartum mothers through training of health workers and integration of family planning services to the maternal and child health services. Despite the identified efforts, the proportion of postpartum women using contraception is still low. This postpartum period presents a rising risk of unwanted conception and often frustrated desire for contraceptive protection (Ross and Winfrey, 2001; Depineres, Blumenthal and Diener-West, 2005). The risk is even greater among the first time mothers who do not know what to expect after their first delivery and rely on the advice and explanations from their female relatives, neighbours and friends (Salway and Nurani, 1998). Although the unmet need for postpartum family planning is high, factors affecting the use of postpartum contraception among the postnatal mothers are not fully known and this calls for such investigation in Ghana. The main purpose of the study is to establish factors that affects the use of postpartum family planning among postnatal mothers in KATH.
Methodology

Study Area

This study was conducted at the Komfo Anokye Teaching Hospital,(KATH) Ghana, a 1000-bed teaching hospital in Kumasi. The hospital is accredited for postgraduate training by the West African college of surgeons. It also provides clinical training for students of nursing, midwifery, emergency nursing, anaesthesia, ear nose and throat, pharmacy and medical laboratory technologists. KATH is bounded on the north by the central police barracks, south and west by 4BN of infantry Uddara barracks and on the east by the main Bantama-Kejetia dual carriage way. KATH is located in Ashanti region, Southern Ghana. The hospital is divided into clinical and non-clinical directorates. The study was conducted in the clinical directorate of obstetrics and gynecology.

Study Population

The study population consists of all the postnatal mothers who attends postnatal care at KATH. By approximation, the number of these mothers was 1000.

Study Type and Design

The study was a cross sectional descriptive study to ascertain the factors that affects the use of postpartum contraception among postnatal mothers. 200 women receiving postnatal services from KATH and were willing to participate in the study were used. The questionnaires was administered after an informed consent was obtained from the respondents. Sampling and data collection was done at the directorates of postnatal, obstetrics and gynecology in the KATH.

Data Collection Tools and Techniques

Data for the study was collected by administering a structured and validated questionnaire from research investigators to patients at the postnatal, obstetrics and gynecology units. The questionnaire was made up of both closed and open ended questions so that respondents can provide adequate responses. For respondents who do not understand the English language, a conscious effort was made by the investigators to get an interpreter to explain the questions in the local language for easy understanding.

Sampling Method and Sample Size

Convenient sampling was used. Subjects were included in the study upon their willingness to take part in the study after the rationale of the study had been explained to them and confidentiality reiterated. A total of 200 subjects were studied.

Data Processing and Analysis

Total of 200 questionnaire were distributed and returned completely filled and were analysed. Data collected was analyzed quantitatively with statistical package for social sciences version 16.0 SPSS and Microsoft Excel 2010 was used to analyze and compute statistical data. Analytical techniques used involved the use of descriptive statistics such as frequency distribution and percentages. Data were then presented using tables, bar and pie charts.

Ethical consideration

Information obtained from subjects was for research only and was treated as strictly confidential; hence, study participants were not required to provide their names on the questionnaire. Participation in this study was voluntary after explaining the rationale and procedures of the study to eligible participants. Also, participants who decide not to participate in
the survey were not coarsed but allowed to do so. The researchers also ensured that the rights of the study participants were respected.

Clearance was sought from the research and development unit of the Komfo Anokye Teaching Hospital and the committee on human research publications and ethics of the Kwame Nkrumah University of Science and Technology.

RESULTS

Demographic and Socio-Economic Characteristics

Age of respondents

<table>
<thead>
<tr>
<th>AGE</th>
<th>Frequency</th>
<th>Percentage (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>15-19</td>
<td>22</td>
<td>11</td>
</tr>
<tr>
<td>20-24</td>
<td>46</td>
<td>23</td>
</tr>
<tr>
<td>25-29</td>
<td>40</td>
<td>20</td>
</tr>
<tr>
<td>30-34</td>
<td>54</td>
<td>27</td>
</tr>
<tr>
<td>35-39</td>
<td>24</td>
<td>12</td>
</tr>
<tr>
<td>40+</td>
<td>14</td>
<td>7</td>
</tr>
<tr>
<td>TOTAL</td>
<td>200</td>
<td>100</td>
</tr>
</tbody>
</table>

Source: Author’s field survey, March, 2014

The age of the respondents ranged from 15 to 49 years. The majority of the respondents were women aged 30-34 years (27%), followed by young adults aged 20-24 years (23%). The oldest women in the sample were aged 40+ years and formed the lowest proportion of 7 percent.

Religion

Figure 1. A diagram showing the religious distribution of the respondents

Source: Author’s field survey, March, 2014

Religious institutions influence contraceptive use among their followers. Some support while others oppose use of contraceptives to regulate fertility. Figure 1 shows that a large majority of the respondents were Protestants (48%), followed by the Catholics with 24 percent and the Muslims accounting for only 20 percent.
Figure 2. Occupation of respondents  
Source: Author’s field survey, March, 2014
Figure 2 shows that the majority of the mothers were housewives accounting for 46 percent, followed by self-employed (24%). About 10 percent were professionals while 9 percent were still in school at various levels. Only 6 percent were unemployed and 5 engaged in casual jobs.

Marital status

Figure 3. Marital status of respondents  
Source: Author’s field survey, March, 2014
Figure 3 shows that a high proportion (50%) of the respondents were married while ten percent were single. A good proportion of respondents was co-habiting (20%).
As observed above, almost half of the respondents (45%) had attained secondary level education, followed by a third of respondents with primary level education. Only less than a fifth (19%) had ever reached tertiary level and only 4 percent had no education.

GENERAL KNOWLEDGE ON FAMILY PLANNING

Knowledge of respondents on the number of contraceptive methods

Table 2: Number of contraceptive methods known by respondents

<table>
<thead>
<tr>
<th>No of contraceptive methods known</th>
<th>Frequency</th>
<th>Percentage (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>1</td>
<td>120</td>
<td>60</td>
</tr>
<tr>
<td>2</td>
<td>44</td>
<td>22</td>
</tr>
<tr>
<td>3</td>
<td>16</td>
<td>8</td>
</tr>
<tr>
<td>4</td>
<td>10</td>
<td>5</td>
</tr>
<tr>
<td>5</td>
<td>6</td>
<td>3</td>
</tr>
<tr>
<td>6</td>
<td>4</td>
<td>2</td>
</tr>
<tr>
<td>Total</td>
<td>200</td>
<td>100</td>
</tr>
</tbody>
</table>

The above table 2 shows that almost all the postnatal mothers (60%) knew at least one modern contraceptive method. The table also shows that the number of methods known ranged from none to six with a mode of two methods known by almost a fourth of the respondents (22%).

Source of Information

From our study, the most frequent source of information about family planning is health talks in the clinics (38%), followed by community health workers (24%) and from peers (20%). The mass media and other books (18%).

Table 3 showing sources of information

<table>
<thead>
<tr>
<th>SOURCES OF INFORMATION</th>
<th>FREQUENCY</th>
<th>PERCENTAGE (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Health Talk</td>
<td>76</td>
<td>38</td>
</tr>
<tr>
<td>Community Health Workers</td>
<td>48</td>
<td>24</td>
</tr>
<tr>
<td>Peers</td>
<td>40</td>
<td>20</td>
</tr>
<tr>
<td>Mass media and books</td>
<td>36</td>
<td>18</td>
</tr>
</tbody>
</table>
Figure 5. A diagram of the prior usage of contraceptives by respondents
Source: Author’s field survey, March, 2014
Less than one-third of the respondents (30%) had used family planning while most of the mothers (70%) reported not having used contraceptives.

Specific contraceptive methods used

Figure 6. Specific contraceptive methods used by respondents
Source: Author’s field survey, March, 2014
About 28 percent of the mothers who reported prior use of contraceptives had used emergency contraceptive, followed by injection (26%) and oral pills (19%). Only 17 percent reported use of condom to prevent conception.

Reasons for stoppage
As asked why they stopped using the methods, 44% of the respondents with prior use of contraceptives had plans to conceive while 13 percent cited side effects. About 31 percent were using the contraceptive methods for occasional protection especially emergency pill while opposition from the partner accounted for only 7 percent. Those who reported not being sexually active were about 5 percent.

**Prenatal Contraceptive Counseling**

**Antenatal attendance**

**Table 4: Number of antenatal attendance by respondents**

<table>
<thead>
<tr>
<th>ANC attendance</th>
<th>Frequency</th>
<th>Percentages(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>6</td>
<td>3</td>
</tr>
<tr>
<td>Once</td>
<td>14</td>
<td>7</td>
</tr>
<tr>
<td>Twice</td>
<td>20</td>
<td>10</td>
</tr>
<tr>
<td>Thrice</td>
<td>40</td>
<td>20</td>
</tr>
<tr>
<td>Four and above</td>
<td>120</td>
<td>60</td>
</tr>
<tr>
<td>Total</td>
<td>200</td>
<td>100</td>
</tr>
</tbody>
</table>

*Source: Author’s field survey, March, 2014*

The table above shows that only 3 percent had not attended antenatal care. It is notable that 60 percent had attended the recommended four or more antenatal care sessions, followed by 30.4 percent who attended antenatal care three times, 8.3 percent attended twice and 6.9 percent care only once.

**Prenatal contraceptive counseling**
Pattern of Substance Use Among Nigerian Air Force (NAF) Personnel at Sam Ethanan Air Force Base, Ikeja-Lagos, Nigeria

Article by Air Commodore Bashir Adam Yakasai (Rtd). MBBS, Cert Av. Med, DC Neurol, DPM, MSc, FMCPsych, MNIM
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Abstract

Objective: The study examined the pattern of Substance Use among the Nigerian Air Force Personnel.

Method: All the participants were airforce personnel. Officers and Men were randomly selected (N=250) and each subject was assessed using: 1) a Health Questionnaire (that assessed socio-demographic variables as well as the pattern of use and consumption of liquor), 2) Alcohol and drug sections of the Schedule for Clinical Assessment in Neuropsychiatry (SCAN), and the 28 – item General Health Questionnaire (GHQ -28). The personnel were informed that completion and returning the questionnaires would indicate consent to participate in the research.

Results: One hundred and ninety males and sixty females comprising officers and men participated. The mean age of the group was 30.9 years, with a range of 21 – 44 years; SD 4.35. One hundred and eight (42.6 percent) were 20 – 29 years, while one hundred and thirty (52 percent) were 30 – 39 years, and Twelve (5.4 percent) were 40 and above years. The difference in mean age between officers and men was not statistically significant following analysis of variance (ANOVA), F=2.59, P=0.148. The most commonly used substances were mild stimulants (coffee and kolanuts), alcohol, cigarette, cannabis, and hypnosadatives in that order. About the same trend was observed for the lifetime use. As many as 158 (63.3 %) of the respondents were current users of alcohol and almost everyone in the sample 92% have used alcohol in their lifetime. Fifteen 6% of the respondents were currently using cannabis, while 18.7% were lifetime users. Disorders were recorded for past year (ie criteria met within the previous 12 months) and lifetime (ever met criteria) using SCAN. Overall, 21 (8.3%) and 6 (2.3%) of the respondents DSM IV diagnostic criteria for alcohol abuse and dependence respectively in the past year; Eleven (4.7%) and 13 (5.3%)met the criteria for nicotine abuse and dependence respectively in the past year; 10 (4.0%) and 3 (1.0%)met the criteria for cannabis abuse and dependence respectively in the past year. A total of 42 respondents (16.8%) scored eight and above on the GHQ-28 scale. Thus the probable psychiatric morbidity rate for the cohort was about 17%.

Keywords: Military, SCAN, GHQ, Substance Use, Psychiatric Morbidity.

Introduction

Substance and alcohol use have historically been common among military personnel. Substances have been used by soldiers to reduce pain, lessen fatigue, and increase alertness or to help them cope with boredom or panic that accompany battle. During the U.S. Civil War, medical use of opium resulted in addiction among some soldiers. In the modern U.S. military, substance use became a recognized problem during the Vietnam War in the late 1960s and early 70s. Approximately 20 percent of Vietnam War veterans reported having used narcotics (e.g., heroin, opium) on a weekly basis, and 20 percent also were considered to be addicted based on reported symptoms of dependence.\(^1\) Similar to substance use, heavy drinking in the military has been an accepted custom and tradition.\(^2\) In the past, alcohol was thought to be a necessary item for subsistence and morale and, as such, was provided as a daily ration to sailors and soldiers. Within the predominantly male U.S. military population, heavy drinking and being able to "hold one's liquor" have served as tests "of suitability for
the demanding masculine military role\textsuperscript{2} A common stereotype has been to characterize hard-fighting soldiers as hard-drinking soldiers. Alcoholic beverages have been available to military personnel at reduced prices at military outlets and until recently during "happy hours" at clubs on military installations\textsuperscript{3}. In addition, alcohol has been used in the military to reward hard work, to ease interpersonal tensions, and to promote unit cohesion and camaraderie\textsuperscript{4}.

Paradoxically, substance abuse are strongly opposed within the armed forces worldwide, because of their negative effects on the health and well-being of military personnel and because of their detrimental effects on military readiness and the maintenance of high standards of performance and military discipline\textsuperscript{5}. In the military, drug abuse is defined as the wrongful use, possession, distribution, or introduction onto a military installation of a controlled substance (e.g., marijuana, heroin, cocaine), or intoxicating substance (other than alcohol). Alcohol abuse is defined as alcohol use that has adverse effects on the user's health or behaviour, family, community, or the Department of Defence.

Pattern of substance use has been studied in many populations around the world. However, findings on the risk factors for substance use disorder in the military have remained inconsistent due to variations in methodology. There are few military based studies which have assessed the pattern of substance use among the Air Force in Nigeria. Therefore, this paper is a cross sectional study that tries to address the problems of substance use in the NAF.

Methods

The study was conducted at the Sam Ethnan Base, Ikeja-Lagos, Nigeria. The Sam Ethnan Airforce Base, is the largest base in the Nigerian Air Force (NAF), with a population of about 2000 personnel consisting of officers, air men and air women mostly living with their families. All the subjects involved in this study were members of the Nigerian Air Force irrespective of their ages, rank and length of service years (although a minimum age of 18 years was observed). Personnel, who are physically as well as mentally fit and had no military charges, were allowed to participate. Each subject was randomly assessed using; 1) a Health Questionnaire (that assessed socio-demographic variables as well as the pattern of use and consumption of liquor), 2) Alcohol and drug sections of the Schedule for Clinical Assessment in Neuropsychiatry (SCAN), and the 28 – item General Health Questionnaire (GHQ - 28). The personnel were informed that completion and returning the questionnaires would indicate consent to participate in the research.

Results

The result of this study would be presented under the following headings:

a. The socio-demographic characteristic of the group.

b. Prevalence and pattern of substance use and related disorders.

c. Relationship between substance use disorders and socio-demographic variables.

d. Psychiatric morbidity rates among the respondents as determined by the GHQ.

Socio-demographic characteristic of the group. Table 1, summarises the socio-demographic characteristic of the respondents. One hundred and ninety males and sixty females comprising officers and men participated. The mean age of the group was 30.9 years, with a range of 21 – 44 years; SD 4.35. One hundred and eight (42.6 percent) were 20 – 29 years, while one hundred and thirty (52 percent) were 30 – 39 years, and Twelve (5.4 percent) were 40 and above years. The difference in mean age between officers and men was not statistically significant following analysis of variance (ANOVA), F=2.59, P=0.148.
Table 1. Socio demographic characteristic of the subjects

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Frequency</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sex:</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>190</td>
<td>76</td>
</tr>
<tr>
<td>Female</td>
<td>60</td>
<td>24</td>
</tr>
<tr>
<td>Total</td>
<td>250</td>
<td>100</td>
</tr>
<tr>
<td><strong>Age Group (years)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>20 – 29</td>
<td>108</td>
<td>42.6</td>
</tr>
<tr>
<td>30 – 39</td>
<td>130</td>
<td>52</td>
</tr>
<tr>
<td>40 and above</td>
<td>12</td>
<td>5.4</td>
</tr>
<tr>
<td>Total</td>
<td>250</td>
<td>100</td>
</tr>
<tr>
<td><strong>Ranks</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Airman/woman</td>
<td>215</td>
<td>76.3</td>
</tr>
<tr>
<td>Officers</td>
<td>35</td>
<td>23.7</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td>100</td>
</tr>
<tr>
<td><strong>Marital status</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Single</td>
<td>120</td>
<td>48</td>
</tr>
<tr>
<td>Married</td>
<td>119</td>
<td>47.6</td>
</tr>
<tr>
<td>Divorce/ Widowed</td>
<td>11</td>
<td>4.4</td>
</tr>
<tr>
<td>Total</td>
<td>250</td>
<td>100</td>
</tr>
<tr>
<td><strong>Educational Status</strong></td>
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<td></td>
</tr>
<tr>
<td>Secondary</td>
<td>135</td>
<td>56.3</td>
</tr>
<tr>
<td>Diploma</td>
<td>73</td>
<td>31.4</td>
</tr>
<tr>
<td>Degree</td>
<td>42</td>
<td>16.3</td>
</tr>
<tr>
<td>Total</td>
<td>250</td>
<td>100</td>
</tr>
</tbody>
</table>

Prevalence of Substance Use

Table 2 presents the prevalence of substance use. The most commonly used substances were mild stimulants (coffee and kolanuts), alcohol, cigarette, cannabis, and hypnosadatives in that order. About the same trend was observed for the lifetime use. As many as 158 (63.3 %) of the respondents were current users of alcohol and almost everyone in the sample 92% have used alcohol in their lifetime. Fifteen 6% of the respondents were currently using cannabis, while 18.7% were lifetime users.

Table 2. Prevalence of Substance Use

<table>
<thead>
<tr>
<th>Substances (n=250)</th>
<th>Current Use (%)</th>
<th>Lifetime Use (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alcohol</td>
<td>158 (63.3%)</td>
<td>230 (92%)</td>
</tr>
<tr>
<td>Cigarette</td>
<td>72 (29%)</td>
<td>140 (57.7%)</td>
</tr>
<tr>
<td>Cannabis</td>
<td>15 (6.0%)</td>
<td>47 (18.7%)</td>
</tr>
<tr>
<td>Mild Stimulants</td>
<td>180 (72.2%)</td>
<td>241 (96.7%)</td>
</tr>
<tr>
<td>Hypnosedatives</td>
<td>3 (1.3%)</td>
<td>97 (38.7%)</td>
</tr>
<tr>
<td>Amphetamine</td>
<td>0 (0.0%)</td>
<td>19 (7.6%)</td>
</tr>
<tr>
<td>Cocaine/Heroin</td>
<td>Nil</td>
<td>Nil</td>
</tr>
</tbody>
</table>

Current usage pattern of commonly used substances. In Table 3, while a significant proportion of current users of cigarette and cannabis were daily users, a high proportion of current users of alcohol tended to use it on a weekly (40%) and monthly (30%) basis. No current use was recorded for amphetamine and heroine, so also no daily use was noted for hypnosedatives.

Table 3. Current Usage Pattern

<table>
<thead>
<tr>
<th>Substances</th>
<th>N</th>
<th>Daily Use (%)</th>
<th>Weekly Use (%)</th>
<th>Monthly Use (%)</th>
<th>Occasional Use (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alcohol</td>
<td>158</td>
<td>8 (5.3)</td>
<td>63 (40)</td>
<td>47 (30)</td>
<td>39 (24.7)</td>
</tr>
</tbody>
</table>
Prevalence of Substance Use Disorder. Table 4 shows the prevalence of substance use disorders in the subjects. Disorders were recorded for past year (i.e criteria met within the previous 12 months) and lifetime (ever met criteria) using SCAN. Overall, 21 (8.3%) and 6 (2.3%) of the respondents DSM IV diagnostic criteria for alcohol abuse and dependence respectively in the past year; Eleven (4.7%) and 13 (5.3%) met the criteria for nicotine abuse and dependence respectively in the past year; 10 (4.0%) and 3 (1.0%) met the criteria for cannabis abuse and dependence respectively in the past year. No dependence Syndrome was noted for amphetamine, cocaine, and heroin in the past year. The lifetime acute intoxication from alcohol was 2.3%; lifetime uncomplicated withdrawal from alcohol was 0.7%. The prevalence of cigarette abuse was higher among the Other ranks than Officers, but this was not statistically significant, x=2.78, P=0.0952.

Table 4. Prevalence of Substance Use Disorder

<table>
<thead>
<tr>
<th>Substance</th>
<th>Past year Abuse (%)</th>
<th>Lifetime Abuse(%)</th>
<th>Past year Dep (%)</th>
<th>Lifetime Dep (%)</th>
<th>Total Past yr Abuse/Dep (%)</th>
<th>Other Past yr/Disorder (%)</th>
<th>Other Lifetime Dis (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alcohol</td>
<td>21 (8.3)</td>
<td>31 (12.3)</td>
<td>6(2.3)</td>
<td>9 (3.6)</td>
<td>10.6</td>
<td>3 AI (1.0)</td>
<td>6AI (2.3)</td>
</tr>
<tr>
<td>Cigarette</td>
<td>11 (4.6)</td>
<td>29 (11.6)</td>
<td>13(5.3)</td>
<td>21(8.3)</td>
<td>10.0</td>
<td>3 UW</td>
<td>9UW(3.6)</td>
</tr>
<tr>
<td>Cannabis</td>
<td>10 (4.0)</td>
<td>11 (4.6)</td>
<td>3 (1.0)</td>
<td>4 (1.7)</td>
<td>5.0</td>
<td>---</td>
<td>1 (2.5) AI</td>
</tr>
<tr>
<td>Mild Stimulants</td>
<td>4 (1.7)</td>
<td>7 (3.0)</td>
<td>2 (0.2)</td>
<td>5 (2.0)</td>
<td>2.3</td>
<td>2 UW</td>
<td>4UW (1.7)</td>
</tr>
<tr>
<td>Cocaine</td>
<td>2 (0.7)</td>
<td>6 (2.3)</td>
<td>0</td>
<td>0</td>
<td>--</td>
<td></td>
<td>1 (0.25) IA</td>
</tr>
<tr>
<td>Heroin</td>
<td>0</td>
<td>3 (1.0)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>--</td>
<td>--</td>
</tr>
</tbody>
</table>

AI = Acute Intoxication. UW = Uncomplicated Withdrawal.

Preferred Alcohol type. Table 5 shows the preferred alcohol type by the respondents. A significant proportion of alcohol users (62.0%) preferred to use larger beer. Only 6.9% preferred drink locally made preparation such as palm wine, burkutu, pito etc.

Table 5. Preferred Type of Alcohol

<table>
<thead>
<tr>
<th>Alcohol Type N= 158</th>
<th>Frequency</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bear alone</td>
<td>98</td>
<td>62.3</td>
</tr>
<tr>
<td>Bear &amp; Wine</td>
<td>15</td>
<td>9.6</td>
</tr>
<tr>
<td>Bear &amp; Hot</td>
<td>6</td>
<td>4.0</td>
</tr>
</tbody>
</table>
Table 6. Quantity of Alcohol consumed

<table>
<thead>
<tr>
<th>Unit of Alcohol N=158</th>
<th>Frequency</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;5</td>
<td>105</td>
<td>67.03</td>
</tr>
<tr>
<td>5-10</td>
<td>43</td>
<td>27.5</td>
</tr>
<tr>
<td>11-20</td>
<td>10</td>
<td>6.15</td>
</tr>
</tbody>
</table>

Quantity of Alcohol consumed. Table 6 shows the amount of alcohol consumed at a time. A unit of alcohol containing 8mg of alcohol was approximated to half a bottle of bear or wine, a bottle of small stout, a glass of wine, a tot of hot drink. The range was 1-20, with a mean of 4.8. The heavy drinkers tended to drink at same rate on weekdays, and weekends.

Table 7. Quantity of cigarette smoked

<table>
<thead>
<tr>
<th>No of Cigarette Stick N=72</th>
<th>Frequency</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-4</td>
<td>35</td>
<td>48.82</td>
</tr>
<tr>
<td>5-14</td>
<td>23</td>
<td>32.35</td>
</tr>
<tr>
<td>15-20</td>
<td>9</td>
<td>12.94</td>
</tr>
<tr>
<td>21-36</td>
<td>5</td>
<td>5.88</td>
</tr>
</tbody>
</table>

Quantity of Cigarette smoked. Table 7 shows the amount of cigarette smoked. A range of 1-36; mean 7.55. The heavy smokers tended to smoke continuously on a 24 hourly basis.

Table 8. Quantity of daily Cannabis consumed

<table>
<thead>
<tr>
<th>No of Wraps N = 15</th>
<th>Frequency</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>5</td>
<td>35.7</td>
</tr>
<tr>
<td>2</td>
<td>4</td>
<td>30.7</td>
</tr>
<tr>
<td>3</td>
<td>3</td>
<td>17.5</td>
</tr>
<tr>
<td>4</td>
<td>2</td>
<td>16.1</td>
</tr>
</tbody>
</table>

Quantity of Cannabis smoked. Table 8, shows the amount of cannabis smoked. The usual quantity of cannabis consumed was measured in wraps.

Table 9. Age at first use of cigarette

<table>
<thead>
<tr>
<th>Age NO=72</th>
<th>Frequency</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>9-15</td>
<td>11</td>
<td>15.0</td>
</tr>
<tr>
<td>16-19</td>
<td>31</td>
<td>43.13</td>
</tr>
<tr>
<td>20-24</td>
<td>22</td>
<td>31.25</td>
</tr>
<tr>
<td>25-30</td>
<td>8</td>
<td>10.62</td>
</tr>
</tbody>
</table>

Age at first cigarette use. Table 9 shows the age when cigarette was first used. Mean age of officers 19.2, SD = 2.5; mean age of Other ranks 19.3, SD = 3.97. The difference between mean ages of officers and other ranks was not statistically significant, F=1.23, P=0.89.

Psychiatric Morbidity (GHQ Score). A total of 42 respondents (16.8%) scored eight and above on the GHQ-28 scale. Thus the probable psychiatric morbidity rate for the cohort was about 17%. Fourteen out of the 28 items were reported by at least 10% of the respondents. The most frequently reported symptoms were “felt that you are ill”, 23.5% “lost sleep over worry”, 21.3%, “getting any pains in the head”, 19.2% “getting edgy and bad tempered”, many of these were somatic and anxiety symptoms.
**Table 10. Frequency of GHQ Score**

<table>
<thead>
<tr>
<th>GHQ Score</th>
<th>Frequency</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-3</td>
<td>145</td>
<td>58</td>
</tr>
<tr>
<td>4-7</td>
<td>63</td>
<td>25</td>
</tr>
<tr>
<td>8 and above</td>
<td>42</td>
<td>16.8</td>
</tr>
</tbody>
</table>

**Discussions**

Similar to most military personnel, the subjects in this study consists of bastion of young people (mean age, 30.90 SD+4.35%, with males consisting of 76% while the majority were Other Ranks (76.3%). This is comparable with studies elsewhere, for example, the rates of heavy drinking in the United States military is nearly four times higher among young men\(^6\). Interestingly, researches have indicated young people among the civilian population being at greater risk for drug abuse in general and alcohol abuse in particular\(^7,8,9\). However, the rate of heavy drinking in young military men is about twice that of their civilian counter parts as reported in the Department of Defence (DoD) News, April 5, 2012. The high literacy rate among the subjects is a reflection of the normal tendency for the Nigerian Air Force (NAF) to recruit only educated persons, and also to the laudable program of staff development in the NAF.

The life time prevalence of alcohol, and cannabis use in the cohort was 63.3% and 18.7% respectfully. In a much wider study, it was reported that almost half of the active duty service members (47%) reported binge drinking. In addition, 30% of the US soldiers were current users of cigarette smokers\(^5\). This finding is very much similar to our study in which 29% were current users of cigarette. Furthermore, these prevalence rates can be compared with that of general population samples\(^3,8\). Based on work at the middle belt area of Nigeria, it was estimated that about 50% of students and adults drink alcohol regularly\(^8\). The high rate of industrial beer (62.3%) and wine (21.6%) could be attributed to the relatively higher affluence among the military personnel, compared with the civil general population\(^10\).

One of the most common comorbid conditions with SUDs is depression. In the 2005 and 2008 HRB surveys, both Army and Marine Corps service members had the highest rate on a depression symptom screener (24% and 26%, respectively)\(^11\). Furthermore, it was, also found that those service members most likely to screen positive for depression also screened positive for PTSD (71%); reported suicidal thoughts (28%); were partnered, but unaccompanied (23%) or single (21%); and were illicit drug users (21%) or cigarette smokers (21%)\(^6\). By far, the most significant predictor of whether a service member would screen positive for depression was if the member screened positive for PTSD. In a study of service members with OEF and OIF exposure, In a previous study, it was found, that female veterans were at higher risk for a diagnosis of depression than male veterans were, but male veterans had over twice the risk for drug use disorders\(^12\). This finding is similar to our own study in which the probable psychiatric morbidity was 17%, and the most frequent symptoms on GHQ score were “felt that you are ill” in 23.5%, “lost sleep over worry” in 21.3%.

**Limitation of the study**

Several limitations could be identified. Data were collected from only one NAF Base, which would limit the generalizability of findings to other NAF units and formations. In addition, data were collected based on self report and might be misinterpreted by soldiers who do not understand the context of the questionnaires. Another limitation could be the issue of possible bias resulting in giving wrong answers or could be as a result fear of stigmatization or intimidation, even though the study was completely anonymous. Furthermore, the low number of participants and the exclusion of subjects that had other medical problems or military trial could lead to a reduction of the true prevalence of alcohol use and alcohol use disorders.
Conclusion

The life time prevalence of alcohol, and cannabis use in the NAF was 63.3% and 18.7% respectfully, which is comparable with that of the general population. Most of the subjects were young and majority of them belong to the Rank and Files of the NAF. Interestingly, most of our subjects are well educated and had a flare for expensive and branded alcohol drinks. One of the most common comorbid conditions with SUDs is depression. The probable psychiatric morbidity was 17%, and the most frequent symptoms on GHQ score were “felt that you are ill” in 23.5%, “lost sleep over worry” in 21.3%.

Acknowledgement

The author express his gratitude to the Headquarters, Nigerian Air Force, Logistic Command, for allowing the study to be conducted at Sam Ethanan Nigerian Air Force Base, Ikeja- Lagos, Nigeria.

References

A Rare Case Report of Unilateral Involvement of Basal Ganglia and Thalamus in a Case of Hypoxic Brain Injury

Article by Sunil Chowdary Minnekanti, Monika Sai Paida, Sushant Duddala, Nerin Duddala, Snigdha Shanti, Varsha Pulijal
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Abstract

Hypoxic injury of brain can occur at any age from an infant to an adult, also called as global hypoxic ischaemic injury. The patients usually present with a history of asphyxiation, drowning, cardiac arrest or respiratory arrest. Basalganglia, thalami, cerebral cortex (the sensorimotor and visual cortices are predominantly involved, though involvement is often diffuse), cerebellum, hippocampi are the areas usually affected in the brain. Usually the involvement is bilateral in deep nuclei we here present a rare case of unilateral involvement of basal ganglia in a case of hypoxic brain injury.

Introduction

• Hypoxic-ischaemic cerebral injury occurs at any age group, though the aetiology is significantly different in infants, children and adults.
• Older children: Drowning and asphyxiation are the most common causes of.
• Adults: Due to result of cardiac arrest or cerebrovascular disease, with secondary hypoxemia/hypoperfusion.
• The basal ganglia and thalamus are paired deep gray matter structures that may be involved by a wide variety of disease entities. The basal ganglia are highly metabolically active and are symmetrically affected in toxic poisoning, metabolic abnormalities, and neurodegenerative disorders with brain iron accumulation. Both the basal ganglia and thalamus may be affected by other systemic or metabolic disease, degenerative disease, and vascular conditions. Radiologists may detect bilateral abnormalities of the basal ganglia and thalamus in different acute and chronic clinical situations, and although magnetic resonance (MR) imaging is the modality of choice for evaluation, the correct diagnosis can be made only by taking all relevant clinical and laboratory information into account.
• The neuroimaging diagnosis is influenced not only by detection of specific MR imaging features such as diffusion restriction and the presence of hemorrhage, but also by detection of abnormalities involving other parts of the brain, especially the cerebral cortex, brainstem and white matter.
• During the acute period after diffuse cerebral anoxia, the results of conventional MR imaging and CT scanning may be normal, or the images and scans may show only subtle abnormalities. The imaging findings of diffuse cerebral anoxia include obscured grey-white matter junctions, abnormal appearance of deep grey matter nuclei, infarctions in regions between major arterial territories, and laminar necrosis.
• Because of its poor prognosis, a method that rapidly helps in diagnosis of diffuse cerebral anoxia is required. PET and SPECT may be helpful in the diagnosis of diffuse cerebral anoxia, but may be difficult to perform in hypoxic brain damage group patients. The use of diffusion-weighted MR imaging for the diagnosis of acute cerebral infarction has been described, but this imaging technique has not been used to examine patients with diffuse cerebral anoxia.
Case report

- 24 year old male alleged case of poisoning and attempted hanging after poisoning came with history of unconsciousness. On examination there is no history of protrusion of tongue or convulsions or any signs of head injury. The patient was referred from outside hospital for further management. On admission the patient was intubated and is on ventilator support. On examination the patient was sedated, pupils dilated (3mm) sluggishly reactive with minimal eye opening and moving all four limbs. The patient is tachycardic, blood pressure was 110/70 mm Hg and febrile. There was one episode of GTCS after the admission. Based on the history of poisoning and hanging, routine toxicology screen and drug screening were performed. The labs revealed high amounts of cholinesterase of 6244.7 μ/l (2700 – 4100). The routine drug screen was negative. Serum K⁺ was 5.7.

On admission ABG revealed the following findings
- pH of 7.4 (7.35 – 7.45)
- PCo2 27 (35-45) mm Hg.
- PO2 250 (83-1 05) mm Hg.
- Hco3⁻ 1.8. 2 mmol/lt
- K⁺ 3.7 (3.5 – 5) mmol/lt
- Na⁺ 1.33 (135 – 146) mmol/lt.
- Ca²⁺ 1.06 (1.15 – 1.29) mmol/lt.
- Cl⁻ 110 μ/l.
- Anion gap was 4.8 mmol.
- Renal function tests and liver function tests are normal.
- Echo showed mild grade I Mitral regurgitation, aortic valve is sclerotic and is tri leaflet, mitral diastolic flow is altered, Ejection Fraction is 40% with a kinetic left ventricular apex and showed minimal pericardial effusion. Usg abdomen and pelvis revealed no significant abnormality. Ct scan of brain performed on the day of admission did not reveal any abnormality.
- Mri brain was performed 3 days after admission in our institute as the patient is not showing improvement, which revealed the following findings.
- Scattered areas of abnormal hyperintense signal on T2-weighted and FLAIR sequences in right occipital region, right temporo-occipital region, right basal ganglia, right thalamus, right high frontoparietal region and left high frontoparietal region and these areas showed diffusion restriction.
- The signal abnormality also involved bilateral peri-Rolandic cortical regions with predominant involvement of the cortex with involvement of the subcortical white matter in right occipital regional. The left basal ganglia and left thalamus appear normal.
- The rest of the brain parenchyma, cerebellum and brainstem does not reveal any abnormality.
DWI images show area of diffusion restriction in bilateral high frontoparietal region with corresponding hypointensity on ADC maps.

DWI images show area of diffusion restriction in right basal ganglia and right thalamus and right posterior occipital lobe with corresponding ADC maps.
T1 weighted images show minimal hypointensity in the areas of corresponding diffusion restriction and minimal hyperintensity on T2 weighted images.

T1 weighted images show mild vacuity in the continuity of the body of the right corpus callosum which is confirmed on the DTI imaging showing less “fa” value.
Non contrast 2D-TOF angiography revealed non occlusion of both vertebral arteries and no dissection of bilateral ICA’s.

**Discussion**

Regardless of the cause of injury, the common underlying physiopathologic processes that result in hypoxic ischaemic injury is decreased cerebral blood flow (ischemia) and reduced blood oxygenation (hypoxemia). In general, infants and children are more likely to suffer asphyxia events, which result in hypoxemia and brain hypoxia. With prolonged hypoxemia there is cardiac hypoxia which leads to diminished cardiac output which results in brain ischemia. Thus, brain injury resulting from asphyxia is the consequence of ischemia with superimposed cardiac hypoxia. In fact, acute hypoxemia without superimposed ischemia is less likely to cause injury, unless there is prolonged hypoxia. Adults more frequently suffer brain ischemia as a result of cardiac arrest or cerebrovascular disease, with secondary hypoxia due to reduced blood flow. It is well known that global hypoxic-ischemic insults do not affect all brain structures uniformly. Rather, certain tissues in the brain are more likely to be injured and are injured earlier than others, a concept known as selective vulnerability.

The patterns of observed injury reflect dysfunction of selected excitatory neuronal circuits, which causes a complex cascade of unwanted biochemical events and, ultimately, selective neuronal death. Brain ischemia causes a change of metabolism from oxidative phosphorylation to anaerobic metabolism, which is highly inefficient. This change causes rapid depletion of adenosine triphosphate (ATP) and causes lactate accumulation within cells, and eventual loss of normal cellular membrane function. Depolarization of presynaptic neuronal cell membranes causes a massive release of excitatory neurotransmitters in particular, glutamate. In immature brains, glutamate binds predominantly to N-methyl-D-aspartate (NMDA) receptor–mediated calcium ($\text{Ca}^{2+}$) channels. Activation of NMDA receptors results in an influx of $\text{Ca}^{2+}$ into postsynaptic neurons, which triggers a number of cytotoxic processes, including activation of membrane phospholipases and production of the oxygen free radicals (such as nitric oxide) that damage cell membranes and internal constituents. Damage to mitochondria may ensure, causing further loss of ATP production and, ultimately energy depletion. Severe energy depletion results in rapid cell death from necrosis. With lesser degrees of energy depletion, neurons may survive the initial insult, only to undergo a delayed form
of programmed cell death known as apoptosis. Apoptosis appears to play a significant role in injury to the immature brain.

Adopted from Benjamin Y. Huang, MD, MPH ● Mauricio Castillo, MD Hypoxic-Ischemic

Brain Injury: Imaging Findings from Birth to Adulthood

From the model just described, we can draw the following conclusions:

• The areas of the brain with the highest concentrations of glutamate or other excitatory amino acid receptors are more susceptible to excite toxic injury that occurs as a result of hypoxicischemia.

• The areas of the brain with the greatest energy demands become energy depleted most rapidly during hypoxic ischemia, and are therefore injured early on.

• Because of delayed cell death from apoptosis, some injuries may not be evident until days after the initial insult has occurred.

• These factors help to explain the relatively specific patterns of injury that can be observed in patients with Hypoxic ischaemic injury. In any given patient, the sites in the brain that tend to be most vulnerable to hypoxic injury will be determined largely by the maturity of the brain, which is a function of patient age and, in infants, gestational age at birth.

• This is why Hypoxic ischaemic injury in the perinatal period differs from Hypoxic ischaemic injury in adults or even in older infants and the imaging appearance of Hypoxic ischaemic injury differs between term and preterm neonates.

• One must be aware of the degree of brain maturity at the time of the insult when interpreting studies for suspected Hypoxic ischaemic injury.

• The severity of a hypoxic ischemic insult also plays an important role in determining the distribution of injuries in the brain.

• Episodes of severe hypoxia-ischemia result in a different injury pattern compared with less severe insults.

• Duration of insult also seems to be a key determinant of the pattern of injury in HII, since insults of short duration usually do not result in brain injury.
• It has been suggested that, in the paediatric population, an arrest must typically last at least 15 minutes for brain injury to occur.

**Blood supply to the basal ganglia and thalamus**

- **Posterior Inferior Cerebellar Artery (PICA in blue).**
The PICA territory is on the inferior occipital surface of the cerebellum and is in equilibrium with the territory of the AICA in purple, which is on the lateral side. The larger the PICA territory, the smaller the AICA and vice versa.\(^{2-6}\)

- **Superior Cerebellar Artery (SCA in grey).**
The SCA territory is in the superior and tentorial surface of the cerebellum.

- **Branches from vertebral and basilar artery.**
These branches supply the medulla oblongata (in blue) and the pons (in green).

- **Anterior Choroidal artery (AchA in blue).**
The territory of the Ach artery is part of the hippocampus, the posterior limb of the internal capsule and extends upwards to an area lateral to the posterior part of the cella media.

- **Lenticulo-striate arteries.**
The *lateral* LSA's (in orange) are deep penetrating arteries of the middle cerebral artery (MCA). Their territory includes most of the basal ganglia. The *medial* LSA's (indicated in dark red) arise from the anterior cerebral artery (usually the A1-segment). Heubner's artery is the largest of the medial lenticulo-striate arteries and supplies the anteromedial part of the head of the caudate and anteroinferior internal capsule.

- **Anterior cerebral artery (ACA in red).**
The ACA supplies the medial part of the frontal and the parietal lobe and the anterior portion of the corpus callosum, basal ganglia and internal capsule.

- **Middle cerebral artery (MCA in yellow).**
The cortical branches of the MCA supply the lateral surface of the hemisphere, except for the medial part of the frontal and the parietal lobe (anterior cerebral artery), and the inferior part of the temporal lobe (posterior cerebral artery). The deep penetrating LSA-branches are discussed above.

- **Posterior cerebral artery (PCA in green).**
P1 extends from origin of the PCA to the posterior communicating artery, contributing to the circle of Willis. Posterior thalamoperforating arteries branch off the P1 segment and supply blood to the midbrain and thalamus. Cortical branches of the PCA supply the inferomedial part of the temporal lobe, occipital pole, visual cortex, and splenium of the corpus callosum.
Diagrammatic representation of the blood supply of human brain parenchyma

In our case scenario the possibility of unilateral involvement of the basal ganglia and thalamus might be due to the cause of unilateral compression of the lateral lenticulo-
striate branches and the penetrating branches of posterior cerebral artery (P1 segment) on left side during the alleged incident of hanging which spared the left basal ganglia and thalamus.(2,4)

Conclusion

Hypoxic ischaemic injury can be occurred in both children and adults due to various causes MR imaging plays a crucial role in evaluating subtle changes of hypoxic brain injury. Though there is overlap of findings on MRI a clinical discussion and observing the clinical details, history and symptoms help the radiologist in narrowing down the possible diagnosis of the cause of hypoxia. MR angiogram or CT angiogram may be necessary to identify the dissection in vertebral arteries in a case of hanging.

Bibliography

Knowledge Attitude and Practices of Commercial Drivers Towards HIV/AIDS and Prevention in Ose Local Government Area Ondo State Nigeria

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Abstract

The presented article on ‘Reducing bias in open-label trials where blinded outcome assessment is not feasible: strategies from two randomized trials’ provides strategic approach towards creating unbiased approach were blinding in the study is not possible. The study has been supported by two randomized trials which have been well accepted before.

Introduction

The article for review is taken from ‘Trials Journal’ and the topic is ‘Reducing bias in open-label trials where blinded outcome assessment is not feasible: strategies from two randomized trials’. The review is mainly divided into Critical Review, conclusion and references.

Critical Review

Generally it is observed that blinding of the study involving devices, surgical interventions, non-pharmacological interventions are more difficult to blind as compared to traditional drug trials. It is necessary to use blinded outcome assessment to prevent bias in case of open study and this blinded outcome assessment requires use of independent clinician and independent adjudication committee. But there are instances were neither independent clinician presence nor adjudication committee is possible to bring blinded assessment. These have been explained in the given study ‘Reducing bias in open-label trials where blinded outcome assessment is not feasible: strategies from two randomized trials’ by Brennan C Kahan. Single approach use for introducing blindness is by modification of outcome assessment definition. The approach has been explained by giving example of two randomized trials, TRIGGER Trial and TAPPS Trial.

However it is not always possible to modify the outcome assessment and thereby may be difficult to reduce bias in all open label study. A randomised trial can be methodologically sound and not be double blind or, conversely, double blind and not methodologically sound.

Although double blinding suggests a strong design, it is not the primary indicator of overall trial quality. Moreover, many trials cannot be double blinded. Such trials must, therefore, be judged on overall merit rather than an inapplicable standard based on double blinding. Methodological investigations tend to show that double blinding prevents bias but is less important, on average, in prevention of bias than is adequate allocation concealment.

Double blinding proves difficult or impossible in many trials. For instance, in general, surgical trials cannot be double blinded. Specifically, a trial that compares degrees of pain associated with sampling blood from the ear or thumb cannot be double-blinded. If researchers do not describe their trial as double-blind or the equivalent, it could still be scientifically strong. Apart from assessment of the other methodological aspects of the trial, readers would have to assess how much bias might have ensued due to absence of blinding. Readers should identify if anybody was blinded in the trial and what benefits might have accrued.
Conclusions

Overall the article presents what it means by the topic itself. The two cited examples of the trials also justify what the author wants to convey to the reader. But still there are number of open label studies were blinding is not possible and chances of bias may remains.

References


An Accessment of the Management of Post Operative Pain in Children
Admitted to the Pediatric Surgery Unit of the Korle-bu Teaching Hospital (kbth)

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Background

The oxford dictionary defines pain as a “highly unpleasant physical sensation caused by illness or injury”. It is also defined by the International association of pain as “an unpleasant sensory and emotional experience associated with actual or potential tissue damage” (Fisher, 2000). Now internationally it has been accepted that, pain should be expected, carefully and efficiently restricted in children irrespective of how old or mature they are and how severe their source of pain is considered to be (Fisher & Morton 1998).

A number of researches have been done in the area of pediatric pain and this has led to an improvement in the understanding of pain in children by both their parents or guardians and their clinical health care team. This not withstanding there is still some amount of challenge with the evaluation of pain in children.

Even though internationally so many studies have been conducted in the area of pediatric pain assessment and management, in Ghana there has been little or no study conducted in this area. Even obtaining local information about the assessment of post operative pain in children was not fruitful. As a result one cannot prove that post operative pain in children in Ghana who undergo one surgery or another receives the best control therapy.

This study is to assess the management of post operative pain in children in the biggest tertiary hospital in Ghana and information gathered could inform further studies in this area that can help improve the care given to children when it comes to the management of their post operative pain.

Literature review

There have been the believe of certain misconceptions that have influenced the under management of pain in children. For instance, neonates and infants are thought to have under developed nervous system and for that reason their ability to sense pain or feel pain is lower than that of adults but this is not true since research has proven that structures needed for perception of pain in humans are present around the 25th week of gestation and so the perception of pain can occur even intrauterine (Anand and Carr, 1989).

A lot of changes have occurred in the management of pain since it was first reported that children’s pain is under treated. There have been advances like a good understanding of pain in children during their developments and how to manage acute pain in children (Howard. R.F., 2003). This acquired knowledge has not been widely utilized or translated into custom clinical practice. Recently it was discovered that the pain experienced in early part of a child’s life may lead to long term consequences (Howard. R.F., 2003). It has been realized that factors like the timing of pain, degree of injury and the nature of analgesia administered may be important determinants of the long term outcome of infant pain (Howard. R.F, 2003)

Post operative pain defined “as a sudden or long persisting pain that is experienced after a surgical procedure” (www.articlesbase.com). Post operative pain is an expected phenomenon. However, its passage beyond acceptable limits is a common and costly experience (Coll et al, 2004)
The process of post operative pain management is always initiated before the surgery is done and this is because, it has been realized that good pain prevention reduces the severity of pain felt after the surgery has been done. Even though there is fast progress in the management of postoperative pain in children, children who have undergone surgery do not have their pain after the surgery being well managed because of complexity in the evaluation of the child level of pain and also fear of the possible addictive effect of pain relievers that belong to the opioid group (Lee and Jo, 2014). It is agreed that it is a bit difficult to have a faultless pain assessment method for children and pain relieving medications that do not have any adverse effect at all on them but a good assessment of the child’s pain and a good pain relieving approach designed by considering how young the child is, the kind of surgery that the child is to undergo, the kind of disease condition that the child had that necessitated the surgery with administration of a combination of the different pain relieving medications can improve the reduction of post operative pain in children (Lee and Jo, 2014).

Research has proven that considerable pain stimulation devoid of appropriate analgesia, will not only cause intolerable pain at the time of the stimulation but will result in the production of ‘pain memory’ which subsequently produces an inflated response to any form of stimulated pain (Taddio A et al, 1994) (Taddio A et al, 1995) (Taddio A et al, 1997).

Two decades ago, there was a survey that revealed that 40% of children that had undergone one kind or another surgical procedure felt moderate or severe postoperative pain and out of this group, 75% of them received analgesia that was not enough to control their pain (Marther L, Mackie J, 1983).

A survey conducted by Lawrence Marther and Josephine Mackie in 1983 came up with findings that indicated there was some level of prevalence of post operative pain perception in children. It had a study population of 170 children who had undergone a surgery of a sought. Out of the number who had pain after the surgery, 16% did not receive any analgesic. 39% of patients who needed opioid analgesics did not receive it and instances where the patient needed both opioid and non-opioid analgesics, there was the use of just the non-opioids in 25% of that group of patients (http://www.articlesbase.com). Another finding from this survey confirmed that post operative pain in children was not well managed.

In Sweden there was a study conducted by M Karling et al, 2007 to access the incidence of postoperative pain in children, the inadequate treatment of pain in children and also a look at the pain management structure in the country. It was a nationwide survey and it resulted in the following findings; 23 % of children on admission at hospitals had moderate to severe post operative pain. 45% of the clinicians and nurses who were respondents attested to the fact that post operative pain management in children could be done better.

Elizabeth Cummings et al also conducted a study on the prevalence and source of pain in pediatric patients. It involved the interviewing of some parents and their children on admission. As part of findings from the above study, it was realized that children were not receiving enough analgesia therapy. Neither the clinical care givers nor the parents of the children were seen by the children as helping with analgesia care. This study also confirmed that many of the children endured unnecessary height of pain whilst on admission (Cummings et al, 1996).

The process of managing pediatric post operative pain has seen much improvement over the last ten years since there came into existence of practical methods and valid tools which aid in assessing pain in children. At this point I must admit that the level of work or effort put into the management of postoperative pain in adults is so much higher than that invested in to the control of post operative pain in children who undergo one surgery or the other and this is attributable to the fact that only little is known clinically about pain in children, there is still much research work that has to be conducted in this area and the fear of having children suffer the adverse effects of opioid used as pain reduction medication by certain pediatricians (Lee and Jo, 2014).
Pain assessment in children

The assessment and treatment of pain in children and its functional consequence present a considerable unmet challenge. The assessment of pain in children can be very difficult and this has resulted in the design of different pain assessment tools for all the various age ranges of children (D Baroudi, 2007) Most scores allocate a numerical value to one of the following dimensions: cognitive, physiological, sensory, behavioral, and even facial expression (D Baroudi, 2007).

Among the pain assessment tools are the CR IES (Jacques, 2009), FLACC (Jacques, 2009), Mc Gill Pain Questionnaire (Jacques, 2009), Numerical Rating Pain scale (Jacques, 2009), Wong Baker faces pain scale (Jacques, 2009), Comfort Observer pain scale (Jacques, 2009), CRIES (Krechel and Bildner, 1995)

This is a pain scale that is used to access pain in neonates and infants who are six months and below. It is an observer-rated tool which access at the subject’s cries characteristics, oxygenation, vital signs facial expression and sleeplessness (Jacques, 2009)

FLACC

This is an acronym for face, legs activity, crying and consolability. This scale is an observer-rated scale which is made for children within the ages of 2years -7years. It can be used even on adult patients who cannot communicate their pain verbally. The assessment is between 0-10 (Jacques, 2009). A study was done in 1996 to access the validity of accessing post operative pain in children using the FLACC and it was realized that, it provided a simple structure for quantifying pain behaviors in children who may not be able to put into words the presence or severity of pain (Markel et al, 1996)

Numerical rating pain scale

The most common pain assessment tool used in the hospital settings is this one. This tool is designed such that patient can either verbally or by placing a mark on the scale to indicate his or her level of pain from 0 to 10. This tool is usually administered to children who are nine years and above (Jacques, 2009)

Wong baker faces pain scale (Wong et al, 2001)

This tool puts together pictorial and numerical presentations to enable the patient rate his or her pain level. It has six faces in all with each face assigned a numerical value (Jacques, 2009)

Comfort pain scale (Jacques, 2009)

This tool is used when the patient whose pain is to be accessed cannot verbally describe his or her level of pain nor can he or she rate the level of pain. It can also be applied to children, adults with cognitive impairment patients with learning disabilities and patients in ICU under sedation. The scale is rated from 9-45

Mc Gill pain scale (Jacques, 2009)

This scale utilizes the ranking of a painful event with words in groups provided. Once the patient ranks the pain, the one administering the questionnaire allocates a pain rating index which is a numerical score to the patient rating.

A precise evaluation of pain in the diverse age groups in children and the efficient control of postoperative pain are continuously being developed.
Medications used in pediatric post operative pain management

Management of pain and anguish should be the main concern for all clinicians. It has been proven as wrong in initial reviews that the inadequate treatment of pain in infants and children is not right. (Walco et al, 1994). In the 1970’s and 1980’s, there were surveys done and these indicated that infant and children were less likely to receive postoperative analgesics than adults (Schechter et al, 1986).

In children, the pharmacokinetics and pharmacodynamics of analgesics change during their development as a result, different hepatic-enzyme systems for drug metabolism mature at different rates as they develop (* Currently the use of patient – controlled systemic administration of opioid pain relievers in combination with the administration of nonsteroidal anti-inflammatory (NSAIDS) pain relievers as well as the use of local pain relievers at the site of operation either with or without the addition of adjunctive therapy have resulted in an improved and efficient control of post operative pain in children.

Opiod analgesics

It has been realized that when opioid analgesics are dosed well and monitored well after administration, they are useful in controlling moderate to severe post operative pain in children (Matthews, 2008). The age of children influences their response to opioid analgesics when they are given because it varies very much by age (Matthews, 2008). In neonates there is evidence that opioid analgesics can cause respiratory distress due to the fact that their respiratory system is not fully developed (Goldschneider et al, 2001)

Non – opioid analgesics

These include Acetaminophen, Non-Steroidal Anti-inflammatory Drugs (NSAIDS) and they are used most often as first choice drugs for the management of mild to moderate pain in children (Sutters et al, 2004). These groups of analgesics are readily available and have relatively safer spectrum of use so are usually used in the management of pediatric pain in general.

Acetaminophen

This is a metabolite of Phenacetin. It is the most widely used antipyretic used all over the world. Acetaminophen alone is a weak analgesic agent when used in the management of post operative pain (Kokinsty and Thornberg, 2003). Recently it has been shown by researches that the dosage of acetaminophen required to provide analgesia is higher than the traditional dosages used for controlling pyrexia in children, in addition it has been proven that the bioavailability of rectally administered acetaminophen is lower than the orally administered acetaminophen. The Intravenously administered acetaminophen (propacetamol) is said to provide the best bioavailability of acetaminophen. (Kokinsty and Thornberg, 2003).

NSAIDS

Over the last 10 years, NSAIDS have been very useful in the management of post operative pain in children. Usually NSAIDS are effective in the management of mild to moderate post operative pain in children (Kokinsty and Thornberg, 2003).

In Ghana most hospitals do not have any pain management protocol for children. The use of pain assessment tools in pain assessment is not common but pediatric surgery has developed so much that most pediatric surgery cases of Ghanaian children are treated in Ghana. Since post operative pain management is very necessary this study seeks to know how post operative pain is assessed and managed in Ghana and to expose the areas that need to be looked at.
Aim

TO ACCESS THE POST OPERATIVE PAIN MANAGEMENT NEED OF PEDIATRIC PATIENTS ADMITTED TO THE PEDIATRIC SURGERY WARD OF THE KBTH.

Objectives

1. WHAT GUIDES THE SELECTION OF ANALGESICS USED AT THE PEDIATRIC SURGERY WARD OF KBTH
2. HOW WELL IS THE POSTOPERATIVE PAIN OF PATIENTS CONTROLLED?

Method

The Pediatric surgery unit of the Korle -Bu Teaching Hospital will be the study site. It is a unit with a bed capacity of 27. It has a nursery capacity of 10, a ward for toddlers and another ward for young children as well as older children who are not more than thirteen years of age. The unit has four consultant pediatric surgeons, resident doctors that pass through on rotation and house officers who come there to pursue their houseman ship. The unit has two principal nurses in charge of the unit, two senior nurses, some nursing officers and student nurses who are posted to the unit to undertake their practical training.

A prospective study was preceded with a four days piloting of the data collection tool for accessing the pain in the children this was from the 21st of October, 2014 to the 24th of October 2014. During the piloting period, certain factors which were earlier on omitted from the data collection tool (appendix 2) such as; indication for the surgical procedure,, the date on which the assessment was being done, and a session for comments was identified and so the data collection tool (appendix 2) was modified.

The study actually started on the 3rd of November, 2014 and ended on the 7th of November 2014.

The study included all patients who had undergone a surgical procedure within 24 hours of the 3rd of November and the subjects were monitored for seventy-two hours since that is the duration for managing most post operative pain in children who have undergone surgery at the ward. The study excluded all patients who had undergone surgery 24 hours before 3rd of November, 2014.

Data collection was in two parts. The first part, involved the administration of a questionnaire (appendix 1) to the Doctors and nurses at post on the ward during the study period.

The questionnaire was in three parts. The first part looked at the Demographics of the clinical care staff (Doctors and Nurses) the second part sought to know the choice and the reason for analgesics that are prescribed for post operative pain management and the third part sought the knowledge of the clinical staff about the assessment of pain in their patients.

The second part of the data collection involved the use of a data collection tool (appendix 2) designed to assess the pain of the patients. As a guide, FLACC pain assessment tool (appendix 3) and the NIP’s pain scale (appendix 4) was used to assess the pain of patients on admission. The assessment of pain was done every six to eight hours since that was when most of the patients had their analgesics administered. As part of data collected, it was recorded when analgesics were administered or not administered.

The study was for academic purposes and was fully anonymous but very well explained to all stake holders, ethical approval was not sorted for. This was because I could not have enough time to meet the requirements of my institutions ethical approval. Also patients were not asked to sign informed consent.
Results

Characteristics of Health Care professionals at the Pediatric surgery ward

Reasons for clinicians’ first choice analgesic used post surgeries.
First choice analgesic used at the pediatric surgery ward of KBTH

Characteristics of patients on the pediatric surgery ward.

<table>
<thead>
<tr>
<th>Age of Patient</th>
<th>Number</th>
<th>Percentage</th>
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<tbody>
<tr>
<td>Neonate</td>
<td>4</td>
<td>36.4</td>
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<tr>
<td>1-3 years</td>
<td>4</td>
<td>36.4</td>
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<tr>
<td>4-7 years</td>
<td>3</td>
<td>27.3</td>
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The total number of patients on the ward during the study period was 11 and out of this, 72.7% were males and 27.3% were females.

Types of Analgesic given at post op at the pediatric surgery ward.
Discussion

There was a total of 7 clinicians and 4 nurses on the Pediatric surgery ward as of the time of the study. Majority of the clinicians were consultants and only 2 of the nurses accepted to answer the questionnire. It was observed that most of the clinicians said their first choice post operation analgesic would be paracetamol the nurses said if they were allowed to prescribe, the would have prescribed pethidine as the first choice analgesic for post operative pain management.

The question of what informed the choice of analgesics by clinicians and nurses for the patients, 44.44% which was the highest ascribed their choice to guidelin es but unfortunately there was no written down guidelines or protocol any where on the ward with information on analgesic choices for post operative pain management.

Considering the duration for post operative analgesic therapy, 77.78% of the clinicians and nurses said that they would give analgesic until patient has no pain anymore before they stop. This study brought out the fact that no clinicians did not prescribe opiod analgesics as first choice for their patients and the reason some gave was that even when they prescribe the opiod analgesics the nurses are reluctant to give.

When it came to pain assessment of the patients it was realised there was no regular pain assessment for the patient on the ward once their analgesic was being given nobody looked out for expressions of pain in the patients. As for the use of the pain scale for the assessment of patients pain it was totally absent. Also 88.89% of the clininicians and nurses attested to the fact that they prefered accessing pain level by either talking to the patient or to the parent and only 11.11 % mentioned that they would want to use the pain scale to access pain level of the patients. Also the Kokinsky and Thornberg guide to post operative pain control in children had stated that a good postoperative care in the hospital should involve a professional management of pain with the help of nurses experienced in the assessment and administion of suitable analgesics in order to reduce the discomfort of pain afterient the surgery. Also for out- patient cases, the patients parents or guardians are suppose to be given the necessary information as to how to access and manage the post operative pain in the patient when they get home. Unfortunately, this suggeston by the above guideline is not being adhered to on the pediatric surgery ward since there was no trained professional helping with the management of pain on the ward.
The only indication used as assessment for pain was excessive crying or wailing in the children. There was an instance during the study when a patient who had undergone Right Hemiotomy was being given only suppository paracetamol for 48 hours after surgery but when the patient’s pain level was assessed it was at 8. Then the data collector alerted the clinician on the ward of the need to have the patient analgesics reviewed and this was done by adding Ibuprofen to the analgesics after which the pain assessed went as low as 0. This was not fare on the child.

Comparing this study to one conducted in 1983 by Marther and Markie, almost every child who underwent surgery had an analgesic prescribed and given to him/her within twenty four hours post op; but in the 1983 study 16% of the patients did not have analgesic prescribed for them at all.

Most of the patients who had ‘around the clock’ analgesic given had a pain level as low as 0. But most of those who kept missing their Intravenous Paracetamol due to difficulty in line assessment or unavailability of the drug had higher levels of pain.

One obvious observation was the fact that most of the clinicians and nurses did not usually consider the possible non-pharmacological means by which they could reduce pain in the patients. Even though most of the stated that distracting the patient’s attention could help no one ever made the attempt to use that method to control pain in the patients who appeared to be in pain even after analgesics have been given.

Looking at the surgical interventions done during the period, Hypospadias repair was the highest number of intervention done and in most of these patients pain scores were as low as 0 even on post –op day 1 with patients being given only rectal or oral paracetamol. According to the Martha and Merkie guideline it may be necessary to add Intravenous Opioid medications to the analgesic combination for such patients but it looked just the use of Acetaminophen was enough pain relief for the patients who underwent such surgeries.

Conclusion

The post operative need of the patient who undergo surgery at the pediatric surgery ward of the Korle-bu Teaching Hospital is somehow being met but much work has to be done to improve it. Patients are never well assessed for their post operative level when they get to the ward.

Recommendation

1. There should be a trained professional available at the ward at all times to help with the assessment and management of post operative pain in the patients.
2. There is a need to develop a pain management guideline for the ward where the different types of surgeries and the suggested analgesics required for pain management would be stated. As part of this written protocol, it should be mandatory to have the pain level on the ward assessed and recorded at regular intervals.
3. Since research has indicated that Intravenous Acetaminophen works better and faster that the rectal and oral route administered ones, it would be very expedient for the pharmacy department of the hospital to procure some for the Pediatric pharmacy unit so it would be readily available for use.

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**Acknowledgements**

All the clinicians and nurses at pediatric surgery ward (kbth)
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Clin. Pharm Frankline Acheampong (Surgical Medical Emergency Unit Pharmacy, KBTH)
Data Management in Clinical Research

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Abstract

Clinical data management helps to produce a drastic reduction in time from drug development to marketing. Team members of CDM are actively involved in all stages of clinical trial right from inception to completion. They should have adequate process knowledge that helps maintain the quality standards of CDM including case report form (CRF) designing, CRF annotation, data designing, data-entry, data validation, discrepancy management, medical coding, data extraction and data locking are assessed for quality at regular intervals during the trial. Presently there is an increased demand to improve the CDM standards to meet the regulatory requirements and stay ahead of the competition by means of faster commercialization of product. With the implementation of regulatory complaint data management tools. CDM team can meet these demands. Additionally, it is becoming mandatory for companies to submit data electronically. It is advocated that CDM professionals should meet appropriate expectations and set standards for data quality and also have a drive to adapt to the rapidly changing technology. Pls refer Binny Krishnankutty, Shantala Bellary, Naveen B. R. Kumar et al 2011 Data management in clinical research an overview Indian Journal of pharmacology 44(2):168-172. doi 10.4103/0253-7613.93842

Definition

Data management is defined as a system for managing large amount of data ref Oxford advance learners dictionary. While the encyclopedia Wikipedia defines clinical data management in clinical research as defined by the National Institute of Health (NIH) as the ultimate goal of clinical research data management (CRDM) is to ensure that data support the conclusion drawn from research. It also stipulates that clinical data management (CDM) is a critical phase in clinical research, which leads to generation of high – quality, reliable and statistically sound data from clinical trials. Clinical data management assures collection, integration and availability of data at appropriate quality and cost ref https://en.m.wikipedia.org/wiki/clinical-data assessed on the 20th of June 2015

Introduction

The primary objective of clinical data management (CDM) is to provide high quality, reliable data for reporting randomized controlled trials (RCTs) in line with good clinical practice (GCP) requirements. In treatment trials of neglected Tropical diseases (NTDs) in endemic countries, CDM systems need to be efficient and AFFORDABLE (key issue), the challenges of poor infrastructures, license costs associated with GCP-complaint software and limited human resources to provide the required expertise are daunting, but it is argued that high quality CDM for NTDs can be achieved and the challenges can be overcome through the use of open-access tools ref Raymond Omollo, Michael Ochieny and Tansy Edwards 2014 innovative approaches to clinical Data management in resource limited settings using open source technologies PLOS Neglected Tropical diseases 2014 sen.8 (9). e3134.

Keywords: NEGLECTED TROPICAL DISEASES, Good clinical practice soft complaint software, clinical data management systems, data management e-CRF,
Good clinical data management practices validation, clinical data interchange standard

Discussion

Clinical data is intended to find answers to the research question by means of generating data for proving or disproving hypothesis Binny Krishnankutty 2011 The quality of data generated plays an important role in the outcome of the study Clinical data management is a relevant and important part of a clinical trial. All researchers try their hands on CDM knowingly or unknowingly. Clinical data management is the process of collection, cleaning and management of subjects data in compliance with regulatory standard, the primary objective of CDM processes is to provide high quality data by keeping the number of errors and missing data as low as possible and gather maximum data for analysis to meet the objectives best practices are adopted to ensure that data are complete, reliable and processed correctly. Pls refer Ptizer quality management in clinical trials 2009,030209

Components for generating clinical data

1) Creating, implementing, and upholding standard operating procedures (SOPs) for trial execution
2) A quality scientific and medical design of the protocol
3) Clinical investigation and site pre-assessment and selection
4) Regulatory agency and ethics committee approval
5) Developing and providing appropriate informed consent (Language transparency of benefits and risks) and obtaining ethics committee approval of the informed consent process
6) Investigators meetings and training
7) Adequate recording and reporting data
8) Periodic monitoring
9) Audits

Many soft ware tools are available for data management and these are called clinical data management systems (CDMS) used in pharmaceutical companies are commercial but a few open source tools are available as well as. The commonly used ones in pharmaceutical companies are mostly commercial but a few open source tools are available as well ref lu and Su publisher 2010 (Open access journal of clinical trials 2, 93-105 clinical data management current status, challenges and future directions from industry perspective). Commonly used CDM tools are oracle clinical, clintrial, macro, rare and e clinical suite, In terms of function ability these soft ware tools are expensive and need sophisticated information technology infrastructure to function. Additionally some multinational pharmaceutical grants use custom made CDMS Tools to suite their operational needs and procedures. Among the open source sophisticated tools the most prominent ones are open clinical, open CDMS, Trial DB and phosco. These CDM software are available free of cost and are as good as their commercial counterparts in terms of function ability. These open source software can be downloaded from their respective web site –ref Binny Krishnankutty et al 2011

In regulatory submission studies maintaining an audit trail of data management activities is of paramount importance. These CDM tools ensure the audit trail and also help in the management of discrepancies. According to the roles and responsibility, multiple user IDs can be created with access limitation to data entry, medical coding, data designing or quality check. This ensures that each user can access only the respective function ability allotted to that user ID and cannot make any other change in the data base. For responsibility where changes are permitted to be made in the data. The software will record the change made, the user ID that made the change and the time and date of the change. For audit purposes (audit trail) During a regulatory
audit the auditors can verify the discrepancy management process, the changes made and can confirm that no unauthorized or false changes were made.

**Regulatory, guidelines and standard in CDM**

Akin to other areas in clinical research, CDM has guidelines and standards that must be followed since the pharmaceutical industry relies on the electronically captured data for the evaluation of medicines. There is the need to follow good practices in CDM and maintain standards in electronic data capture. These electronic records have to comply with the code of Federal Regulation (CFR) 21 CFR Part 11. This regulation is applicable to records in electronic Format that are created, modified, maintained, archived, retrieved, or transmitted. This demands the use of validated systems to ensure accuracy, reliability, and consistency of data with the use of secure, computer generated, time stamped audit trails to independently record the data and time of operator entries and actions that create, modify, or delete electronic records. Adequate procedures and control should be put in place to ensure the integrity, authenticity, and confidentiality of data. If data have to be submitted to regulatory authorities, it should be entered and processed in 21 CFR Part 11 complaint systems. Most of the CDM systems available are like this in pharmaceutical companies as well as in contract research organizations which ensure this compliance. Binny Krishnankutty 2011 Good clinical data management practices (GCDMP) provide guidance on the accepted practices in CDM that are consistent with regulatory practices by high-lightening the minimum standard and best practices. Clinical Data Interchange standard consortium (CDISC) a multidisciplinary non-profit organization has developed standards to support acquisition exchange, submission and archival of clinical research data and metadata. This includes data about the individual who made the entry or a change in the clinical data, the date and time of entry or change and details of changes that have been made among the standards. Two important aspects are the study data tabulation model implementation guide for Human clinical trials (SDTMIG) and the clinical data acquisition standard harmonization (CDASH) standards available free from cost from the CDISC website (www.cdisc.org). The SDTMIG Standards describe the details of model and standard technologies for the data and serves as a guide to the organization. CDASH V 1.1 (5) defines the basic standard for the collection of data in a clinical trial and enlists the basic data information needed from a clinical regulatory and scientific perspective (CDISC).

**The CDM process**

The CDM process like a clinical trial begins with the end in mind. This means that the whole process is designed keeping the deliverable in view. As a clinical trial is designed to answer the research question. The CDM process is designed to deliver an error-free, valid and statistically sound database. To meet this objective, the CDM process starts early even before the finalization of the study protocol.

**Review and finalization of study document**

The protocol is reviewed from the database designing perspective, for clarity and consistency.

During the review the CDM personnel will identify the data items to be collected and the frequency of collection with respect to the visit schedule. A case report form (CRF) is designed by the CDM team as this is the first step in translating the protocol specific activities into data that is generated. The data fields should be clearly defined and be consistent throughout. The type of data to be entered should be evident from the CRF. For example, if weight has to be captured in two decimal places, the data entry field should have two data boxes placed after the decimal. Also, the units of
measurements e.g. centimeters, meters or kilograms should be mentioned next to the data field. The case report form CRF should be self explanatory, and user friendly. Along with the CRF the filling instructions called CRF Completion guidelines) should also be provided to study investigators for error free data acquisition. The CRF is done according to study data tabulation model implementation guide for human clinical trials (SDTMIG) or any other convention followed internally. Based on this a data management plan (DMP) is developed.

DMP Document is a road map to handle data under foreseeable circumstances and describes the CDM activity to be followed in the trial. PLs refer CDISC clinical data interchange standards consortium.

Database designing

Databases are the software application which are built to facilitate the CDM tasks to carry out multiple studies. Generally these tools have built in compliance mechanisms with regulatory requirements and are easy to use. System validation is conducted to ensure data security, during which system specification, user requirements and regulatory compliance are evaluated before implementation. Study details like objectives, interval visits of investigators, sites and patient are defined in the database entry. These entry screenings are tested with dummy data before moving them to the real data capture ref Binny Krishnankutty 2011

Data collection and C2

Data collection is done using case report forms (CRF). The entries made in the CRF will be monitored by the clinical research associate CFR for completeness and filled up CFRs are retrieved and handed over to the CDM team. CRF are tracked for missing pages and illegible data are not lost.

In case of missing or illegible data, a clarification as obtained from the investigator and the issue is resolved.

Class C2

Definition –class 2 is a security rating established by the US National computer security centre (NCSC) and granted to products that pass Department of Defence (DOD) Trusted computer system Evaluation criteria (TCSEC) tests A C2 rating ensures the minimum allowable level of confidence demanded for Government agencies and offices and other organizations that process classified or secure information. TCSEC Standards were established in the 1985 DOD document Department of Defense trusted computer systems Evaluation criteria known unofficially as the “Orange Book “ PLs refer Margaret Rouse sep 2008 WhatLs.com and –Searchsecurity.com

Data entry and discrepancy management

Data entry takes place according to guidelines prepared along with the DMP. This is applicable only in the case of paper CRF retrieved from the sites. Usually double entry data is performed where in the data is entered by two operators separately. The second pass entry (entry made by the second person) helps in verification and reconciliation by identifying the transcription errors and discrepancies causes by illegible data. More over double data entry helps in getting a cleaner database compared to a single data entry. Earlier studies have shown that double data entry ensures better consistency with paper CRF as denoted by a lesser error rate. DISCREPANCY MANAGEMENT –This is also called query resolution. Discrepancy management includes reviewing discrepancies investigating the reason and resolving them with documentary proof or declaring them as irresolvable. Discrepancy management helps in cleaning the data and gathers enough evidence for
deviations observed in the data. Almost all CDMS (clinical data management systems) have a discrepancy management base where all discrepancies are recorded and stored with audit trail.

When discrepancies are found they are referred to investigators for clarification. The CDM team reviews all discrepancies at regular intervals to ensure that they have been resolved. The resolved discrepancies are recorded as closed. Some of these may include spelling errors. Ref Binny Krishnankutty

**Medical coding and database locking**

Medical coding helps in identifying and properly identifying the medical terminology associated with the clinical trial. Classification of events, medical dictionaries available on line are used. Technically, this activity require needs the knowledge of medical terminology, understanding of disease entities, drugs used and a basic knowledge of the pathological processes involved. Functionally it also requires knowledge about the structure of electronic medical dictionaries and the hierarchy of classification available in them.

Commonly used medical dictionary for coding is the medical dictionary for regulatory activities (MEDDRA) is used for the coding of adverse events as well as other illnesses and World Health organization –drug dictionary Enhancement (WHO-DDE) is used for coding the medications, other dictionaries are WHO-ART. Some pharmaceutical companies customize dictionaries to suit their needs and meet their operating procedure.

Medical coding helps in classifying reported medical terms on the CRF to standard dictionary terms in order to achieve data consistency and avoid unnecessary duplication. An investigator may use different terms for the same adverse event but it is important to code all of them to a single standard code and maintain uniformity in the process. The right coding and classification of adverse events and medication is crucial as an incorrect coding may lead to masking of safety issues or highlight the wrong safety concern related to the drug.

After a proper quality check and assurance, the final data validation is run. If there are no discrepancies, the SAS (STANDARD ANALYSIS SYSTEM) Data sets are finalized in consultation with the statistician. All data management activities should have been completed prior to database lock. To ensure this, a pre-lock checklist is used and completion of all activities is confirmed. This is done as the database cannot be changed in any manner after locking once approval is obtained from all stakeholders.

SAS (statistical Analysis System) is a software suit developed by SAS Institute for advance analysis, multivariate analysis, business intelligence, data management and predictive analysis Ref SAS Institute North Carolina state university 1966-1976 https://en.m.wikipedia.org/wiki/sas The data base is then locked and clean data is extracted for statistical analysis Generally no modification of the data base is possible but in case a critical issue or for other important operational reasons privileged users can modifier the data. However in this contest privileged user has not been properly defined. Any adjustment will require proper documentation and an audit trail has to be maintained with sufficient justification for updating the Locked database. Data extraction is done from the final database after locking. This is followed by archival.

**The roles of team members in CDM team**

In the CDM team different roles and responsibilities are attributed to the team. The minimum educational requirement for a team member in CDM should be a graduate in life science and knowledge of computer application. Ideally medical coders should be medical graduates, however in the industry paramedical graduates are also
recruited as medical coders. Some key roles are essential for all CDM Teams. The list of roles stated herein can be considered as minimum requirements for a CDM team.

- Data manager
- Database programmer/Designer
- Medical coders
- Clinical data coordinator
- Quality control associate
- Data entry associate

The data manager is responsible for supervising the entire CDM process. The data manager prepares the DMP, approves the CDM procedures and all internal documents related to CDM activities. Controlling and allocating the data base access to team members is also the responsibility of the data manager.

Different professional organizations have outlines on clinical data management. There is the International Network of clinical data management (INCDMA) The INCDNA aims at the promotion of collaboration among clinical data management groups around the world. It is active International forum for discussion of and feedback on current topics of relevance to the discipline of CDM. It is composed of members of the boards of the SCDM, ACDM (UK), DMB (FRANCE), PSDM (THE NETHERLANDS) Who participate in the in the INCDMA proceedings and funding. It also regroup Dm leaders and subject matter experts from Europe, North America, Israel, Japan China and Australia pls refer https://www.acdm.org.uk and https://en.wikipedia.org/wiki/clinical-data-management

**Conclusion**

Clinical data management has evolved in response to the ever increasing demand from pharmaceutical companies to fast track the drug development process and from regulatory authorities to put quality systems in place to ensure generation of high quality data for accurate drug evaluation. To meet this expectation there is the graduate shift from the paper based to the electronic system of data management.

Developments in the technological front have positively impacted on the CDM process and systems there by leading to encouraging results on speed and quality of data been generated.

THE biggest challenge from the regulatory perspective would be in standardization of data management process across organizations and development of regulations to define the procedure to be followed and the data standards from industry perspective, the biggest hurdle would be the planning of data management systems in a changing operational environment where the rapid pace of technological development outdates the existing infrastructure. In spite of these CDM is evolving to become the standard based clinical research entity by striking a balance between the expectation from and constraints in the existing systems driven by technological development and business demand.

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A Review on the Drugs Approved By US-FDA and DCGI

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Introduction

Drugs: Drug is the chemical substance may be synthesized or derived naturally and is use for its therapeutic effect. It plays a vital role in life it is meant to diagnose, mitigate, cure, prevent, or treat or modify the physiological condition. Drug is meant for the safeguard of public health.

Importance of the medicines: medicines are considered to be one of the vital need of the human being. One has to rely upon this once or oftenly in their life time in order to maintain their physical and mental health. In ancient times the illness was considered to be gods wish but after certain period the revolution came and now that is era and till date continuous introduction of drugs to the patient need is available. After continuous Discovery and introduction of the drug the public health is being improved. And the mortality rate compare to ancient time has been reduced.

But there are lot more risks are also associated with a drug along its benefits if not taken cautiously some of major among them are:

1. ADR (adverse drug reaction)
2. drug addiction
3. SAE (serious adverse event)

1 ADR (ADVERSE DRUG REACTION): it is some untoward reaction of a drug other than its therapeutic effects.

2. Drug addiction: these are those drugs also known as opioids drugs some times greatly required. But these drugs as the name suggested are habit forming.

3 SAE: this is known as serious adverse event may be associated with that particular medicine or may be by any other medicines but this event can lead to permanent disfuction of body or may even death of patient.

FDA and its role in drug approval

The food and drug administration in usa is the organization which responsible for approving and non. approving of the drug. the main aim of FDA is to keep uneffective and unsafe drugs off the market to ensure, protect and increase the good public health. just to ensure that the public good think that if the drug is approved it means it met all the standard for its safety and efficacy when a research molecule is researched then the pharmaceutical company file for IND (investigational new drug) to FDA. The IND file by company contains whole data of preclinical study i.e trials performed on animals. The number of sheet would be around of 100000 pages in which the whole information about the new drug is written after reviewing the data if the criteria meets the standard then FDA gives approval for clinical trails for that particular drug. Each year FDA approve wide range of new drugs and biological products some of the products are new one or may be already in market but are seeking approval of FDA either for its other therapeutic effect or may be in combination to increase the efficacy.

In order to review the drug in proper way by the FDA the drugs are classified and the new innovative drug is considered to be as NEW MOLECULE ENTITY.

Following are the stages which a drug undergo with to come in market and at every and new stage the company has to file to FDA:-

1. Preclinical trials: inventing product are testing on animals
2. clinical trials:-
   Phase 1: perform on healthy volunteers to check the safety of product
   Phase 2: Perform on patients to check the safety and efficacy of product
Phase 3: perform on larger population of patient to make sure the safety and efficacy in larger population.

Phase-4: It is also known as post marketing of product done after launching of the product to market on periodic basis.

There are enormous numbers of the drugs which have been researched and many of these are in pipeline to come in market. It take a lot of time around 10-12 yrs it take to come a researched drug from lab to market. Only 5 in 5000 drugs are approved for trials on human body after preclinical trial by FDA.

Reasons of not approving much drugs in recent time and then sudden increase in approvals

The industry and FDA both play very important role in approval of a drug. There were a sudden decline in the approval of the drugs in past years because of the reason that the pharmaceutical company’s r&d process that is they are not meeting the criteria for safety and efficacy and many other parameters which result into long term decline in pharmaceutical R&D productivity which ultimately led to decrease in probability of success and increased cost for discovery and development of drug. In order to avoid it the biopharmaceutical company taken the initiative to improve their r&d status and reducing their fixed costs by outsourcing it to CROS.

The average number of approval rate over time

From 2004-2012 CDER has 26 NME average approval per anum but in 2012 CDER had approved 39 NME and in 2013 it was 27. The number of approval of the drug remains steady and the maximum number of approval were in 2014 that is total 41 approval of novel drugs in past decades.

1. The reason for sudden increase in approving of new drugs is emergence of drug for life threatening diseases through accelerated approval of drug from FDA.
2. The time reduce by FDA in reviewing data process for NME.
3. The inclination of pharmaceutical companies toward r&d requirement to meet the standard

The innovative therapies approved in past few years given major advances in the field of oncology, cardiovascular disease, type 2 diabetes, hepatitis C and in HIV.

The novel drug of 2014:-

Following are the drugs approved by us-fda in 2014

<table>
<thead>
<tr>
<th>Drug name</th>
<th>Active ingredients</th>
<th>Approval date</th>
<th>What it is used for</th>
</tr>
</thead>
<tbody>
<tr>
<td>Opdivo</td>
<td>Nivolumab</td>
<td>12/22/2014</td>
<td>To treat patient with unressectable or metastastics melanoma who no longer respond to other drugs</td>
</tr>
<tr>
<td>Rapivab</td>
<td>Peramivir</td>
<td>12/19/2014</td>
<td>To treat influenza in adult patient</td>
</tr>
<tr>
<td>Zerbaxa</td>
<td>Cetolazane/tazobactum</td>
<td>12/19/2014</td>
<td>To treat patient with intra abdominal infection</td>
</tr>
<tr>
<td>Viekira pak</td>
<td>Ombitasvir, paritaprevir,</td>
<td>12/19/2014</td>
<td>To treat patient with chronic hepatitis c with genotype 1 infection and complicated urine infection</td>
</tr>
<tr>
<td></td>
<td>ritonair Tablets</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lynnparza</td>
<td>Olaparib</td>
<td>12/19/2014</td>
<td>To treat advance ovarian cancer</td>
</tr>
<tr>
<td>Xtoro</td>
<td>Finafloxacin otic susp</td>
<td>12/17/2014</td>
<td>To treat acute otitis eternal</td>
</tr>
<tr>
<td>Blincyto</td>
<td>Blinatumomab</td>
<td>12/3/2014</td>
<td>To treat patient with philadelphia chromosome-</td>
</tr>
<tr>
<td>Drug</td>
<td>Description</td>
<td>Approval Date</td>
<td>Use Case</td>
</tr>
<tr>
<td>----------</td>
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<td>--------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Esbriet</td>
<td>Pirfenidone</td>
<td>10/15/2014</td>
<td>For treat patient with idiopathic pulmonary fibrosis</td>
</tr>
<tr>
<td>Ofev</td>
<td>Nintedanib</td>
<td>10/15/2014</td>
<td>For treat patient with idiopathic pulmonary fibrosis</td>
</tr>
<tr>
<td>Lumason</td>
<td>Sulfur hexafluoride lipid Microsphere</td>
<td>10/10/2014</td>
<td>For patient whose ultrasound images is hard to see with ultrasound wave</td>
</tr>
<tr>
<td>Akynzeo</td>
<td>Netupitant and palonosetron</td>
<td>10/10/2014</td>
<td>To treat patient with nose and vomiting for chemotherapy patient</td>
</tr>
<tr>
<td>Harvoni</td>
<td>Ledipasvir/sofosbuvir</td>
<td>10/10/2014</td>
<td>To treat patient with chronic hepatitis c with genotype 1</td>
</tr>
<tr>
<td>Trulicity</td>
<td>Dulaglutide</td>
<td>9/18/2014</td>
<td>To treat adult with type 2 diabetes</td>
</tr>
<tr>
<td>Movantik</td>
<td>Naloxegol</td>
<td>9/16/2014</td>
<td>To treat opioid induced constipation</td>
</tr>
<tr>
<td>Keytruda</td>
<td>Pembrolizumab</td>
<td>9/4/2014</td>
<td>To treat patient with advance unresectable melanoma where other treatments fails to work</td>
</tr>
<tr>
<td>Cerdelga</td>
<td>Eliglustat</td>
<td>8/19/2014</td>
<td>For the long term treatment in adult patient with type 1 goucher disease</td>
</tr>
<tr>
<td>Plegridy</td>
<td>Peginterferon</td>
<td>8/15/2014</td>
<td>To treat patient with relapsing form of multiple sclerosis</td>
</tr>
<tr>
<td>Belsomra</td>
<td>Suvorexant</td>
<td>8/13/2014</td>
<td>To treat patient for inducing sleep</td>
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<td>Orbactiv</td>
<td>Oritavancin</td>
<td>8/6/2014</td>
<td>To treat patient with adult infection</td>
</tr>
<tr>
<td>Jardiance</td>
<td>Empagliflozin</td>
<td>8/1/2014</td>
<td>To improve glycemic control in adult with type 2 diabetes</td>
</tr>
<tr>
<td>Striverdi</td>
<td>Respimat</td>
<td>7/31/2014</td>
<td>To treat patient with chronic pulmonary diseases</td>
</tr>
<tr>
<td>Zydelig</td>
<td>Odelalisib</td>
<td>7/23/2014</td>
<td>To treat patient with three type of blood cancer</td>
</tr>
<tr>
<td>Kerydin</td>
<td>Tavaborole</td>
<td>7/7/2014</td>
<td>For the treatment of onychomycosis of toenails</td>
</tr>
<tr>
<td>Beleodaq</td>
<td>Belinostat</td>
<td>7/3/2014</td>
<td>To treat patient with peripheral t-cell lymphoma</td>
</tr>
<tr>
<td>Sivextro</td>
<td>Tedizolid phosphate</td>
<td>6/20/2014</td>
<td>To treat adult with skin infection</td>
</tr>
<tr>
<td>Jubila</td>
<td>Efinaconazole</td>
<td>6/4/2014</td>
<td>To treat mild to moderate fungal infection</td>
</tr>
<tr>
<td>Dalvance</td>
<td>Dalbavancin</td>
<td>5/23/2014</td>
<td>To treat skin infection</td>
</tr>
</tbody>
</table>

The 41 drugs approved by FDA in 2014 contributes a major role in public health and these 41 drugs are placed and divided according to their categories. Few are discussed below:

1. **First in class drugs**: these are those new drugs which are using for new and unique mechanism to treat the medical condition following are the first in class medicines approved by FDA in 2014:

<table>
<thead>
<tr>
<th>s.no</th>
<th>Drugs</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Harvoni</td>
<td>To treat patient with chronic hepatitis C</td>
</tr>
<tr>
<td>2</td>
<td>Keytruda</td>
<td>To treat patient with unresectable or metastatic melanoma</td>
</tr>
<tr>
<td>3</td>
<td>zontivity</td>
<td>To reduce risk of thrombotic cardiovascular events</td>
</tr>
</tbody>
</table>

ACCELERATED APPROVAL: These drugs are those drugs which get early approval because of their urgent demand in public health for a serious or life threatening illness for better treatment over the used drugs. After approval of these drugs, the drug must undergo additional testing to confirm the benefits.

Following are the drugs approved as accelerated drugs by FDA in 2014:

<table>
<thead>
<tr>
<th>s.no</th>
<th>Drug</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Beleodaq</td>
<td>To treat patients with peripheral T-cell lymphoma</td>
</tr>
<tr>
<td>2</td>
<td>Keytruda</td>
<td>To treat patients with melanoma</td>
</tr>
<tr>
<td>3</td>
<td>Northera</td>
<td>To treat patient neurogenic orthostatic hypotension</td>
</tr>
<tr>
<td>4</td>
<td>Zydelig</td>
<td>To treat patient with 3 types of cancer</td>
</tr>
<tr>
<td>5</td>
<td>Blincyto</td>
<td>To treat patient with Philadelphia chromosome-negative</td>
</tr>
<tr>
<td>6</td>
<td>Lynparza</td>
<td>To treat patient with ovarian cancer</td>
</tr>
<tr>
<td>7</td>
<td>Opdivo</td>
<td>It is human programmed death receptor-1 blocking</td>
</tr>
<tr>
<td>8</td>
<td>Zyakdia</td>
<td>To treat metastatic non-small cell lung cancer</td>
</tr>
</tbody>
</table>

DCGI and its role in approving drugs

The drug controller general of India was established in 1998 the govt added schedule ‘Y’ to DRUG AND COSMETIC ACT-1940 schedule Y has detailed information for clinical trial and pre-clinical trials. However the pre-clinical trial is not approved in India. Though for the approval for the new drug to become approve and come in the market the same procedure like in us has to follow in india also. For the approval of the drug it is very necessary that the drug should meet all the criteria or guidelines provided in schedule Y. Then the application should be submitted to ethical committee. A clinical trial can only be performed after approval from DCGI for every next phase of the trial for the particular drug the application should be submitted to ethics committee and DCGI. DCGI is having the power to terminate the clinical trial in mid if the result or the data produce is not up to mark. In 2012 the pharmaceutical company were told to submit the safety report for the new drug in six months.

Drugs approved by DCGI in India 2014

The drugs approved by DCGI are mainly the drug which are already in market or approved already. They come in approval either in combination or with other therapeutic effect unlike previous or for further safety and efficacy purpose. Following are the drugs which were approved by dcgi in 2014:-

<table>
<thead>
<tr>
<th>Drug</th>
<th>Approval date</th>
<th>Therapeutic use</th>
</tr>
</thead>
<tbody>
<tr>
<td>Toleridone tartrate extended release tables 2/4mg</td>
<td>31/01/2014</td>
<td>For the treatment of overactive bladder</td>
</tr>
<tr>
<td>Botezomib for injection 3.5mg</td>
<td>28/01/2014</td>
<td>For the treatment of overactive bladder</td>
</tr>
<tr>
<td>Paclitaxel inj. Concentrated for nano dispersion 100 nd 300 mg</td>
<td>22/02/14</td>
<td>For the treatment of breast cancer after failure of combination therapy</td>
</tr>
<tr>
<td>Heparin sodium topical solution</td>
<td>16/1/2014</td>
<td>For the treatment of fluctuence of post infusion superficial thrombophlebitis</td>
</tr>
<tr>
<td>Medicine</td>
<td>Date</td>
<td>Indication</td>
</tr>
<tr>
<td>----------------------------------</td>
<td>----------</td>
<td>-----------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Eltrombopag olamine tab 25/50mg</td>
<td>7/4/2014</td>
<td>To treat patient with hepatitis</td>
</tr>
<tr>
<td>Decitabine lyophilized powder</td>
<td>9/4/2014</td>
<td>For elderly patient to treat secondary acute myeloid leukemia</td>
</tr>
<tr>
<td>for injection</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Glycopyrronium inhalation powder</td>
<td>1/4/2014</td>
<td>To treat chronic obstructive pulmonary disease</td>
</tr>
<tr>
<td>Micafungin sodium for inj</td>
<td>2/5/2014</td>
<td>To treat fungal infection</td>
</tr>
<tr>
<td>Apixaban tab 2.5mg</td>
<td>16/5/2014</td>
<td>Prevention of stroke and systemic embolism in adult patient with non-valvular</td>
</tr>
<tr>
<td>Mometasone furoate nasal spray</td>
<td>21/5/2014</td>
<td>To treat perennial allergic rhinitis</td>
</tr>
<tr>
<td>50 mcg</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tadalafil 10mg,20mg</td>
<td>30/7/2014</td>
<td>For erectile dysfunction</td>
</tr>
<tr>
<td>Hydroxychloroquine sulphate</td>
<td>28/7/2014</td>
<td>To treat patient with type 2 diabetes</td>
</tr>
<tr>
<td>Nevirapine extender release</td>
<td>1/7/2014</td>
<td>To treat patient with HIV-1</td>
</tr>
<tr>
<td>tab 400mg</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cerebrolysin inj</td>
<td>25/7/2014</td>
<td>To treat amelioration of cranial injury</td>
</tr>
<tr>
<td>Artesunate powder</td>
<td>2/7/2014</td>
<td>To treat patient with severe falciparum malaria</td>
</tr>
<tr>
<td>Lactobacillus brevis CD logenges</td>
<td>9/8/2014</td>
<td>Prevention of radiotherapy and chemotherapy induced oral mucositis in cancer</td>
</tr>
<tr>
<td>100mg</td>
<td></td>
<td>patients</td>
</tr>
<tr>
<td>Rivaroxaban tab 15/20mg</td>
<td>2/9/2014</td>
<td>To treat patient with deep vein thrombosis and to prevent DVT and pulmonary</td>
</tr>
<tr>
<td>Hydroxychloroquine tab 300mg</td>
<td>9/8/2014</td>
<td>embolism</td>
</tr>
<tr>
<td>Ginko biloba extract</td>
<td>9/12/2014</td>
<td>To treat patient dementia, vertigo and tinnitus</td>
</tr>
<tr>
<td>Bendamustine hydrochloride inj</td>
<td>19/9/2014</td>
<td>To treat patient with chronic lymphocytic leukemia</td>
</tr>
<tr>
<td>25mg</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Metformin ER750mg</td>
<td>25/9/2014</td>
<td>To improve glycemic control in type 2 diabetes</td>
</tr>
<tr>
<td>Sorafenib tsylate tab 200mg</td>
<td>25/9/2014</td>
<td>To treat patient with thyroid carcinoma refractory</td>
</tr>
<tr>
<td>Deferasirox dt 100/400mg</td>
<td>26/9/2014</td>
<td>Treatment of chronic iron overload in patient with non-transfusion dependent</td>
</tr>
<tr>
<td>Imatinib mesilate 100/400 cap</td>
<td>9/9/2014</td>
<td>thalassemia</td>
</tr>
<tr>
<td>Olanzepine pamoate powder</td>
<td>14/10/14</td>
<td>To treat patient with schizophrenia</td>
</tr>
<tr>
<td>Rivastigmine tranderal patch</td>
<td>28/10/2014</td>
<td>To treat patient with severe dementia of the alzheimer's disease</td>
</tr>
</tbody>
</table>
### Conclusion

The revolution in drug discovery and its approval is proved as boon for public health. It results in improved health both mentally and physically in human race. The pace of drug approval is quite high in present time as compare to past few years. The high rate of approval of drug is good initiative by the government authorities to maintain and sustain good public health. Specially in case of life threatening illness like cancer, HIV, cardiovascular and many more. By approving these drugs on fast basis and keeping all quality and standard of these drugs in mind many lives can be saved in time. This is good move for both india and usa. Population. Specially in india as india is developing country and illness rate and variety of illness is more here than in any other country and due to lack of heigene and lack of awareness the chances are more to spread of dieases in contagious way specially in rural area. So it is very necessary demand for approval of these drugs so that preventive action can be taken against illness in time.

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