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A Comparison of Effectiveness of Efavirenz and Nevirapine - Based First-Line HIV Treatment in Patients Attending Coast Provincial General Hospital, Kenya

Article by Philip K. Naluande¹, Michael M. Gicheru², Michael F. Otieno³
¹ Clinical and Laboratory Standards Institute (CLSI-AFRICA), Kenya
² Kenyatta University- Department of Medical Laboratory Sciences
³ Kenyatta University - Department of Zoological Sciences
E-mail: pnaluande@yahoo.com

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Abstract

The objective of this study was to compare the effectiveness of Efavirenz and Nevirapine based First-line HIV treatment in patients attending comprehensive care centre in Mombasa. This was a prospective comparative study. The target population was HIV positive adult patients eligible for HAART. A total of 251 patients were enrolled in the study and followed up for 12 months. All ARV naive patients with CD4 count < 350/ul with WHO stage 3 or 4 and eligible for HAART were randomly into Efavirenz and Nevirapine based regimens (D4T/3TC/EFV and D4T/3TC/NVP) and followed up for a period of twelve months. Laboratory tests were done for each patient every three months by testing for Haemoglobin, Liver enzyme test (ALT), Creatinine and CD4 cell count. The study showed that first-line regimens of Efavirenz and Nevirapine were effective in suppressing HIV/AIDS infection with improvement in CD4 count (P<0.05). There was also improvement in haemoglobin levels and body weight among the patients on both regimens in the study. However, elevation of ALT and Creatinine were noted in both treatment groups, but this did not warrant drug discontinuation (P>0.05). Efavirenz based regimen appeared to be superior to Nevirapine based regimen on CD4+ profiles and renal function (P<0.05). There was no significant difference in haemoglobin levels, body weight and ALT enzyme for patients on both treatment groups. The findings demonstrated that D4TC/3TC/EFV and D4TC/3TC/NVP combinations were safe, well tolerated and effective in suppressing HIV progression in advanced HIV infected patients.

Acronyms and abbreviations

<table>
<thead>
<tr>
<th>Acronym</th>
<th>Definition</th>
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<tbody>
<tr>
<td>AE</td>
<td>Adverse Event</td>
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<tr>
<td>AIDS</td>
<td>Acquired Immune Deficiency Syndrome</td>
</tr>
<tr>
<td>ALT</td>
<td>Alanine aminotransferase</td>
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<tr>
<td>ART</td>
<td>Antiretroviral therapy</td>
</tr>
<tr>
<td>ARV</td>
<td>Antiretroviral</td>
</tr>
<tr>
<td>CCC</td>
<td>Comprehensive Care Centre</td>
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<tr>
<td>CD4+</td>
<td>Cluster of Differentiation</td>
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<tr>
<td>CPGH</td>
<td>Coast Province General Hospital</td>
</tr>
<tr>
<td>CNS</td>
<td>Central Nervous System</td>
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</table>
**VCT** : Voluntary Counselling and Testing (for HIV)  
**WHO** : World Health Organization.  
**WBC** : White Blood Cell Count

**Introduction**

**Background information**

Antiretroviral have been widely used in developing countries, yet little has been done to find out the treatment outcome of these drugs by assessing the immunological and virological parameters of an individual’s immune system in relation to the clinical response. Hence, it is important to follow the progression of HIV/AIDS patients through laboratory monitoring, as well as to review the acceptability and tolerability of ARV’s which contribute to adherence, as this will help in treatment decisions by clinicians as they can decide to continue treatment, change a particular regimen or discontinue therapy at the appropriate time. This decision will often be based on the occurrence of side effects, or increased toxicity or non-adherence to antiretroviral drugs. ART has significant toxicity that requires monitoring. Laboratory tests performed on a regular basis are usually used to detect severe toxicity, before it becomes clinically apparent and harmful. These tests, however, are costly and require patient visits, phlebotomy and appropriate infrastructure and equipment.

**Limitations**

The most important limitation in the study was the exclusion of co-morbidities and opportunistic infections like tuberculosis, which can induce important selection bias.

Secondly, lack of viral load testing was also another limitation of the study considering that viral load detection in blood is a good indicator of viral suppression and drug effectiveness. Thirdly, another limitation was the lack of calculation of body mass index (BMI) as an important anthropometric measurement to assess nutrition status of patients on HAART.

**Materials and methods**

**Study site**

The study was carried out in Mombasa County at the Coast Provincial General Hospital (CPGH). The County has approximately 939,370 people (KNBS, 2009) and is a Cosmopolitan Centre with a balanced population of both the youth and older people. The Centre was selected because it offered free services sponsored by Family Health International (FHI) and Ministry of Health (MOH) to all willing clients for Voluntary Counseling and Testing Services, and also that it formed the bulk of population of Mombasa District.

**Research design**

A Prospective longitudinal cohort study of HAART regimens given to ARV naïve HIV infected adult patients at Coast Provincial General Hospital. Clients were randomised into Efavirenz and Nevirapine based regimens (D4T /3TC / EFV and D4T /3TC / NVP) and followed up for a period of twelve months. Screening of patients was done at the Comprehensive Care Centre (CCC) after being referred from VCT clinics, outpatient clinics and the wards. Patients were then screened for eligibility criteria which included laboratory examination for liver enzymes, hemoglobin, renal function, CD4 Cell count and clinical assessments by the clinician. Patients who were eligible for HAART based on their CD4 count as per eligibility criteria were selected to be part of the study and followed up to one year (12 months).
Data collection technique

Laboratory measurements

Ten (10) mls of blood were obtained for Haemoglobin, CD4 count and also for Liver enzyme assay (ALT) and Creatinine at baseline, 3 months, 6 months, 9 months and 12 months duration. Enzyme Linked Immunosorbent Assay (ELISA) test for HIV was used to confirm HIV positive status. Whole blood sample drawn in EDTA containing tubes was used to determine T-helper cells (CD4 count). Absolute numbers of CD4 was calculated as well as white blood cell count using the coulter counter as per manufacturer’s instructions. Biochemical parameters which include Liver enzyme test (ALT) were used to assess the liver response in patients treated with ARV’s by determining the values of these parameters at baseline and at intervals of three (3) months after commencement of ARV therapy for up to one year.

Statistical analysis

Data analysis was done using SPSS Version 11.0 statistical software. Basic characteristics of the study samples were summarised using simple proportions and means, median and inter quartile ranges. Further analysis was done to perform one way ANOVA comparing more than two means followed by Post hoc Student Newman Keul for multiple comparisons. Independent t-test was used to calculate if there was any significant difference between the two treatments. Study subjects were followed from HAART initiation to the earliest of death, loss to follow up, development of toxicity or end of twelve months.

Results

Analysis of Patients body weight

Body weight increased for both of the two treatment groups after initiating antiretroviral therapy for the first six months (Table 4.1) and tapered over time between 6 months and 9 months period for the two treatment groups. The mean weight increased between 9th month and 12th month (1 year) period with a mean of 62.1 kg 95% CI (60.6 - 63.5) compared to baseline which was 55.6 kg ( 95% CI 54.1- 57.1. The average increase in body weight for patients on EFV over the 12 months period was 2.2 kg whereas for patients on NVP was less than 2 kg. There was no significant difference on the body weight for both patients on EFV and NVP groups p > 0.05 as measured at 6 months. However, patients in both treatment groups experienced slight increase in weight between the 9th month and 12th month follow up period respectively.

Table 4.1. Body weight in kilograms of patients in the EFV and NVP study groups

<table>
<thead>
<tr>
<th>Time in months</th>
<th>Efavirenz</th>
<th>Nevirapine</th>
<th>p - value</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 months</td>
<td>56.21±12.59</td>
<td>54.75±10.38</td>
<td>0.347</td>
</tr>
<tr>
<td>3 months</td>
<td>57.49±12.29</td>
<td>56.48±10.18</td>
<td>0.504</td>
</tr>
<tr>
<td>6 months</td>
<td>59.18±12.31</td>
<td>58.80±10.00</td>
<td>0.797</td>
</tr>
<tr>
<td>9 months</td>
<td>59.49±12.29</td>
<td>58.30±10.29</td>
<td>0.432</td>
</tr>
<tr>
<td>12 months</td>
<td>62.49±12.29</td>
<td>61.30±10.29</td>
<td>0.432</td>
</tr>
</tbody>
</table>

Immunological changes

Immunological variables were measured on a maximum of 5 occasions. There were significant differences in CD4 lymphocyte subsets between patients on EFV and patients on NVP treatment arm ( p < 0.01) at the 6th, 9th and 12th month respectively.
The profiles of these values showed that EFV based regimen was superior in improvement of CD4+ count compared to NVP based regimen as shown in Table 4.2 below.

**Table 4.2. Mean CD4 + cells for patients in the study CD4 + Cells/mm3**

<table>
<thead>
<tr>
<th>Time in months</th>
<th>Efavirenz</th>
<th>Nevirapine</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 months</td>
<td>133.75±91.98</td>
<td>165.11±61.33</td>
<td>0.001</td>
</tr>
<tr>
<td>3 months</td>
<td>171.32±103.38</td>
<td>139.74±63.65</td>
<td>0.003</td>
</tr>
<tr>
<td>6 months</td>
<td>200.07±114.28</td>
<td>161.39±68.33</td>
<td>0.001</td>
</tr>
<tr>
<td>9 months</td>
<td>270.07±114.28</td>
<td>231.39±68.33</td>
<td>0.001</td>
</tr>
<tr>
<td>12 months</td>
<td>365.07±114.28</td>
<td>326.39±68.33</td>
<td>0.001</td>
</tr>
</tbody>
</table>

The comparison of differences in immunological parameters between the baseline period, 3 months, 6 months, 9 months and 12 months for both EFV and NVP patients are well illustrated in table 4.2 above. The means of the differences between changes for EFV and NVP were significantly different (p < 0.001). The data on CD4 count confirm that patients at enrolment had lower levels of CD4 cell count at the onset of the study for both groups. In addition, the data indicate that the mean absolute numbers of CD4 count were slightly higher for the patients on NVP regimen compared to EFV regimen at the baseline with means of 165.11 (103.78 – 226.44) and 133.75 (41.77 – 225.73) respectively. The mean absolute CD4 cell count for patients on both regimens increased to the 12th month period suggesting positive immune response following HAART therapy. During the first 6 months of ART, the number of CD4+ T cells typically increased by 30 cells to 60 cells/mm³ of blood. This burst was then followed by a second, faster phase of T cell repopulation with an average rate increase of 70 cells / mm³ in the 9th month of ART.

**Hemoglobin levels during the study period**

Hemoglobin levels increased for patients in both arms of treatment (EFV and NVP) group up to the 6th month. However, there was a sudden decline of hemoglobin levels towards the 9th month. Hemoglobin levels increased further from 9th month to 12th month during the study. There was no significant difference in haemoglobin levels of patients on EFV and NVP regimens throughout the study (p > 0.05) (Table 4.3).

**Table 4.3. Mean of hemoglobin (g/dl) during the 12 months study period**

<table>
<thead>
<tr>
<th>Time in months</th>
<th>Efavirenz</th>
<th>Nevirapine</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 months</td>
<td>10.49±2.40</td>
<td>10.03±2.29</td>
<td>0.135</td>
</tr>
<tr>
<td>3 months</td>
<td>11.18±2.39</td>
<td>10.92±2.30</td>
<td>0.406</td>
</tr>
<tr>
<td>6 months</td>
<td>11.88±2.52</td>
<td>11.82±2.39</td>
<td>0.858</td>
</tr>
<tr>
<td>9 months</td>
<td>11.58±2.39</td>
<td>11.33±2.33</td>
<td>0.145</td>
</tr>
<tr>
<td>12 months</td>
<td>11.98±2.39</td>
<td>11.73±2.35</td>
<td>0.420</td>
</tr>
</tbody>
</table>

Reference ranges for Hemoglobin: Adult Male: 13.0g/dl – 18.0 g/dl and Adult Female: 12.0g/dl – 15.0g/dl
Liver enzymes (ALT) before and after initiation of HAART

The monitoring of patients through the two ARV regimens allowed the analysis to be done for toxicity. There was no significant difference in the mean values of ALT enzymes for patients on EFV based regimen and NVP based regimen from baseline to the 12th month (p > 0.05). Nevertheless, the hepatic biological tolerance during EFV or NVP based regimen was generally good in months 3 and 6. The majority of the mean values of ALT enzymes studied were above normal ranges except for those at baseline (Table 4.4).

Table 4.4. Mean liver enzymes alt (U/L) for patients during the study

<table>
<thead>
<tr>
<th>Time in months</th>
<th>Efavirenz</th>
<th>Nevirapine</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 months</td>
<td>49.81±3.48</td>
<td>44.83±4.40</td>
<td>0.379</td>
</tr>
<tr>
<td>3 months</td>
<td>67.86±5.13</td>
<td>62.39±5.29</td>
<td>0.485</td>
</tr>
<tr>
<td>6 months</td>
<td>85.80±9.21</td>
<td>90.38±14.55</td>
<td>0.780</td>
</tr>
<tr>
<td>9 months</td>
<td>126.57±12.13</td>
<td>137.89±21.40</td>
<td>0.620</td>
</tr>
<tr>
<td>12 months</td>
<td>165.99±18.30</td>
<td>183.32±31.09</td>
<td>0.608</td>
</tr>
</tbody>
</table>

Reference ranges for ALT enzyme: Adult Male and Female: 7 U/L – 55 U/L.

The comparison of ALT enzymes after initiation of HAART has shown that changes in these parameters were similar in both HAART regimens. The early hepatic biological tolerance during EFV or NVP based regimen was generally good and similar. However, significant increases in the enzyme values for ALT were observed with the NVP based regimen when compared with EFV regimen. There were also 16 cases of clinical toxicities which later resolved. Ten were associated with Stavudine and Nevirapine with mainly peripheral neuropathy, lipodystrophy and CNS symptoms.

Creatinine trends of patients in the study

The Creatinine levels increased minimally for all patients from onset of ARV’s up to a maximum of 154 umol / L at the end of the follow up. There was significant difference of Creatinine levels for the two regimens with Nevirapine giving higher values than Efavirenz regimen (p < 0.001). (Table 4.5). At endpoint patients on EFV regimen had Creatinine mean of 135.61±0.89 compared to NVP mean of 151.04±3.30. However, none of the patients reached a Creatinine level of >300 umol / L to warrant drug discontinuation or regimen change.

Table 4.5. Mean creatinine levels (umol/L) for patients on EFV and NVP

<table>
<thead>
<tr>
<th>Time in months</th>
<th>Efavirenz</th>
<th>Nevirapine</th>
<th>p -value</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>74.16±2.60</td>
<td>75.19±3.37</td>
<td>0.808</td>
</tr>
<tr>
<td>3</td>
<td>91.47±1.51</td>
<td>94.49±3.29</td>
<td>0.405</td>
</tr>
<tr>
<td>6</td>
<td>115.83±1.21</td>
<td>123.15±3.23</td>
<td>0.036</td>
</tr>
</tbody>
</table>
Reference ranges for Creatinine: Adult Male: 80.0 U/L – 115.0 U/L and Adult Female: 53.0 U/L – 97.0 U/L

**Discussion**

**Effect of HAART on CD4 profiles**

The study has demonstrated clinical benefits in terms of CD4 cell count and weight increase well into the end of first year of follow up. The finding of a rapid rise in CD4 cell counts during the initial few weeks of therapy followed by a slower rise for the patients in the current study are consistent with earlier reports on CD4 cell kinetics conducted in the USA. In addition, the mean CD4 cell increase seen in patients in this study at one year after antiretroviral therapy initiation is similar to the response seen in studies conducted in Europe (Lifson et al., 2011). As such, the mean CD4 cell increase seen at later time periods reflect responses to both primary and secondary regimens (about 10% of the patients in the study switched to second line therapy). Alternatively, individuals in the current study may have different hepatic regeneration capacities at the initiation of ART. For this study population, CD4+ cells had continued to increase up to 12th month period.

In fact, even among highly advanced patients in our study who initiated HAART with CD4 cell counts below 200 cells/mm3, subsequent increase in CD4 cell count was most strongly predicted following treatment with HAART. Previous studies showing that CD4 cell counts <350 cells/mm3 may preclude a CD4 cell count response may have been confounded by patient non adherence (Kenneth et al., 2013).

The main immunologic outcome observed was the change in CD4 cell count over time. A switch in therapy occurred if the ART regimen recorded at follow up was different from the regimen initially started. Any individual drug substitution or regimen change was considered a switch. Dose reduction however, was not considered an ART switch. The time of the first switch defined the time of reaching the outcome. If the physician recorded a symptom during a clinic visit believed to be attributed to ART, a toxicity event was considered to have occurred.

Deaths were recorded based on physicians or family notification on the discontinuation. Official records such as death certificates were not usually available. The primary end point was mortality from all cases in the 12 months after starting HAART. Changes in CD4+ cell counts in the first 3, 6, 9 and 12 months were secondary end point measurements used in this analysis. Time was measured from the start of HAART and ended at the earliest of the date of death, the date of the last follow up visit or month 12 after starting HAART.

**Effect of HAART on body weight changes**

The current study found that mean body weight gains mirrored CD4 cell increase immediately following antiretroviral therapy initiation and this correlated with the findings of Barnejee et al. (2010) which showed that HAART had a positive effect on growth in HIV 1 infected individuals. HAART had modestly favourable effects on body composition, particularly in patients with greater pretreatment immunosuppression and virological suppression. In a previous study HIV-1 infected individuals and especially children experienced a continued gain in body weight after starting HAART (Denue et al., 2013). However, body weight was found to have subject variability with consistent mean body weight increases among the NVP based and EFV based treatment arms in the study period.
Effect of HAART on liver enzyme (ALT)

All HAART drugs have a potential of causing severe hepatotoxicity (Adikwu et al., 2013). The results of this study tie with those obtained by another study by Lucien et al. (2010) which showed that HAART was associated with low level hepatotoxicity at therapy initiation, regardless of drug class. The lack of significant difference in the proportion of patients who experienced an increased enzyme activity between these two ARVs regimens could be due to the fact that Stavudine toxicity present on both arms of treatment could have masked the actual toxicity experienced by NVP. In another related study, patients who have been on HAART had significantly elevated ALT and AST levels but mild toxicity (Shakirat et al., 2014). Our study was also comparable with that of Kalyesubula et al. (2011) who in their retrospective cohort study determined the incidence of hepatotoxicity associated with (NNRTI) in a group of HIV infected patients who received EFV and NVP and the rate was similar among the treatment groups.

The findings in the current study were also comparable to those of Emily et al. 2010 who showed in a study on liver injury after receiving Nevirapine; that elevated liver enzymes was observed in their cohort. Other studies that showed similar results with our study are those on early hepatotoxicity during the first 12 weeks of treatment (Adikwu et al., 2013). In their analysis, the frequency of hepatotoxicity was 17% in the group receiving NVP and 0% in the EFV group. In another related study, data confirmed an increased risk of early hepatotoxicity associated with the use of NVP (Shakirat et al., 2014). The proportion of patients who had elevated ALT activity had tripled with each ARV therapy from month 3 to month 6. The increased activity of ALT was reported as a potential side effect of most ARVs used in the treatment of HIV infection. Kalyesubula et al. (2011) concluded in their study that hepatotoxicity occurs during HAART therapy and was more common in patients receiving NVP than those using EFV which is consistent with results of this study.

It has been reported in another study by Lucien et al., (2010) that some patients who experienced serious liver toxicity with NVP did not develop hepatotoxicity during subsequent treatment with EFV, suggesting that toxicity was related to ARV and not to specific class (Lucien et al., 2010). The high incidence rate of severe hepatotoxicity in the first 3 months of initiating ART necessitates the need for more frequent and careful monitoring of ALT levels early during therapy.

Effect of HAART on renal function

In our study, none of the patients had renal failure but the study showed that closer monitoring of renal function is essential in all HIV patients on HAART. This result is consistent with the study of Mainasara et al. (2014) which showed that HAART of Stavudine, Lamivudine and Nevirapine improve renal creatinine clearance functions among the HIV positive patients. Similar results were also obtained by Robert et al. (2015) on the study of predictors of renal outcome in HIV associated nephropathy.

HAART and other medical therapies for HIV related infections have been associated with both short and long term toxicities including nephrotoxicity.

Effect of HAART on haemoglobin levels

The present findings show that there is an association between anemia, decreased survival, and increased disease progression in patients with HIV infection. In our study, low platelets counts resolved in patients on ART and were probably not drug related. Thus monitoring of hemoglobin would have been enough to detect nearly all of the significant cases of anaemia. Metabolic abnormality associated with potent antiretroviral regimens including NVP may revert at least partially with time and after replacing NVP by EFV as observed in this study. In a different study haemoglobin changes following HAART varied by sex and age, but remained significantly associated with prognosis in both sexes (Florence et al., 2011). Also studies from other developed countries suggest that use of HAART reduces the risk of anemia in patients with HIV infection and improves hemoglobin values in many patients who are already anemic at the time of HAART initiation (Simbarashe et al., 2013). Our study showed decreased anemia.
with HAART use, which supports data from prior studies which showed that patients on HAART had improved hemoglobin levels and less incidence of anaemia (Chauhan et al., 2011). Similarly, studies by Zelalem et al. (2014) found that HAART was an effective treatment for anaemia of HIV infection, and the potential mechanisms that might be involved included a reduction in opportunistic infections and the anaemia of chronic disease, and an improvement in nutritional status. Lower body mass index was also associated with a high risk of anaemia.

Conclusions

The results from this study demonstrated that D4TC/ 3TC/ EFV and D4TC/ 3TC/ NVP combinations were safe, well tolerated and effective in increasing CD4 Cell counts and suppressing HIV progression in advanced HIV infected patients.

Recommendations for future steps

Patients with HIV should have their CD4 cell count monitored regularly before and after commencement of HAART before they reach immunological failure. The findings support the ongoing feasibility of early ART roll out in the country. Therapeutic monitoring may be a useful tool for the administration of HAART in the future. In the future, closer monitoring of renal function and adverse effects of HAART should be enhanced as these parameters appear elevated with time as patients continue to use the drugs. Renal function and Liver function should therefore be monitored on a regular basis in patients with HIV receiving any antiretroviral agent.

References


Patients’ Perception on Benefits of Medications for treating diabetic Peripheral Neuropathic Pain

1 Pharmacy Supervisor. PHCC /MSc in Clinical Pharmacy
2 Senior Cons. of Neurology /HGH (Hamad General Hospital)
3 Consultant of family medicine /PHCC (Primary Health care Corporation)
4 Senior Consultant of family medicine/PHCC
5, 7, 12, 15, 16, 17 Senior Pharmacist/PHCC
6, 8, 9, 10, 11, 13, 14 Pharmacist/PHCC
E-mail: ayousif50@gmail.com

Abstract

Background: About 16% of the adult Qataris at ages of 20 to 79 were diabetic. The prevalence of peripheral diabetic neuropathy in Arabic ranged between 38-94% in diabetic. Medications in studied were Amitriptyline, Carbamazepine, Celecoxib, Diclofenac, Duloxetine, Fluoxetine, Gabapentin, Imipramine, Meloxicam, Paracetamol and pregabalin.

The specific objective; how the DPNP patients would perceive the benefits of medications Secondary objectives; which medication(s) perceived to restore a patient’s quality of life. In addition, which medications could realize a 50% benefits for releasing DPNP.

Setting: participants selected randomly, when attended their routine appointments in six health centers under in Qatar.

Sample size: 646 DPNP participants

Inclusion criteria: Diabetic from 18 years and above, taking medications to treat DPNP for duration of at least three weeks.

Exclusion criteria: Patients taking same medications for other ailments, diabetic less than 18 years old, and those with difficulty in communication.

Results: Participants showed abilities to perceive the benefits of their medications, and their impact on some domains of quality of life. Gabapentin perceived by average percent of 70.70 % to be beneficial in the above mentioned domains. Imipramine perceived by 24% beneficial. Fluoxetine not completely perceived as beneficial. Nonsteroidal anti-inflammatory drugs studied perceived to be less than 50% beneficial. Conclusion: Patient’s perception on benefits of medications may be of high importance factor in medication selection. Anticonvulsants perceived to be more beneficial than other medications group. Recommendations: Consider patient’s preferences in selection medications.

Keywords: Patients’ perception, diabetic peripheral neuropathy medications.

Introduction

Diabetic peripheral neuropathy (DPN) is a common complication of diabetes mellitus. It usually affects the legs and feet. It may cause an injury of sensation or pain. DPN often begins gradually and the symptoms may be a burning sensation or numbness that starts in the toes and /or the balls of the feet and spreads upwards. Sometimes, the skin may become so sensitive that the slightest touch is painful. Symptoms may also include unexpected severe pain, and electric shock-type pains or intense aching. At times, the DPNP may be just noticeable and at other times, it may be almost intolerable. DPNP commonly deteriorates at night. This can cause or worsen sleep disorders.

In some people, DPNP may have an impact on an individual’s quality of life (Davies M, et al. 2006). DPNP may interfere with a patient's mood, sleep, energy, mobility, work, social activities and their enjoyment of life (Galer BS, et al, 2000). DPN occurs in 30 to 50 percent of patients with the diabetes, Barrett AM, et al. 2007)
Controlling hyperglycemia, which may highly worsen pain, is essential step in relieving the DPNP (Lee JH, et al 1990).

In June 2013 Action on Diabetes (AOD), a joint initiative by the Supreme Council of Health in State of Qatar and other organizations, they completed a public screening campaigns that have been carried across malls in Doha, capital of Qatar. The results of these screening campaigns come as a statement from (AOD); that about 16% of the adult Qatari population between the age of 20 and 79 suffers from diabetes. Studies in the Arab world show prevalence of neuropathy ranging between 37-94% in diabetic foot cases, (Almoutaz Alkhier et al. 2011)

Bener A, et al (2009) has reported that; the overall prevalence of diabetes mellitus (DM) among adult Qatari population found to as high as (16.7%) with diagnosed DM (10.7%) and newly diagnosed DM was (5.9%).

The generic medications that are used to treat DPNP include tricyclic antidepressants like amitriptyline, imipramine (Saarto T and Wiffen PJ. 2007). Wernicke JF et al.( 2006) has reported that the newer anticonvulsants like pregabalin, gabapentin and serotonin-norepinephrine reuptake inhibitors e.g. duloxetine they can be used for treating DPNP.

Some other medications are prescribed in PHCC in Qatar include carbamazepine and some non-steroidal anti-inflammatory like diclofenac, celecoxib, meloxicam, paracetamol. PHCC does not permit use the following medications of opiate, venlafaxine, lidocaine batches and capsaicin cream in the health center for treating the DPNP. Rationale or justification of the current research is referred to in general shortage of studies or research that have observed patients’ perceptions on the benefits of medications that they took to treat their ailments.

Depending on internet search has not shown any study, particularly carried in the State of Qatar about the patients’ perceptions of the benefits of the medications, but the current study has been the first study about the patients’ perception of the benefits of medications to treat DPNP. In accession to that, higher prevalence of diabetes mellitus among adult Qatari population was high (16.7%), as good as the higher occurrence of diabetic peripheral neuropathy pain at a rate of 30 to 50 percent of patients with diabetes mellitus.

The specific aims of the current study are to know how diabetic patients, with diabetic peripheral neuropathic pain perceive the benefits of medicine used to handle it. The secondary aim is; which medication can restore patient quality of liveliness. Consequently, which medication realizes a 50% of the benefits and release diabetic peripheral neuropathic pain in five domains that add up in the self-assessment questionnaire used in the present work.

Materials and methods

Setting

Data samples collected from six randomly selected health centers. Two health centers from each region; from Northern region health centers of Al Gharafa and Madinat Khalifa, from central region health centers of Umm Ghuwailina and West Bay from, and health centers of Abu Nakhla and Mesaimeer from Western Region. The study carried from 30 April 2015 to 30 April 2016.

Study design

It was an observational and qualitative study. The setting was a random selection of diabetic patients on medication(s) to treat DPNP, and they attended their routine appointments in six health centers.

Criteria of inclusion

- Applied to both male and female who were at the age of 18 years or older.
- Participants who were taking medications to treat DPNP for a duration of at least three weeks at the time of collecting data and patient’s participation.

Exclusion criteria

- Patients who were taking same medications for treating other ailments, epilepsy.
- Patients who was less than 18 years old.
- Patients have disability that prevents them from natural communication.
Background information to the sample design

The targeted population for this present study is all citizens and expatriates in State of Qatar, who receive medical care and medications treatment for diabetic peripheral neuropathy pain at any of twenty one health centers in the country, which are under the administration of Primary Health Care Corporation (PHCC).

The overall prevalence of diabetes mellitus among adult Qatari population is high (16.7%) with diagnosed DM (10.7%) and newly diagnosed DM is 5.9%, (Bener A, et al, 2009).

Sample design

The sample for the current study will be from 4388 diabetic patients, they form the diabetic population in the six health centers, where the study is carried. More details about the criteria of selection, sample size, subsample size from selected sites and method of data collections are in the next chapter.

The names of health centers written in bold in table 1 above were the six randomly selected sites where from the data collected. Randomization of selecting health center was done by using an online Random Choice Generator.

Sample size

The following simple formula (Daniel, 1999) used to calculate the adequate sample size n=Z2 x P (1-P / d2 ).

Where n = sample size,
\( d = \) Absolute error or precision (in proportion of one; if 5%, \( d = 0.05 \).
\( Z = Z \) statistic for a level of confidence = 1.96 as 95% is considered confidence level and 0.05 significance level.
\( P = \) expected prevalence or proportion of DPNP in Qatar =

The DPNP prevalence in Qatar is \( P=37.1\% \) (S. JAMBART et al, April 2011)

Sample size = \( 1.96 x 1.96 x 0.37 \) (1-0.371) = \( 3.8416 x 0371 x 0.629 = 0.05 x 0.05 \) \( 0.0025 \)

\( = 3.8416 x 0.2335 \frac{9}{9} = 358.58 \) patients

Therefore, the sample size for the present study was 384 DPNP patients / participants. As the data collection through using a questionnaire, a non-response rate considered. The non-response rate for previous surveys conducted in Qatar has been relatively small, about 5%–10%, similar to the rate got in studies carried in countries with a similar level of development to Qatar (World Health Survey Qatar, 2006).

In this study the non-response rate of 20%, assumed to the required sample size

Sample size x Nonresponse rate = 358.58 x 20 = 71.716 = 72 patients

By adding this result of expected nonresponse rate to the calculated size sample size, the total targeted sample size reaches four hundred sixty one 430.31 = (358.8 +71.71) Multiply sample size 430.37 by 1.5 (design effect (deff) .In general, for a well-designed study, the design effect usually ranges from one to three. 430.37 x 1.5 = 645.55 = 646 patients. Therefore, the current study sample size is 646 patients.

This done in order reach the target 359 participants, which were the diabetic patients taking medications treatment to treat DPNP.

To allocate subsample per each of six-selected health centers, the total sample size broke down depending on diabetic (type1 and type 2) patients registries in the six-health centers, see table 1.

The Following calculations was done to allocate subsample of diabetic patients (n) in each, health center multiplied by the total sample size 461 participants, and then divided by the total number of diabetic patients (4388) in all the six health centers. See below table 2.

To find a subsample size from each health center, here below equation, used.
Sampling technique

Data collected from all the six selected health centers on face-to-face an interview to answer a modified structured Self-Assessment Questionnaire (SAT). This questionnaire clinically validated (Ingela Wiklund et al, 2013) among patients with post herpetic neuralgia.

All investigators received very well and structured training; they became well informed about the study questionnaire and technique to carry out a face-to-face interview in the proposed time for the interview. An investigator after getting a generic consent form a participant, then an interview ran for 20 to 30 minutes.

Participants were nonprobability selected. Participants were attending on their normal manner to visit the selected primary health centers during the data collection duration. The participants were receiving medication(s) for the treatment of DPNP, at the time of the data collection.

Procedure of data collection

All interviews were face – to – face interview. Investigators and / or data collectors got a participant’s consent form before starting the interview. The SAT bilingual modified questionnaire used in all the six data collection sites. All data collected in a paper -based questionnaires.

The data collected from an eligible participant who coped with required inclusion criteria; patient on DPNP medications treatments for at least three to thirteen weeks, age from 18 years and above, no communication barriers. Patients would like to participate and they used same the medications for other medical conditions, for example, patients were using anticonvulsants medications for epilepsy, patients have mental disorders or psychic problems and were using anti-depressant medications, which can be used to relief DPNP.

Most interviews took from 20 to 30 minutes. Investigator / data collectors took a very high care not to influence the respondents’ answers. The interviews carried not to affect patients – flow, and the interviews within the health center during the working hours for and in an office, pharmacy-counselling room. Only one questionnaire used for one participant and the participant chose by ticking one answer from the five given answers per each question. The participant had full freedom to answer the questionnaire rather than to carry an interview with investigator or data collector.

Six hundred forty six, 646, modified SAT questionnaires used to collect data from all the six data sites collection to reach the sample for this current study.

Data analysis

After conducting, the sampling procedure designated above. The actual sample size was 511 participants from all the six sites. Therefore, the overall response rate achieved was 79.1%. = \( \frac{511 \times 100}{646} \). Before the analysis done, the 511 collected data were and any uncompleted answered questionnaire removed from the analysis. The uncompleted ones found to be 167 i.e. only 344-anwsered questionnaire and valid for analysis.

Therefore, only data collected from 344 respondents had been completed and entered into a spreadsheet for analysis. Data analyzed to test frequency and Chi-square test using Statistical Package for the Social Sciences (SPSS), version (IBM SPSS Statistics 24). Statistical significance is determined to have \( p \)-value of 0.05 and 95% is considered for confidence level.

The analysis conducted for this study was simple tabulations of the data against the important and studied subcategories. These categories were, in general, sex,, DPNP severity, duration of treatment, patients’ perceptions on medications benefits, nature and status of the work, nationality Qatari, and non-Qatari composed of all other nationalities of the expatriates in Qatar.
Results

The graph 1 below shows some clinical characteristics of the participants. Three hundred and forty four participants disclosed information describing their DPNP assessment before starting taking medications, which expected to be before the time of collecting data. Data collected on answering the question of; how the participants would express their DPNP before taking medications? To answer this question, the participants given, a scale from 0 = (no pain), 5 = (moderate pain) to 10= (worst pain).

One more question asked a participant, for how long he or she has taken medication(s) for treating DPNP in the time of collecting the data.

Depending on the participants’ perceptions on their DPNP they experienced, they accordingly put into three groups. The first group resembles participants who experienced mild DPNP. The second group those who experienced moderate DPNP, and the third group they experienced severe DPNP.

Results obtained put in the see graph 1, which revealed that the first group, experienced mild DPNP formed about 9.9% (34/344) of the total participants. Those who described or assessed their DPNP as moderate pain, second group, formed a percentage of 40.1% (138/344). The third group represented by participants who experienced severe DPNP and they formed a 50% (172/344) from the total participants.

The third group was 50%, those who experienced severe DPNP reflected the importance of diabetes complications occurrence and necessity of addressing the treatment of these diabetic complication.

The current study contained mainly four durations for using DPNP medications, and accordingly the participants grouped. A participant had to choose one of these groups, to indicate for how long he or she has taken the DPNP medications. The given treatments durations covered both acute and chronic DPNP.

First group took the DPNP medications for durations of less than three weeks, when they accepted to take an interview as participants in this study. Second group, they took the medication for more than three weeks but for less than three months. The third group took DPNP medications for more than three months but for less than twelve months at the time of collecting data. Forth group took DPNP medications for more than twelve months at the time of collecting data.

In addition, graph 1 below shows the durations of taking the DPNP by the participants. The first group represented by 3.5 %( 12/344), they took medications for a duration started from zero time when a participant sensed DPNP up to three weeks, and medications taken . The second group formed 24.1 % (83/344) of the participants took the DPNP medications for a duration of more than three weeks but less than three months. The third participants group formed 40.7 % (140/344) they took DNPN medications for more than three months, but less than one year, i.e. for less than twelve consecutive months. The fourth participants group formed 31.7 % (109/344) they took medication(s) to treat DPNP for more than one year, i.e. for more than twelve successive months.
Table 1. DPNP participant’s information

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Frequency</th>
<th>Percentage %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nationality</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-Qatari</td>
<td>270</td>
<td>78.50%</td>
</tr>
<tr>
<td>Qatari</td>
<td>74</td>
<td>21.50%</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>120</td>
<td>34.90%</td>
</tr>
<tr>
<td>Male</td>
<td>224</td>
<td>65.10%</td>
</tr>
<tr>
<td>Age in years</td>
<td></td>
<td></td>
</tr>
<tr>
<td>18-30</td>
<td>7</td>
<td>2.00%</td>
</tr>
<tr>
<td>31-50</td>
<td>116</td>
<td>33.70%</td>
</tr>
<tr>
<td>51-66</td>
<td>166</td>
<td>48.30%</td>
</tr>
<tr>
<td>&gt; 66</td>
<td>55</td>
<td>16.00%</td>
</tr>
<tr>
<td>Work status</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Employee</td>
<td>180</td>
<td>53.50%</td>
</tr>
<tr>
<td>No-work</td>
<td>137</td>
<td>38.70%</td>
</tr>
<tr>
<td>Retired</td>
<td>27</td>
<td>7.80%</td>
</tr>
<tr>
<td>Work nature</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Labor</td>
<td>49</td>
<td>27.22%</td>
</tr>
<tr>
<td>Office</td>
<td>131</td>
<td>72.78%</td>
</tr>
<tr>
<td>Total</td>
<td>180</td>
<td>100%</td>
</tr>
</tbody>
</table>

Table 2. Frequencies of uses of medications by 344 participants

<table>
<thead>
<tr>
<th>Medication</th>
<th>Frequency</th>
<th>Percentage %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amitriptyline 10 mg</td>
<td>8</td>
<td>2.33</td>
</tr>
<tr>
<td>Carbamazepine 200 mg</td>
<td>12</td>
<td>3.49</td>
</tr>
<tr>
<td>Celecoxib 200 mg</td>
<td>3</td>
<td>0.87</td>
</tr>
<tr>
<td>Diclofenac 50 mg</td>
<td></td>
<td>1.029</td>
</tr>
<tr>
<td>Duloxetine 60 mg</td>
<td>83</td>
<td>24.13</td>
</tr>
<tr>
<td>Fluoxetine 20 mg</td>
<td>1</td>
<td>0.29</td>
</tr>
<tr>
<td>Gabapentin 300 mg</td>
<td>157</td>
<td>45.64</td>
</tr>
<tr>
<td>Imipramine 10 mg</td>
<td>5</td>
<td>1.45</td>
</tr>
<tr>
<td>Meloxicam 15 mg</td>
<td>5</td>
<td>1.45</td>
</tr>
<tr>
<td>Paracetamol 1000 mg</td>
<td>3</td>
<td>0.87</td>
</tr>
<tr>
<td>Pregabalin 150 mg</td>
<td>22</td>
<td>6.4</td>
</tr>
<tr>
<td>Pregabalin 75 mg</td>
<td>43</td>
<td>12.5</td>
</tr>
<tr>
<td>Tenoxicam 20 mg</td>
<td>1</td>
<td>0.29</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>344</strong></td>
<td><strong>100%</strong></td>
</tr>
</tbody>
</table>

Table 2 above gives frequencies and percentages of medications used to treat 344 DPNP participants during the study from 30, April 2015 to 30, April 2016.

It found that gabapentin 300 mg capsule without any combination with other DPNP medications used by 45.64% (157 / 344) participants at the .Then followed by duloxetine 60 mg capsule used by 24.13% (83 / 344) participants, without any combination with another DPNP medication. Pregabalin 75 mg capsule without any combination with another DPNP medication, was used by only 12.5 % (11/344) participants. But pregabalin 150 mg capsule, without any combination with another DPNP medication, found to be used only by 22/344 participants at the rate of 6.4%. On the other hand, all the other DPNP medications included in this study, they used at rates of 0.29 % (1/344) to 3.49 % (12/344) of participants.

The Chi - tests on version IBM SPSS Statistics 24 performed to find comparative analytic results for gender (120 females and 244 males) against the main five questions in the modified SAT questionnaire.

Table 2 shows the frequencies of uses of medications by 344 participants. Gabapentin 300 mg used by 157 participants, it was the highest medication used in the current study, followed by duloxetine 30
mg, pregabalin 75 mg, used by 43, pregablin 150 mg used by 22 and carbamazepine 200 mg used by 12 participants. The other medications included in the study used by less than 10 participants.

Table 3 is established to put together all the percentages of the 344 participants’ perceptions on the benefits of the medications used in the current study for treating and relieving the diabetic peripheral neuropathy. The participants expressed their assessment by answering five questions to elucidate the DPNP consequences; like acuity of the pain, impacts on quality of life, influences on daily activity, if the participant would undergo the same medication treatment in the future. In addition to that to perceive which medication(s) alleged by at least by 50% of the participants to relieve the DPNP.

Discussion

This study is a cross section study. It targeted to detect the ability of diabetic patient in Qatar, can perceive the benefits of the medications they used for treating diabetic peripheral neuapathy pain (DPNP).

The study ran in six health centers out of twenty- one health center in under the management of Primary Health Care Corporation (PHCC) in Qatar. These six health centers selected randomly to represent whole State of Qatar.

The non-response rate for previous surveys conducted in Qatar was relatively small, about 5%-10%, (World Health Survey Qatar, 2006). In this study the nonresponse rate found to be 20%. The sample size for the present study was 646 participants with DPNP.

After conducting, the sampling procedure designated above. The actual sample size was 511 participants from all the six sites. Therefore, the overall response rate achieved was 79.1% = (511 x 100)/646.

Before the analysis done, the 511 collected data cleared by removal of incomplete answered questionnaires. Only 344 fully answered questionnaires analyzed.

Table 1 explicates frequencies and percentages of DPNP participants information non-Qatari expatriates formed the higher percent of the diabetic participants experienced DPNP than Qatari participants. So, expatriates experienced the most harmful of diabetes complications, peripheral neuropathy more than the Qatari diabetic patients. This occurred at the ratio of 270:74 (3.65:1) non-Qataris: Qatari respectively. It is almost every four non-Qataris diabetic patients experience DPNP opposite to one Qatari. Although failure to keep blood sugar levels as close to normal cause developing DPND, other socio-economically factors, and being away from the mother home may play role in aggravation of the complication of diabetes like DPNP.

Depending on the ages, the participants divided into four groups of age. Results of the current study revealed that the 33.7 % (116/344) participants in the group in 51-65 years old, and 48.3% (166/344) in the group of age 31-50 of the participants suffered from DPNP. Collectively the participants at the ages from 31 to 50 years are the mostly workers and employees and productive. This may have direct influences on private and / or the general economic productivity as well as other fields of commerce and lastly the national economy. Therefore the DPNP has impact on diabetics and their productivity and, hence quality of life and daily activity.

From the results, it noted that the employees 53.5% (180/344) suffered from DPNP more than those who do not have work 38.7% (137/344) or retired 7.8% (27/344).

Amongst the employees who suffered DPNP, who works at offices 72.78% (131/344) were more than labors 27.22% (49/344) with DPNP. Because the DPNP is, a major complication of uncontrolled diabetes. These results may give signals of that employees who work at offices were less controlling blood sugar, or because of sedentary, or limited movements and low activity in comparison to the labors.

Graph 1 shows grouping of the participants according to the acuity of the DPNP. Half of the participant’s 172/344 experienced severe DPNP, followed by 40% of the participants experienced moderate DPNP. Only 10% of the participants suffered mild DPNP. These result may give indication of poor glucose blood control, and this settle with studies that related severity of DPNP with poor glycemic control. The beneficial effect of successful glycemic control on painful symptoms is limited to small studies (Aristides Veves, Miroslav Backonja, Rayaz A. Malik, and 30- July 2007). ‘Improvement in controlling blood glucose with insulin has improved harshness of symptoms (Christopher H Gibbons, Roy Freeman, and April 2010)’. 
In addition, graph 1 shows frequencies and percent of durations through which the participants used DPNP medications. Mostly The participants used the DPNP medications for long duration, from three weeks up to more than twelve months. The durations reflected the nature of DPNP and its chronicity has an impact on patients’ quality of life and their daily activity. One hundred - forty participants (40.7%) used DPNP medications for more than three months and less than twelve months. Hundred – nine (31.7%) of the participants used DPNP medications for more than 12 months. Eighty-three (24.1%) of the participants used DPNP medications for duration of more than 3 weeks and less than 3 months. Only twelve (3.5%) participants used DPNP medications for less than 3 weeks for treating DPNP. In human fear in particular appears to play a central role in the duration of pain, catastrophizing thoughts lead to pain related fear’ (McCracken LM, Gross RT, Dec.1993), (Vlaeyen JW, Kole-Snijders AM, Boeren RG, van Eek H. 1995).

It can be summarized from the graph 1 most of diabetic patients experienced DPNP and used medication for long duration. But it is not only uncontrolled blood sugar is causes of experiencing severe DPNP and necessitates longer duration of treatment, other factors of fear, depression and anxiety may also be indicators for central nervous system physiology that play a substantial role in the durability of pain (Katona C, Peveler R, Dowrick C, et al. 2005).

The results revealed by the current study regarding the durations for treating DPNP, exactly the durations of three months to twelve months, and a duration of more than twelve months, lie within the range of 30% to 65% (Katona C, Peveler R, Dowrick C, et al. 2005).

Table3 established to put all together the percentages of the 344 participants’ perceptions on the benefits of the medications for treating and relieving DPNP. Participants’ perceptions on the beneficial of DPNP medications covered the beneficial on the following; relieving of diabetic peripheral neuropathy accompanied consequences like pain, impacts on quality of life, influences on daily activity, if the participant would undergo the same medication treatment in the future.

The participant’s perceptions averages on the benefits of the DPNP medications, collected after the answering the five questions in the questionnaire used for the present study. All these averages for each medication added together and then divided by five to get the average of benefits that participants’ perceived in all the five questions for that medication.

All the participants’ perceptions on each medication collected from the five answered questions added together, then divided by five to get the average of benefits for each DPNP medication. Medications having same generic name and different strength considered as different medications as the dose difference has different efficacy .See the last right column in the table 3.

The findings averages percentages of participants’ perceptions more than 50% on the benefits of the DPNP medications to relieve the DPNP pain, they arranged here from highest percentage to the lowest one: 80% diclofenac, 70.70% gabapentin 300 mg, 68.33 % carbamazepine 200 mg, 57.5% amitriptyline 10mg, 54.89% pregabalin 75 mg, 50.84% duloxetine 60 mg.

The following averages percentages of participants’ perceptions less than 50% on the benefits of the medications used for treating DPNP, arranged here from highest percent to the lowest one :46.67% celecoxib 200mg, 44.55% pregabalin 150 mg, 40%tenoxicam 20 mg,32 % meloxicam 15 mg 26.67% paracetamol 1000mg,24% imipramine 10 mg, 0% fluoxetine 20 mg .
Table 3. Realized percentages of perceptions on the benefits of DPNP medications. (n = number of participants took the medication.)

<table>
<thead>
<tr>
<th>Medications</th>
<th>1-How do you assess your pain relief after treatment in this study?</th>
<th>2-How do you assess your activity level after treatment in this study?</th>
<th>3-How has your quality of life changed after treatment in this study?</th>
<th>4-Would you undergo this treatment again?</th>
<th>5- How do you compare this treatment to the previous treatment?</th>
<th>Average Percent of realized in the five Domains %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amitriptyline 10 mg(n=8)</td>
<td>87.5% (7/8)</td>
<td>50%(4/8)</td>
<td>75%(6/8)</td>
<td>37.5%(3/8)</td>
<td>37.5%(3/8)</td>
<td>57.5%</td>
</tr>
<tr>
<td>Carbamazepine 200 mg(n=12)</td>
<td>83.33%(10/12)</td>
<td>66.67%(8/12)</td>
<td>58.33%(7/12)</td>
<td>75%(9/12)</td>
<td>58.33%(7/12)</td>
<td>68.33%</td>
</tr>
<tr>
<td>Celecoxib 200 mg(n=3)</td>
<td>66.67%(2/3)</td>
<td>66.67%(2/3)</td>
<td>66.67%(2/3)</td>
<td>33.33%(1/3)</td>
<td>0%(0/3)</td>
<td>46.67%</td>
</tr>
<tr>
<td>Diclofenac 50 mg(n=1)</td>
<td>100%(1/1)</td>
<td>100%(1/1)</td>
<td>100%(1/1)</td>
<td>0%(0/1)</td>
<td>100%(1/1)</td>
<td>80%</td>
</tr>
<tr>
<td>Duloxetine 60 mg(n=83)</td>
<td>81.93%(63/83)</td>
<td>37.35%(31/83)</td>
<td>14.46%(12/83)</td>
<td>72.29%(60/83)</td>
<td>48.19%(40/83)</td>
<td>50.84%</td>
</tr>
<tr>
<td>Fluoxetine 20 mg(n=1)</td>
<td>0%(0/1)</td>
<td>0%(0/1)</td>
<td>0%(0/1)</td>
<td>0%(0/1)</td>
<td>0%(0/1)</td>
<td>0%</td>
</tr>
<tr>
<td>Gabapentin 300 mg(n=157)</td>
<td>82.17%(129/157)</td>
<td>65.61%(103/157)</td>
<td>71.34%(112/157)</td>
<td>78.34%(123/157)</td>
<td>56.05%(88/157)</td>
<td>70.70%</td>
</tr>
<tr>
<td>Imipramine 10 mg(n=5)</td>
<td>20%(1/5)</td>
<td>60%(3/5)</td>
<td>20%(1/5)</td>
<td>20%(1/5)</td>
<td>0%(0/5)</td>
<td>24%</td>
</tr>
<tr>
<td>Meloxicam 15 mg(n=5)</td>
<td>20%(1/1)</td>
<td>60%(3/5)</td>
<td>60%(3/5)</td>
<td>20%(1/5)</td>
<td>0%(0/5)</td>
<td>32%</td>
</tr>
<tr>
<td>Paracetamol 1000mg(n=3)</td>
<td>66.67%(2/3)</td>
<td>0%(0/3)</td>
<td>33.33%(1/3)</td>
<td>0%(0/3)</td>
<td>33.33%(1/3)</td>
<td>26.67%</td>
</tr>
<tr>
<td>Pregabalin 150 mg(n=22)</td>
<td>63.64%(14/22)</td>
<td>40.91%(9/22)</td>
<td>50%(11/22)</td>
<td>45.45%(10/22)</td>
<td>22.73%(5/22)</td>
<td>44.55%</td>
</tr>
<tr>
<td>Pregabalin 75 mg(n=43)</td>
<td>65.12%(28/43)</td>
<td>65.12%(28/43)</td>
<td>65.12%(28/43)</td>
<td>48.84%(21/43)</td>
<td>30.23%(13/43)</td>
<td>54.89%</td>
</tr>
</tbody>
</table>
Tenoxicam 20 mg (n=1)
100% (1/1)
0% (0/1)
0% (0/1)
40% (0/1)
60% (0/1)
The higher percentage of perceptions on the benefits for treating DPNP above 50%, reported by one participant, who took diclofenac 50 mg. This result for diclofenac 50 mg couldn’t be considered and clinically was insignificantly as it was used by one participant.

Gabapentin 300 mg perceived by the average of 70.70% to be beneficial to relieve the DPNP. So gabapentin 300 mg, whatever the dose and frequency in the current study, was the highest medication that realized more than 50% in releasing DPNP in comparison to the medications included in this study.

It is also noted that other anticonvulsants; carbamezpine200 mg, pregablin 75mg realized more than 50% to be beneficial in DPNP. Pregabalin 150 mg, it was exception, as it found to be perceived by less than 50% to be beneficial in DPNP.

Duloxetine 30 mg, an antidepressant used in this study realized percentage more than 50% beneficial to the participants. But Imipramine 10 mg compared perceived by less than 50% to be beneficial in treating DPNP. Fluoxetine 20 mg used by on participant, and it failed completely to be perceived as beneficial for treating DPNP.

All the nonsteroidal anti-inflammatory drugs; celecoxib 200mg mg, tenoxicam 20 mg, meloxicam 15 mg and paracetamol 1000 mg in the present study perceived to be less than 50% beneficial to the participants. The only exception was diclofenac 50 mg, see above.

List of Abbreviations

<table>
<thead>
<tr>
<th>Acronym</th>
<th>Description</th>
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<tbody>
<tr>
<td>AIDS</td>
<td>Acquired Immune deficiency Disease</td>
</tr>
<tr>
<td>AND</td>
<td>Autonomic Diabetic Neuropathy</td>
</tr>
<tr>
<td>Anti-TNF</td>
<td>Anti- Tumor Necrosis Factor</td>
</tr>
<tr>
<td>AOD</td>
<td>Action on Diabetes</td>
</tr>
<tr>
<td>CRPS</td>
<td>Complex Regional Pain Syndrome</td>
</tr>
<tr>
<td>DFDs</td>
<td>diabetic foot disorders</td>
</tr>
<tr>
<td>DPN</td>
<td>Diabetic Peripheral Neuropathy</td>
</tr>
<tr>
<td>FDN</td>
<td>Focal Diabetic Neuropathy</td>
</tr>
<tr>
<td>GCC</td>
<td>Gulf Cooperation Council</td>
</tr>
<tr>
<td>HGH</td>
<td>Hamad General Hospital</td>
</tr>
<tr>
<td>HIV</td>
<td>Human Immunodeficiency Virus</td>
</tr>
<tr>
<td>HMRC</td>
<td>Hamad Medical Research Center</td>
</tr>
<tr>
<td>IASP</td>
<td>International Association for the Study of Pain</td>
</tr>
<tr>
<td>I.V</td>
<td>Intravenous</td>
</tr>
<tr>
<td>LANSS</td>
<td>Leeds Assessment of Neuropathic Symptoms and Signs Pain Scale</td>
</tr>
<tr>
<td>NP</td>
<td>Neuropathic pain</td>
</tr>
<tr>
<td>NSAIDs</td>
<td>Non-steroidal Anti- Inflammatory</td>
</tr>
<tr>
<td>SAT</td>
<td>self-assessment treatment</td>
</tr>
<tr>
<td>PASW</td>
<td>Predictive Analytics Software</td>
</tr>
<tr>
<td>(applied statistical software)</td>
<td></td>
</tr>
<tr>
<td>PBS</td>
<td>Pharmaceutical Benefits Scheme</td>
</tr>
</tbody>
</table>

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A Clinical Research Tool that can Decrease Pharmaceutical Study Costs, Improve Subject Recruitment and Increase Patient Retention and Adherence

Article by Nicole C. Hank,
Perseverance Research Center, LLC
E-mail: nhank@prcresearcheducation.com

Abstract

Clinical trials are a key research tool for advancing medical knowledge and patient care. They ultimately gear towards ameliorating and improving diagnosis and treatment of all diseases by introducing novel interventions and therapies. Essential to conducting a clinical trial is randomizing the proper study population through recruiting eligible participants based on inclusion and exclusion criteria, and ensuring study completion and adherence of study patient participation. Although these may seem simplistic, patient recruitment, retention and adherence are the most difficult challenges in clinical trials. While patient recruitment is one of the key elements to study completion, over 80% of clinical trials shockingly do not finish on time. Devising a potential strategy is vital in overcoming recruitment barriers; however, it is very costly and cumbersome. Lambda Health, LLC is in the process of creating a clinical research tool that can interface with EMR, in hopes of increasing patient retention through proper site selection, and setting reminders to patients about medication dosing, diary documentation, study procedures and visits scheduling. Ideally through implementing this tool into clinical trials, less effort and money will be spent on recruitment and the rates of adherence and retention will increase.

Keywords: Patient recruitment, retention rates, patient adherence, cost-effective, clinical research tool.

Introduction

The key determinants of a successful clinical trial are based on the success or failure of recruitment and retention of study participants. Most clinical trials fail to meet recruitment goals, which in turn, leads to study delays, early trial termination, increased study costs, or inability to draw conclusions at trial completion due to loss of statistical power. A study recently conducted by Carlisle, et. al (2015) found that 19% of registered trials that closed or were terminated in 2011, either failed to meet accrual goals and an alarming 86% of all U.S. clinical studies fail to recruit the required number of subjects on time. When a study struggles with study patient recruitment, the scientific and financial viability is significantly impacted. It can create uncertainty about the efficacy of a treatment, which can then delay bringing a potentially effective therapy to market. Slow acquisition of study patients may also impact financial investments of agencies funding a study, possibly leading agencies to suspend or even terminate the study and fund less reliable but more rapid recruiting studies. Since poor recruitment is a crucial factor in conduct in all clinical trials, pharmaceutical companies have spent billions of dollars investigating the barriers to recruitment and devising potential strategies such as piloting the recruitment process, financial and educational incentives for clinicians, newsletter and reminders for patients, amending study protocols, assisting with patient travel, and networking with various healthcare professionals. In the United States, the average cost per patient, between the years 2008-2013, had increased by 157%, according to Medrio data (http://medrio.com/partners/the-top-5-cost-drivers-in-phase-i-clinical-trials/2015). These costs have been attributed to subject recruitment to avoid early study closure or trial failure. Participant recruitment to clinical trials has been called “the most difficult and challenging aspect of clinical trials,” (McDonald, 2011) with flaws in recruitment identified as one of the main reasons for the failure of clinical studies.
Study recruitment

Recruiting patients into a clinical trial takes careful planning and flawless execution from multiple key players. Although the site is often responsible for contributing the majority of patients needed to meet enrollment targets, several study personnel are ultimately responsible for patient recruitment, which essentially starts with site selection. Although Sponsors feel confident in their selections based from site feasibility questionnaires and site initiation visits; a site or PI may not be able to recruit patients as needed and required by a Sponsor. Poorly performing sites has long been a challenge for the industry and increasing protocol complexity has created new challenges with feasibility. According to research from FUFTS CSDD nearly 40 percent of all amendments occur before the first study volunteer receives first dose (http://csdd.tufts.edu/news/complete_story/pr_ir_jan_feb_2016) mostly because of slow enrollment. In fact, it has been determined that most of investigative sites under enroll, 11% of sites fail to enroll a single patient and only 13% exceed their enrollment target (FUFTS CSDD, 2013 http://csdd.tufts.edu/news/complete_story/pr_ir_jan-feb_2013). These recruitment and retention problems create not only major delays and increased pharmaceutical costs, but also delay approval in a potential effective, ground breaking therapy. With augmentation of study costs and extensive time and effort spent in the process of clinical trial recruitment, improving the rate of recruitment and retention is warranted. The industry has begun to recognize that there is an issue, pouring an increasing amount of money into the process but seeing results plateau. TUFTS Center for the Study of Drug Development (2014, http://csdd.tufts.edu/news/complete_story/pr_tufts_csdd_2014_cost_study) concluded that total capitalized cost per approved new compounded grew at an 8.5% compound annual rate while rates of drug approval, in relation to cost, dropped significantly. If increased funding is not the answer to recruitment then what is? Although there isn’t one specific answer for study costs increasing, delays in study trial completion, and therapies not being approved, new strategies have been implemented by pharmaceutical companies.

Social networking like Facebook and Twitter not only help companies spread the word about a specific trial but assist with reducing the cost per patient while targeting specific demographic populations (Clinical Trial Media, 2011). Social media has been an effective method for generating pre-qualified patient referrals and lowering the overall cost per randomized patient. In 2009, Acurian, a leading provider of clinical trial patient recruitment and retention solutions for the life sciences industry, generated 54% of their pre-qualified patient referrals through social networking channels and proprietary online health channels (June 2011 http://www.healthcaretrendsnewsletter.com/2010/07/social-media-for-patient_recruitment-only-the-beginning/).

In addition to social networking, sponsors have also been working with online communities such as Patients Like Me and Clinical Trial Awareness, which allow patients to monitor and submit data on the effects of novel drugs. This has opened new ways of testing treatments and accelerating patient recruitment into clinical trials as well as reducing the cost of conducting a clinical trial (Brownstein et al, 2009). In addition to social media, and online community marketing, pharmaceutical companies have also created Clinical Research Recruitment Specialist positions for primarily assisting sites with patient recruitment. These specialists typically visit sites, assist with additional marketing materials and provide sites with additional funding for radio, TV and other marketing avenues. While this has been productive and successful, this can be quite costly. So why is recruiting patients for clinical trials such an arduous, expensive task? Some sites believe study designs are getting too difficult to recruit patients, while others believe sites are inaccurately estimating how many eligible patients they have and how many they can enroll. Regardless of the reason, a new, improved, less costly strategy needs to be implemented.

Feasibility

In clinical research, feasibility is the precursor to site selection. Before a site is even selected to participate, sponsors provide feasibility questionnaires that are completed by a potential site. Recruitment factors including proper patient population of the disease of interest, determining subject eligibility, listing of competitive enrolling trials, estimating total number of subjects a site can enroll and in what time frame,
are typically the standard questions asked in a feasibility questionnaire. Assessing these and other factors allow a sponsor to choose which sites are most appropriate for a particular clinical research study, and who may be the most successful in recruiting based on site responses. Estimating enrollment potential for a clinical trial is a typical part of the feasibility process; however, patient enrollment remains one of the greatest challenges in the clinical research industry. In fact, most trials end up doubling their original timelines to meet enrollment goals, and 48% of sites under-enroll study patients (Tufts, 2013). Sponsors go through a thorough feasibility process to ensure a site is adequate and has the large patient population to enroll patients from, yet there are still issues with patient recruitment. If a site inaccurately or overestimates subject eligibility, this could lead to unsuccessful trials. Accurately reporting a sites patient population during the feasibility plays such a large role in site selection since approximately 80% of study patients are utilized from within a site’s own database and the remaining 20% are typically recruited from various outreach methods. (Centerwatch, 2016). As expected, a site’s principal investigator and the study coordinator are crucial to patient recruitment. After a site is selected, one of the first steps of recruitment is searching within the site’s database. However, if a site overestimates their ability to recruit study patients, they will spend extensive time and effort prescreening. Once a site finds a patient who may be eligible, the potential patient must then be contacted and educated about the study and properly consented. Once a patient is identified, consented and enrolled in the study, it is also the site’s responsibility to ensure the patient is always updated and made aware of appointments, study procedures, and drug dosing to ensure patient adherence and retention.

Patient retention

Adequate subject enrollment also provides a foundation for projected subject retention which is a vital component in evaluating patient data. Although, recruitment is a major issue and one of the largest issues plaguing clinical trials, retention and adherence are just as critical. In reality, retaining study patients from start to finish can be just as challenging as patient recruitment. Clinical trials face serious consequences from dropouts through study delays, increased study costs, as well as missing data that essentially compromises the results and integrity of a study. According to a recent study, dropout rates are between 30-40% in clinical trials (Alexander, W. 2013). Although it is a patient’s right to drop out from a trial, for any reason, at any given time, which is thoroughly explained in the informed consent process, there are many reasons why patients withdraw. Despite good intentions of finishing a study, many participants end up dropping out for a variety of reasons. While some dropouts are due to uncontrollable circumstances, others are preventable. Of course, subjects have the right to discontinue participation in research at any time. However, more can be done to prevent withdraws and lower dropout rates.

Communication issues

Even with pharmaceutical companies spending billions of dollars in recruitment, withdrawal of patients from clinical studies is not an uncommon phenomenon and is inevitable in some circumstances. Lack of efficacy of the drug being tested, the occurrence of adverse and intolerable side effects, lack of patient follow-up, or simply patient withdrawal of consent during the clinical trial are some reasons encountered (Gabriel & Macodo, 2011). Although patient retention is the strategy and tactics designed to keep patients enrolled in clinical trials, and from discontinuing participation and dropping out, patient adherence, which is a level of compliance a patient has with taking their medication as prescribed, is just as important. Today, the average trial adherence rates are only 43-78% (Zonana, 2015) which is a main reason why most clinical trials fail. Some patients may simply forget while some may not have a clear understanding of the importance of taking medication properly or finishing a trial. Data from noncompliant patients can affect trial results to such an extent that they can make or break a drug making it to market, thus why it is imperative that sites need to create a strategy for better medication adherence.
How to improve recruitment, retention and adherence

Improving both patient recruitment and retention can be achieved through better site and patient communication. The aim of fostering strong links between pharmaceutical companies, clinical trials and potential patients is obviously a concerted goal for all involved in the process. The question, of course, is how can this aim be achieved and how can the number of patients recruited and retained be increased? Through creating a Tool that can be utilized among all sites and implemented into EMRs, and into smart phones, can open new lines of communication as well as strengthen those that already exist. Let’s start with initial feasibility of a site. If a site was able to accurately and properly estimate how many patients at their site may be eligible to participate, this can help sponsors accurately chose a site during site selection, leading to increased patient recruitment, and lowered costs spent on unnecessary recruitment strategies. Although patient retention can be out of our control due to uncontrollable circumstances, if patients had better communication with site personnel, this may help with patients wanting to remain in a study. Since patients tend to forget when they should take their medications, when to fill out their diary, or even remembering when their study visit is, if they had constant reminders on their phone, this could improve patient retention and adherence. Lambda Health, LLC, is in the process of creating a clinical research tool that could integrate inclusion and exclusion criteria into multiple EMR systems through importing HL7 data into a database and apply faceted search and analytics across the data based on specific feasibility questions.

Methods

Lambda Health, LLC is in the process of developing a tool that would be used strictly for clinical research to accommodate studies of different interventions or disease states. This tool will have the capability of matching eligibility criteria to relevant data fields and flagging potential trial subjects to investigators. It will also be able to provide a pharmaceutical company with more accurate estimate of patients that may be eligible to participate. Ideally patient questionnaires and surveys can be linked to can also be linked in the EMR to provide additional context to clinical data. This tool with also be utilized as a portal, which will only be utilized and accessed by each site’s clinical team. This portal will provide updates and communication between the clinical staff and the patient. In addition, this clinical research tool will have the capability to be utilized as a phone application, utilized by study patients to keep track of study timelines, procedures, and any pertinent study information. Once a patient in consented and is randomized (enrolled) into a study, a member of the site’s clinical team will register the patient into the study and provide them a subject number and access code. The patient, with the help of the site’s clinical team, will be able to download the app from the app store and sign in with the provided access code. Only the designated members of the site’s clinical team and the patient will have access to this information, and the patient will only be identified and registered with a subject number. Once a patient has successfully been registered into the app, they will be able to receive updates, access pertinent study information that pertains to them, and contact the clinical team with any inquiries. This clinical application will serve as a guide to the patient throughout the course of the study, reminding the patient when to take their medication, clinic visit dates and times, change in dosing schedules, prohibited medications, as well as an online tool to track adverse events and log concomitant medication in real-time. Through this constant patient interaction, eliminating missed visits, improper medication dosing, and keeping track of real time adverse events and concomitant medications, it is hopeful that through this clinical research tool, data collection will be streamlined and patient retention and study adherence will exceed pharmaceutical companies’ expectations. This clinical research tool is currently being conducted in a local Investigator Initiated Trial in Scottsdale Arizona. Data and effectiveness and find tuning of this tool is anticipated to be released in late 2018.

Regulations

Lambda Health has experience with building mobile apps and mobile-specific UI/UX design that can achieve HIPAA and other compliance standards in technical implementation as well as has adequate healthcare domain expertise and experience with knowledge of HIPAA compliance. With this tool, Privacy
issues and information governance are among the most complex aspects of implementing such a tool for clinical research. All data will be encrypted and secure to follow HIPAA guidelines. Patients will have a unique subject ID and unique password that only they will know. The only personnel that has access to the portal are members of the site’s study team that will also have their own username and access code.

Since this is a new concept, we anticipate all study sites would need to consent their patient population regarding how their EMRs will be used and by whom. Language regarding a phone app would be integrated into the informed consent process that will have to be IRB approved. Developing optimal procedures for ensuring patients that are informed and protected, balanced with minimizing barriers to research is a major consideration as technology in clinical research advances.

Discussion

In clinical research, patient retention is a key factor in ensuring the success of a study; however, it is often overlooked and undervalued. Most of the time, effort and pharmaceutical costs are spent on patient recruitment and not retention. Poor clinical trial recruitment and retention is therefore likely to impede the successful evaluation of new and existing interventions, and prevent greater efficiency in clinical development. Keeping patients in clinical trials to ensure successful and long-term data-gathering requires careful planning and pro-active strategies. Attention needs to be directed to the individual needs of patients and site staff in relation to specific demands of the research protocol. Some patients may simply forget while some may not have a clear understanding of the importance of taking medication properly or finishing a trial. These are issues that can be aided by proactively planning strategies to educate patients on the importance of complying with all components of clinical protocol, to include medication instructions along with the value of completing a clinical trial. If sites had the capability to accurately report their study population and study eligibility, pharmaceutical companies wouldn’t need to spend an obscure amount of money on recruiting strategies. Through implementing a clinical tool that can be implemented into a myriad of EMRs for site feasibility as well as has the capability of sending text message reminders to study patients, is an easy, inexpensive way to help patients remember to take medication and to remind them of upcoming study visits, therefore increasing retention and adherence.

Conclusion

Clinical research tools are a promising resource to improve the efficiency of clinical trials and to capitalize on novel research approaches. Through utilizing EMRs as useful data sources to support comparative effectiveness research and new trial designs that may answer relevant clinical questions as well as improve efficiency and reduce the cost of recruiting in clinical trials. Initial experience and early testing on such a clinical research tool has been encouraging, and accruing knowledge will continue to transform the application for clinical research. The pace of technology has produced unprecedented analytic capabilities, but these must be pursued with appropriate measures in place to manage security, privacy, and ensure adequacy of informed consent. Whether such a clinical research tool can be successfully applied to the conventional drug development in clinical trials remains to be seen and will depend on demonstration of data quality and validity, as well as realization of expected efficiencies. While there are no easy answers when dealing with both study retention and patient adherence, a clinical application that can interface with a sites electronic medical records strategies and tactics that address the major hurdles patients face to comply with the protocol, as well as educate patients on the expectations and assure their understanding of a clinical trial is essential. Through constant communication and engagement, the importance of taking study medication as directed and attended regularly scheduled study visits will hopefully create higher patients retention rate as well as higher adherence rates.
References

Cross Sectional Quantitative Survey in People for Disease Perception and Social Behaviour for Allergic Rhinitis

Article by Amrit Bhalchandra Karmarkar
PhD (Clinical Research) Scholar, Texila American University, South Guyana
E-mail: abkarmarkar@gmail.com

Abstract

The disorder with very common symptoms such as sneezing, itching, nasal congestion and rhinorrhea often remains undiagnosed in many individuals in the world. This is called as allergic rhinitis. According to WHO, this affects 10-30% of world population. Prevalence of allergic rhinitis is around 7.8% in USA, 5.9% in France and 29% in United Kingdom (UK). However, in India no such study of prevalence was conducted in particular to study allergic rhinitis. Considering this fact, current study was aimed to determine disease perception and effect of allergic rhinitis on social behaviour in adult and elderly population in the areas of Mumbai metropolitan region in India using cross sectional survey methodology. Survey research of such type helps in gathering information not available from other sources. Disease perception and social behaviour assessments will help to understand psychosocial characteristics in population. Effect of allergic rhinitis on quality of life can also be investigated from this research. Questionnaire was designed and responses were collected by both online and offline modes. In total, 240 numbers of respondents agreed to participate. From the results, it was found that many respondents suffer from symptoms of sneezing, itching and nasal congestion which are cardinal symptoms of allergic rhinitis. From the results it was found that 66.67% of respondents have been diagnosed with allergic rhinitis from physician.

Keywords: allergic rhinitis, cross sectional survey, disease perception, social behaviour, India, clinical trials.

Introduction

The disorder with very common symptoms such as sneezing, itching, nasal congestion and rhinorrhea often remains undiagnosed in many individuals in the world. (Skoner DP, 2001). This is called as allergic rhinitis. World Allergy Organization (WAO) defines this disorder as a nasal disorder wherein an immune system produces response to allergen which is IgE mediated (WAO, 2016). WAO in depth review on allergic rhinitis suggests that around 400 million people suffer in the world from allergic rhinitis and most of the cases are undiagnosed and undertreated (Scarupa MD and Kaliner MA, 2015). According to World Health Organization (WHO), this affects 10-30% of world population (WHO, 2011). Prevalence of allergic rhinitis is around 7.8% in United States of America (USA), 5.9% in France and 29% in United Kingdom (UK). However, in India no such study of prevalence was conducted in particular to study allergic rhinitis. Unofficially, it was suggested by researchers that approximately, 20-30% of Indians suffer from at least one allergic disease (Prasad R and Kumar R, 2013). Only data from study conducted in year 1964 suggests that prevalence of allergic rhinitis was 10% in India (Viswanathan R, 1964). Allergic rhinitis and its impact on asthma (ARIA) initiative in its Asia Pacific workshop report highlights the fact that this disorder has not received attention of both physicians and patients (Shah and Pawankar, 2009).

Most of the patients of allergic rhinitis often ignore this order as they feel it as common cold and their symptoms. However, it was observed that allergic rhinitis reduces quality of life (QOL) significantly. In particular, it affects social behavior of patient (Scadding et al. 2008). Therefore, it is decided to estimate disease perception and effect of allergic rhinitis on social behaviour using cross sectional survey in adult and elderly population. Children will not be included in survey because their inability to understand symptoms, pathology and treatment of disorders.
Methods

As emphasized above, Survey research of such type helps in gathering information not available from other sources (Grill JD et al., 2015; Smith SK et al., 2015; and Marcano Belisario JS et al., 2015). Disease perception and social behaviour assessments will help to understand psychosocial characteristics in population. Effect of allergic rhinitis on quality of life can also be investigated from this research. Before making study protocol, 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. This involved conversation with one female ENT physician with 25 years’ experience. This conversation serves as essential step in design of questionnaire for protocol.

Preparation of draft of protocol for cross sectional quantitative survey

After pre-pilot study, relevant literature search was done and draft protocol of quantitative cross sectional survey was written. Protocol contained outline such as introduction, study design, brief information of disease, and 18 multiple choice questions. This protocol was then subjected to pilot study.

Pilot study

Draft of protocol of cross sectional quantitative survey was sent to Dr. Indrajeet Gonjari, Research Guide, Texila American University, South Guyana and also discussed with one MD; two MBBS; one MS (ENT).

Finalisation of protocol for cross sectional quantitative survey

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

Summary of study design

This study is prospective observational (quantitative cross sectional questionnaire based survey evaluation) study wherein common public or general population will enrolled as participants. Participants were be provided with questionnaire on allergic rhinitis. Participants have to select one option from multiple choices provided in that question. Quantitative evaluation of responses was done via data analysis.

Purpose

Purpose of present study is to determine disease perception and social behaviour in general population with cross sectional quantitative survey method.

Study population

General population or common public with age above 18 years can participate in study.
Both male and female were allowed to take part in study.

Study setting

Study was carried out in adult and elderly population in Mumbai metropolitan region of India using offline and online questionnaires.

Inclusion criteria

Participant (i.e. general population / public) must satisfy following requirements:

- Age 18 years and above
- Gender: Both male and female
- No history of psychotic condition
Exclusion criteria

Participant should not have
- Age below 18 and above 70
- Any psychotic conditions

Study population and sample size

Study involved use of questionnaire based survey of adult and elderly population. Children were excluded due to lack of their knowledge about symptoms. Sample size of around 100 was expected.

Study duration

Study was conducted from 01 November 2016 to 15 March 2017.

Ethical considerations

As this is non-interventional study in general population, no ethical approval was obtained. Confirmation of regarding approval was obtained from board of studies of Texila American University, South Guyana.

Participant recruitment or advertising

Participants were approached directly and also using social media platforms such as Facebook, Twitter, WhatsApp, and website postings to get greater number of responses to questionnaire.

Outcome measures

Following outcome measures will be identified from questionnaire.
- Disease perception
- Social behaviour
- Awareness of symptoms
- Diagnosis, and treatment patterns

Recording, data collection and analysis

Questionnaire responses were collected via both offline and online modes. Data was entered in Microsoft Excel 2007 and data was represented graphically in form of bar graphs. Wherever applicable, percentage analysis will be done. Data analysis and representation will be done using Microsoft Excel 2007.

Results

Survey research of such type helps in gathering information not available from other sources (Grill JD et al., 2015; Smith SK et al., 2015; and Marcano Belisario JS et al., 2015). From the current research, following observations were obtained.

Response rate

As mentioned in methods, current research was carried out in both online and offline ways. In total, 350 respondents were approached. Out of them, 240 respondents actually replied to the survey. In total, response rate was found to be 68.57%. Out of total respondents, 58.33% respondents were participated using online mode and 41.67% were from offline mode.

Gender and mode of response of survey

In this survey, participants have taken part in both online and offline mode. Figure 2 represents this data graphically.
Average travel time for work

As travel time for work is most important factor in Mumbai, it has taken into consideration. During travel, different mode of transport i.e. rail, and road are used daily by people. Certainly this may have impact on causation of allergic rhinitis. Table 1 highlights this fact.

Table 1. Average travelling time for work

<table>
<thead>
<tr>
<th>Travelling time for work</th>
<th>Percentage of Respondents</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 to 0.5 hour</td>
<td>6.25</td>
</tr>
<tr>
<td>0.5 to 1 hour</td>
<td>38.33</td>
</tr>
<tr>
<td>1 to 1.5 hour</td>
<td>34.58</td>
</tr>
<tr>
<td>1.5 to 2.0 hour</td>
<td>15.83</td>
</tr>
<tr>
<td>2.0 or more</td>
<td>5.00</td>
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</tbody>
</table>

Response about different nasal symptoms

Participants were asked about whether they have any of such symptoms such as symptoms on one side of nose; thick, green or yellow discharge from nose; post nasal drip (down back of the throat) with thick mucus and/or runny nose; facial pain; recurrent nosebleeds; and loss of smell. Figure 2 graphically represents the data.
Symptoms lasting at least one hour on most days

Participants were asked about whether they experience symptoms such as watery runny nose, sneezing especially violent and in bouts, nasal obstruction, nasal itching, conjunctivitis (red, itchy eyes) for at least one hour on most days, or during season if their symptoms are seasonal. Following responses were obtained and are represented graphically in Figure 3.

Grade of troublesome of symptoms

Participants were asked how troublesome these symptoms are to them. Following responses were obtained.
Figure 4. Troublesome allergy symptoms

Causes of symptoms

According to literature, different causes of allergic rhinitis were studied (Scarupa MD, & Kaliner MA, 2015). These include pollen from trees, flowers and grasses; mould (both indoor and outdoor), furred animals (especially cats, dogs and mice), dusty places, and air pollution. Following responses were outlined in Figure 5.

Figure 5. Cause of symptoms vs. percentage of respondents

Effect on activities of respondents

Question was asked to respondents about how symptoms affect their activities. This included disturbance in sleep, restriction in daily activities, and restriction in participation in school or work. Following responses were obtained and are represented in Figure 6.
**Figure 6.** Effect of symptoms on activities of respondents

**Duration of symptoms and its effect on meeting with people**

Participants were asked about how long these symptoms last and do they have effect on meeting with people. Following observations were obtained and are represented graphically in Figure 7 and 8.

**Figure 6.** Duration of symptoms
Figure 7. Response of respondents that avoid meeting with people due to symptoms

From the figure 7 it could be said that around 48.75% respondents avoid meeting with people due to nasal and other symptoms.

**Effect on quality of life**

Respondents were asked about how allergic rhinitis symptoms have affected their quality of life. Figure 8 graphically represents the data.

**Effect on mood**

Question was asked to participants about whether they get irritated, depressed easily or little or not at all due to symptoms of allergic rhinitis. About 27.92% replied that they get irritated easily, and 25.42% replied that they get depressed easily. Figure 9 represents the data.
Effect on mood due to symptoms

Question was asked to participants about how symptoms affect to their work and private life. Following responses were obtained and are shown in Figure 10.

Effect on relations

Explanation of allergic rhinitis

Question was based on how participants explain allergic rhinitis. Whether they explain it to others in detail, or does not explain or avoid it or even don’t know how to explain. This was represented as follows in Figure 11.
Figure 11. Explanation of allergic rhinitis

Allergy testing and type of allergy testing

Participants were asked about whether they have done allergy testing. Only 15.83% of participants responded that they have done allergy testing. Further, what type of allergy testing was done was asked to respondents who replied yes to above question, following results were obtained.

Figure 12. Type of allergy test done by respondents

Family member with allergy

Around 72.92% of respondents replied that they have some of the family members who have allergic rhinitis or some other allergic diseases. 27.08% replied that they do not have allergic family member.
Diagnosis of allergic rhinitis

Out of total respondents, 66.67% of respondents replied that they have been diagnosed with allergic rhinitis and 33.33% said they have not been diagnosed with disease.

Type of physician from which treatment was sought

Question was asked about from which type of physician they have received treatment. In India, MBBS and MD (Allopathic); BAMS and MD (Ayurvedic); BHMS and MD (Homeopathic); BUMS and MD (Unani) systems of medicine are generally available to population. From the results, it is suggested that allopathic treatment option is most preferred amongst population.

![Type of Physicians vs. Percentage of respondents](chart)

**Figure 13.** Type of physician from which treatment is taken

Type of treatment

Regular medicine, symptomatic medicine and combination of two therapies are options for treatment of allergic rhinitis treatment. In around 53.13% of respondents regular therapy was provided. Figure 14 shows data of these results.
Effectiveness of therapy and choice of second opinion

Participants were asked about how effective therapy was there for allergic rhinitis. Data from results is shown in Figure 15.

They were also asked about whether they opted for second opinion from any other physician. Only 13.75% respondents have taken second opinion and 86.25% respondents have not opted for second opinion.
Discussion

Current study was aimed to determine disease perception and effect of allergic rhinitis on social behaviour in adult and elderly population in the areas of Mumbai metropolitan region in India using cross sectional survey methodology. Survey research of such type helps in gathering information not available from other sources. Disease perception and social behaviour assessments will help to understand psychosocial characteristics in population. Effect of allergic rhinitis on quality of life can also be investigated from this research.

Questionnaire was designed and responses were collected by both online and offline modes. In total, 240 numbers of respondents agreed to participate. Out of 350 respondents who were approached, only 240 actually participated. This means that only 68.57% responded the survey. According to Jack Fincham (2008), goal of the study should be collection of at least 60% of responses. For survey based research, ≥ 80% should be there to appropriately represent population. Reaching only 68.57% is limitation of the current research. This may be due to limited study time period and unawareness of allergies and allergic diseases in population (Nulty DD, 2008).

Travelling with allergies is difficult and travelling incurs exposure with allergens such as pollens, air pollution, etc. In Mumbai, average travelling time for 38.33% of respondents was up to 1 hour and for 34.33% was up to 1.5 hours. Blum SW et al (2015) have suggested that travelling time increases burden of allergic rhinitis in United States.

Mode for conduction of this research were both online and offline surveys. Offline or paper based surveys provide original material related to survey methods, and also we can get number of recommendations from the respondents additionally. However, targeting participants by visiting their home or office becomes a tedious task and also it increases cost of conduction of the study. In case of online surveys, the convenience of response can be achieved and survey link can be easily sent to respondent’s smart phone or email id (Evans JR and Mathur A, 2005). Due to this fact, response of online questionnaire was found more than offline in current survey. This fact is also highlighted when gender based filter is applied to responses of the study. Both males and females preferred online mode more than paper based survey.

Symptoms on one side of nose, thick green or yellow discharge of mucus, post nasal drip, facial pain, recurrent nose bleeds, and loss of smell are generally not found in Allergic rhinitis (Refer Figure 2). Presences of any one of these symptoms indicate alternative diagnosis and referral of specialist is recommended. Results of the study indicate that most respondents are not experiencing these symptoms. Out of these symptoms, facial pain, loss of smell, and post nasal drip are seen in sinusitis. In this case, specialist should be consulted. However, any one of symptoms such as watery runny nose, sneezing, nasal itching and obstruction, and conjunctivitis (including red itchy eyes) indicate possibility of allergic rhinitis. Findings of the study (Figure 3) indicated that most of participants (50-60%) are having possibility of allergic rhinitis. These findings are in accordance with guideline of Allergic Rhinitis and its impact on Asthma (ARIA) (2007).

Question was asked to participants about how troublesome these symptoms are. According to results, 32.92% reported it to as mild, 26.67% respondents reported it is moderately troublesome and 12.08% reported it as severe. This indicates allergic rhinitis to them. These findings are in accordance with statements made by Wallis RS (1982).

Increase in allergen exposure and reduced immunity are important factors from which allergic rhinitis could occur. Exposure to allergens such as pollen, moulds, furred animals, dust, air pollution are some these allergens. (Mandhane SN et al. 2011).

It was found that for participants where symptoms were there, disturb in sleep, daily activities, and participation in school work were hampered. In most of the respondents, symptoms were found to last for more than 4 days a week. This had impact on meeting with people. These findings are in accordance with ARIA guidelines. This indicates persistent form of allergic rhinitis. (Bachert et al, 2002). “A subjective value a person places on satisfaction with own life is called as Quality of Life”. Figure 8 indicates that allergic rhinitis affects quality of life of an individual. This finding is in accordance with findings of Spanish study which suggests that allergic rhinitis affects quality of life more than that of diabetes, hypertension and depression (de la Hoz Caballer B, 2012).
Marshall PS et al (2002) have evaluated effect of allergic rhinitis due to pollens and found that fatigue and alterations in mood occur due to it. According to him, this could be change in biochemical reactions in central nervous systems due to which mood changes occur. Sansone RA and Sansone LA (2011) have evaluated relationship of allergic rhinitis on mood and anxiety syndromes. Results of current research are in accordance with these studies. In total 73.33% (Figure 9) (i.e. total of 27.92% who get irritated easily, 25.42% who get depressed, and 20.00% who have little effect on mood levels) of respondents witnessed changes in mood due to allergic rhinitis. Similar effect was observed with relationships of allergic rhinitis respondents (Figure 10). Also in this study, participants were asked about how they explain symptoms of disease. Most of the respondents, however, do not know how to explain symptoms to others. This suggests need of awareness programs on allergic rhinitis.

In total, 84.17% respondents have not done allergy testing. Out of those who did allergy testing, 50.00% have done with skin prick testing, 7.89% with specific IgE testing, and 42.11% are not aware of which testing was done. Therefore, this suggests need for awareness of allergic testing which is integral part of diagnosis and treatment. Similar facts were suggested by Kalpakliglu AF et al (2011).

Around 72.92% of respondents said that their family member has allergic rhinitis. Genetic segregation studies and investigations in twins have suggested genetic basis of causation of allergic rhinitis. Studies on chromosome 2, 3, 4, and 9 revealed the fact of genetic hereditary link between allergic rhinitis (Davila I, 2009). De Yun Wang (2005) has also highlighted the same fact.

It was found that 66.67% respondents have diagnosed with allergic rhinitis. In India, different options for treatment are available. Allopathic treatment is most preferred and then ayurvedic and homeopathic therapies are preferred by respondents. Regular medicine, symptomatic medicine and combination of two therapies are options for treatment of allergic rhinitis treatment. In around 53.13% of respondents regular therapy was provided. Figure 14 shows data of these results. According to ARIA guidelines, effectiveness of treatment of allergic rhinitis is very less. Results from Figure 15 represent the data (Mandhane SN, 2011). Seeking second opinion to other physician is the other way to confirm the diagnosis and treatment of disease. In the current research, only 13.75% respondents have taken second opinion and 86.25% respondents have not opted for second opinion. Gendo and Larson (2014) used method of second opinion to confirm the diagnosis of suspected allergic rhinitis.

Conclusion

Disease perception and social behaviour assessments helped in gathering data about allergic rhinitis. Parameters such as nature of symptoms, troublesome behaviour of symptoms, cause of symptoms, how they affect daily activities and how long they last, effect on meeting with people and quality of life, effect on mood and relationships were investigated. Also other factors such as allergy testing, type of allergy testing, diagnosis, treatment, duration and effectiveness of treatment were studies. Thus, survey type of research helped in gathering information not available from other sources, especially about psychosocial characteristics in population. From the results it can be concluded that prevalence of allergic rhinitis is significant in population. However, awareness and treatment strategies need to be improved. Further research will be conducted on opinions of physicians about treatment pattern and awareness about allergic rhinitis in population.

References

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(Accessed on 01 September, 2016)


A Comparative Study of Stress level of Male and Female Nurses in ICU

Article by Jolly Sabu
Clinical Research, Texila American University, India
E-mail: jollymoolakkatt@yahoo.com

Abstract
The purpose of this study is to assess the perceived stress in male and female nurses working in ICU. According to the World Health Organization, stress is a significant problem of our times and affects both physical as well as the mental health of people. ... Stress coping methods are the cognitive, behavioral and psychological efforts to deal with stress.

Introduction
Stress has always been part of human life. Stress is a physical or emotional state of response present in a person as a result of dynamism in life. It is intensified in a nonspecific response to an internal or external environmental change or threat.

Stress is a condition wherein any factors interact with the individual to change (disrupt/enhance) her/his psychological or physiological conditions so that the persons mind and body are forced to deviate from its normal way of functioning. Stress in human life is often experienced with tension, anxiety, worry, and pressure. It is an accepted fact that stress is useful in life but it can have either beneficial or detrimental effects. They can be physical, social, emotional, intellectual, and spiritual. World Health Organization is of the opinion that work place stress is estimated to cost companies more than 300 million dollars a year due to poor performance, absenteeism and health costs.

Professional stress or job stress poses a threat to physical health. Work related stress in the life of organized workers, consequently, affects the health of organizations. Numerous studies have indicated that job stress is significant in nursing. It was found that job stress brought about hazardous impacts not only on nurses’ health but also their abilities to cope with job demands. This will seriously impair the provision of quality care and the efficacy of health services delivery. In particular, the job stress of nurses working in acute and specialized care units has been widely studied. Heavy work load, poor staffing, dealing with death and dying, inter-staff conflict, strain of shift work, careers and lack of resources and organizational support has been identified as the major source of job stress. It has also been found that nurses experience job stress differently. Some studies found that stress level was significantly higher in junior nurses than in the senior nurses.

1. The purpose of this research is to assess the professional stress level of male and female staff nurse working in ICU’s
2. To compare the professional stress level among both the male and female staff nurses in ICU’s.
3. To co-relate the findings with demographic variables.
4. Early identification of stress in staff nurses.
5. To inform the nursing administrators to implement the strategies to reduce stress in the nursing staff.

Limitations
a) The study will be limited to 60 staff nurses working in different ICUs of Hospitals in Al Ain City.
b) Those who are willing to participate in the study and those who are present during the period of data collection.
c) The extraneous variables like age, sex, income, type of family were beyond the investigator’s control.
d) The study was limited to the experience level of the researcher.
Method

The conceptual framework adapted for the study was based on Lazarus’s Transactional model of stress. The focus of this model, the first stage in his model is primary appraisal where the subject analyzes the stressor and determines if it will be positive or negative, exciting or harmful, etc. The second stage is secondary appraisal, where the subject determines if he or she can cope with the given stressor. Even if the stressor is determined as harmful in the first stage, if the subject decides he or she can cope with it in the second stage, stress will be kept at a minimum.

The steps undertaken for gathering and organizing the data collected were: research approach, research design, study setting, population under study, sample and sampling techniques, criteria for selection of samples, development and description of tools, pilot study, data collection and plan for data analysis.

Research approach

A research approach tells the researcher what data to collect and how to analyze it. It also suggests possible conclusion to be drawn from the data.

According to Polit and Hungler “Research is systematic inquiry that uses disciplined methods to answer questions or solve problems. The ultimate goal of research is to develop, refine, and expand a body of knowledge.”

It is a fact finding investigation with adequate interpretation. It is designed to gather descriptive information and provides information for formulating more sophisticated study: Data collection by using one or more appropriate methods; observation, interviewing and mail questionnaire.

In view of the nature of the problem under study and to accomplish objectives of the study descriptive survey approach which is exploratory in nature was considered appropriate to describe professional stress among male and female staff nurses working in ICU in selected Hospitals of AlAin city.

Company profile

Al Noor hospital: is one of the leading private hospitals in Al Ain where all the patients are accommodating in accordance to the mantra “You are in safe hands. Hospital is accredited by JCI, maintained 3 consecutive times and ISO certification will attest to its quality services. Bed capacity of 52 beds with 7 in ICU, 4 Operation Theatres and other critical services are readily available here.

NMC Hospital: is a multispeciality hospital provides quality and trusted healthcare services to the people of Al Ain and the surrounding area. The hospital is affiliated with all major national as well as international insurance companies and engages direct billing with insurance companies and third party administrators.82 patient beds, 7 ICU beds and 5 operation beds are available here.

Oasis Hospital: has been serving the residents of the eastern region since beyond 1960. It is the first private hospital accredited in the emirate of Abu Dhabi for JCI with a vision to be the hospital of choice in Al Ain and the neighboring community. It has 109 beds with 7 ICU beds, 4 Operation theatres and other critical services.

Problem statement

A comparative study has been assess the professional stress level of male and female staff nurses working in ICU of selected hospitals in Al Ain city.

Nursing work situation has certain demands. Meeting demands can lead to psychological distress. Stress at work is a real problem both to the organization and its workers. Stress can be physical and psychological and often leads to decreased quality of life and poor organizational performance. Stressors at work can cause stress and individuals exposed to these stressors will experience stress in their personal life and which will ultimately affect their performance at work. Stress at work refers to occupational phenomenon associated with specific situations, characteristics of the work cause environment including individual perceptions and reactions in the context of the workplace.

Nursing provides a wide range of potential workplace stress. Nursing is a work environment that is notable for high work stress and high demands. Stress is also associated with high levels of emotional, cognitive, and physical strain. Nursing is a typically stressful and emotionally demanding work. As such the burden of care giving has generally produced stress and distress among healthcare professionals. Nurses engage in physically demanding tasks on a daily basis and are often for occupational burnout and
physical complaints merely due to high demands at work. This consequently results in increased dissatisfaction with their career. The current study concerns with management of workplace stress in critical care setting. The studies associated high turnover among healthcare professionals with high levels of work strain and stress and low levels of work satisfaction.

There are various factors that can influence the stress in the critical nursing staff. Some of the factors include

(A) Lack of confidence and competence in critical care area.
(B) New technologies, change in leadership work environment
(C) Lack of capacity to care for self. With new roles and new expectations,
(D) Limited training in the new work tasks,
(E) increased consumption of healthcare goods and services,
(F) short-age of nursing staff and insufficient competence at work task

As can be seen, an increased level of stress can lead to high staff turnover, low quality of care and organizational inefficiency the present study could be considered important for understanding stress management and can be managed by some of the following strategies.

- Nursing professionals working in the hospital settings will be able to find opportunities to teach and improve the knowledge of nurses regarding stress and its better management.
- Mastery of working environmental demands and sufficient resources and improved communication will be helpful to resolve the stress and improve coping abilities among nurses.
- Sound knowledge and clinical assessment skills among nurses will be important factors in reducing stress and improving coping abilities.
- Implications for practice include fostering planned discussion, sessions and continued education to improve counseling skills related to bereavement among nurses will be necessary for preventing stress and promoting coping abilities.
- Nursing professionals working in the hospital settings will be able to find opportunities to teach and improve the knowledge of nurses regarding stress and its better management.
- Mastery of working environmental demands and sufficient resources and improved communication will be helpful to resolve the stress and improve coping abilities among nurses.
- Sound knowledge and clinical assessment skills among nurses will be important factors in reducing stress and improving coping abilities.
- Implications for practice include fostering planned discussion, sessions and continued education to improve counseling skills related to bereavement among nurses will be necessary for preventing stress and promoting coping abilities.
- Research approach: Quantitative approach
- Research design: Comparative descriptive design
- Setting: 3 Hospitals in AL AIN City
- Sampling technique: Convenient sampling technique
- Sample size: 60 (30 male and 30 female)
- Population: ICU staff nurse
- Study duration: 90 days.

Result

Section-I deals with percentage distribution of samples. This shows that equal number of male (50%) and female (50%) staff nurses are participated in the study, the 66.7% of the male and 76.7% of female samples are in the age group of 21 -25 years and remaining 33.3% and 23.3% are in the age group of 26-30 years. No samples have age more than 30 years.

Majorities of the male and female staff nurses, 66.7% are completed general nursing and 33.3% are completed BSC nursing. 50% of the male staff nurses and 56.8% of female staff nurses have experience in between 0-2 years. 26.7% males and 30% of females are in the 2-4 year experience group and 23.3% of males have experience in between 4-6 years.

No one has experience more than 6 years.
Section-I: Description of demographic data

Table 1. Frequency distribution of staff nurses as per demographic variables

<table>
<thead>
<tr>
<th>Demographical data</th>
<th>Males</th>
<th></th>
<th>Females</th>
<th></th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Frequency</td>
<td>Percentage</td>
<td>Frequency</td>
<td>Percentage</td>
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<tr>
<td>Age</td>
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<tr>
<td>21-25yrs</td>
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<td>26-30yrs</td>
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<td>36 and above</td>
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<td>BSC Nursing</td>
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<td>33.4</td>
<td>10</td>
<td>33.4</td>
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<tr>
<td>GNM</td>
<td>20</td>
<td>66.6</td>
<td>20</td>
<td>66.6</td>
</tr>
<tr>
<td>ICU Experience 0-2 yrs</td>
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<tr>
<td>2-4 yrs</td>
<td>15</td>
<td>50.0</td>
<td>17</td>
<td>56.8</td>
</tr>
<tr>
<td>4-6 yrs</td>
<td>8</td>
<td>26.7</td>
<td>9</td>
<td>30.0</td>
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<tr>
<td>&gt; 6 yrs</td>
<td>7</td>
<td>23.3</td>
<td>2</td>
<td>6.6</td>
</tr>
</tbody>
</table>

N=60

Data presented in table 1 shows that majority of staff nurses were from age group between 21-25 years, i.e. 20(66.7%) are males and 23(76.7%) are females. Staff nurses having BSC (N) and GNM degree were equal in both sex i.e. 10(33.4%) BSC (N) and 20(66.6%) GNM. Among the male nurses 15(50%) are from non-experienced group and 15(50%) are from experienced group. Whereas among females only 17(56.8%) are from non-experienced and 13(43.2%) are from experienced group.

Section-II: Findings related to professional stress among staff nurse

Table 2. Frequency distribution of male and female staff nurses as per professional stress level in ICU.

<table>
<thead>
<tr>
<th>Professional stress level</th>
<th>Gender</th>
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<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Male</td>
<td></td>
<td>Female</td>
</tr>
<tr>
<td></td>
<td>Frequency</td>
<td>Percentage</td>
<td>Frequency</td>
</tr>
<tr>
<td>No stress</td>
<td>13</td>
<td>43.3%</td>
<td>8</td>
</tr>
<tr>
<td>Mild stress</td>
<td>15</td>
<td>50%</td>
<td>19</td>
</tr>
<tr>
<td>Moderate stress</td>
<td>2</td>
<td>6.7%</td>
<td>3</td>
</tr>
<tr>
<td>Total</td>
<td>30</td>
<td>100</td>
<td>30</td>
</tr>
</tbody>
</table>

N=60

Table 2 describes that among total population of 60 staff nurses mild stress group consisted of 19(63.3%) females compared to only 15(50%) male staff nurses, whereas no stress was observed among 13(43.3%) male and 8(26.7%) female staff nurses.
Figure 1. Frequency distribution of male and female staff nurses as per professional stress level

Data represented in the above cone diagram describes that most of the staff nurses in both group have mild stress, and no stress has been observed among majority of the male staff nurses.

Figure 2. Bar diagram showing the age wise distribution of professional stress level among male and female staff nurses
Number of female staff nurses in the mild stress group is higher than the number of male staff nurses whereas in no stress group number of male staff nurses are higher than female staff nurses among the age group of 21-25 years. In 26-30 years of age group the numbers of males are higher than females in no stress group and same in mild stress group.

Discussion

Professional stress is the result of interaction between characteristics of individual persons, resources and stress factors which are physical, mental or social, related to the work environment. Professional stress among nurses is associated with a variety of personal and institutional factors. Working in areas such as the emergency room or the intense care unit, patients require a greater level of care. These situations can require immediate response by the nursing staff and can often cause high stress levels. The present study was assessing professional stress among male and female staff nurses working in ICUs of selected hospitals in Al Ain city. The level of stress has been classified in this study as no stress, mild stress, moderate stress and severe stress. The findings of this study have been discussed with reference to the objectives and hypothesis.

In this study we have equal number of male and female staff nurses are there. The most of the male and female samples 72% are in the age group of 21-25 years. 66.6% of the samples are completed general nursing and more than 50% of the samples have experience less than 2 years.

Descriptive research approach was used to assess the stress level of staff nurses from Oasis hospital, Al Noor hospital, NMC hospital. The sample size was 60, 30 male and 30 female staff nurses taken by non-probability convenience sampling technique. Both male and female BSC and GNM nurses were included in the study and ANM staff nurses were excluded from the study. David Fontana’s professional life stress scale was modified to assess the stress level of male and female staff nurses working in ICU. In the questionnaire there are 2 sections 1st section deals with the demographical data and the 2nd section contains 18 objective type questions to assess the stress level of the staff nurses. 15 to 20 minutes were taken to fill the questionnaire. According to score the samples are classified into no stress, mild stress, and moderate stress. There 21 samples have no stress and 34 have mild stress and 5 have moderate stress, nobody has severe stress in the sample. The average score obtained by the male staff nurses and female staff nurses were 11.6 and 12.7 respectively.

The study conducted in managing stress in nursing professionals in this study majority of nurses (59/90-65%) perceived stress, supported that stress in ICU is high compare to other areas. Stress was found to be significantly more in wards and ICU rather than operation theater (p<0.05) stress was found to be less in staff nurses having less than 50% of mark in 12th standard as computed too others. Work stress was greater perceived cause of stress in nurses conflict between work and home was major factor.

In this study two sample t test were used to compare the stress level of male and female staff nurses. The values found by ‘t’ test is -0.74 and ‘p’ value 0.232 shows that there is no significant change in the professional stress of male and female staff nurses. Detail description of the data were shown in the section III.

Co-relation between the Professional stress and demographical variables are done by Chi square test. ‘p’ values of all the demographical variables were found to be greater than 0.05 that indicate that there is no association between demographical variables and professional stress.

The study conducted on Job stress and intention to quit in newly-graduated nurses during the first three months of work in Taiwan supporting the finding shown above in this study. To identify job stress and intention to quit in newly-graduated nurses during the first three months of their work at two different levels of hospitals and to understand factors that may influence their retention. Subjects experienced somewhat stressful conditions (Mean = 2.89, SD 0.62) and 31.5% intended to quit. Job stress was the highest at 0-1 month and the intention to quit was highest at 1-2 months. The intention-to-quit group had significantly higher job stress with regard to roles/interpersonal relationships than the intention-to-stay group \[t(144) = 2.65, p = 0.009\]. Logistic regressions indicated that higher job stress (odds ratio = 2.26; 95% CI 1.14-4.51), working at a medical centre (odds ratio = 3.61; 95% CI 1.10-10.92) and not having had a clinical practicum in the working hospital (odds ratio = 2.41; 95% CI 1.01-5.77) were significant predictors associated with the intention to quit.
Conclusion

The conclusion drawn from the findings of the study are as follows:

The two sample t test was used to compare the professional stress levels of male and female staff nurses working in ICUs and found that there is no significant change in the stress level of male and female staff nurses. The associations were checked with demographical variables by using chi-square test and found that demographical variables have no association with professional stress.

Early identification of stress in staff nurses will help in increase the work performance and good patient care without any physical and mental problems. This will give an idea to top order for plan educational and stress management programs to reduce the stress levels in staff nurses and increase quality of patient care and productivity. Professional stress is the result of interaction between characteristics of individual persons, resources and stress factors which are physical, mental or social, related to the work environment. Professional stress among nurses is associated with a variety of personal and institutional factors. Working in areas such as the emergency room or the intense care unit, patients require a greater level of care. These situations can require immediate response by the nursing staff and can often cause high stress levels. The present study was assessing professional stress among male and female staff nurses working in ICUs of selected hospitals in Al Ain city. The level of stress has been classified in this study as no stress, mild stress, moderate stress and severe stress. The findings of this study have been discussed with reference to the objectives and hypothesis

The findings of the study can be used in the following areas:

- Nursing practice
- Nursing education
- Nursing administration
- Nursing Research

Acknowledgement

I sincerely thank the Almighty God for his glorious blessing infinite mercy, abundant love and spiritual guidance all the way through my life.

I would like to thank the Management of the organizations for allowing me to study their organizational structure and on the activities who shared their valuable time even during their office timings, and gave me full support and beneficial information’s and tips to study and complete the project.

A Special gratitude I give to my colleagues whose contribution in stimulating suggestions and encouragements.

References

The Impact of Prostate Specific Antigen Testing on Incidence of Prostate Cancer cases in Zimbabwe

Article by Assam Musonza¹, Professor Lynn Zijenah², Victor T. Nyanhete³
¹Ph.D, in Clinical Research, Zimbabwe
²P.O Box A178 Avondale Harare, Zimbabwe
³158 Marks Road Daylesford Gweru, Midlands, Zimbabwe.

E-mail: assammuso@gmail.com / assammuso@yahoo.co.uk¹, lzijenah@gmail.com², victort92@gmail.com³

Abstract

Prostate cancer is the leading cancer causing death in Zimbabwean men according to the Zimbabwe National Cancer Registry. By 2004 prostate cancer had become the most common cancer in Zimbabwean men. The incidence of prostate cancer shows strong age, race and geographical dependence. The prostate specific antigen (PSA) is a serine protease produced by cells of the prostate gland. The PSA blood test measures the level of PSA in man’s blood and is used as a biomarker for prostate cancer (PCa). Unfortunately the PSA is prostate specific but not PCa specific. PSA testing started in Zimbabwe in 1995. The specific objectives of the study were: (i) to determine the age range most affected by PCa, (ii) to evaluate the impact of PSA testing on PCa cases in Zimbabwe. The study was a retrospective cross sectional study. Secondary data of all histology confirmed cases of PCa were obtained from the Zimbabwe National Cancer Registry (ZNCR) and analysed. Graph Pad Prism 7.03 was used to statistically analyse the data. The two-tailed T-test was employed to compare the number of pre-PSA cases against the number of post PSA era cases. 5277 PCa cases covering a thirty year period were retrieved. The first ten years (1986-1995) were the pre PSA era period and the next twenty years (1996-2015) were the post PSA era. The median age was 71 (IQR 64-78) years. There was a significant difference between number of PCa cases of the pre-PSA era (1986-1995) and the first post PSA era 1996-2005, and the second PSA era (2006-2015) (p =0.0042 and p=0.0028 respectively. This showed the impact that PSA testing had on PCa in Zimbabwe (2006- 2015). The study showed that the age group most affected by PCa was the 64-78 years.

Keywords: Prostate cancer, Cross Sectional Study, Prostate Specific Antigen, PSA impact, age group, Zimbabwe.

Introduction

PCa also known as carcinoma of the prostate is the most common cancer among men only second to skin cancer in the world (Ferlay et al 2013). In Zimbabwe PCa is the leading cancer causing death in men (ZNCR report 2014)

Risk factors

The incidence of PCa shows strong age, race and geographical dependence (Center et al 2012 and Babb 2014. Autopsy studies have shown an age dependent risk of finding microscopic foci of what is considered to be PCa, from age 30 and up (Sakr, Haas, Cassin, Pontes and Crissman 1993), Soos, Tsakiris, Szanto, Turzo, Haas and Dezso 2005).

There is a large variation of the incidence of PCa in the world. The highest incidence is found in African-Americans and lowest in Chinese men (Hsing and Devesa 2001). The difference being about 40 fold.

The incidence rates of PCa in Africa are increasing at an alarming rate (Boyle and Levin 2008). PCa is the most commonly diagnosed cancer among men in Southern Africa and Western Africa including South Africa, Zimbabwe, Nigeria and Cameron (Jemal, Bray, Forman, O’Brien, Ferlay, Center and Parkin 2012).
Heredity form of PCa constitutes approximately five per cent of the cases (Bratt, Kristofferson, Lundgren, and Olsson 1999). This is diagnosed on the pedigree with three relatives in different generations with the disease or three first degree relatives or early onset (before 55 years of age) among two relatives. The risk of dying from the disease increases if the relatives are young at diagnosis (Groomberg, Wiklund and Damber 1999). This raises the aspect of high incidence in African-Americans and Africans in general, whether genetics plays a major role. It has not been established that this is the case but certain genes and DNA mutations have been implicated. A lot of work is underway to elucidate this. It has been established that there is no size fit all with regard to PCa treatment (Isaacs and Kainu, 2001).

In Zimbabwe, since 2004 PCa cases have increased by 104 per cent (ZNCR 2012 Report). An in depth understanding of which age group is most affected and what the impact of PSA testing on PCa cases is required. The study was undertaken to seek answers to these questions.

**Screening for PCa**

The tests most commonly used to screen for PCa are the Digital Rectal Examination (DGE) and the PSA blood test. In the DGE, a doctor or nurse inserts a lubricated gloved finger into the rectum to estimate the size of the prostate and feel for lumps. This is very subjective and not very accurate. There are high chances of missing the tiny lumps and of under or overestimating the size of the prostate. Others use ultra sound scan to screen, the transrectal ultra sound scan is adjudged to be more superior. The PSA measures the level of PSA in the blood. The PSA is a serine protease normally secreted by the prostate in large amounts into the seminal plasma but only tiny amounts enter the blood stream hence low biological reference range of 0-4.0ng/ml. Prostatic diseases like PCa, Benign Prostatic Hypertrophy (BPH), urinary tract infections and prostatitis disrupt the integrity of the basal cell layer and basement membrane which leads to leakage of PSA into the blood stream (Andriole et al 2004). Therefore the PSA test is prostate specific but not PCa specific, which compromises its screening role. More biomarkers that are PCa specific and sensitive are required.

A biopsy is the main tool that’s used to confirm and diagnose PCa. Small pieces of tissue are removed from the prostate and examined under the microscope by a histopathologist to check for cancer cells. A bone scan, computed tomography (CT or CAT) scan and Magnetic Resonance Imaging (MRI) are also used to find out if the cancer has spread.

The study used archived data collected and kept by the ZNCR. All confirmed PCa cases with their demographic data were retrieved electronically and the data was analysed.

**Methodology**

**Research design**

The study was a retrospective cross-sectional study using secondary data collected by the ZNCR. All confirmed PCa data obtained from the entire country was retrieved and analysed.

**Sampling technique**

A convenience type of sampling was employed. All the available data on prostate cancer from the ZNCR from 1986-2015 was retrieved and analysed.

**Data collection**

An electronic data set of all confirmed PCa patients was obtained from the ZNCR after the study was approved by the Medical Research Council of Zimbabwe (MRCZ). There were no names of patients to safeguard patient confidentiality. Information on each numbered patient included: registry number, year of diagnosis, age, race and district of residence and the histopathological diagnosis. The data set was from 1986 to 2015. 1986 -1995 was the pre PSA testing era and 1996 –2015 was the post PSA testing era.

**Data analysis**

All the data was transferred onto an excel spread sheet and grouped into individual years (30) and the years in ascending order. The data was then grouped into five year groups for comparison using the
two tailed T-test, the pre PSA years versus the post PSA era. The 1986 -1995 group was reference group for comparing with post PSA groups 1996-2005 and 2006-2015 groups. Graph Pad Prism 7.03 was employed to analyse the data. Significance level was 95 % / p value 0.05.

**Results**

A dataset with a total of 5 277 confirmed PCa cases was obtained from the ZNCR on an excel spread sheet and analyses. There were 1191 (22.6%) cases in the period January 1986 to December 1995. This was the era before PSA testing (pre-PSA era). 1996-2005 (first post-PSA era) had 37.0% (n=1955) PCa cases. And the second post-PSA era 2006-2015 had 40.4% (n=2131) cases (Fig 1 & 2).

There was a significant difference in the number of cases between the pre-PSA era and the two post-PSA eras (p=0.0042 and 0.0028) respectively. The number of cases between the two post-PSA periods, was not significantly different (p =0.8262).

The youngest patient was 9 years and the oldest was 99 years of age. The median age was 71 (IQR 64-78) years. There were 26 (0.5%) PCa cases in the under 40 years age group, 116 (2.2%) PCa cases in the 41-50 years age group, 703 (13.3%) between 51-60 years of age and the over 60 years constituted 84% (n=4432) of all the PCa cases (Fig 3).

Out of the 5 277 confirmed cancer cases, 255 (4.83%), had PSA results in their reports. Their median age was 76 (IQR 70-82) years. The median PSA level was 76.16 (IQR 32.95-287.29) ng/ml. 92% of all the PCa cases were adenocarcinomas (Fig 4).

![Zimbabwe PCa cases over 30 years](image)

**Figure 1**: Total number of PCa cases over 30 years

Prostate Cancer Cases in Zimbabwe

Figure 2. Prostate Cancer cases vs. Age in Zimbabwe. The number PCa cases per age group in brackets.

Figure 3. PCa cases per 5 years over 30 years.
Figure 4. Types of PCa diagnosed over 30 years

92% (n= 4829) Adenocarcinomas, 5.8% (n=38) squamous cell carcinoma.

Discussion

The study showed that the majority of the PCa cases were over 60 peaking at 99 years of age years of age confirming that PCa is a disease of the old in Zimbabwe just like it is in the rest of the world. The median age was 71 (IQR 64-78) years, meaning that fifty per cent of the PCa cases were in the 64-78 years age group. According to these results PSA screening would really benefit the 40-55 years age group considering the slow growing nature of most of the prostate tumours (Neal et al., 2000). Most PCAs found in comparatively young men (45-55 years) appear to be more aggressive and have high mortality rates (Salinas et al., 2014).

The 26 (0.5%) PCa cases found in the under 40 years of age group would require further investigation as far as risk factors e.g., genetics are concerned. It has however been pointed out by Bubenborderf et al., (2000), and Soos et al., (2005), that autopsy studies have shown an age dependant risk of finding microscopic foci of what is considered to be PCa from the age of 30 years. Considering their observation, the 0.5% PCa cases in the under 40 years would be expected.

The median age of 71 years is similar to the Swedish one of 69 (The National board of health and welfare Sweden 2008) and to the earlier study by this author (Musonza 2016) of 75 years (IQR 70-82) years using a much smaller sample size. In America the median age is 66 and in Europe it is 69 (Guzzo, Drach, Wein, 2016). These are all in agreement with results obtained in this study. There is no indication of ethnic or racial difference as far as the most affected age group is concerned.

PSA is organ specific and not PCa specific. Many men can live and die with PCa and not of PCa (Whitmore 1994). This is confirmed by the disparity for all ages between incidence and mortality rates e.g., in 1993 65 000 men out of 165 000 died in the USA (Whitmore 1994). The fact that most PCas are
slow growing and indolent but will raise the PSA level which can lead to biopsies and treatment to an otherwise ‘friendly’ tumour which would not cause any symptoms is a disadvantage of PSA testing. Other prostatic diseases like Benign Prostatic Hyperplasia (BPH), prostatitis and urinary tract infections can also raise the PSA levels (Caplan & Kartz 2002).

The impact of PSA on the increase in PCa cases in Zimbabwe is demonstrated in the study. The study shows a significant increase in the number of PCa cases after the introduction of PSA testing from 1191 (22.6%) cases to 1955 (37%) and 2131 (40.4%) p value = 0.0042 and 0.0028 respectively. A comparison of the two ten year post PSA periods do not show any significant difference 37% compared to 40.4% (p= 0.8262).

Therefore the introduction of PSA testing in 1996 had the effect of increasing the prevalence of PCa in Zimbabwe according to the results of this study. The non-specificity of PSA then brings in the debate of over diagnosis and over treatment. The United States Preventive Services Task Force (USPSTF) has issued guidelines discouraging screening using PSA (Moyer 2012). However PCa cases in the United States peaked after PSA testing was introduced, levelled off, new cases came down and mortalities declined (Moyer 2012). This debate about PSA screening requires more time and more studies in our own environment. There is need for more research on over diagnosis and over treatment because of PSA testing. At present early diagnosis using PSA screening has prolonged lives.

USPSTF and The Cancer Council of Australia have argued that the quality of life has been affected by procedures and over treatment that follow the treatment of indolent tumours as a result of PSA testing. Indolent tumours are slow growing and depending on the age, they would be outlived by other conditions with no symptoms at all. Watchful waiting has been proposed as a more practical way of dealing with raised PSA with no symptoms (Heijnsdijk, Wever and Auvinen et al 2002).

The introduction of PSA testing in Zimbabwe has revolutionised PCa diagnosis, treatment, monitoring treatment and prolongation of life. As more information is becoming available on the role of certain genes in PCa pathogenesis, more studies need to be carried out in Zimbabwe to combat men’s number one cancer.

**Limitations and recommendations**

The use of secondary data, despite its cost effectiveness always has limitations because it would have been collected for other purposes like policy making, planning, and statistics or for answering different research questions, not the study’s objectives. It is very difficult to exclude errors and omissions in the data if there are any. Certain vital information like treatments and outcomes was not available in this particular data set. It would have been very useful in the evaluation of the impact of age and PSA testing. The race and ethnic criteria was not taken into account due to the dominance by one major group.

It is recommended that more studies in collaboration with other groups be done to get more insight into PCa in Zimbabwe. The debate about over diagnosis and over treatment needs to be seriously looked at by all stakeholders including the patients themselves.

**Conclusion**

The age group most affected by PCa in Zimbabwe is the 64-78 years with a median age of 71 (IQR 64-78) years. 84% of all the PCa cases in this study were above 60 years of age. The introduction of PSA testing had the effect of suddenly increasing the number of PCa cases in Zimbabwe. There was a significant difference between the pre-PSA era and the two post-PSA eras (p=0.0042 and p=0.0028) respectively. More studies are required on PCa for us to understand if there are other risk factors involved, now that we know the most affected age group. PCa is a major health problem in Zimbabwean men and needs better screening methods that detect the aggressive types of PCa, more awareness among men and access to diagnosis and treatment.
References


An Open-Label, Balanced, Randomized, Two-Treatment, Two-Period, Two-Sequence, Single-dose Crossover Pilot Oral Bioequivalence Study of Ritonavir Capsules 100 mg with NORVIR® Ritonavir Capsules Soft Gelatin 100 mg of Abbott Laboratories, USA in Healthy, Adult, Male, Human Subjects Under Fasting Conditions

Article by Venkatesh Pandi
Clinical Research, Texila American University, India
E-mail: drvenkat22@gmail.com

Abstract

Background: The present study was conducted to investigate the bioequivalence of Ritonavir Capsules 100 mg with that of NORVIR® Ritonavir Capsules Soft Gelatin 100 mg.

Patients and methods: This study was an open-label, balanced, randomized, two-treatment, two-period, two-sequence, single dose crossover pilot oral bioequivalence study. Study was conducted in 12 healthy, adult male subjects with age ranging from 18 to 45 years. The total duration (excluding screening) of subject participation in a study was approximately 11 days including washout period of 07 days between each dosing. The estimation of Ritonavir in human plasma is carried out by using LC/MS/MS method in Bioanalytical laboratory. The pharmacokinetic parameters assessed were AUC₀₋₅, AUC₀₋∞, C₅₀, AUC₀₋₅/AUC₀₋∞, T₅₀, kₑ, and t₀.

Results: The geometric mean ratios (90% confidence intervals) of the test drug/reference drug for Ritonavir were 100.8 (83.64-121.51) for AUC₀₋₅, 102.1 (85.39-122.01) for AUC₀₋₅₉, and 97.5 (81.19-117.08) for C₅₀. The 90% confidence intervals of the test/reference AUC₀₋₅, AUC₀₋∞, C₅₀ ratio of Ritonavir were within the acceptance range for bioequivalence. In this study, single dose of Ritonavir 100 mg capsule was well tolerated by both groups of subjects under fasting conditions.

Conclusion: It was concluded that the two Ritonavir capsules formulations (the test and reference products) were bioequivalent in terms of the rate and extent of absorption.

Introduction

Situations in which bioequivalence studies are required:

- When significant changes are made in the manufacture of the marketed formulation, and
- When a new generic formulation is tested against the innovator’s marketed product.

Bioequivalent simply means that one brand or dosage form of a drug or supplement is equivalent to a reference brand or dosage form of the same drug or supplement in terms of various bioavailability parameters measured via in vivo testing in human subjects.

The purpose of the study to compare and evaluate the single-dose oral bioavailability of Ritonavir Capsules 100 mg with NORVIR® Ritonavir Capsules Soft Gelatin 100 mg of Abbott Laboratories, USA in healthy, adult, male, human subjects under fasting conditions.

General regulatory considerations for BA/BE studies

The processes of study design and workflow of BA/BE studies are presented in brief in below. The general considerations for the advancement of conducting BA/BE studies are:

- Study design and protocol.
- Bio analysis.
- Selection of appropriate analysts.
- BE metrics and data treatment.
- Statistical approaches and analysis.
Materials and methods

Design and conduct of the study

Study design

The study should be designed in such a way that the formulation effect can be distinguished from other effects. If the number of formulations to be compared is two, a two-period, two-sequence crossover design is often considered to be the design of choice.

In the present study the design followed was:

An open-label, balanced, randomized, single dose, two-treatment, two-sequence, two-period, crossover bioequivalence study.

Conduct of the study

Clinical phase

Preparation of protocol

Protocol is defined as a document signed and dated by the investigator and the sponsor that fully describes the objective(s), design, methodology, statistical considerations and organization of a study. The study protocol may also give the background and rationale for the study but these could be provided in other study protocol-referenced documents. The protocol includes all the details regarding the investigational product, the details regarding the administration of the drug, Pharmacokinetic (PK) sample withdrawal time-points, safety assessment parameters etc.

A protocol is prepared by the investigators of the study or his designee (usually a clinical pharmacologist and reviewed by various departments like analytical, statistical, QA to make necessary changes). The following chart gives an overview regarding the preparation of the protocol:

Ethical considerations

Basic principles

The study was conducted according to Good Clinical Practice, the Declaration of Helsinki, Guideline for Good Clinical Practice and all Applicable regulations and guidance.

Institutional review board

An institutional review board / independent Ethics committee reviewed this protocol and the study started only after the approval of the protocol by the institutional review board / independent Ethics committee.

Independent Ethics Committee (IEC) consists of a board of members who look into the ethical issues of the study to be conducted. The study operations can be initiated only after the protocol is approved by IEC.

An IEC should safeguard the rights, safety, and well being of all trial subjects. Special attention should be paid to trials that may include vulnerable subjects. The investigator may provide information on any aspect of the trial, but should not participate in the deliberations of the IEC or in the vote/opinion of the IEC. An IEC may invite nonmembers with expertise in special areas for assistance.

Informed consent

Designated clinical research personnel informed the subjects before initiation of the study through an oral presentation regarding the purpose, procedures to be carried out, potential Hazards and rights of the subjects during the course of the study.

ICF is designed as per the ICH-GCP and local regulatory requirements. ICF is conducted in order to get the consent from the volunteer to participate in the study. Volunteers were given all the information regarding the study including:

- Details of Investigational products
- Adverse events that may occur during the study
• The total blood loss
• The compensation to be given at the end of the study
• Regulations to be followed while participating in the study

Volunteers were given the freedom to withdraw from the study at any point of time, during the study. This consent is taken as a part of the ethical issue in conducting a BA/BE study. Every care was taken to protect the health of the volunteers. The volunteers signed on this form and gave their consent for participating in the study. Once they were enrolled in to the study, they were called ‘subjects’. The enrollment in the study started with the “check-in” process.

**Protocol training**

After the approval of the protocol, it is discussed among the investigators of the study. The summary of the protocol that includes:

• The name of the investigational product (drug to be administered to the subjects)
• Dose to be administered
• Type of study whether it is a single center study, a fast or fed study, analyst study etc.
• Number of subjects to be enrolled in the study
• Kind of study etc, and other minute details like the Clinical Pharmacology unit (CPU) in which the subjects would be housed etc.

This summarized version of the protocol is discussed among the personnel in the facility to train them in the protocol.

**Registration of volunteers**

For recruiting volunteers for a study suitable volunteers are selected from the database. New people are informed and registered in the database after they gave the written consent. Generally, healthy male, adult volunteers in the age group of 18-45 years are preferred according LIC height and weight chart.

**Screening**

The screening was carried out after taking an initial informed consent from volunteers for study screening procedures.

Each subject was undergone a screening procedure for health assessment, which consists of a complete medical history, physical examination with vital signs, clinical laboratory evaluations, 12-lead ECG and Chest X-ray PA view. The physical examination findings, ECG and the laboratory tests were considered as valid for maximum of 21 days prior to the dosing (drug administration) in first period of the study. Chest X-ray PA view will be taken within 6 months prior to dosing (drug administration) of period-1.

**Clinical/laboratory diagnostic tests**

<table>
<thead>
<tr>
<th></th>
<th>Hematology:</th>
<th>Red blood cell count, White blood cell count, Differential white blood cell count, Hemoglobin estimation, Plat count, MCH, MCV, MCHC, RDW, Mean Plat Volume, HCT, Erythrocyte sedimentation rate (ESR), Blood grouping and RH typing.</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>Biochemistry</td>
<td>Serum creatinine, Blood urea, SGOT (AST), SGPT (ALT), Serum alkaline phosphatase, Total bilirubin, Blood sugar / Plasma Glucose (Random), Serum electrolytes (Sodium, Potassium and Chloride)</td>
</tr>
<tr>
<td>3</td>
<td>Serology</td>
<td>HIV (1 &amp; 2) antibodies, HbsAg (Hepatitis B surface antigen), HCV antibodies, VDRL/ Syphilis.</td>
</tr>
<tr>
<td>4</td>
<td>Urine analysis</td>
<td>Color/Apperance, Transparency, pH, Specific gravity, Glucose, Proteins, Ketones, Bilirubin, Blood, Urobilinogen, Urine microscopic examination.</td>
</tr>
</tbody>
</table>
Inclusion criteria
Subjects fulfilled all of the following criteria before including the subjects into this study:

- Healthy Male subjects aged between 18 to 45 years (inclusive of both).
- Body mass index of ≥ 18.5 kg/m2 and ≤ 24.9 kg/m2 and weight ≥ 50 kg.
- Healthy according to the laboratory results and physical examination, performed within 21 days prior to the commencement of the dosing in Period-1.
- Have normal ECG, Chest X-ray and vital signs.
- Subject clinical laboratory values are within normal limits or clinically insignificant as determined by physician or principal investigator to be of no clinical significance.
- Light smokers, Ex-smokers or Non-smokers (A light smoker is defined as someone smoking 10 cigarettes or less per day, Ex-smoker being defined as someone who completely stopped smoking for at least 12 months before day 1 of this study).
- Subjects able to communicate effectively and provide written informed consent.
- Subjects willing to adhere to protocol requirements as evidenced by written informed consent approved by an Independent Ethics Committee (IEC).

Exclusion criteria
Subjects were not allowed for study participation if he meets any of the following criteria:

- Any history of allergy or hypersensitivity to Ritonavir or related drugs.
- Positive test result for hepatitis B surface antigen (HBsAg), VDRL/ Syphilis, hepatitis C virus antibody (HCV Ab) or HIV-1 antibody or HIV Type 2 (HIV-2) antibody (HIV Ab).
- The study drug shall not be contraindicated for medical reasons (as stated in protocol section 3.0) to any of the study participants.
- Any history or presence of significant cardiovascular, pulmonary, hepatic, renal, gastrointestinal, endocrine, dermatological, neurological or psychiatric disease or disorder.
- History of significant alcoholism (> 3 units of alcohol per day) within one year prior to drug administration.
- History or presence drug abuse in the past one year.
- History of smoking more than 10 cigarettes per day.
- Any history or presence of cancer.
- Any history of difficulty in donating blood.
- Had clinically significant abnormal values of laboratory parameters.
- Blood pressure is <100/60 or >140/90 mmHg (Systolic blood pressure/ Diastolic blood pressure).
- Pulse rate less than 60 beats/minute and more than 100 beats/minute.
- Usage of any prescribed medication during last 14 days or OTC medicinal products, herbal products during the last 7 days preceding the first dosing.
- Any clinically significant illness during 3 months before screening.
- Participation in a drug research study/donation of blood within past 90 days.
- Consideration by the investigator, for any reason, that the subject is an unsuitable candidate to receive Study drug.

Subjects with positive for breath alcohol test, urine screen for drugs of abuse [(Cannabinoids (Marijuana / Tetra Hydro Cannabinoids-THC), Cocaine, Opiates (morphine), Amphetamine, Barbiturates, and Benzodiazepines] at the time of check-in for each period were excluded from the study.

Check-in process
The volunteers who gave their consent to participate in the study were enrolled in the study i.e. the check-in process. During this process it was checked whether the person has met all the inclusion/exclusion criteria and cleared the screening process.

They were undergone vital examination and Medical examination again to ensure they are fit for participation in the study. They would be changing into the uniforms provided to them in the facility. Once the check-in of the volunteer is completed he would be called as ‘subject’. The subjects were provided with all the requirements they need including recreational activities like movies and games,
newspapers. The check in day is called as Day 0. The subjects were given standardized dinner after which they would be fasting overnight for 10 hours.

**Tests performed before check-in of each period**

Subject’s urine was screened for drugs of abuse like cocaine, cannabinoids, amphetamines, barbiturates, benzodiazepines and opiates at the time of check-in for each period. Alcohol breath test was performed for all subjects before check-in into each period of the study. Subject will be rejected / withdrawn from the study if the result is positive for alcohol.

**Number of subjects**

Total 12 healthy, adult male subjects, 18 to 45 years old volunteers were enrolled in this study.

**Housing**

All Subjects were checked-in into the clinical facility at 10.50 hrs before dosing on 31 Jul 2014 & 08 Aug 2014 in period-01 & period-02 respectively. They were checked-out 24 hours after dosing on 02 Aug 2014 & 10 Aug 2014 in each period period-01 & period-02 respectively.

**Randomization**

The test and reference products were assigned to each subject in a sequence according to a predetermined randomization schedule prepared by using SAS software 9.1.3 version. The randomization schedule prepared is as follows:

<table>
<thead>
<tr>
<th>Subject ID</th>
<th>Sequence</th>
<th>Period-01</th>
<th>Period-02</th>
</tr>
</thead>
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<tr>
<td>1</td>
<td>1</td>
<td>A</td>
<td>B</td>
</tr>
<tr>
<td>2</td>
<td>2</td>
<td>B</td>
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</tr>
<tr>
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<tr>
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</tr>
<tr>
<td>12</td>
<td>1</td>
<td>A</td>
<td>B</td>
</tr>
</tbody>
</table>

**Dispensing**

As per the randomization schedule a qualified registered pharmacist dispensed the investigational products under the supervision of Quality Assurance personnel on 31 Jul 2014 & 08 Aug 2014 in period-01 & period-02 respectively. Remaining drug products were stored in their original container as retention samples. The test and reference product were stored in humidity chamber below 25°C and 60% RH ±5%.

The dispensed tablets were transferred to the drug-dispensing containers as unit doses. The drug-dispensing containers used for dispensing were properly labeled for the study number, period number, subject number, treatment code, initial and date of the person dispensing the product.
The details of the investigational products were as follows:

<table>
<thead>
<tr>
<th>Product</th>
<th>Test</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment ID</td>
<td>A</td>
<td>B</td>
</tr>
<tr>
<td>Product Name</td>
<td>Ritonavir Capsules 100 mg</td>
<td>NORVIR® Ritonavir Capsules Soft Gelatin 100 mg</td>
</tr>
<tr>
<td>Manufactured / Distributed by</td>
<td>--</td>
<td>Abbott Laboratories, USA</td>
</tr>
<tr>
<td>Strength</td>
<td>100 mg</td>
<td>100 mg</td>
</tr>
<tr>
<td>Dosage Form</td>
<td>Capsules</td>
<td>Capsules</td>
</tr>
<tr>
<td>Route of Administration</td>
<td>Oral</td>
<td>Oral</td>
</tr>
</tbody>
</table>

**Dosing of investigational product**

All subjects were fasted for at least 10 hours prior to scheduled time for dosing. As per the randomization schedule, one tablet of test (A) product i.e., Ritonavir Capsule 100 mg or one tablet of reference (B) product i.e., NORVIR® Capsule Soft Gelatin 100 mg was administered to each subject with 240 mL of water at ambient temperature on 01 Aug 2014 and 09 Aug 2014 in period-01 and period-02 respectively by trained study personnel.

Subjects were instructed not to chew or crush the capsule or tablet but to consume it as a whole. Compliance for dosing was assessed by a thorough check of the oral cavity immediately after dosing. Administration of investigational products was carried out while the subjects were in sitting posture and they were instructed to remain seated for two hours after dosing in each period except when clinically indicated to change the posture or in case of any natural exigency. Thereafter, the subjects were allowed to engage in normal activities while avoiding severe physical exertion.

**Diet and water**

Subjects were fasted for 10 hours before dosing in each period. Drinking water was prohibited for two hours before and two hours after dosing. At other times, drinking water was provided ad libitum. Meals or snacks were provided at 4 hr (lunch), 8 hr (snacks), 12 hr (dinner) and 24 hr (check-out breakfast) after dosing in each period.

**Restrictions to subjects**

**Smoking**

All subjects were instructed to abstain from smoking for at least 24.00 hours prior to dosing till last sample collection in each period.

**Medications**

Subjects were asked about their medication history in the past, particularly last 14 days for usage of any prescribed medication and last 7 days for the usage of any OTC medicinal products, herbal products preceding the first dosing and were instructed not to take any medication until completion of the study.

**Diet**

All subjects were instructed to abstain from any xanthine-containing food or beverages (tea, coffee, chocolates, soft drinks etc.), grapefruit juice or related products and alcohol or related products for at least 24.00 hours prior to dosing till the last sample collection in each period and were prohibited from consuming above mentioned products, during their in house stay. Subjects were instructed not to consume/chew any tobacco containing products {pan masala, gutkha, supari (betel nut)} etc. from...
24.00 hours prior to dosing of each period and till last sample collection in each period.

Activity

All subjects were dosed at the fixed time and were remained in sitting position for the first 2.00 hours following drug administration except while going for sampling and medical examination/vitals or clinically indicated/for natural exigency. Further subjects were ambulatory but they were advised to avoid severe physical exertion.

Drinking water

Drinking water will be prohibited for two hours before and two hours after dosing. At other times, drinking water will be provided ad libitum.

Collection of blood samples

The sampling schedule should be planned to provide an adequate estimation of $C_{\text{max}}$ and to cover the plasma concentration time curve long enough to provide a reliable estimate of the extent of absorption. This is generally achieved if the AUC derived from measurements is at least 80% of the AUC extrapolated to infinity. For most drugs, 18 to 30 samples, including a pre-dose sample, should be collected per subject per dose. This sampling should continue for at least three or more terminal half lives of the drug\textsuperscript{16}. The exact timing for sample collection depends on the nature of the drug and the input from the administered dosage form. The sample collection should be spaced in such a way that the maximum concentration of the drug in the blood ($C_{\text{max}}$) and terminal elimination rate constant ($\text{t}_1/2$) can be estimated accurately.

According to the literature $T_{\text{max}}$ is 2 hours and $T_1/2$ ranged between 3 - 5 hours for Ritonavir after oral use, the below sampling schedule is decided using above $T_{\text{max}}$ and $T_1/2$ values.

In this study, in each period, a total of 21 (1 x 6 mL) venous blood samples were collected from each subject as per the following schedule:

Pre-dose (0.00 hr), 0.33, 0.67, 1.00, 1.50, 2.00, 2.50, 3.00, 3.50, 4.00, 4.50, 5.00, 5.50, 6.00, 7.00, 8.00, 10.00, 12.00, 16.00, 24.00 and 36.00 hours post dose in each period.

Blood loss

The total blood loss combining both the periods [including 291 mL for pharmacokinetic analysis, 19 mL of discarded heparinized blood prior to each post-dose sample collected through cannula (except for pre-dose and ambulatory samples), about 10 mL blood collected for pre-study screening and about 10 mL blood collected for post safety assessment] did not exceed 291 mL.

Sampling procedure

Blood samples were collected through an indwelling cannula placed in a forearm vein. Heparin lock technique was used to prevent the clotting of the blood. At each sampling time point, blood sample was withdrawn and transferred to a sample collection tube containing K$_2$ EDTA as anticoagulant. Before each blood sample is collected except for pre-dose sample (0.00 hours) and ambulatory sample (36.00 hrs), 0.5 mL of heparinized blood was withdrawn and discarded to prevent heparin interference with sample analysis. For ambulatory sample collection i.e. 36.00 hrs, direct venipuncture was done.

The pre-dose blood sample was collected before dosing and the post-dose samples were collected within ± 2 minutes from the scheduled sampling time during in-house stay. For the ambulatory samples, the sampling was done within ± 60 minutes from the scheduled sampling time. During collection of blood sample at each time point the mid-point of the minute was considered to calculate the nearest minute, which was recorded on the appropriate form. The deviations greater than mentioned in the protocol from the scheduled sampling time were reported as protocol deviations.

Sample separation and storage

After collection, blood samples were placed in ice water bath till start of centrifugation. Within 30 minutes from the time of collection, the blood samples were placed in a refrigerated centrifuge and then spun at 3000 rpm for 10 minutes at 4°C. As soon as possible, the plasma obtained was separated
and transferred into two different polypropylene tubes/RIA vials. Each tube/vial will be labeled with Project No., Period No., Subject No., Sampling time point and Aliquot No. 1 mL of plasma was separated and transferred into aliquot 1 and the rest of plasma into aliquot 02.

All samples were stored at a temperature of -20°C or below for interim storage at the clinical site until transferred to analytical site.

Sample sorting

Once all the samples from the subjects were collected, the samples are sorted. The sorting was done by separating the aliquots containing samples of different time points of each subject into easy sealing bags. Various conditions are maintained while sorting the samples, like the maintenance of low temperatures. Sorting was done in presence of dry ice to prevent the exposure of samples to room temperature and also to prevent their degradation due to thawing. These bags were sealed into various boxes and stored in the deep freezer, which are later handed over to the bio-analytical department with proper documentation for further processing.

Safety monitoring

Subjects were monitored for their well being by recording vital signs. Clinical Examination was carried out and recorded at check-in, before dosing and at checkout. Vital signs (sitting blood pressure, pulse rate and oral temperature) measurement was carried out and recorded at check-in, before dosing of investigational products (in the morning of the day of dosing), at 1, 2, 4, 6, 8 (within ± 45 minutes) hours after dosing and at checkout. Clinical examination and measurement of vital signs were also being carried out at other times during the conduct of the study when the attending physician felt it necessary.

About 10 mL of blood was collected from all the subjects for safety evaluation [haematology and biochemistry] at the end of the study.

The normal vital signs range is as follows:

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Temperature</td>
<td>97.8°F-99°F</td>
</tr>
<tr>
<td>Pulse Rate</td>
<td>60-100 beats/min</td>
</tr>
<tr>
<td>Respiration Rate</td>
<td>14-20/min</td>
</tr>
<tr>
<td>Systolic BP</td>
<td>100-138 mm of Hg</td>
</tr>
<tr>
<td>Diastolic BP</td>
<td>60-88 mm of Hg</td>
</tr>
</tbody>
</table>

If any adverse event is observed either by clinical staff or reported by subjects at times other than scheduled times will also be recorded.

Reporting of adverse events

A total of three AE’s (One AE during period 01 in-house and Two AE’s during post study safety evaluation) during the study.

Subject number 08 had experienced the adverse event (Dizziness) during period 01 in-house of the study which was possibly related to the study drug and mild in intensity and resolved completely without sequel.

Post study safety evaluations of laboratory parameters were found to be within acceptable limits for all the subjects except for subject number 02 & 10. Subject number 02 was found to have (Increased total bilirubin levels) while evaluating the post study safety reports which was mild in nature and possibly related to the study drug and considered as completely resolved on 25 Aug 2014.

Subject number 10 was found to have (Increased SGPT levels) while evaluating the post study safety reports which was mild in nature and possibly related to the study drug and considered as completely resolved on 25 Aug 2014.

In this study, single dose of Ritonavir 100 mg capsule was well tolerated by this group of subjects under fasting conditions.

Withdrawal criteria

Subjects will be withdrawn from the study by the principal investigator or co-investigators for any
of the following reasons during the course of the study:
1. If the subject suffers from significant illness
2. If the subject requires concomitant medications which may interfere with pharmacokinetic of
   the study drug
3. If the subject has entered the study in violation of the inclusion and the exclusion criteria
4. If the subject is found to be non co-operative
5. If the subject decides to voluntarily dropout from the study

Note
- Any such subject withdrawals will be reported for reasons for withdrawal (if any).
- Medical examination of the subject will be done at the time of withdrawal / dropout.
- The plasma concentration data from subjects who are withdrawn due to adverse events will be
  presented, but will not be included in the statistical analysis.

There were no withdrawals in this study.

Check out process

After the completion of the study the subjects were checked-out. In the check out process the
subjects undergo a medical check up to ensure that they are healthy even after participating in the
study.

The study cycle was repeated after the washout period when the subjects are crossed over to other
treatment.

Their post study medical check-up includes the blood test. Once the subjects finish giving their
blood samples they are paid their compensation.

Washout period

Subsequent treatments should be separated by periods long enough to eliminate the previous dose
before the next one (adequate wash out periods). There should at least 7 half lives of the drug as
washout period between two treatments administrations.

In the present study drug administration in first period was followed by a washout period of 07
days before subjects were switched over to the other treatment in the second period.

Total duration of subject participation in the study

The total duration (excluding screening) of subject participation in a study was approximately 11
days including washout period of 07 days between each dosing. The duration of the total study with
dates is explained in detail in below table.

<table>
<thead>
<tr>
<th>Activity</th>
<th>Date</th>
<th>No. of subjects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Screening</td>
<td>10 Jul 2014 – 30 Jul 2014</td>
<td>25</td>
</tr>
<tr>
<td><strong>Period-01</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Check-in</td>
<td>31 Jul 2014</td>
<td>12</td>
</tr>
<tr>
<td>Dosing</td>
<td>01 Aug 2014</td>
<td>12</td>
</tr>
<tr>
<td>Check-out</td>
<td>02 Aug 2014</td>
<td>12</td>
</tr>
<tr>
<td><strong>Period-02</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Check-in</td>
<td>08 Aug 2014</td>
<td>12</td>
</tr>
<tr>
<td>Dosing</td>
<td>09 Aug 2014</td>
<td>12</td>
</tr>
<tr>
<td>Check-out</td>
<td>10 Aug 2014</td>
<td>12</td>
</tr>
</tbody>
</table>

Accountability procedures for the investigational products:

Accountability was maintained for each unit of the investigational products by recording in
appropriate forms. Drug store custodian and principal investigator were responsible for maintaining
the accountability. The unused samples were sent back to the sponsor after completion of the study.

68
Subject compensation

The subjects were compensated for the overall inconvenience borne during the study. In case of dropouts / withdrawal of a subject before completion of the study, the amount of proportionate compensation to the dropout / withdrawal subject was as follows:

<table>
<thead>
<tr>
<th>S. No.</th>
<th>Reasons of Withdrawal from the Study</th>
<th>Compensation</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Principal Investigator / Medical Officer withdraw the subjects from the study based on medical decision.</td>
<td>Full payment</td>
</tr>
<tr>
<td>2.</td>
<td>After the initiation of the study, subject withdraws on his own free will.</td>
<td>50% proportionate participation dues</td>
</tr>
<tr>
<td>3.</td>
<td>The subject is withdrawn from the study on humanitarian grounds, with the permission of the Principal Investigator / Medical Officer.</td>
<td>100% proportionate participation dues</td>
</tr>
<tr>
<td>4.</td>
<td>Subject is dropped from the study due to violation of requirements of the study by the Principal Investigator / Medical Officer after signing the Informed Consent Form but before receiving any medications</td>
<td>No payment</td>
</tr>
<tr>
<td>5.</td>
<td>Subject is withdrawn from the study by the Principal Investigator / Medical Officer because of willful misinformation on present and /or past medical illness/history.</td>
<td>No payment</td>
</tr>
</tbody>
</table>

Bioanalytical phase

The estimation of Ritonavir in human plasma is carried out using LC/MS/MS method in Bioanalytical laboratory.

Analytical method details

Name of the Drug- Ritonavir
Name of the Analyte- Ritonavir

Instruments/equipments

The following instruments and equipments were used in the estimation of Ritonavir (analyte). Except LC/MS/MS, instruments and equipments of similar performance or equivalent configuration shall also be used for estimation of Ritonavir (analytes) using this analytical method.

Major equipment involved

<table>
<thead>
<tr>
<th>Equipment</th>
<th>Make</th>
<th>Model</th>
</tr>
</thead>
<tbody>
<tr>
<td>LC/MS/MS</td>
<td>Applied Biosystems</td>
<td>API 300</td>
</tr>
</tbody>
</table>

Pharmacokinetic and statistical phase

Based on the plasma concentrations of Ritonavir, the following pharmacokinetic parameters were calculated by using “Non-compartmental model” for Treatments A and B:

- Primary pharmacokinetic parameters: AUC_{0-t}, AUC_{0-∞}, C_{max}.
- Secondary pharmacokinetic parameters: AUC_{0}/AUC_{0-∞}, T_{max}, k_{el} and t_{1/2}.
- All pharmacokinetic analysis was carried out using WinNonlin Version 5.1.
- Statistical analysis was done from subject pharmacokinetic parameters using validated SAS® Version 9.1 software procedures.
Brief representation of work flow of bioavailability/bioequivalence study

Abbreviations: ANDA, abbreviated new drug application; PK, pharmacokinetics.
Results

Pharmacokinetic data

Mean (SD) of Pharmacokinetic Parameters of estimated for test product (A) and reference product (B) were as follows:

<table>
<thead>
<tr>
<th>Parameters (Units)</th>
<th>Test Product (A)</th>
<th>Reference Product (B)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean ± SD</td>
<td></td>
</tr>
<tr>
<td></td>
<td>N=12</td>
<td>N=12</td>
</tr>
<tr>
<td>*T&lt;sub&gt;max&lt;/sub&gt; (hr)</td>
<td>3.25 (1.00-4.50)</td>
<td>4.50 (3.00-5.00)</td>
</tr>
<tr>
<td>C&lt;sub&gt;max&lt;/sub&gt; (ng/mL)</td>
<td>1513.179 ± 670.6014</td>
<td>1549.371 ± 659.5110</td>
</tr>
<tr>
<td>AUC&lt;sub&gt;0-t&lt;/sub&gt; (ng. hr/mL)</td>
<td>12030.037 ± 5460.2195</td>
<td>12233.229 ± 7219.2410</td>
</tr>
<tr>
<td>AUC&lt;sub&gt;0-inf&lt;/sub&gt; (ng. hr/mL)</td>
<td>12759.075 ± 5480.7590</td>
<td>12852.744 ± 7416.2866</td>
</tr>
<tr>
<td>K&lt;sub&gt;el&lt;/sub&gt; (1/hr)</td>
<td>0.141 ± 0.0366</td>
<td>0.134 ± 0.0378</td>
</tr>
<tr>
<td>t&lt;sub&gt;v&lt;/sub&gt; (hr)</td>
<td>5.375 ± 2.1283</td>
<td>5.602 ± 1.7037</td>
</tr>
<tr>
<td>AUC_&lt;sub&gt;_∞&lt;/sub&gt;_El (ng/mL)</td>
<td>6.348 ± 2.8361</td>
<td>5.206 ± 1.3835</td>
</tr>
</tbody>
</table>

For T<sub>max</sub>, Median (Min, Max) are presented.

Statistical data

The statistical results obtained for the drug during the fasting study were as follows:

Statistical Results of Assessment of Bioequivalence of Ritonavir under fasting Conditions (Ritonavir 100 mg capsules (Form A) vs NORVIR® Ritonavir Capsules Soft Gelatin 100 mg (Form B))

<table>
<thead>
<tr>
<th>Parameters (Units)</th>
<th>Geometric Least Squares Means</th>
<th>90% Confidence Limits (%)</th>
<th>(A / B) %</th>
<th>Intra Subject CV %</th>
<th>Post-hoc Power (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Test product (A)</td>
<td>Reference product (B)</td>
<td>(A vs. B)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>C&lt;sub&gt;max&lt;/sub&gt; (ng/mL)</td>
<td>13993.530</td>
<td>1429.272</td>
<td>81.19-117.08</td>
<td>97.5</td>
<td>25.1</td>
</tr>
<tr>
<td>AUC&lt;sub&gt;0-t&lt;/sub&gt; (ng. hr/mL)</td>
<td>11005.510</td>
<td>10917.029</td>
<td>83.64-121.51</td>
<td>100.8</td>
<td>25.6</td>
</tr>
<tr>
<td>AUC&lt;sub&gt;0-inf&lt;/sub&gt; (ng. hr/mL)</td>
<td>11756.376</td>
<td>11517.708</td>
<td>85.39-122.01</td>
<td>102.1</td>
<td>24.5</td>
</tr>
</tbody>
</table>

The 90% CI for Cmax, AUC<sub>0-t</sub> and AUC<sub>0-inf</sub> were not within 80.00-125.00% range.

Discussions

- In this study, single oral-dose of Ritonavir 100 mg Capsule was compared to NORVIR® 100 mg Soft Gelatin Capsule of Abbott Laboratories, USA, in normal, healthy, adult, male human subjects under fasting condition.
- In this study the pharmacokinetic parameters of test formulation was compared with the reference formulation in normal, healthy, adult, male human subjects under fasting condition.
- From the individual concentration vs time curves and the pharmacokinetic profiles, it was observed that the rate and extent of absorption parameters i.e. C<sub>max</sub>, AUC<sub>0-t</sub> and AUC<sub>0-inf</sub> under fasting condition were found to be dissimilar for both reference and test treatment of Ritonavir.
- The 90% CI of Ratio estimates of Ritonavir Capsules 100 mg versus NORVIR® Soft Gelatin Capsules 100 mg were [81.19-117.08], [83.64-121.51] and [85.39-122.01] for C<sub>max</sub>, AUC<sub>0-t</sub> and AUC<sub>0-inf</sub>, respectively. All of these were within acceptable range of 80 to 125 % for C<sub>max</sub>, AUC<sub>0-t</sub> and AUC<sub>0-inf</sub>.
Conclusion

As per the 12 subject’s results, the test formulation - Ritonavir 100 mg Capsules was determined BIOEQUIVALENT to a single dose of reference formulation - NORVIR® 100 mg Soft Gelatin Capsules when both products were tested under fasting conditions in healthy, adult, human study participants.

Overall, a single dose of Ritonavir 100 mg Capsules and a single dose of NORVIR® 100 mg Soft Gelatin Capsules (Abbott), when given under fasting condition seem to have been equally tolerated by both groups comprising of 12 healthy, adult male human participants.

References

[5]. ICH Harmonized Tripartite Guideline; Guideline for Good Clinical Practice; E6 (R1); Current step 4 version dated 10 June 1996.
What Contributes to the Progression of Rheumatoid Arthritis?

Article by Abdirahman Hassan
PhD, Texila American University
E-mail: awale_hassan@hotmail.com

Abstract

Rheumatoid Arthritis is an autoimmune disorder and it is the most common autoimmune and inflammatory arthritis in adults (Helmetc, et al, 2008), the disease mainly affects joints of the body such as knees, hands and hips. The ideology of this inflammation is unknown (Fishman, 2010). However, there are several factors that mainly contribute to the initiation and the progression of the Rheumatoid Arthritis this include gender, age, environmental factors, malnutrition and genetic makeups. The disease occurs approximately 1% of the population. It is more common in women than the male; about 80% of the cases are seen on the population between the ages of 35-50 year (Fishman, 2010). The management intervention of this disease must be started sooner rather than later, the treatment should be widely comprehensive including pain management, reducing swelling and supporting the patients to receive proper treatment that aims to cure the disease and the condition. Radiographic image should be taken to evaluate the extent of the damages on joints. This study investigates the factors that contribute the progression of the Rheumatoid Arthritis.

Keywords: Rheumatoid Arthritis, Autoimmune disorder, inflammatory arthritis.

Introduction

Definition: Rheumatoid Arthritis (RA) can be defined as an autoimmune disease in which the body immune system mistakenly attacks itself and this autoimmune disease particularly targets synovial tissues, cartilage and bone and causes inflammation and stiffness in the joints and the tissues around. If the symptoms are persistent without intervention, the joint will get damaged and this will lead patients to disability if immediate treatment was not introduced; the most important symptoms for immune medicated arthritis are joint pain, swelling, heat and redness. It is obvious that rheumatoid Arthritis results abnormal inflammation to the joints but this not limited to joints and there are other parts and organs in the body that RA can have negative impact on it such as eyes, lungs and blood vessels and therefore the symptoms and signs varies and patients can show the following signs and symptoms such as loss of energy, low grade fever, weight loss and anaemia. The other signs that some patients showed can be rheumatoid nodule where lamp can be seen under the skin, this tumour is not cancerous.

In Rheumatoid Arthritis, there is no single sign or pattern of signs and symptoms that we can use as a measurement to diagnose this disease, the symptoms may varies in their nature and for some people severe and clear symptoms can be seen on particular time but on some occasions less obvious symptom presented by the patients. Likewise, some patients present symptoms on one joint on a time and bilateral on the other times and it is widely accepted by clinicians that, Rheumatoid Arthritis patients presents symptoms of being sick and tired and they might frequently show a degree of low grades of fever, as mentioned above mainly RA patients consider this disease chronic and they expect that its treatment will last longer and continues for life and therefore prolonged presence of RA will cause more damage to the joints and eventually this will lead to complete disability and deformation to the effected bones.
Figure 1. These figures show the early stages of bone deformation in RA patient.

**Rheumatoid arthritis epidemiology**

Epidemiologically, Rheumatoid Arthritis affects 1% of the population in general. However, Canadian people who affected by RA is about 16% of total population, approximately 4.2 million Canadians aged 15 or older are mainly current suffering RA (Figure. 1a).
Figure 1a. Prevalence of rheumatoid arthritis in Canadian populations

What causes rheumatoid arthritis?

Rheumatoid Arthritis is an autoimmune disease in which no known aetiology and causes have been identified. However, there are several factors that mainly contribute to the initiation and the progression of the Rheumatoid Arthritis this includes gender, age, environmental factors, malnutrition and genetic makeups and maybe other factors as previously stated.

Test and diagnosis

Patients with RA usually present with chief complain of pain and stiffness in many joints. The wrists, proximal interphalangeal joints, and metacarpophalangeal joints are main the parts of body where inflammation take place. Stiffness is severer in the morning and it might last for several hours. Clear swelling due to synovitis can be obvious and visible (Figure, 2and2a). During the medical examination synovial thickening is observable and also palpable on joint examination. Joint discomfort or arthralgia is common sign that patients present before the onset of clinically apparent joint swelling. Further sign and symptoms of weight loss, and low-grade fever, and fatigue may occur with active disease.

An attempt to create guideline to recognise the early symptoms to begin early intervention joint committee from the American College of Rheumatology and European League against Rheumatism collaborated to create new classification criteria for RA.

The aim of the new criteria are facilitation to diagnose RA earlier in patients who may not meet the 1987 American College of Rheumatology classification criteria and this joint criteria are formulated in 2010. These criteria will not involve or not included presence of rheumatoid nodules or radiographic erosive changes, because both of them are not present in early stage of RA.

The role of autoantibody

The presence of autoantibody is characterised as a presence of autoimmune disease but presence of rheumatoid factor is not represent the presence of autoimmune disease, but RF is one of the test ordered by the physician yet it not definitive answer for autoimmune disease since many other condition and disease can show high level of RF therefore Rheumatoid factor is not specific for RA and may be present in patients with other diseases, such as hepatitis C, and in healthy older persons.

As Szekanecz et al have stated that Anti-citrullinated protein antibody (ACPAs) was discovered as new serological marker for rheumatoid arthritis and (ACPAs) has grater sensitive and specificity and these characteristics plays important role in disease pathogenesis. Regarding molecular biology level and protein level in diagnostic laboratories and about 80% of rheumatoid arthritis patients are either
positive in Rheumatoid factor or ACPAs or both. Anti-perinuclear Factor (APF) and anti-keratin antibodies are the first autoantibody family that recognise citrullinated epitopes of filagrin.

In diagnostic process the presence and the absent of citrullinated proteins rheumatoid arthritis is important, discovery of citrullinated epitopes used as target for anti-filaggrin antibody facilitated the existence of generations of anti-citrullinated peptide antibody assays. Similarly, anti-CCP2 assays possess high diagnostic sensitivity and specificity, and they also show important predictive and prognostic value in RA (Synoms Et., al 2000).

Although, anti-Sa antibody was been identified many year ago, new scientific studies suggested that anti-Sa is linked to citrullinated vimentin, and therefore it is recognised as a member of the family of ACPAs. Likewise recently identified anti-mutated citrullinated vimentin (anti-MCV) assay showed the similar diagnostic performance with anti-CCP2 ELISA. In diagnostic process the combination of anti-CCP2 and anti-MCV assays showed high certainty to laboratory diagnostics of RA. It is clearly certain that ACPA family needs to expand and there are room for improvement to develop new strategies for RA diagnostics and treatment including designing and developing new cutting-age bioassays.

![Diagram](image)

**Figure 3.** Shows events take place in both Innate and Adaptive immune system and the process of antibody antigen interaction with inflammation process

To investigates the patient with suspected RA, physicians and medical team such as biomedical scientist need to perform series of tests, such as nuclear antibody test, particularly in juvenile forms of the disease. Other tests are of equal importance are CRP and ESR as they are the indicative methods for increase of RA, the level of theses test can used as a marker of activity and response to medication. Because RA is systemic disease that can affect any part of the body and it’s not affecting only joints, bones and muscles the investigation process needs to be well crafted and carefully planned process. Joint aspirations known as Arthrocentesis is done, where sterile syringe and needle is directly taken fluid from joints mainly knees and hand joins for double benefits, one being elevation of pain and the fluid to be analysed for further investigation. However, in some case a dose of cortisone is injected into effected joints by trained professions to reduce pain.

Normally after initial test is completed such as blood tests other diagnostic equipment are employed. Taking radiographic images of hands and feet should be performed to evaluate for characteristic of the bone damage. An X-rays is useful in the latter stage of RA and it can clearly show bone erosion and for further investigation and evaluation of the extent of the damage bone density scans, ultrasound and magnetic resonance imaging must be used.
Figure 3a & 3b. Shows the image of X-ray taken from RA patient.

Diagnostic procedure must be continues such as complete blood count (CBC) with differential, liver functions test (LFT) and renal function test (RFT) to avoid treatment that cause further damage to the patients with liver and kidney problems, this medication can include but not limited to non-steroid anti-inflammatory drugs (NSAID).

**Treatment**

The role of treatment comes after diagnosis procedure of Rheumatoid Arthritis is completed and the type of treatment and procedure must be agreeable between medical team and patient and the negatives and positives should be discussed including duration of the regimen, positive outcomes and drug side effects. Female patient must be given extra care and possible pregnancy must be ruled out. The main objectives of the treatment must not be intended the elevation of pain only. However, pain management, reducing swelling and preventing deformity is fundamental stages for effective RA treatment. The treatment should be comprehensive including pain management, reducing swelling and supporting the patients to receive proper treatment that aims to cure the disease of the conditions, radiographic image should be taken to evaluate the extent of the damages on joints.

Figure 4. The figure shows the difference between normal join, Osteoarthritis and Rheumatoid Arthritis

A group of drugs that are used to treat Rheumatoid Arthritis are the important medication available and this drug called Disease-modifying antirheumatic drugs (DMARDS) This drug helps patients with rheumatoid arthritis. Their main object is to decrease pain and inflammation. However, they are not painkiller but they change the underlying disease, rather than treating the symptoms. The reduction of the swelling and managing pain will slows down the progression of the disease and thus prevents joint damage. This drug can be divided into biologic and non-biologic, or biological and conventional nononcocal antibodies and recombinant receptors that block cytokines and promote the inflammatory
cascade that causes the symptoms of the Rheumatoid Arthritis are the examples of biologic DMARDs drug.

Table.1. the above table shows the approved biological DMARDs and related drugs in development

<table>
<thead>
<tr>
<th>Agent</th>
<th>Status</th>
<th>Properties</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infliximab</td>
<td>Approved</td>
<td>Chimaeric monoclonal antibody to TNF</td>
<td>First biological DMARD to be clinically tested; trials showed that TNF blockade is clinically effective short- and long-term.</td>
</tr>
<tr>
<td>Etanercept</td>
<td>Approved</td>
<td>Construct of TNFRII and the Fc portion of IgG1</td>
<td>Efficacy in RA comparable to infliximab used as a monotherapy or combination therapy.</td>
</tr>
<tr>
<td>Adalimumab</td>
<td>Approved</td>
<td>Human monoclonal antibody to TNF</td>
<td>Efficacy in RA comparable to infliximab used as a monotherapy or combination therapy.</td>
</tr>
<tr>
<td>CDP570</td>
<td>In study</td>
<td>PEGylated Fab fragment of CDP571, a humanized antibody to TNF</td>
<td></td>
</tr>
<tr>
<td>PEG-TNF-RI</td>
<td>In study</td>
<td>PEGylated form of soluble TNF-RI</td>
<td></td>
</tr>
</tbody>
</table>

**IL-1-blocking agents**

<table>
<thead>
<tr>
<th>Agent</th>
<th>Status</th>
<th>Properties</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anakinra</td>
<td>Approved</td>
<td>IL-1R antagonist</td>
<td>Clinically effective as a monotherapy and in combination with MTX.</td>
</tr>
<tr>
<td>IL-1 trap</td>
<td>Phase I</td>
<td>Construct of two IL-1R chains with an IgG-Fc domain</td>
<td></td>
</tr>
</tbody>
</table>

*See ONLINE TABLE 2 for a more detailed version, including adverse events. Years shown are those of the first approvals in a major pharmaceutical market. Anti-TNF therapies are described in REFES 61, 80-91; IL-1 blocking agents are described in REFES 92-96. DMARD, disease-modifying anti-rheumatic drug; IgG1, immunoglobulin G1; IL-1, interleukin-1; IL-1R, interleukin-1 receptor; MTX, methotrexate; RA, rheumatoid arthritis; TNF, tumour necrosis factor; TNF-R, tumour necrosis factor receptor.

The effect of these drugs might not been seen quickly and it usually takes several weeks to work for the patients. Although, there are number of DMARDs that are used for treatment of RA, it is important to mention one of these important drugs Methotrexate can be an excellent example. Methotrexate is the most frequently used drug for the treatment of the RA, and it has been on the market for decades and it’s the first-line prescription in patients with active rheumatoid arthritis, most the patients tolerate but there are number of side effects. Leflunomide is considered as the alternative to methotrexate but it has more gastrointestinal side-effects, similarly hydroxychloroquine is will elicit good affect when used as a mono-therapy, however, synergic drugs are more effective than mono-therapy but in most cases the combined drugs might show greater adverse effects. Tumour necrosis factor inhibitors (TNFi) belong to the group of biologic drugs that are the most studied and the first-line of biological therapy.
Table 2. Small-molecule DMARDs in clinical use

<table>
<thead>
<tr>
<th>Agent</th>
<th>First used</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gold salts</td>
<td>1920s</td>
<td>Relatively long period of administration before clinical effects are seen; rarely used today</td>
</tr>
<tr>
<td>Sulphasalazine</td>
<td>1940s</td>
<td>Second most common DMARD used in Europe during the 1990s</td>
</tr>
<tr>
<td>Antimalarials†</td>
<td>1950s</td>
<td>Less efficacious than other DMARDs, but also less toxic</td>
</tr>
<tr>
<td>Methotrexate</td>
<td>1950s</td>
<td>Gold-standard therapy</td>
</tr>
<tr>
<td>d-Penicillamine</td>
<td>1960s</td>
<td>One of the more toxic DMARDs; rarely used today</td>
</tr>
<tr>
<td>Azathioprine, mycophenolic acid</td>
<td>1960s</td>
<td>Some clinical benefit</td>
</tr>
<tr>
<td>Cyclosporine A, tacrolimus, sirolimus</td>
<td>1980s</td>
<td>Efficacious, but relative toxicity has precluded widespread use</td>
</tr>
<tr>
<td>Minocycline</td>
<td>1990s</td>
<td>Mildly beneficial</td>
</tr>
<tr>
<td>Leflunomide</td>
<td>1990s</td>
<td>Overall, has similar effects to sulphasalazine and methotrexate</td>
</tr>
<tr>
<td>Glucocorticoids</td>
<td>1950s</td>
<td>Rapid anti-inflammatory effects, but also qualities of DMARDs; however, have long-term side effects</td>
</tr>
</tbody>
</table>

*See ONLINE TABLE 1 for a more detailed referenced version. †Chloroquine, hydroxychloroquine. DMARD, disease-modifying antirheumatic drug.

Prescribing such medication to patients who are suffering a significant thrombocytopenia and those with renal failure must be evaluated by specialist in this field and benefit must outweighs the damage and safety of the patients must not be compromised. Several considerable studies concluded that the administration of the Methotrexate drug contraindicated in patients with hepatic disease, particularly hepatitis C, and those with significant renal impairment. Before using TNF inhibitor, as a biological therapy, tuberculin test must be performed to rule out TB. As reported by (ref) use of TNF inhibitor reactivates Hepatitis B.

**NSAIDS and corticosteroids**

The process and steps of treating the RA usually involves administrations of NSAIDs using the corticosteroids for controlling pain and inflammation. Using these medications should be in a short time and should not be used for long period.

**Complementary therapies**

There are very controversial idea that says malnutrition and the kind of food consumed can greatly contributes the RA, on the other hand there is another opinion supporting that some sort of mutations can passively decrease the effect RA and can be used as medication this maturation including vegetarian and Mediterranean diets.
Figure 5. This figure shows the sample of the food that RA patients need to consume to reduce the RA inflammation.

However, there is no enough evidence to support neither of the claims. Similarly, other unconfirmed studies indicate that acupuncture therapy helps and reduce tendency and pain in joints.
Several studies show that smoking is a genuine factor that increases the progression of the RA and physician must advise patients to quit or at least minimizing the quantity of cigarettes they consume per day, as this reduction can contribute and causes to slow the progression of the disease and enhance the quality of human life.
Exercise and physical therapy

Various studies show that moderate and regular exercise positively contributes the reduction of inflammation and thus improves the quality of life of Rheumatoid Arthritis patients. However, there is no evidence based results that concludes concrete relationship between the exercise and complete relief of the disease. Prescribing regular physical exercise has not been adopted yet. RA treatment is not timely respond medication and this might depend on the patient’s attitude, the mechanism of the treatment and drug intervention regimen chosen and the duration of the treatment.

The main object of management of RA in early disease is to reduce disease activity, to prevent loss of function, and to control joint damage. It is important to know that this procedure requires adequate time to achieve an expected outcome and through process with enough duration of time can be achieved positive results and the control for further damage to the bones and joints that were affected by RA.

Joint replacement

The option of joint replacement for Rheumatoid Arthritis patients comes after the control of disease progression, and other treatments are not showing satisfactory results or when there is structural damage to a joint or the tissues around it. There are several types of joint surgeries including total joint replacement. However, the most common ones are hip replacement, knee replacement, shoulder replacement and finger replacement. The orthopaedic surgeon will evaluate the damage and they should be satisfied that the joint replacement will be best option for the patients and this be bring pain relief and therefore movement will improved.

Discussion and conclusion

Rheumatoid Arthritis is an autoimmune disease that affects all joints particularly hips, knees hands and fingers(Figures 1, 1a, 1b) Public health practitioners in both UK and US stated that approximately 1% of adult population of United Kingdom and United States of America has this chronic disease (Luqmani, 2009). Over the past decades, Rheumatoid Arthritis affected negatively the life of many people around the world, and this hugely contributed the increase of disability of millions of people, resulting spending billions of pounds to support RA victims around the globe. However, these financial supports have greatly improved their socio-economic burden caused by this disease. Researchers have tried to invent and discover effective medicine, surgery and devices to support patients, in order to achieve acceptable outcomes.

To critically evaluate the scientific research done by experts of the field, did not achieve acceptable results. A number of research studies have suggested various types of interventions but again this intervention did not yield tangible results and the reason being, the approach was not well formulated and therefore, unnecessary time, effort, and financial means were spent unwisely. The study of the mechanism of autoimmune disease took many years as well, yet the exact biological mechanism is not fully understood. Pain management is very crucial but temporary pain relief without disturbing the resources of the inflammation is just tedious work without expectation of fruitful result. Failure to achieve acceptable outcomes is merely wasting time and resources. The aim and the object of any study that attempting discovery and development of new medication, device or surgery for RA is not only to halt and manage the pain temporarily. The least investigated approach to improve the well-being of the RA patients is prevention strategy, as said before, prevention is better than the treatment. Genetic predisposition is a valid factor, however, environment and food and lack of exercises also plays an important role in the prevalence of Rheumatoid Arthritis. The molecular understanding of RA is important for seeking answers of questions regarding the mechanisms of inflammatory responses, mechanisms of tissue destruction, genetic analysis and the effect of food consumed and malnutrition in general. Although some scientists arguing that there is a lot to be done about understanding of molecular mechanisms. On the other hand, there are well established immunologist who arguably stated that scientific development have achieved enough understanding of the mechanisms of cell communication and the regulation of immune responses, not only that but also the mechanism cell mediated immune responses and tissue injury, and the process of injury and cell damage. (Smith, 2002) concludes that the knowledge of cell process and communication is very satisfying and therefore effective treatment has been developed. In fact, the newer treatments represent the “tip of the iceberg,” says (Smith 2002).
Nevertheless, this scientific hypothesis is eventually an opinion that is not widely welcomed by the wide range of the scientific society, particularly immunologists and therefore, there is a lot to be done. The distance to the destination to reach conclusion is very far and rigorous research and development is important to celebrate the achievement of RA been eradicated or cured. Despite intensive research, the cause of this autoimmune disorder is mysterious. And for this reason the cells or gene factor that is responsible for the progression of RA is also remains elusive. However, several studies suggested that white blood cell specially macrophages plays particular important role in progression of the RA, we cannot rule out the vital roles that other inflammatory cells in the progression of this disorder (Fishman, 2010). As Fisher stated in the Synovium, macrophages are well able to present antigen and to activate T-cells and furthermore the infiltration of the macrophage in to the synovium will reflect with severity and the progression of the RA (Maruotti et al. 2007). Fisherman concluded that “Macrophage-derived cytokines, such as tumours necrosis factor alpha (TNF-a), appear to play a critically important role in the induction and perpetuation of the chronic inflammatory processes in rheumatoid joints as well as in the systemic manifestations of this disease” (Grossman and Brahn 1997).

References

Mechanism of Bacteriophage Lytic Enzyme in Phage Therapy against Streptococcal Infection by in Silico Approach

Article by Chethan Kumar S1, VinodKumar C.S2

1Research Coordinator, S. S. Institute of Medical Sciences and Research Centre, India
2Professor, Department of Microbiology, S. S. Institute of Medical Sciences and Research Centre, India

E-mail: chethan_kumar@outlook.com

Abstract

Lysins or Lytic enzymes of Bacteriophage are highly evolved molecules produced to release their progeny by hydrolyzing the bacterial host cell wall. Now days, due to Multi Drug Resistance in many streptococcal infections; this mechanism is exploited as an alternative therapy against traditional antibiotic therapy. But in the treatment of phage therapy the mode of action is still unclear in the literatures. This study will evidence the probable mode of mechanism by the lysin in the breakage of host cell wall by In Silico approach. 3-D structure of Lysin was retrieved from Protein Data Bank and structure of peptidoglycan is retrieved from the PubChem. Docking studies was performed using Hex 6.3 taking lysin as receptor and peptidoglycan as ligand. Results were visualized in PyMol molecular visualization software. Docking studies showed the hydrophilic interaction between the peptidoglycan and lysin. The interacting residue of lysin belongs to CHAP domain which is responsible for the amidase catalytic activity which results in the breakage of cell wall for the release of their progeny. Molecular interactions between the lysin and peptidoglycan showed the possible mechanism for lysin which is responsible for breaking the major bonds in peptidoglycan layer for the release of bacteriophage progeny inside the host bacterial cell. This study will give the further evidence for the mode of action and by understanding this mechanism further improved therapies can be achieved in the Multi Drug Resistance bacterial infections.

Keywords: Bacteriophage, Streptococcus spp, Multi Drug Resistance bacterial infections, Lysin, Peptidoglycan, Docking studies.

Introduction

With the rising prevalence of antibiotic-resistant bacteria\textsuperscript{1,2} alternatives to treatment with antibiotics are receiving increased attention. One such alternative is the possible therapeutic use of bacteriophages - viruses that parasitize and kill bacteria. When first discovered early in the previous century, the potential to use phage against pathogenic bacteria to cure infections, so-called “phage therapy”, was immediately grasped, but the emergence of antibiotics put this goal on the back burner\textsuperscript{3,4}. However, as multi-drug resistant bacteria have become an enormous public health problem, there is a renewed interest in phage therapy. At our centre, bacteriophages for MDR Staphylococcus aureus, Pseudomonas aeruginosa, Klebsiella pneumonia, Acinetobacter baumannii, Enterococci species, E.coli and Streptococcus species has been isolated and utility of these phages to rescue wound infections in animal model has been studied\textsuperscript{5-10}.

Bacteriophage typically encodes holins and lysins as part of their lytic system to achieve virus exit from the host bacterial cell\textsuperscript{11}. Holins are responsible for forming pores in the cytoplasmic membrane, following which lysins, having accumulated in the cytoplasm, are responsible for degradation of the peptidoglycan layer i.e., cell wall. Damage to this layer results in rapid cell rupture and concomitant virus release through loss of osmotic integrity. So lysins play a very important role in the lysis of bacterial cell
wall that results the potential therapeutic effect against multi drug resistant bacteria in foot infections of type II diabetes mellitus.

Lysins derived from phage that infect Gram-positive bacteria are generally composed of a single polypeptide consisting of an N-terminal catalytic domain and a C-terminal cell wall binding domain (CBD) held together by a short flexible linker [12]. In some rare cases, two or three catalytic domains may be linked to a single binding domain [13,14]. With few exceptions, the catalytic domain is usually represented by one of four families of peptidoglycan hydrolases: N-acetylmuramidases, N-acetylmuramidases (lysozymes), N-acetylmuramoyl-L-alanine amidases and endopeptidases [15].

The Streptococcal C1 phage lysine, PlyC, is the most potent lysine described to date. PlyC is furthermore unique among the Gram-positive lysins in that it consists of two separate proteins—a single 50-kDa PlyCA subunit that is suggested to form a complex with at least eight 8-kDa PlyCB subunits [16]. PlyCA is known to contain an active cysteine-histidine dependent amino hydrolases/peptidase (CHAP) domain, a fold distantly related to the papain-like cysteine-protease family, with Cys 333 and His 429 shown to be essential for amidase catalytic activity [16]. The PlyCB octamer is suggested to represent the CBD because purified material lacking the PlyCA subunit was able to specifically bind Streptococcus pyogenes, S. subris, S. equi, and groups C and E Streptococci, but not other bacterial species (i.e., Streptococcus agalactiae, and Streptococcus mutans) [16].

Materials and methods

The bacteriophage for Streptococcus pyogenes was isolated from different sources of water by the method of Smith and Huggins [17]. In vitro confirmation of bacteriophage activity was done on bacterial lawn, prepared on nutrient agar plates employing 1.0ml of 24hr culture by flooding and draining out the excess. Wells were dug into the agar by employing a sterile cork borer and the 20 µl phage suspension were loaded into each of the well. Sterile distilled water served as the control. The plates were incubated at 37°C for 24 hr. There after the zone of inhibition, if any, was recorded. The plaques if obtained were further passaged on the same target bacterial host and other members of the same genus to reconfirm its diversified activity [8].

Computational methods

To understand the replication process of bacteriophage, an In Silico method is approached to provide more evidence that how this will be achieved inside the host cell. The experimentally solved 3-Dimensional structure of Lysin is retrieved from the Protein Data Bank (http://www.rcsb.org/pdb/home/home.do) and Peptidoglycan is retrieved from the PubChem (http://pubchem.ncbi.nlm.nih.gov/). Peptidoglycan sdf extension file retrieved from the PubChem is converted into pdb using Open Babel software. Docking of Lysin and Peptidoglycan is performed using Hex 6.3 software and obtained result is visualized in PyMol software.

Results

Streptococcus phage isolated formed plaques on 88% of Streptococcus species isolated from diabetic foot infection specimens. The 3-Dimensional structure of Lysin was retrieved from Protein Data Bank bearing the PDB ID: 4F88 (Table 1, Fig 1), consists of 465 amino acid residues and Peptidoglycan was retrieved from PubChem bearing the accession number of CID 9816401 (Fig 1). The retrieved Lysin file consists of two complete PlyC molecules. One molecule was removed using PyMol software to perform docking studies. Docking studies revealed that oxygen atom of Peptidoglycan is showing hydrophilic interaction with hydrogen atom of Valine 388 in Lysin (Fig 2).

Discussion

The discovery of antibiotics was a leap in modern medicine. They have been able to stop the growth or kill many different kinds of microorganisms. However, bacteria have proven to be much more innovative and adaptive than we imagined and have developed resistance to antibiotics at an ever-increasing pace.
Bad practices and mismanagement have only exacerbated the situation. We could soon return to a state of medical health that was as dire as that which occurred prior to antibiotic use. The situation has reached such a decisive point that the World Health Organization (WHO) has cautioned of a return to a “pre-antibiotic era”. The bacteriophages used in animal experiments have proved that they can resolve wound infection effectively than antibiotics [6-10]

Docking study on phage and the host revealed that PlyC consists of two components. A catalytic subunit or domain called PlyCA and binding subunit or domain called PlyCB. The binding domain is responsible for binding in peptidoglycan layer whereas catalytic subunit is responsible for breakage of major bonds in peptidoglycan layer, results in bacterial lysis.

In PlyCA there are two distinct catalytic domains to achieve cell lysis. One is CHAP (Cysteine-Histidine-dependent Aminohydrolase/Peptidase) domain, residue ranges from 309 to 465 amino acids, responsible for amidase catalytic activity and second one is GyH (Glycosyl hydrolase) domain, residue ranges from 1 to 205 amino acids, responsible for glycosidase activity.

From this result, we can understand that the interaction showing amino acid residue Valine 388 lies in the CHAP domain and this domain is responsible for the amidase catalytic activity. Due to this catalytic activity, the breakage of major carbon-nitrogen bonds of the Peptidoglycan in the cell wall will occur. This results in the degradation of bacterial cell wall and facilitates virus egress from the host. This is how we can predict the bacterial infections are countered in the Streptococcal infections. The studies on utility bacteriophages reinforces that the phages could be used in a situations where there is no substitutes available for treating multi-resistant strains or as a valuable adjunct to antibiotics when the bacteria are still susceptible.

Conclusion

Molecular interactions between the lysin and peptidoglycan showed the possible mechanism for lysin which is responsible for breaking the major bonds in peptidoglycan layer for the release of bacteriophage progeny inside the host bacterial cell. This study will give the further evidence for the mode of action and by understanding this mechanism further improved therapies can be achieved in the Multi Drug Resistance bacterial infections.

Tables and figures

<table>
<thead>
<tr>
<th>PDB ID</th>
<th>Organism</th>
<th>Sequence ID</th>
<th>Amino acid residues</th>
</tr>
</thead>
<tbody>
<tr>
<td>4F88</td>
<td>Streptococcus phage C1</td>
<td>Q7Y3F1</td>
<td>465</td>
</tr>
</tbody>
</table>
Figure 1: Three-Dimensional structure of Lysin and Peptidoglycan
Figure 2. (a) Docking results of Lysin and Peptidoglycan, (b) Interaction between Hydrogen atom of Valine 388 and Oxygen atom of Peptidoglycan in cartoon representation

References


An Evaluation of Drug Dosage Calculation Knowledge and Proficiency among Newly Hired Nurses in Private Tertiary Care Hospital, Islamabad, Pakistan

Article by Nuzhat Sultana
Director Nursing Education Services, Shifa International Hospital Islamabad, Pakistan
Email: nuzhatsultana@hotmail.com

Abstract

Background: Drug dosage calculation and administration is an important function of nurses. The key professional role of nurses is to ensure safe drug dosage calculation while performing medication administration. Medication errors are a common cause of adverse events that may result due to wrong drug dosage calculation. The assessment of nurse's knowledge related to drug dosage calculation has not been conducted at the time of commencing their employment in the study hospital.

Purpose: The purpose of this study was to assess the drug dosage calculation knowledge and proficiency among our newly hired nurses before and after the training session.

Method and design: Participatory Action Research (PAR) approach was selected using pre and post -test to assess the newly hired nurse's knowledge and proficiency related to drug dosage calculation. Data was collected after IRB approval at private tertiary hospital, Islamabad, Pakistan.

Sample: Purposive sampling technique was adopted (n=135) all nurses on their commencement of employment from July 2016 to October 2016 participated in the study after the informed consent.

Findings: The study results showed the significant improvement in drug dosage calculation knowledge and proficiency among the study participants while comparing pre-test and post-test results.

Conclusion: The study concluded in the light of pre-test and post-test results that there is an intense need to review the nurse's drug dosage calculation knowledge and proficiency at the time of employment as nurses are key player in drug preparation and administration.

Keywords: Drug dosage calculation, conceptual skills in mathematics, proficiency, an evaluation of drug dosage, essential competency, dosage calculation knowledge, numeracy.

Introduction

Drug dosage calculation and administration is an important function of nurses. The key professional role of nurses is to ensure safe drug dosage calculation while performing medication administration. Literature indicates that medication errors are a common cause of morbidity and mortality that may results due to wrong drug dosage calculation (Cheragi, Manoocheri, Mohammadnejad, & Ehsani, 2013; Fleming, Brady, & Malone, 2014; Freedman et al., 2002; Shamsuddin & Shafie, 2012). Joint Commission 2008 report high lights medication safety considering it as global issue in patient care (Wright, 2010). The current literature warns that medication errors are most common mistakes worldwide that are threat to patient safety and resulting in escalation of mortality rate, length of hospital stay and related costs (Cheragi, et al., 2013). Further a literature review indicates that there is lack of research in the area of drug dosage calculation proficiency of the nurses that could lead to serious medication errors and threat to patient safety (Wright, 2010). Therefore, this study was planned with the purpose to assess the drug dosage calculation knowledge and proficiency among our newly hired nurses using pre-test and post test approach.

Study question

What is the level of knowledge and competence of newly hired nurses related to drug dosage calculation, as compared to before and after receiving the drug dosage calculation training module at Shifa International Hospital, Islamabad?
i. Are our newly hired nurses proficient in drug dosage calculation and conversion system for oral, intramuscular, intravenous and continuous intravenous infusions?

ii. Are our newly hired nurses skillful in micro and macro drug dosage calculation?

iii. Are our newly hired nurses accurate to calculate blood transfusion rate and inotropic infusions (lifesaving drugs)?

The study aimed to answer the above mentioned questions. The study results indicated the significant difference in nurse's knowledge and proficiency in drug dosage calculation as compared to before and after the intervention. The pre-test shows (n=40) 29.63% performed poor, (n=39) 28.89% achieved average score, (n=48) 35.56% of the nurses scored good or very good and very few (n=8) 5.92% achieved excellent scoring 40.5- <50. While in post-test (n=111) 82.22% achieved excellent and (n=58/111) 42.96% achieved 100% accuracy score.

Limitations of the study: The study sample was small and could not generalize the results. However, the implication of the study is in nursing practice, nursing education, nursing research and nursing administration that warrant future researches.

Literature review

Drug dosage calculation errors

Recent literature defines wrong drug dosage error as an inconsistency between the dose administered and the dose prescribed (Wright, 2010). Medication safety is a major concern and a global issue related to quality and safety of patient care (Savage, 2015; Shamsuddin & Shafie, 2012). A study conducted on economic measurement of medical errors in hospital setting reported that 44,000 to 98,000 medical errors cause serious adverse event every year in the United States (David, Gunnarsson, Waters, Horblyuk, & Kaplan, 2013). An empirical study identified that drug dosage calculation errors remained under- investigated and calls an immediate consideration for future studies (Wright, 2010).

Mathematical and dosage calculation proficiency is very important skill for nurses in order to ensure patient safety and delivery of quality care (Athanasakis, 2012; Cheragi, et al., 2013; Fleming, et al., 2014; Savage, 2015; Sulosaari et al., 2015; Wright, 2004). Recent review of literature reports that presently medication errors are focused in healthcare in the light of official reports in United States and the United Kingdom that highlighted the significant of medication errors occurring in hospitals. A study conducted to evaluate the drug dosage calculation proficiency of registered nurses on commencement of new employment reported that majority of the nurses lack the drug dosage calculation skill (Fleming, et al., 2014). A recent study conducted in Tehran, Iran reported that drug errors are a major problem in nursing care as medication errors are not reported by nursing staff, study suggested that nurse managers must encourage nurses to report medication errors timely (Cheragi, et al., 2013). A study conducted in Finland on drug dosage calculation proficiency among graduating nursing students found that one-fifth of the students failed the numeracy test due to poorly organized medication dosage calculation module (Grandell-Niemi, Hupli, & Leino-Kilpi, 2001).

Nurses training need for drug dosage calculation

A significant proportion of errors hint skill and knowledge deficiencies among nurses (Westbrook, Rob, Woods, & Parry, 2011).

In United Kingdom according to the audit commission National Health Service report (2001) adverse events due to medication errors resulted in nearly 20% of the deaths that requires immediate attention cited in (Shamsuddin & Shafie, 2012). Another study conducted in Australia also reported that the tutorial sessions enhanced the accuracy of students’ medication dosage calculation and understanding the application of correct formula and identifying errors of drug dosage calculation (Coyne, Needham, & Rands, 2013). A recent study indicated that drug dosage calculation skills among practicing nurses was greater than graduating nursing students. This study results also indicate that the nurses develop medication knowledge during the first year of practice therefore, the study suggest the need to put more emphasis for on-the-job-training in drug dosage calculation and pharmacological aspect to develop their competence (Simonsen, Daehlin, Johansson, & Farup, 2014). Literature further indicates that the most frequent type of drug calculation errors are resulted from
conceptual errors that needs the attention for nurses in-service education for drug dosage calculation (Blais & Bath, 1992).

Another study identified that the nursing students are not competent in the process of medication therapy both from their own and their clinical instructor's perspectives that calls an urgent need to take actions to strengthen the students’ skills in medication administration and dosage calculation (Zare, Purfarzad, & Adib-Hajbaghery, 2013).

The findings of several research studies have identified the lack of drug dosage calculation skills among nurses (McMullan, Jones, & Lea, 2010; Shamsuddin & Shafie, 2012; Sohrevardi, Mirjalili, Jarrahzadeh, Mirjalili, & Mirzaei, 2014; Tshiamo, Kgositau, Nsayagae, & Sabone, 2015; Westbrook, et al., 2011; Zare, et al., 2013) and threat to patient safety (Cheragi, et al., 2013; David, et al., 2013; Fleming, et al., 2014). A recent study identified lacking in nursing curricula that should develop the nurse’s competence in pharmacology and drug dosage calculation during the basic nursing training. The study results suggest that mathematical and conceptual drug dosage calculation skills “should be identified as a distinct competency in nursing curricula and continuing education program” p. 305 (Fleming, et al., 2014).

Adverse out-comes

Drug dosage miscalculation leads to medication errors that may result in serious adverse outcomes (Cheragi, et al., 2013; Fleming, et al., 2014). Presently health care reform in United states is taking positive initiatives in health policy and health care systems generally and specifically in hospitals while “Medicare has eliminated payments to hospitals for hospital- acquired conditions” p. 305 (David, et al., 2013).

Current literature indicates that drug dosage calculation is essential nursing proficiency that is so important to ensure patient safety and quality care (Athanasakis, 2012; Cheragi, et al., 2013; Fleming, et al., 2014; Shamsuddin & Shafie, 2012; Tshiamo, et al., 2015). A recent study indicates that main cause of medication errors caused due to lack of pharmacological knowledge and study further shows that there was no statistically significant relationships between medication errors and nurses years of working experience, age, and working shifts (Cheragi, et al., 2013). A study conducted in Malaysia to assess the knowledge level of nurses related to preparation and administration of drugs indicated that intravenous medications errors cause most of life threatening situations (Shamsuddin & Shafie, 2012). A recent study conducted in intensive care unit suggested that supervision to the nurses administering medications by more experienced ICU nurses in regular intervals is helpful in preventing medication errors (Agalu, Ayele, Bedada, & Woldie, 2012).

A study conducted in Norway showed nurses poor knowledge and highest mean risk of medication error calling the immediate attention as nurses regularly have complete responsibility for medication management and drug dosage calculation and administration (Simonsen, et al., 2014). current literature reports that there is evidence that deaths from medication errors have been on the rise (Aronson, 2009).

Empirical literature suggested that nursing training program should give high importance on drug dosage calculation skills (Shamsuddin & Shafie, 2012; Simonsen, et al., 2014). A recent study done in Australia indicated that intravenous drug administrations have a higher risk and severity of error than other medication administrations. A significant proportion of errors hint skill and knowledge deficiencies among nurses (Westbrook, et al., 2011).

Intravenous drug errors

Literature reports that 61% of serious adverse out-comes were associated with intravenous medication cited in (Shamsuddin & Shafie, 2012). A study conducted in Iran showed that the most common type of medication errors (34.26%) were linked with the intravenous injection doses faster than the recommended rate (Sohrevardi, et al., 2014). An observational study done in UK indicated that 265 intravenous (IV) drug errors were identified out of 483 drug preparations and 447 drug administration's (Taxis & Barber, 2003). A study conducted in Australia for continuous infusions of IV fluids (parenteral nutrition and non-electrolyte) identified that the most common errors observed were wrong administration rate (Han, Coombes, & Green, 2005). A study done in three countries UK,
Germany and French identified that wrong dilutions and wrong rate of infusion administration were observed frequently, study suggested that intravenous infusions must be considered as a high risk interventions. These findings call urgent attention to develop effective policy and procedures for safe intravenous infusion therapy (Cousins, Sabatier, Begue, Schmitt, & Hoppe-Tichy, 2005).

A study conducted in Malaysia reported that 61% of life threatening errors were linked with intravenous medications (Shamsuddin & Shafie, 2012). A recent study reported that medication errors had been made by 64.55% of the nurses while, 31.37% of the participants reported potential medication errors identified and caught on the edge of occurrence related to wrong dosage and infusion rate (Cheragi, et al., 2013).

Another study indicates that during the assessment of knowledge level related to drug administration skills found less than 50% of nurses able to calculate correct dosage of IV medications (Shamsuddin & Shafie, 2012). Adverse out- come occur among hospitalized patients, in United States medical errors has been estimated 3.7% to 16.6% of hospital admissions cited in (Freedman, et al., 2002). A recent study conducted in Norway showed nurses poor knowledge and highest mean risk of medication error calling the immediate attention as nurses regularly have complete responsibility for medication management and drug dosage calculation and administration (Simonsen, et al., 2014). current literature reports that there is evidence that deaths from medication errors have been on the rise (Aronson, 2009).

Empirical literature suggested that nursing training program should give high importance on drug dosage calculation skills (Athanasakis, 2012; Cheragi, et al., 2013; Fleming, et al., 2014; Savage, 2015; Shamsuddin & Shafie, 2012; Simonsen, et al., 2014; Tshiamo, et al., 2015). A recent study done in Australia indicated that intravenous drug administrations have a higher risk and severity of error than other medication administrations. A study conducted in Finland revealed that Practicing nurses (n = 62) were deficient with the skills they needed for accurate medication calculation, while 35% of the nurses achieved a score of ≥ 90 and most errors were made when calculating intravenous drug dosage calculations (Grandell-Niemi, et al., 2001).

**Methodology**

**PICOT** approach was used to address the issue of drug dosage calculation proficiency of nurses on commencing their employment as follow:

- **Problem**: A worldwide and well known Drug dosage calculation errors in hospital setting.
- **Population**: Newly recruited nurses at Shifa International Hospital, Islamabad, Pakistan.
- **Intervention**: Drug dosage Calculation Training Module
- **Comparison**: Pre-test and post-test.
- **Outcome**: Participants who scored 100 % in post-test micro and macro dosage calculation were privileged to administer medication via oral, intramuscular (IM), intravenous (IV) and continuous infusion therapy.
- **Time**: July 2016 to October 2016.

**Study design**

Participatory Action Research (PAR) approach was selected using pre and post test to assess the newly hired nurse's knowledge and skills related to drug dosage calculation. PAR is a teamwork between researcher and study participants in identification of the problem and finding its solution. The aim of PAR is realization and action including knowledge enhancement as researcher put efforts to empower study participants in developing and using new information (Polit & Beck, 2004).

**Setting**

The study was conducted in Shifa International Hospital, Islamabad, Pakistan that is 500 bedded private tertiary hospital comprised of more than 100 critical beds (medical and surgical including pediatrics and neonatal). Shifa International Hospital also provides special services like cardiac surgery, renal transplant, liver transplant, corneal transplant hip and knee replacement inclusive many more special services.
Sample

Purposive sampling technique was adopted (n=135) all nurses on the commencement of their employment from July 2016 to October 2016 were selected to participate in the study at Shifa International Hospital, Islamabad Pakistan. Using pre-test and post-test approach for drug dosage calculation module in Nursing Education services successful nurses were to be assigned in different clinical areas Emergency Room (ER), Medical wards (male and female), Surgical ward (male and female), Stroke unit, Intensive care units: (Medical ICU, Medical step down, Surgical ICU and Surgical step down).

Data collection

Data was collected after the approval of Institutional Review Board (IRB) and the informed consent of the study participants from July 2016 to October 2016. The study tool contained 6 components to assess micro and macro drug dosage calculation proficiency of the nurses carrying total 50 marks. According to our hospital policy the study participants were expected to achieve full marks 50/50 (100%) with no chance of error in drug dosage calculation to be privileged for medication administration. A recent literature cited many examples where nursing institutions pass nurses for medication administration even they achieved 70% score. Literature further argues that how 70% passing marks are acceptable when even small error may cause serious adverse event (Fleming, et al., 2014).

Study tool

A study tool taking before and after intervention approach assessed nurse's knowledge and proficiency for drug dosage calculation comprised of 6 components: metrics conversions, oral drug dosage, injections dosage, drips rate, blood and blood products rate and inotropic infusion related to life saving drug dosage calculations.

Questions in component 1: There were 10 questions to assess the metrics conversion skills carrying 1 mark each (total 10 marks). Question in component 2: contained 5 questions to assess oral dosage calculation carrying 2 marks each (total 10 marks). Question in component 3: comprised 5 questions to assess injections dosage calculation carrying 1 mark each (total 5 marks). Question in component 4: There were 5 questions for drip rate calculation carrying 2 marks each (total10 marks). Question in component 5: consisted 5 questions to calculate blood and blood products rate carrying 2 marks each (total 10 marks). Similarly, questions in component 6: There were 2 questions posed to judge the calculation skills in inotropic infusion related to life saving drug dosage calculation carrying 2.5 marks each (total 5 marks).

Internal and external validity of the tool was established by expert nurses 3 faculty members from Nursing Education Services and 5 on-board expert nurses working on clinical side. Pilot testing was done on 10% of the study sample that was excluded from the actual study. Conceptual framework teaching learning process: assessment, planning, implementation and evaluation was used to guide the study (Billings & Halstead, 2005).

Data collection procedure

Upon completing hiring process in Human Resource Department on 4th day all newly employed nurses joined Nursing Education Services for 3 weeks orientation program as part of routine. Every month average 30 to 35 new nurses are employed to catch the nurse’s shortage in the hospital. First day in Nursing Education Services all new nurses are pre-tested for their professional competencies and nursing knowledge including drug dosage calculation proficiency prior to commence the orientation program in Nursing Education Services department. The pre-test for drug dosage calculation was administered to each new group of nurses and based on pre-test results, 10 hours drug dosage calculation workshop (2 hours every day for 5 days) was conducted and each individual nurse was provided with rigorous exercises and examples of all types of drug dosage calculations under the close supervision of 2 nursing instructors and researcher to understand the concepts of micro and macro drug dosage calculations, standardized formulas and conceptual skills in mathematics. The study participants were provided with individualized assistance and coaching in addition to drug
dosage calculation practice, standard formulas and workbooks. Small group work and individual home assignments for practice were also provided with guided teaching resources. While post-test was administered when the study participants felt comfortable and ready to attempt.

Data analysis

Pre-test and post-test responses were analyzed using SPSS (version 16). Descriptive statistics were applied using t-test with alpha <0.05 for comparison between pre-test and post-test score.

Results

Demographic characteristics

The sample constituted of nurses (n=135) who recently joined study hospital and were inducted for orientation program. The socio demographic data of the study subjects were analyzed using descriptive statistics and were presented in terms of frequency and percentage. Majority of the participants (n=98) 72.6% were females, aged between 21-25 Years (n=104) 77.1%. Education wise most of the participants (n=133) 98.6% had General Nursing 3 Years Diploma most of them had additional one year specialty diploma in Midwifery/ ICU/ Cardiac/ Psychiatric/ Anesthesia/Accidental Emergency, while large number of participants (n=92) 68.1% were fresh graduates (Table 1).

<table>
<thead>
<tr>
<th>Variables</th>
<th>f</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>98</td>
<td>72.6</td>
</tr>
<tr>
<td>Male</td>
<td>37</td>
<td>27.4</td>
</tr>
<tr>
<td>Age</td>
<td></td>
<td></td>
</tr>
<tr>
<td>21-25</td>
<td>104</td>
<td>77.1</td>
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<tr>
<td>26-30</td>
<td>26</td>
<td>19.2</td>
</tr>
<tr>
<td>31-35</td>
<td>5</td>
<td>30.7</td>
</tr>
<tr>
<td>Education</td>
<td></td>
<td></td>
</tr>
<tr>
<td>BScN (4 years) / Post RN</td>
<td>2</td>
<td>1.4</td>
</tr>
<tr>
<td>General Nursing Diploma¹</td>
<td>133</td>
<td>98.6</td>
</tr>
<tr>
<td>Experience in Year</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fresh</td>
<td>92</td>
<td>68.1</td>
</tr>
<tr>
<td>1-3</td>
<td>38</td>
<td>28.3</td>
</tr>
<tr>
<td>4-6</td>
<td>5</td>
<td>3.6</td>
</tr>
</tbody>
</table>

¹ Additional One Year Specialization: Midwifery (97), ICU (6), Cardiac (11), Psychiatric (3), Anesthesia (3) Accidental Emergency (1).

Micro and macro drug dosage calculation proficiency data of 6 items was analyzed using SPSS (version 16). Descriptive statistics were applied using t-test with alpha <0.05 for comparison of pre-test and post-test score. Item 1: conversions part showed pre-test mean score 2.42 ±1.52 and post-test mean score 4.64±0.65. P-value < 0.05, paired t-test showed that the nurses gained significant knowledge after the education session. Item 2: oral dosage calculation showed pre-test mean score 5.31 ±3.19 and post-test mean score 9.60±0.96. P-value < 0.05, paired t- test found the significant enhancement of knowledge in post-test scores. Item 3: injection dosage calculation showed pre-test mean score 4.12±3.15 and post-test mean score 9.36±1.49, P-value < 0.05, paired t- test proved the significant increase in nurses knowledge in post-test. Item 4: drips rate calculation illustrate that pre-test mean score 2.30±2.11 and post-test mean score 4.65±1.08. P-value < 0.05, paired t- test observed that the nurses gained significant knowledge after the intervention of education session. Item 5: blood and blood product rate calculation showed pre-test mean score 4.12±3.89 and post-test mean score 8.92±2.50. P-value < 0.05, paired t- test established the significant improvement in nurses knowledge in post-test. Item 6: inotropes infusion rate calculation related to life saving drugs showed pre-test mean score 0.94 ±2.57 and post-test mean score 7.93±3.48. P-value < 0.05, paired t-test found the
significant enhancement of knowledge in post-test. While the overall paired t-test knowledge score in all 6 components achieved in pre-test by the respondents showed the mean score 19.21 ±16.43 and post-test mean score 45.01±10.16. P-value <0.05, Paired t-test revealed that the nurses gained significant knowledge after the education session (Table 2).

Table 2. Pre- test and post- test items wise scores (n135)

<table>
<thead>
<tr>
<th>Items question (Total marks)</th>
<th>Pre-test score</th>
<th>Post-test score</th>
<th>P-value (Sig. 2-tailed)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean ± Std. Deviation</td>
<td>Mean ± Std. Deviation</td>
<td></td>
</tr>
<tr>
<td>Metrics Conversions (10)</td>
<td>2.42 ± 1.52</td>
<td>4.64 ± 0.65</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Oral dosage calculation (10)</td>
<td>5.31 ± 3.19</td>
<td>9.60 ± 0.96</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Injections dosage calculation (5)</td>
<td>4.12 ± 3.15</td>
<td>9.36 ± 1.49</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Drips rate calculation (10)</td>
<td>2.30 ± 2.11</td>
<td>4.65 ± 1.08</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Blood and blood product rate calculation (10)</td>
<td>4.12 ± 3.89</td>
<td>8.92 ± 2.50</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Inotropic Infusion rate calculation (5)</td>
<td>0.94 ± 2.57</td>
<td>7.93 ± 3.48</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Overall score</td>
<td>19.21 ± 16.43</td>
<td>45.01 ± 10.16</td>
<td>&lt; 0.006</td>
</tr>
</tbody>
</table>

In overall pre-test (n=40) 29.63% received the score between 0-10 (poor) and (n=39) 28.89% of the participants received the score between 10.5 -20 (average). While (n=48) 35.56% of the participants scored between 20.5-40 (good and very good) and only few (n=8) 5.92% of the study participants scored 40.5-<50 (excellent). While in post-test the majority of the study participants (n=111) 82.22% received the score between 40.5- ≤50 (excellent) while (n=58/111) 42.96% achieve 100% accuracy score in safe drug dosage calculation. While some of the study participants (n=23) 17.04% scored 20.5-40 that is good and very good (Table 3).

Table 3. Distribution of overall knowledge scores (n=135)

<table>
<thead>
<tr>
<th>Knowledge Score</th>
<th>Pre-test f (%)</th>
<th>Post-test f (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Poor (0-10)</td>
<td>40 (29.63)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Average (10.5-20)</td>
<td>39 (28.89)</td>
<td>1 (0.74)</td>
</tr>
<tr>
<td>Good (20.5-30)</td>
<td>25 (18.52)</td>
<td>7 (5.19)</td>
</tr>
<tr>
<td>Very Good (30.5-40)</td>
<td>23 (17.04)</td>
<td>16 (11.85)</td>
</tr>
<tr>
<td>Excellent (40.5-≤50)</td>
<td>8 (5.92)</td>
<td>111 (82.22)(^1)</td>
</tr>
</tbody>
</table>

\(^1\) (n=58/111 achieved 100% accuracy in post test)

The analysis of score comparison qualification wise shows that there is no much difference in drug dosage calculation scores of the study participants acquiring general nursing 3 years diploma alone or having additional one year specialization courses as only few (n=7/121) 5.18% achieved pre-test score 40.5-<50. Pre-test score of nurses having 3 years nursing diploma (n=12) 8.8% also shows severe deficiency in drug dosage calculation skills that was significantly improved in post-test scores. However, BscN graduates (n=2) 1.48% performed much better in pre-test scoring 30.5-<50 who were also able to score 100% in post test. However, overall post-test scores improved significantly. (Table 4).
Table 4. Score comparison qualification wise (n=135)

<table>
<thead>
<tr>
<th>Score</th>
<th>BScN(^1) (n=2)</th>
<th>Gen. Nursing (n=12)</th>
<th>Gen. Nursing diploma Plus One year specialization (n=121)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Diploma</td>
<td>Midwifery</td>
<td>ICU</td>
</tr>
<tr>
<td>Pre-test</td>
<td>Post-test</td>
<td>Pre-test</td>
<td>Post-test</td>
</tr>
<tr>
<td>Poor (0-10)</td>
<td>-</td>
<td>6</td>
<td>30</td>
</tr>
<tr>
<td>Average (10.5-20)</td>
<td>-</td>
<td>2</td>
<td>30</td>
</tr>
<tr>
<td>Good (20.5-30)</td>
<td>-</td>
<td>2</td>
<td>19</td>
</tr>
<tr>
<td>V. Good (30.5-40)</td>
<td>1</td>
<td>2</td>
<td>16</td>
</tr>
<tr>
<td>Excellent (40.5-≤50)</td>
<td>1</td>
<td>2</td>
<td>8</td>
</tr>
<tr>
<td>Total</td>
<td>2</td>
<td>2</td>
<td>12</td>
</tr>
</tbody>
</table>

\(^1\) Post RN BScN + One year community nursing (n=1), Generic BScN (n=1)
Score comparison of the study participant’s experience-wise shows that there is no much difference in pre-test score between fresh graduate and experienced ones. While pre-test score shows that only few fresh nurses (n=4) 2.97% achieved 40.5-<50 score that is same for experienced ones. However, majority (n=134) 99.25% scored 20.5-≤50 that is good, very good and excellent level (Table 5).

Table 5. Score comparison with work experience of the study participants (n=135)

<table>
<thead>
<tr>
<th>Score</th>
<th>Fresh (n=92)</th>
<th>Experience</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pre-test</td>
<td>Post-test</td>
</tr>
<tr>
<td>Poor (0-10)</td>
<td>29</td>
<td>12</td>
</tr>
<tr>
<td>(%)</td>
<td>(21)</td>
<td>(9)</td>
</tr>
<tr>
<td>Average (10.5-20)</td>
<td>26</td>
<td>12</td>
</tr>
<tr>
<td>(%)</td>
<td>(20)</td>
<td>(9)</td>
</tr>
<tr>
<td>Good (20.5-30)</td>
<td>18</td>
<td>4</td>
</tr>
<tr>
<td>(%)</td>
<td>(13)</td>
<td>(3)</td>
</tr>
<tr>
<td>Very Good (30.5-40)</td>
<td>15</td>
<td>11</td>
</tr>
<tr>
<td>(%)</td>
<td>(11)</td>
<td>(8)</td>
</tr>
<tr>
<td>Excellent (40.5-≤50)</td>
<td>4</td>
<td>77</td>
</tr>
<tr>
<td>(%)</td>
<td>(3)</td>
<td>(57)</td>
</tr>
<tr>
<td>Total</td>
<td>(68)</td>
<td>(68)</td>
</tr>
</tbody>
</table>

The analysis of score comparison qualification wise shows that there is no much difference in drug dosage calculation scores of the study participants acquiring general nursing 3 years diploma alone or having additional one year specialization courses as only few (n=7/121) 5.18% achieved pre-test score 40.5-<50. Pre-test score of nurses having 3 years nursing diploma (n=12) 8.8% also shows severe deficiency in drug dosage calculation skills that was significantly improved in post-test scores. However, BscN graduates (n=2) 1.48% performed much better in pre-test scoring 30.5-<50 who were also able to score 100% in post test. However, overall post-test scores improved significantly. (Table 4).

Score comparison of the study participant’s experience-wise shows that there is no much difference in pre-test score between fresh graduate and experienced ones. While pre-test score shows that only few fresh nurses (n=4) 2.97% achieved 40.5-<50 score that is same for experienced ones. Inability to calculate accurate dosages contribute to serious medication errors cited in (Fleming, et al., 2014). However, in post-test majority (n=134) 99.25% scored 20.5-≤50 that is good, very good and excellent level (Table 5).

**Discussion**

Empirical literature highlighted the serious concern about nurse’s drug dosage calculation proficiency (Cheragi, et al., 2013; Fleming, et al., 2014; Shamsuddin & Shafie, 2012; Tshiamo, et al., 2015) and threat to patient safety (Cheragi, et al., 2013). There is lack of research in this area (Wright, 2010). Therefore, the current study was planned to evaluate the drug dosage calculation proficiency of registered nurses commencing employment.

Nursing Education Services at study hospital conducts drug dosage calculation proficiency pre-assessment of newly employed nurses that is part of three weeks orientation program as routine. As
Drug Dosage Calculation and Safe Medication Administration Certification is basic requirement for nurses before starting in clinical areas at Shifa International Hospital. This orientation package includes drug dosage calculation proficiency module as well.

The study participant were taken in to confidence and assured that this exercise is to assess their knowledge and skills related to drug dosage calculation as an essential skill required for nurses so, they should not worry in case they do not score pre-test adequately. They were explained that during work hours, well designed training module will be provided to them to develop their competence in drug dosage calculation enabling them for safe medication preparation and administration. In addition, confidentiality and individual respect and dignity were observed all the time.

The study participants were found to be very enthusiastic to learn the drug dosage calculation proficiency that motivated them for informed consent with the right to with-draw any time during the study. The study cohort verbalized that this is first time for them to attend such structured program to build their competence in drug dosage calculation. During the course of the program the study participants took high interest to learn the mathematical concepts and standardized formulas to be used for drug dosage calculation. However, the learning capacity and pace varied for each individual that was taken care of by the concerned faculty members to facilitate the cohorts in learning throughout the whole process. This part of the information corresponds with previous researches that drug calculation proficiency must be developed among nurses on practice side through in-service education (Fleming, et al., 2014; Shamsuddin & Shafie, 2012; Wright, 2010). Moreover, nursing curricula must address the nursing students need for capacity building in drug dosage calculation BscN level (Anthanasakis, 2012; Fleming, et al., 2014; Sohrevardi, et al., 2014; Sulosaa, et al., 2015; Tshiamo, et al., 2015).

The empirical literature supports that nursing curriculum needs to be reviewed for effective integration of drug calculation proficiency and pharmacological knowledge otherwise student may graduate from the program with-out acquiring drug dosage calculation knowledge and proficiency that is prime important for nurses role cited in (Tshiamo, et al., 2015) lack of teaching opportunities regarding drug dosage calculation for nursing students and in-service activities for practicing nurses cited in (Fleming, et al., 2014).

The current study identified that years of nursing experience and additional specialty diploma had no influence on the level of score achieved by the study participants. The study results are similar to previous study done in Malaysia (Shamsuddin & Shafie, 2012). In Pakistan this study result may be due to nurse's dependency on physicians that they receive calculated dosage prescriptions and they are system dependent in practice to verify such orders related to safe drug dosage calculation. However, this area needs further researches to identify the factual causes of knowledge and skill deficiency on nurses part related to drug dosage calculation. As literature supports that there is lack of research that medication errors are due to nurses poor numeracy skills (Fleming, et al., 2014).

While analyzing the main questionnaire comprised 6 components scenario based micro and macro drug dosage calculation suggested that item 1: conversions part that was based on 10 questions allocated 1 mark for each question showed pre-test mean score 2.42 ±1.52 majority of the study participants (n=104) 77% achieve the score 0-30 that shows lack of nurses drug dosage calculation skills. The study results are congruent with previous literature (Fleming, et al., 2014; Shamsuddin & Shafie, 2012). While post-test showed mean score 4.64±0.65. P-value < 0.05 and paired t- test showed that majority of the nurses (n=127) 94% achieved score 30-≤50 very good and excellent showing significant improvement after the drug calculation training. While item 2: oral dosage calculation was based on 5 questions allocated 2 marks for each question pre-test showed the mean score 5.31 ±3.19 while majority scored 0-30 and only (n=31) 22.96% scored 30.5-<50. Previous literature also indicated that nurses lack the drug dosage calculation skills (Cheragi, et al., 2013; Fleming, et al., 2014; Shamsuddin & Shafie, 2012). Post-test showed significant improvement of mean score 9.60±0.96. P-value <0.05 while paired t- test found the significant enhancement of knowledge among nurses after attending drug dosage calculation module.

Item 3: injection dosage calculation also contained 5 questions and allocated 1 mark for each question showed pre-test mean score 4.12±3.15 majority (n=104) 77% of the nurses scored 0-30 previous study support this result (Cheragi, et al., 2013; Fleming, et al., 2014; Shamsuddin & Shafie,
2012). While post-test showed mean score 9.36±1.49, P-value <0.05. Paired t-test proved the significant increase in nurse’s knowledge.

The results of Item 4: drips rate calculation contained 5 question that was allocated 2 marks each (total 10 marks) illustrate that the pre-test mean score 2.30±2.11 showing that majority (n=104) 77% scored 0-30. Similar studies suggested lack of nurses’ knowledge in drip dosage calculation (Cheragi, et al., 2013; Fleming, et al., 2014; Shamsuddin & Shafie, 2012). Post-test mean score improved 4.65±1.08. P-value<0.05 paired t-test observed that nurses gained significant knowledge after the intervention of drug dosage calculation session.

A study conducted in Australia for continuous infusions of IV fluids identified that the most common errors observed were wrong administration rate (Han, et al., 2005). A study done in three countries UK, Germany and French identified that wrong dilutions and wrong rate of infusion administration were observed frequently, study suggested that intravenous infusions must be considered as a high risk interventions. These findings call urgent attention to develop effective policy and procedures for safe intravenous infusions (Cousins, et al., 2005).

The study findings of item 5: related to blood and blood product rate calculation that was allocated 10 marks to 5 questions showed pre-test mean score 4.12±3.89 and post-test mean score 8.92±2.50. P-value < 0.05. Paired t-test established the significant improvement in nurse’s knowledge in post-test.

Item 6: inotropic infusion rate calculation related to life saving drug was allocated 5 marks for 2 questions that showed pre-test mean score 0.94 ±2.57 and post-test mean score 7.93±3.48. P-value < 0.05. Paired t-test found the significant enhancement of knowledge in post-test. Empirical literature supports continuing education of the nurses that help reducing medication errors and especially high teaching priority for the new and complex medications coming in the hospitals (Anderson & Townsend, 2010).

In overall pre-test (n=40) 29.63% showed Knowledge score poor (0-10) and (n=39) 28.89% of the participants showed knowledge score average (10.5-20), while (n=48) 35.56% of the participants obtained score 20.5-40 good and very good. However, only few (n=8) 5.92% of the study participants scored excellent 40.5<50.

While in overall post-test the majority of the study participants (n=111) 82.22% performed excellent and secured the highest score 40.5≤50; while (n=58/111) 42.96% achieve 100% accuracy score for safe drug dosage calculation and showing the significant impact of training session. In the study hospital newly hired nurses were assessed and given the opportunity to develop their competence in drug dosage calculation through this study as nurses’ drug dosage calculation proficiency is very important for patient safety and delivery of quality care. In addition, we can control preventable medication errors and adverse events by reducing the chance of error by developing nurses’ competence in drug dosage calculation. Moreover, we can make health care cost effective by shortening the length of stay in the hospital. Finally, we can gain public trust through provision of error free care or reduced medication errors rate.

The paired t-test knowledge score achieved by the respondents showed pretest mean score 19.21 ±16.43 and post-test mean score 45.01±10.16. P-value < 0.05, Paired t-test revealed that the nurses gained significant knowledge after the education session (Table 4).

All the study participants (n=135) who were graduated from the different nursing educational institutions from all over the country failed the numeracy pre-test and could not achieve the required accuracy level in drug dosage calculation. Only (n=2) 1.48% who had BscN degree achieved the pre-test score 30<50. However, the passing marks were 50/50 (100%) to reach the safe drug dosage calculation. However study participants failing in the pre-test were given 10 hours hands-on workshop along with practice questions and hospital drug dosage calculation protocol and guide as resource material to get themselves familiar with standard formulas to be used for accurate dosage calculations in different clinical situations. The training was facilitated by 2 nursing instructors and principal investigator.

The achievement of this study was that in post-test (n=58) 42.96% of the study participants achieved 100% accuracy for safe drug dosage calculation and privileged for medication administration. While majority of the nurses (n=77) 57% could not achieve 100 % accuracy in post-test. So they were advised to re-appear for another post test or to repeat the modular program
according to their comfort level until they reach to expected level of accuracy in drug dosage calculation. They were planned to be given extra time and support at their pace to help them to clarify difficulties and the key concepts involved in drug dosage calculation by arranging special tutorials. While these re-do results are not included in this study.

The study results suggested that at the commencement of employment nurses drug dosage calculation is extremely poor in the study hospital. It is very important for hospitals to assess this vital skill of nurses at the time of hiring. So, nurses lacking drug dosage calculation skills may be polished prior to assign them on clinical areas in order to ensure patient safety and quality care. This is most important area that is under investigated and warrants future researches (Wright, 2010). Drug dosage calculation knowledge and skill is essential competency for nurses that should be given high importance for in-service education and refresher trainings on regular basis. Similarly, Drug dosage calculation proficiency must be included in basic nursing curriculum so the newly graduate nurses acquire the knowhow of accuracy in drug dosage calculation once they join nursing jobs. The study findings supports that nursing curricula needs to be reviewed keeping in mind the importance of developing nurse’s competence in pharmacology and drug dosage calculation knowledge and skills. previous empirical researches also suggested that drug dosage calculation skills must be acknowledged as an essential competency in basic nursing training and continuing education program for practicing nurses (Athanasakis, 2012; Cheragi, et al., 2013; Fleming, et al., 2014; Shamsuddin & Shafie, 2012; Tshiamo, et al., 2015; Wright, 2010).

Test of significance

Null Hypostasis: Stated that mean score of pre-test = mean score of post-test
Alternative Hypostasis: Stated that mean score of pre-test ≠ mean score of post-test

The mean score of pre-test was 19.21 and the mean score of post-test was 45.01, so there was enough evidence to reject H0.

P-value for all the pre-test and post-test responses was calculated using t-test. In all of the components a significant difference was observed as all 2-sided significance value for the complete set of questions came out to be highly significant < 0.005.

Limitation

Limitation of the current study was a small sample size that comprised of only 4 month data. This would have been appropriate if data was collected at least over the 12 months period for generalization of the study findings. Although this study limits the generalization of the findings, the results supports the need for further research on a larger sample of the nurses commencing employment. A much larger study sample will validate the reliability and confirming the findings of this study.

Conclusion

In conclusion, nurses have vital responsibility to ensure safe drug administration to the patients. Several studies proved that nurses lack drug dosage calculation proficiency (Cheragi, et al., 2013; Fleming, et al., 2014; Shamsuddin & Shafie, 2012; Tshiamo, et al., 2015). The pre-test of current study statistically established that the study participants were deficient of knowledge and proficiency regarding drug dosage calculation at commencement of employment. However, the post-test statistically proved that structured education program was highly effective to improve the knowledge and skill related to drug dosage calculation among nurses at the time of commencing employment.

The study results also showed that years of experience has no influence on the level of score achieved by the study participants. It may be due to nurses are not provided with effective training opportunities related to drug dosage calculation in-spite of their vital role in medication administration. Low scores in nurse’s drug dosage calculation should be taken serious as such calculation errors and conceptual mistakes could cause life threatening medication errors or even deaths. In the light of current study it is recommended that drug dosage calculation skill must be considered key proficiency of the nurses that should be addressed aggressively in basic nursing curriculum as well as in-service education for on board nurses.
In addition, this important skill must be assessed at the commencement of nurse's employment and they should be provided adequate training related to drug dosage calculation knowledge and proficiency in the interest of patient safety.

Empirical literature suggested that there is prime need to understand the causes of medication errors through universal and standardized reporting mechanisms (Michaels et al., 2010).

Although the sample size was small and the study findings cannot be generalized even then study has the implication on nursing practice, education, administration and research. Further, interventional/experimental research is warranted on larger sample to generalize the findings of this study.

**Implication of the study**

**Nursing practice**

At the time of commencement of employment nurses must be assessed for this important proficiency related to drug dosage calculation and provide them chance to up-date their related knowledge. Moreover, on- board nurses should be highly supported to polish their drug dosage calculation proficiency on regular basis. Hospitals must have standardized mechanism in-placed for nurse's in-service education and training related to drug dosage calculation to ensure patient safety.

**Nursing education**

Basic nursing curriculum must provide more hours to develop drug dosage calculation skills among student nurses. Nursing faculty members must acquire drug dosage calculation proficiency so they are enabled to teach and mentor students effectively.

**Nursing administration**

The nurse administrator can make use of these study findings to encourage the nurses for evidence-based practice and also transfer the knowledge among the student nurses during their clinical placement. In addition, seminars and workshop can be organized to strengthen the knowledge base related to drug dosage calculation.

The findings of the study should be used in basic nursing curriculum as well as basis of in-service education programs for nurses so their knowledge regarding drug dosage calculation may be enhanced.

**Nursing research**

The research findings and research design may be used as an avenue in future researches. The nurse researchers can promote further research on same topic to develop the body of knowledge for generalization of these findings and diverse aspects of the research for further inquiry into the problem.

**Acknowledgement**

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c) IRB and hospital management for providing the opportunity to conduct this study

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Assessment of Prenatal Drug Prescription Pattern at Mbabane Government Hospital

Article by Mphumalanga Moyomuhle Vilakati¹, Sebenta Menon², Alemayehu Lelisa Duga³

¹, ² Swaziland Christian University
³Management Sciences for Health (MSH),

Email: mphumalangavilakati@gmail.com¹, sebentamenon@gmail.com², alexduga4@gmail.com³

Abstract

**Background:** Pregnancy is the time of profound physiological changes in a female’s body. Maternal drug use during pregnancy may pose a teratogenicity risk to the fetus. However, the fact that drugs are needed to mitigate the complications during pregnancy cannot be avoided, therefore, this study is designed to assess prenatal drug prescription pattern at Mbabane Government Hospital.

**Objectives:** Assess prenatal drug prescription patterns at the gynecology and maternity wards at Mbabane Government Hospital in Swaziland.

**Methodology:** A retrospective study was conducted at the maternity and gynecology wards at Mbabane Government Hospital from 3rd – 14th of July 2017. Data was retrieved from in-patient medical records.

**Results:** The study was done by enrolling 218 pregnant women. The most commonly prescribed drugs were the antimicrobial, NSAIDs, nutritional supplements, parenteral solutions and analgesics. The least prescribed were anticonvulsants. A high proportion were prescribed from US-FDA category B (42%), followed by category C (36%) and category A (9%). A small percentage of drugs (6%) were prescribed from drugs with positive evidence of risk (US-FDA category D) and (7%) were prescribed from drugs with proven fetal risk (category X).

**Conclusion/ Recommendations:** A considerable proportion of pregnant women were exposed to drugs, including those with positive evidence of risk and those with proven fetal risk. Healthcare providers must adopt the US-FDA risk category system when prescribing drugs to pregnant women.

**Keywords:** Prenatal; drug prescription pattern; US-FDA pregnancy category.

Introduction

**Background**

Prenatal period is associated with a range of pharmacokinetic and physiological changes which present physiological complications (Ramesh, et al, 2016).

Selection of the best medications to be used during prenatal period to manage disease states is posing challenges to the clinicians. Maternal medications can pose teratogenic risk to the fetus (Uchenna, et al, 2007). Few cases about stillbirths, premature births and babies born with deformities were reported and statistics by WHO states that in Swaziland stillbirth rate per 1,000 total births in 2009 was 18.0 and neonatal mortality rate per 1,000 births in 2013 was 29.8 (WHO, 2013).

A study from Ethiopia reported that the use of overall medications was found to be high during prenatal as well as antenatal period. 52.2% women had at least one prescription only medicines (POM) and over the counter (OTC) medications during pregnancy with the average number of 1.6±0.5 POM and 1.5±0.5 OTC medications respectively (Mohammed, et al, 2013).

Mohammed also mentioned that the prevalence and average number of medication used in the study is comparable with the results done in South Africa (59.3%), Egypt (86%) and Palestine (56%). In Ethiopia, higher proportion of Category-D medications was observed in the third (18.6%) and first (16.1%) trimesters as compared to the second (13.5%) trimester of pregnancy. Similarly, Category-X medications was used higher in third trimester (7.2%) and first (7.1%) trimester than second trimester (6.7%) of pregnancy (Mohammed, et al, 2013).
A study in Mumbai found the percentage that all pregnant women attending outpatient department (OPD) to receive folic acid and iron were; West-Africa (33.33%), Germany (54%), Nepal (72.8%) and Pakistan (79.4%) (Gawde, 2013). Gawde also reported that out of 760 prescriptions, only 292 prescriptions had drugs other than iron, folic acid and calcium lactate. Of 292 prescriptions only 50 prescriptions had drugs belonging to category A (17.1%), 189 (64.7%) prescriptions had category D. Majority of the drugs (apart from iron, folic acid, and calcium supplements) used during pregnancy were from category B, followed by category A and category C (Gawde, 2013).

A study in India reported that iron was prescribed only to 2.8% women in first trimester, 39.3% women in second trimester, 50% women in third trimester where folic acid was prescribed to 74.2%, 32.7% and 2% women in first, second and third trimester respectively (Reddy, et al, 2011).

**Objectives of the study**

**General objectives**

The aim of the study was to assess the prenatal prescription patterns and to identify commonly prescribed drugs and assess them according the US-FDA risk category system at Mbabane Government Hospital (MGH).

**Table 1.** US-FDA-pregnancy category classification system

<table>
<thead>
<tr>
<th>CLASS</th>
<th>DESCRIPTION</th>
</tr>
</thead>
<tbody>
<tr>
<td>Category A</td>
<td>Adequate and well controlled studies have failed to demonstrate a risk to the fetus in the first trimester of pregnancy and there is no risk in later trimesters.</td>
</tr>
<tr>
<td>Category B</td>
<td>Animal reproduction studies have failed to demonstrate a risk to the fetus and there are no adequate and well-controlled studies in pregnant.</td>
</tr>
<tr>
<td>Category C</td>
<td>Animal reproduction studies have shown an adverse effect on the fetus and there are no adequate and well-controlled studies in humans, but potentially benefit may warrant use of the drug in pregnant women despite potential</td>
</tr>
<tr>
<td>Category D</td>
<td>There is a positive evidence of human fatal risk (birth defects, etc.), but the benefits from use in pregnant women may be acceptable despite the risk.</td>
</tr>
<tr>
<td>Category X</td>
<td>Studies in human beings or animals have demonstrated fetal abnormalities or there is evidence of fetal risk based on human experience, and the fetal risk of using the drug in pregnant women clearly outweighs and possible benefit.</td>
</tr>
</tbody>
</table>

**Research methodology**

**Study area and period**

The research was conducted from May up to July 2017 at maternity and gynecology wards in Mbabane Government Hospital (National referral hospital). A retrospective study was conducted at the maternity and gynecology wards in MGH from the 3rd – 14th of July 2017.

**Population**

The target population was all pregnant woman who attended the maternity and gynecology wards in MGH from March to June 2017 and a random sampling method was used.

**Sample size:** The sample size for the study was determined based on the prevalence of drug use during pregnancy. According to a study done by Hanafy et al, 2016, the prevalence prescriptions drug use during pregnancy in Egypt was 83%. By using a single proportion formula taking the prevalence of the drug use during pregnancy as 83%.
Among prescribed. Classification and teratogenic more prescribed by US trimester, trimester antepartum was 8 were were of medicines, taken in incomplete abortion 43(19.7%), followed by ectopic pregnancy 12(5.5%), threatened abortion 8(3.7%) and antepartum hemorrhage 6(2.8%). In the second trimester incomplete abortion 32(14.7%) was the common maternal disorder, followed by pre-clampsia 18(8.3%), inevitable abortion 5(2.3%) anemia 4(1.8%) and urinary tract infection 4(1.8%). In the third trimester of gestation, pre-clampsia 24(11.0%) was the common maternal condition followed by urinary tract infection 10(4.6%), antepartum hemorrhage 3(1.4%), upper respiratory tract infection 2(0.9%) and eclampsia 1(0.5%), respectively (Figure 2).

The gynecology unit admitted the most pregnant women in first trimester (88%), followed by second trimester (86%) and (2%) in third trimester of gestation while the maternity unit admitted (45%) in third trimester, (2%) in second trimester and (0%) in first trimester of gestation.

US-FDA Pregnancy risk classification of medications

A majority of medications prescribed in pregnant women were from category B (41.8%) followed by category C (36.2%), category A (8.5%) category X (7.5%), and category D (6.0%), respectively.

A majority of category A medicines were prescribed at the first trimester (4.4%), followed by the second trimester (3.0%) and then the third trimester (1.1%). Category B had the highest medicines prescribed to pregnant women over all the other trimesters which were; the first trimester (18.1%) had more medicines, followed by the second trimester (16.8%) and the least was the third trimester (7.0). Category C; first trimester (17.6%), (14.3%) and (4.4%) respectively. A relatively high proportion of teratogenic medications from category D (3.2%) and category X (4.2%) were used highly during the first trimester. Second trimester category D and X prescription reduced to (1.0%), (2.9%) respectively and in the third trimester (1.7%), (0.4%) respectively.

Classification of medication category according to therapeutic uses

Among antimicrobials (32.6%): metronidazole (13.6%) and amoxicillin (11.6%) were frequently prescribed. Among NSAIDs (11.6%): diclofenac (9.1%) aspirin (1.9%) were frequently prescribed. Among nutritional supplements (10.0%): ferrous sulfate (3.1%), folic acid (3.0%) and multivitamins (1.7%) were frequently prescribed. Among parenteral solutions (9.6%): ringer’s lactate (6.6%) and normal saline (2.6%) were commonly given to pregnant women. Among exogenous hormones (6.4%): oxytocin (6.1%) was the frequently prescribed. Among analgesics (6.1%): paracetamol (5.0%) and tramadol (1.2%) were commonly given to pregnant women.

Among antihypertensive agents (6%): methyllopa (2.5%), nifedipine (2.4%), and hydralazine (1.0%) were frequently given to pregnant women. Among gastrointestinal drugs (4.2%): hyoscinamine

\[ n = \frac{z^2p(1-p)}{d^2} \]

\[ n = \frac{1.96^20.83(1 - 0.83)}{0.05^2} \]

n = 218 sample size
N: Desirable sample size
z: z value which is the standard deviation of 1.96% at 95% confident interval.
P: Proportion of prevalence of adherence of clinicians to US-FDA pregnancy category system (83% was taken from previous studies (Hanafy et al, 2016)).
d: Margin error on p, approximately 0.05.

Result and discussions

A total of 218 pregnant women were enrolled in the study. Majority of the patients were in age group of 30-34 years (25.7%), followed by 25-29 years (25.2%), 20-24 years (21.1%),15-19 years (7.8%), 40-44 years (6.4%) and the least group was >14 years (0.9%). All the age groups have a mean of 28.64 (SD=6.941) (Table 1). A majority of the patients in the study were in first and second trimesters 87 (39.91%) while in third trimester 44(20.18%) (Figure 1).

During first trimester, the maternal disorders most frequently recorded in the patient medical files were incomplete abortion 43(19.7%), followed by ectopic pregnancy 12(5.5%), threatened abortion 8(3.7%) and antepartum hemorrhage 6(2.8%). In the second trimester incomplete abortion 32(14.7%) was the common maternal disorder, followed by pre-clampsia 18(8.3%), inevitable abortion 5(2.3%) anemia 4(1.8%) and urinary tract infection 4(1.8%). In the third trimester of gestation, pre-clampsia 24(11.0%) was the common maternal condition followed by urinary tract infection 10(4.6%), antepartum hemorrhage 3(1.4%), upper respiratory tract infection 2(0.9%) and eclampsia 1(0.5%), respectively (Figure 2).

The gynecology unit admitted the most pregnant women in first trimester (88%), followed by second trimester (86%) and (2%) in third trimester of gestation while the maternity unit admitted (45%) in third trimester, (2%) in second trimester and (0%) in first trimester of gestation.
(2.9%), and metoclopramide (0.8%) were frequently prescribed. Among anesthetics (2.9%): ketamine (1.8%), and propofol (0.8%) were commonly prescribed to pregnant women. Among bronchodilators (2.0%): salbutamol (2.0%) was commonly prescribed. Among the steroids (1.8%): dexamethasone (1.3%) was prescribed frequently. Among sedatives and hypnotics (1.6%): midazolam (1.6%) was prescribed frequently. Medicines that were not commonly prescribed among the total of 1190 medicines were the diuretics (0.5%), anticonvulsants (0.4%) and antihistamines (0.2%).

Number of drugs per prescription

Prescriptions with 6-10 medicines (57.8%), followed by those with 1-5 medicines (39.9%) and the least were those with 11-15 medicines (2.3%). The mean was 1.62, SD was 0.531 and the range was 2 and average was 6.5.

Table 2. Age wise distribution of prenatal women (N=218)

<table>
<thead>
<tr>
<th>Frequency</th>
<th>Percent</th>
<th>Valid Percent</th>
<th>Cumulative Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>14 and below</td>
<td>2</td>
<td>.9</td>
<td>.9</td>
</tr>
<tr>
<td>15-19</td>
<td>17</td>
<td>7.8</td>
<td>7.8</td>
</tr>
<tr>
<td>20-24</td>
<td>46</td>
<td>21.1</td>
<td>21.1</td>
</tr>
<tr>
<td>25-29</td>
<td>55</td>
<td>25.2</td>
<td>25.2</td>
</tr>
<tr>
<td>30-34</td>
<td>56</td>
<td>25.7</td>
<td>25.7</td>
</tr>
<tr>
<td>35-39</td>
<td>28</td>
<td>12.8</td>
<td>12.8</td>
</tr>
<tr>
<td>40-44</td>
<td>14</td>
<td>6.4</td>
<td>6.4</td>
</tr>
<tr>
<td>Total</td>
<td>218</td>
<td>100.0</td>
<td>100.0</td>
</tr>
</tbody>
</table>

Figure 1. Trimester variations among pregnant women
Figure 2. Distribution of diagnosis in the three trimesters.

Figure 3. US-FDA pregnancy risk classification of medications.

Table 3. Frequency distribution of FDA drug category of the drugs prescribed during prenatal admission.

<table>
<thead>
<tr>
<th>US-FDA category system</th>
<th>Trimester 1</th>
<th>Trimester 2</th>
<th>Trimester 3</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. %</td>
<td>No. %</td>
<td>No. %</td>
<td>No. %</td>
</tr>
<tr>
<td>A</td>
<td>53 4.4</td>
<td>36 3.0</td>
<td>13 1.1</td>
<td>102 8.5</td>
</tr>
<tr>
<td>B</td>
<td>215 18.1</td>
<td>200 16.8</td>
<td>83 7.0</td>
<td>498 41.8</td>
</tr>
<tr>
<td>C</td>
<td>209 17.6</td>
<td>170 14.3</td>
<td>52 4.4</td>
<td>431 36.2</td>
</tr>
<tr>
<td>D</td>
<td>38 3.2</td>
<td>12 1.0</td>
<td>20 1.7</td>
<td>70 6.0</td>
</tr>
<tr>
<td>X</td>
<td>50 4.2</td>
<td>34 2.9</td>
<td>5 0.4</td>
<td>89 7.5</td>
</tr>
</tbody>
</table>
The results of the study showed that out of 218 pregnant women 126 (57.8%) received 6-10 drugs, followed 87 (38.9%) received 1-5 drugs and the least were 5 (2.3%) who received 11-12 drugs. The average of drugs per prescription in this study was 6.5 which is much higher than WHO recommended standard which is 2.0 per prescription. The findings are almost similar with a study conducted in Saudi-Arabia which showed an average of 4.17 drugs per prescription. This is contrasted with a study conducted in Pakistan which showed an average of 1.66 drugs per prescription (Al-Humayyid et al, 2016). A study in USA showed an average of 2.2 per prescription whereas a study in Italy showed an average of 1.8 (Daw et al, 2011).

One reason for the higher number of drugs per prescription was that all of included women were inpatient and they stayed at least 4 days in the gynecology and obstetrics wards. In addition, a quarter of admitted pregnant women had at least one disease and thus this average. Despite this, keeping the mean number of drugs per prescriptions as low as possible is always preferable to reduce the risk to the fetus and the mother also.

Classification of medication categories according to pharmacological classes

Almost all pregnant women who were admitted at the gynecology and obstetrics wards were prescribed antimicrobials (32.6%) especially metronidazole (13.6%) and amoxicillin (11.6%). The next group of commonly prescribed drugs during pregnancy were the NSAIDs (11.6%) mainly diclofenac (9.1%). These two groups were followed by nutritional supplements (10.0%) (Ferrous sulphate (3.1%) and folic acid (3.0%), exogenous hormones (6.4%) (Mainly oxytocin (6.1%) analgesics (6.1%) (Especially paracetamol (5.0%). A similar study was conducted in Ethiopia reported that a majority of drug prescribed to pregnant women were the antimicrobials such as amoxicillin, metronidazole, followed by NSAIDs and nutritional supplements (Mesfin et al, 2015) and also a study conducted in France showed an increase in the prescription of antimicrobials (42%) (Daw et al, 2011).

In contrast, a study conducted in Ethiopia reported that anti-emetics and anti-infectives were the commonly prescribed drugs. This was followed by analgesics especially, paracetamol (6.5%) and NSAID (diclofenac (5.09%) (Kasaye et al, 2015) and another study in Ahmedabad reported that iron salts (78.2%), calcium (77.1%) and folic acid (46.3%) were frequently prescribed drug groups followed by uterine relaxants (24.4%), nutritional preparations (18.5%), antiemetic drugs (14.3%) and antimicrobial agents (11.9%) and others (Harsh, et al, 2012).

This variations in drug groups in prescribing during pregnancy could be due to the fact that diseases vary in different countries. Despite this variation of diseases in countries, intensive assessment of pharmacotherapy given to pregnant women should be done with respect to the US-FDA risk category, the gestational period and the risk-benefit balance of a drug before its prescription so as to prevent fetal harm.
US-FDA pregnancy risk category of medications

This study revealed that 41.8% of medication frequently prescribed during pregnancy were from category B followed by category C (36.2%), category A (8.5%), category X (7.5%) and category D (6.0%). The present findings are comparable with a study conducted in Egypt which showed that category B (41.3%) and category C 30.2% were the most prescribed, then followed by category A (12.1%), category X (0.9%) and category D (0.5%) (Hanafy et al, 2016).

This study is comparable to a study conducted in Oman which have reported that category B and category C medicines were frequently received by pregnant women, this is also similar to a study in USA which showed some pattern where category B (50.0%), followed by category C (37.8%), category A (2.4%) were frequently prescribed (Al-Hamim et al, 2016). However, this study is contrasted with studies where category A, B and C were commonly prescribed drugs. For example, a Nigerian study reported that category A drugs (48.1%) were frequently prescribed, followed by (25.7%) category B, (17.2%) category C and D (5.0%) (Uchenna, et al, 2007). A study by Reddy et al also contrasted the finding of the study in that he reported that a majority of drugs used, were from category A, followed by category B and category D. However, category C and X drugs constituted 2.90 % and 5.71% of drugs used during the third trimester and first trimester, respectively (Reddy, et al, 2011).

Most of public literature shows category D and X as the least prescribed drugs. However, a higher percentage of teratogenic medicines (category D 6.0% and category X 7.5%) were highlighted in the current study, which are considered contraindicated in pregnancy. This was caused by higher admissions due to women being diagnosed with an incomplete abortion, inevitable abortion and missed abortion. The Standard Treatment Guideline (STG) of Swaziland states that in either cases if the risk outweighs the benefit oxytocin (category X) must be prescribed for abortion (STG, 2012).

The current study has not deviated from the study in Ethiopia, which reported that higher proportion of Category-D medications were observed in the third (18.6%) and first (16.1%) trimesters as compared to the second (13.5%) trimester of pregnancy. Similarly, Category-X medications was used mostly in third trimester (7.2%) and first (7.1%) trimester than in the second trimester (6.7%) of pregnancy (Mohammed, et al, 2013). In the Ethiopian study it was also reported that 4% of the pregnant women were prescribed drugs form category D and X whereas a study conducted in Taiwan found that 1.1% were from category D or X drugs 0.6% (Kabed et al., 2009). It is estimated that 3.9-4.6% of the pregnant women in the USA receive category D and X drugs (Andred et al, 2008). This variation is due to the different diseases that women presented during pregnancy.

In the current study, there was a significant decrease in prescribing of category A drugs over the three trimesters (4.4%, 3.0% and 1.1%) respectively. This is due to the fact that these are mainly vitamins and minerals and it is known that in gynecology practice the need of vitamins and minerals decreases as the pregnancy is advancing.

Trends of medication use across pregnancy trimesters

A reduction in the trend of medication use across the trimesters was demonstrated from 39.9% in first trimester and 39.9% in second trimester and 20.2% in the third trimester. This indicates that most of pregnant women participated in the study were mostly in first and second trimester and prescribers were not reluctant to prescribe medication during the first and second trimesters of pregnancy.

The current study is comparable to a study conducted in Egypt where trends of medication use decreased across the trimester; where in the first trimester was 54.0%, 35.4%, 10.6% in second and third trimester, respectively (Hanafy et al, 2016). However, the current study is contrasted with a study conducted in Ethiopia which declared an increased trend in medication use from first trimester 19.2%, to second 26.7% and third 54.0% trimesters (Mohammed et al, 2013). Mohammed suggested that the reason for the increase of use of medications across pregnancy trimesters could possibly be because the majority of pregnant women were in the third (57.2%) and second (26.3%) trimester of pregnancy, respectively (Mohammed et al, 2013).

Different medical conditions over the three trimesters

During first trimester, the maternal disorders most frequently recorded in the patient medical files were incomplete abortion 43(19.7%), followed by ectopic pregnancy 12(5.5%), threatened abortion
8(3.7%) and antepartum hemorrhage 6(2.8%). In the second trimester of gestation incomplete abortion 32(14.7%) was the common maternal disorder, followed by preeclampsia 18(8.3 %), inevitable abortion 5(2.3%) anemia 4(1.8%) and urinary tract infection 4(1.8%). In the third trimester of gestation, preeclampsia 24(11.0%) was the common maternal condition followed by urinary tract infection 10(4.6%), antepartum hemorrhage 3(1.4%), upper respiratory tract infection 2(0.9%) and eclampsia 1(0.5%)

Unlike other studies where nausea and vomiting were encountered in first trimester and mostly UTIs in the second trimester. For example, a study in Ahmedabad contrasted the findings in that it reported that common complaints of women coming to the hospital were abdominal pain (13.8%), vomiting (12.4%), fever (7.5%), cough (3.4%), urinary tract infections (2.7%), and discharge per virginia (2.6%) (Harsh, et al, 2012). A survey conducted in Western Nepal reported that a problem oriented drug use was due to nausea and vomiting (4.7%), dyspepsia (3.1%) and per virginal spotting/bleeding (3.4%), mainly (Sarker et al, 2013).

These study differs from mine, which presented incomplete abortion and ectopic pregnancy in the first trimester, pre-clampsia and urinary tract infections in the second trimester of pregnancy.

This could be due to that the current study included in-patients only and most of them were pregnant women admitted in the gynecology ward (79.82%) and from previous studies it had been noticed that there were little or no incidences where pregnant patient presenting nausea and vomiting were admitted in gynecology unit but only for serious medical conditions.

**Conclusion and recommendations**

Findings of my study showed that all admitted pregnant women were commonly prescribed category B and C medicines, followed by category A, X and D, respectively. However, approximately a quarter of pregnant women were prescribe category D and X which are thought to cause possible fetal harm. Thus, such inappropriate prescription of drugs should not be underestimated since it affect the life of both the mother and the fetus. Therefore, intensive assessment of pharmacotherapy given to pregnant women should be done with respect to the US-FDA risk category, the gestational period and the risk-benefit balance of a drug before its prescription. The prescribing trends among prescribers for pregnancy is more or less rational, but there is a lot to be improve. The lack of awareness in respect to drug prescription and use should be improved with the proper implication of information, education and communication.

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Texila American University Ltd,
Unit T 1/F, Mau Lam Comm Building,
16-18 Mau Lam Street, Jordan,
Kowloon, Hong Kong.
E-mail: ejournal.assist@tau.edu.org
Skype: texila.aco32
Whatsapp: +918056580933