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Compare the Effect of Thiopental and Propofol on Neonatal and Maternal Outcomes after Caesarean Section: Anon-Systematic Review

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Abstract

Background: obstetric anaesthesia recommends that caesarean sections are done under regional anaesthesia, but there are conditions for which regional anaesthesia is contraindicated, so in those conditions general anaesthesia is the only choice.

For general anaesthesia thiopental 4-5mg/kg l and propofol 2,5mg/kg are both used for caesarean section.

Methods: we have reviewed articles from 1989 up to 2016 comparing the use of thiopental to propofol in caesarean sections.

Result: a total of 20 published articles and abstracts from 1989 up to 2016 were reviewed. These articles show that propofol was the best alternative drug for general anaesthesia induction in caesarean section and has few disadvantages according to the neonate Apgar score at one minute.

Conclusions: these articles reviewed show that propofol is currently the most commonly used induction agent and alternative for obstetric general anaesthesia and has better neonatal and maternal outcomes post operation than thiopental.

Keywords: *propofol, obstetric anaesthesia, thiopental, caesarean section*

Introduction

Currently more caesarean sections are done under regional anaesthesia than general anaesthesia. The use of regional anaesthesia is increasing because of failed intubation (Dyer RA 2011) and it has good post-operative analgesia. Currently the use of general anaesthesia in caesarean sections is less than 5% of caesarean deliveries in the United States and United Kingdom (Gilbert J Gran, up to date).

The type of anaesthesia in C/S depends upon the caesarean section indication.

The study compared the effect of thiopental and propofol on neonatal and maternal outcomes. Thiopental and propofol are used for induction in GA for C/S. The purpose of the study was to find which one is the best induction drug in caesarean sections.

Literature review

Introduction

A study done comparing the effect of thiopental and propofol on the Apgar score was done in Uganda at Mulago National Referral Hospital and concluded that there was no significant difference between the two drugs used for induction in women undergoing general anaesthesia for a caesarean section (Tumukunde et al. 2015).

Another study done on pregnant women showed that there is some evidence that propofol may exert neuro developmental effects in animals but the effect on a developing human fetus is not clear (McKenzie 2015). Many anaesthetists use propofol for C/S at a dosage of 2.8mg/kg but a previous study done showed that there is no advantage to neonates in using propofol (Dyer 2011).

Thiopental is no longer available in many western countries. Propofol is the alternative. In China thiopental is not available and ketamine was recommended as the drug of choice for induction in caesarean sections by the Obstetric Anaesthesia Society (Huang, Gao 2016).

Thiopental has been used routinely for caesarean sections since 1930 as an anaesthetic induction agent. It has disadvantages such as hypotension and a potentially reduced Apgar score.

Propofol is widely used for the induction and maintenance of anaesthesia for other types of surgery, but not for caesarean section.

Agents used in general anaesthesia

Intravenous induction drugs

These are drugs that, when given intravenously in an appropriate dose, cause a rapid loss of consciousness. This is often described as occurring within "one arm-brain circulation time", which is simply the time taken for the drugs to travel from the site of injection (usually the arm) to the brain, where they take effect. They are used:

- To induce anesthesia prior to other drugs being given to maintain anesthesia.
- As the sole drug for short procedures.
- To maintain anesthesia for longer procedures by intravenous infusion.
- To provide sedation.

The concept of intravenous anesthesia was born in 1932, when Wesse and Schrapff published their report on the use of hexobarbitone, the first rapidly acting intravenous drug. Two years later in 1934, sodium thiopental was introduced into clinical practice by Waters and Lundy, and it is still widely used today. A number of other drugs have come since then. The commonest drugs currently in use can be classified according to their chemical structure and include:

- Barbiturates
- Phenols
- Imidazoles
- Phencyclidines
- Benzodiazepines

Barbiturates and phenols will be discussed below.

Pharmacokinetic

On entering the blood stream, a percentage of the drug binds to the plasma proteins, with the rest remaining unboundor "free". The degree of protein binding will depend upon the physical characteristics of the drug in question. These include lipid solubility and degree of ionization. The drug is carried in the venous blood to the right side of the heart, through the pulmonary circulation, and via the left side of the heart into the systemic circulation. The majority of the cardiac output passes to the brain, liver and kidney (often referred to as "vessel rich organs"); thus a high proportion of the initial bolusis delivered to the cerebral circulation. The drug then passes along a concentration gradient from the blood into the brain. The rate of this transfer is dependent on a number of factors:

- The arterial concentration of the unbound free drug
- The lipid solubility of the drug
- The degree of ionization.

Unbound, lipid soluble, unionized molecules cross the blood-brain barrier the quickest.

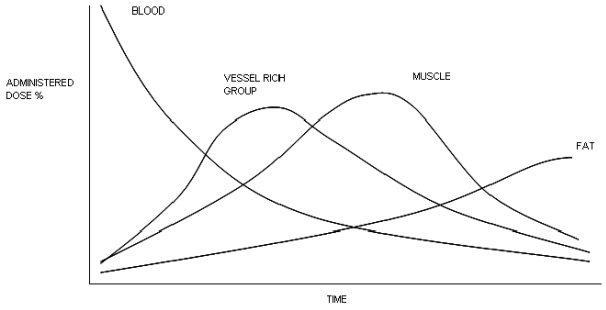
Once the drug has penetrated the CNS tissue, it exerts its effects. Like most anaesthetic drugs, the exact mode of action of the intravenous drugs is unknown. It is thought that each drug acts at a specific receptor – GABA-A, NMDA and acetylcholine receptors have all been studied as potentials it esofaction.

Following the initial flooding of the CNS and other vessel-rich tissues with non-ionized molecules, the drug starts to diffuse through other tissues that do not have such a rich blood supply. This secondary tissue up take, predominantly by skeletal muscle, causes the plasma concentration to fall, allowing the drug to diffuse out of the CNS down the resulting reverse concentration gradient. It is this initial redistribution of the drug in to other tissues that leads to the rapid awakening seen after a single dose of an induction drug. Metabolism and plasma

clearance have a much less important role following a single bolus, but are more important following in fusions and repeat doses of a drug.

Fat makes little contribution to the early redistribution of free drugs following a bolus due to its poor blood supply (vessel-poor tissues), as seen on the diagram below. However, following repeat doses or in fusions, equilibration with a dipose tissue forms a drug reservoir, often leading to the delayed awakening we observed most with obese patients.

Drug distribution in various tissues against time following an iv bolus of thiopental



Effect on cardiac output

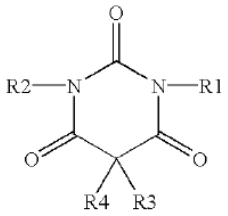
In the case of patients in shock, cesare an section (due to physiological changes), and elderly patients, cardiac output is reduced and the body compensates by diverting an increased proportion of cardiac output to the cerebral circulation in order to preserve cerebral blood flow. Thus a greater proportion of any given drug will enter the cerebral circulation. In these situations, the induction drug dose must always be reduced. Furthermore, as global cardiac output is reduced, the time taken for an induction drug to reach the brain and exertits effect is prolonged. The slow titration of a reduced drug dose is the key to safe induction in these patients.

Properties of intravenous induction drugs

1. Physical properties
   - Water soluble and stable in solution
   - Stable on exposure to light
   - Long shelf life
   - No pain on intravenous injection
   - Painful when injected in to an artery
   - Non-irritant when injected subcutaneously
   - Low incidence of thrombo phlebitis
   - Cheap
2. Pharmaco kinetic properties
   - Rapid on set in one arm-brain circulation time
   - Rapid redistribution to vessel-rich tissue
   - Rapid clear ance and metabolism
   - No active metabolites
3. Pharmaco dynamic properties
   - High the rapeutic ratio (ratio of toxic dose : minimally effective dose)
   - Minimal cardio vascular and respiratory effects
   - No histaminerel ease/hyper sensitivity reactions
   - No emetic effects
   - No involuntary movements
   - No emergence night mares
   - No hang over effect
   - No adreno cortical suppression

- Safe to use in porphyria

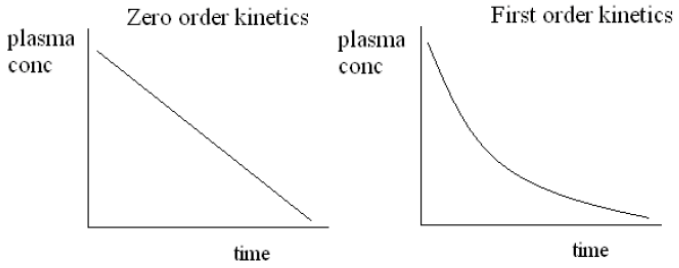
1. Sodium Thiopental



Thiopental (also called thiopentone and pentothal) is a barbiturate, supplied as a pale yellow hygroscopic (attracts moisture from the atmosphere) powder. Ampoules commonly contain 500 mg of sodium thiopental with 6% sodium carbonate in an inert atmosphere of nitrogen. Reconstituted with 20 ml of water, this yields a 2.5% solution (25mg/ml) with a pH of 10.8. The alkaline solution is bacteriostatic and safe to keep for 48 hours. The molecular structure of thiopental is based up on the barbiturate ring – as shown above. A sulphur atom at the carbon R2 position confers the short duration of action.

A dose of 4-5 mg/kg of thiopental produces a smooth on set of hypnosis with good definitive end points within 30 seconds of intravenous injection. Recovery after a single dose is rapid due to redistribution, and there is a low incidence of restlessness, nausea and vomiting.

Thio pentalis 65-85% protein bound in plasma. Metabolism is slow and occurs in the liver. Excretion of metabolites occurs mainly in the urine. Following repeated doses or infusions of thiopental, metabolism follows zero order kinetics; this means that a constant amount of the drug is being eliminated per unit time, irrespective of the plasma concentration. Some drugs are metabolized by first order kinetics; this means that a constant fraction of the drug is eliminated per unit time, i.e. dependent on plasma concentration. Zero order kinetics occur when the metabolic path ways become saturated, leading to an accumulation of the active drug and delayed recovery.



T Thiopental directly depresses the contractile force of the heart, reducing cardiac output and blood pressure. There may be a compensatory increase in the heart rate. It also decreases venoustone, causing pooling of blood in the peripheral veins, and increasing the degree of hypotension, particularly in patients who are hypovolemic (e.g. following hemorrhage).

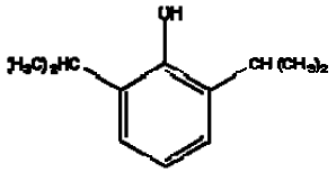
Respiratory depression is common and a period of apneais usually seen following abolus dose. Airway reflexes are well preserved in comparison with propofol; as a result, it is unsuitable for use when inserting a laryngeal mask airway (LMA), which may cause coughing and laryngospasm. Histamine release can occur, which may precipitate bronchospasm.

Thiopental reduces cerebral blood flow, cerebral metabolic rate and oxygen demand. It has potent antic on vulsant properties. Following traumatic brain injury, infusion of thiopental to produce a “barbiturate coma” lowers intra cranial pressure and may improve neurological outcome. This is, however, associated with significant accumulation, causing a prolonged effect with multiple complications.

The porphyrias are a group of diseases characterized by over production and excretion of

porphyrins (intermediate compounds produced during hemo protein synthesis). Acute attacks may be precipitated by drugs, stress, infection, alcohol, pregnancy and starvation. Thiopental may precipitate porphyria due to hepatic enzyme induction in susceptible patients, and therefore should be avoided.

Propofol (2, 6 di-isopropylphenol)



$C_{12}H_{18}O$

Propofolis usually presented as a 1 or 2% aqueous mulsion (tiny fat drop lets in suspension, white colour) containing soya oil, egg phosphatide and glycerol. It is otonicto plasma and has a pH of 7.0 - 8.5. It can cause pain on injection in to small veins.

It is a short-acting general anesthetic drug, with an onset of action of approximately 30 seconds. Recovery from anesthesia is usually rapid. A smooth induction of anesthesia usually follows a dose of 2-2.5mg/kg. Propofol should be titrated against the response of the patient until the clinical signs show the onset of anesthesia. The best end point is loss of verbal contact with the patient.

Following an IV bolus, there is rapid equilibration between the plasma and the highly per fused tissue of the brain as described earlier. Plasma levels decline rapidly as a result of redistribution, followed by a more prolonged period of hepatic metabolism and renal clearance. The initial redistribution half-life is between 2 and 4 minutes. Moderate hepatic orrenalim pairment does not alter the pharmaco kinetics of propofol.

Propofol causes the most marked fall in blood pressure of all the induction drugs. This is mainly due to systemic vasodilatation. There may be an accompanying light increase in heart rate. The fall in blood pressure is dose dependent and is most marked in the elderly and inpatients in shock. This can be minimized by slow injection to avoid in advertent overdose.

With the exception of ketamine, all induction drugs act on the respiratory centre to cause respiratory depression. This effect is the most profound with propofol, and a period of a pnoeais usually seen.

Propofol also markedly reduces airway and pharyngeal reflexes, making it the ideal drug to use with the laryngeal mask.

Propofol has been associated with epileptic form movements, which must not be confused with true seizure activity, on induction and recovery, but it is anti convulsant in normal doses. It has also been shown to reduce cerebral blood flow, metabolic rate and intra-cranial pressure.

An infusion of propofol issued commonly to provide sedation for adult patients undergoing minor procedures and in intensive care units. It is also the most commonly used drug to provide to talintravenous anesthesia.

Experience suggests that propofol is safe to use inpatients susceptible to porphyria and in pregnancy.

Inhalation agents

The inhalation agents used for the maintenance of GA were analysed and it was found that sevoflurane and desflurane had no adverse maternal or neonatal effects, while sevoflurane was associated with more rapid recovery than isoflurane (Dyer 2011). Sevoflurane has been successfully used for anaesthesia induction in patients with need lephobia.

2.2. Muscle relaxant Suxamethonium has been used successfully for rapid sequence of intubation, but in the case of anaphylactic reaction, rocurronium or sugammadex can be used instead.

Opioid use: a study on remifentanil showed that it is effective for intubation in healthy patients, but neonatal respiratory support may be required, especially in preterm.

2.2.5.100% oxygenation in GA leads about 50% and more umbilical venous oxygenation. Endo tracheal Intubation in GA for C/S is standard, but a study shows that a laryngeal mask airway is an alternative to tracheal intubation during elective C/S. Failed intubation delays the surgery and leads to poor oxygenation of the unborn baby, which may yield a poor Apgar score.

Propofol crosses the placenta and can depress neonatal respiration.

Tables of articles reviewed

1. Study Jeffrey Huang, Huan Gao 2016 Methods	Survey of current obstetric anaesthesia practiced in China
Participants	78000 registered anaesthesiologists, members of the New Youth Anaesthesia Forum, responded by on WeChat to a questionnaire on agent use in general anaesthesia for caesarean section. Their response was that propofol is not licensed by manufacturers for use in obstetric anaesthesia.
Interventions	No
Outcomes	The author concluded that anaesthesiologists strongly supported the use of propofol to replace ketamine as the induction agent of choice in caesarean sections. Manufacturers should change the wording of their package inserts with regard to the use of propofol in obstetric anaesthesia.
Notes	This survey was done in China. Other anaesthetists did not support the replacement of ketamine by propofol.

2. Study Munender Mamidi et al 2016 Methods	Comparative randomized study
Participants	A sample of 103 healthy patients were randomized in two groups. Of these, 51 patients received thiopental and 52 patients received propofol.
Interventions	Term pregnant women received 5mg/kg of thiopental or 2.5mg/kg of propofol; maintenance was similar.
Outcomes	Author concluded that propofol appears to be a suitable alternative induction agent for obstetric anesthesia.

3. StudyTumukunde et al. BMC anaesthesiology 2015

Methods	Randomised single blinded clinical trial at Mulago Hospital, in Uganda, ASA1 and 2 included term pregnant women.
Participants	150 term pregnant women, from November 2013 to April 2014
Interventions	Premedication was done with: cimetidine200mg IV, metoclopramide 10mg IV 1-2hours before operation, preoxygenate for 3-5 minutes. General group with thiopental 4mg/kg iv, succinylcholine, oxygen, isoflurane inhalation, then atracurium, nalbuphine 10mg was administered, then halothane was discontinued,

	reversal was given: neostigmine 0.05mg/kg of body weight plus atropine 0.02mg/kg. GA group with propofol had 2mg/kg administered in one minute intravenously, followed by succinylcholine 1,5mg/kg, oxygen, isoflurane inhalation, then atracurium, nalbuphine 10mg was given, then halothane was discontinued, reversal was given: neostigmine 0.05mg/kg of body weight plus atropine 0.02mg/kg. Both groups were intubated. All received 1.5l of crystalloid.
Outcomes	The author concluded that maternal recovery was shorter in the propofol group than in the thiopental group. The Apgar score did not differ significantly whether thiopental or propofol was used as an induction agent in women receiving GA. There was high rate of ICU in the group in which propofol was used for induction.

4. Study Vedat et al.2015 Methods	Patients were selected on a randomized basis.
Participants	70 term pregnant women, divided in two groups T (N=35) and P (N=35), undergoing C/S for any indication.
Interventions	Premedication done with: cimetidine200mg IV, metoclopramide 10mg IV 1-2hours before operation, preoxygenate for 3-5minutes. General group had either thiopental 5mg/kg iv and or propofol 2,5mg/kg then 0,6mk/kg of rocuronium, oxygen, sevoflurane inhalation for maintenance, 15 unit of oxytocin infusion then 10unit bolus, reversal was given: neostigmine 0.05mg/kg of body weight plus atropine 0.02mg/kg.
Outcomes	The author concluded that both propofol and thiopental sodium can be used safely in caesarean sections, and the use of propofol was more advantageous than thiopental because it provided adequate anaesthetic depth and more rapid recovery.
Notes	

5. StudyDadras MM et al. 2013

	Methods Double-blind clinical trial
Participants	230 healthy women who volunteered to undertake caesarean operation were selected and then divided randomly into two equal groups using statistical blocking.
Interventions	One group was treated by propofol while other one was treated by thiopental.
Outcomes	Author concluded that after sufficient fluid therapy, propofol can be a suitable drug to achieve anaesthesia. Moreover, it exerts less impact on cesarean babies' Apgar and stimulates lower levels of nausea and vomiting in mothers.

6. Study Arzu Mercanet al.2012

Methods	Prospective, randomized, clinical study was performed between January 2009 and December 2009 at Saad Specialist Hospital.
Participants	82 term pregnant women. Nulliparity. Sample size was 82 patients divided in two groups, propofol group (N=42) and

	thiopental group (N=40), undergoing elective C/S for any indication.
Interventions	Premedication done with: cimetidine200mg IV, metoclopramide 10mg IV 1-2hours before operation, preoxygenate for 3-5minutes. General group had thiopental 5mg/kg iv, succinylcholine 1mg/kg, oxygen, isoflurane inhalation, then atracurium0.5mg/kg, nalbuphine 10mg was given, then isoflurane was discontinued, reversal was given: neostigmine 0.05mg/kg of body weight plus atropine 0.02mg/kg, 100% oxygen 5mg/kg and propofol 2mg/kg Thiopental 4-5mg/kg.
outcomes	The author concluded that induction agent for caesarean section could be effective in maintaining adequate BIS (bispectral index) levels until neonate delivery. Furthermore propofol used as an induction agent was more effective than thiopental in keeping BIS values levels lower until the delivery of the newborn.

7. Study Maziar Mahjoobifard et al. 2011

Methods	230 patients selected by randomized prospective study.
Participants	230 pregnant healthy women, divided in two groups, thiopental (N=115) and propofol (N=115), undergoing elective C/S for any indication.
Interventions	General group had propofol or thiopental succinyl choline, oxygen/nitrousoxide, isofluraneat 0.25-0.5% for maintenance, reversal given was neostigmine plus atropine.
Outcomes	The author concluded that in elective cesarean sections in which there are no danger to mother and neonate without any contraindication; propofol may be useful as an anaesthetic inducing agent. Despite its reduced effect on the neonatal Apgar score, it induces less post-operative nausea and vomiting for mothers.

8. Study Perisa Golfam et al. 2009

Methods	Double blinded clinical trial study, done for patients scheduled for elective caesarean section.
Participants	60 term pregnant women, sample size was 60 patients divided in two groups, 1st (N=30 for propofol) and 2nd (N=30 for thiopental), undergoing elective C/S for any indication.
Interventions	Premedication done with: cimetidine 200 mg IV, metoclopramide 10mg IV 1-2 hours before operation, preoxygenate for 3-5 minutes. General group had thiopental 4mg/kg iv, or propofol 2.5 mg/kg, Succinylcholine, oxygen, halothaneinhalation, thenatracurium, nalbuphine 10mg was given, then halothane was discontinued, reversal was given: neostigmine 0.05mg/kg of body weight plus atropine 0.02 mg/kg.
Outcomes	The author concluded that propofol had no adverse effect on either mother's hemodynamic or the clinical status of neonates: it can be used as an alternative drug to induce anaesthesia.

9. Study Celleno D et al. 1993

Methods	Randomized, double-blind study
Participants	90 healthy patients undergoing elective cesarean section with general anesthesia.
Interventions	3 groups of 30 patients each receiving thiopental 5 mg/kg, propofol 2.4 mg/kg, or midazolam 0.3 mg/kg for induction of anesthesia.
Outcomes	The author concluded that thiopental still remains the first-choice induction drug for cesarean section. The slow induction time with midazolam may put the mother at risk for pulmonary inhalation. A plane of anesthesia that may risk awareness and potential neonatal depression is the main drawback of the two newer induction drugs.
Notes	

10. Study M Valtonen et al. 1989

Methods	Patients were selected by randomized prospective study.
Participants	32 term pregnant women, divided in two groups, A (N = 16) and B (N = 16), undergoing elective C/S for CPD.
Interventions	General group had thiopental 4mg/kg iv or propofol 2, 5 mg/kg for induction, other drugs were the same.
Outcomes	The author concluded that propofol was found to be similar to thiopentone in induction characteristics and in the effects on neonates. Recovery times after anesthesia were shorter with propofol, and this fact may be advantageous in some situations. Propofol appears to be a suitable alternative to thiopentone as an induction agent for anesthesia in elective caesarean sections.
notes	

Methods

We carried out a non-systematic literature review of articles comparing propofol to thiopental from 1989 to 2016.

Findings

Out of all the articles read, Celleno et al (1993) said that thiopental remains the first line choice for C/S and others concluded that propofol can be used as an alternative in pregnancy for C/S.

Conclusions

Most of the studies read show that GA for C/S is a challenge for the modern anaesthesiologist, because the physiological changes during pregnancy make the GA difficult. In the case of general anaesthesia, propofol can be used as an alternative, but manufacturers advise against using it in pregnancy.

Recommendations

Many articles support the use of propofol in pregnancy. This is practice based rather than research based. We are not sure of its safety in obstetric use. Manufacturers still contraindicate it for obstetric use.

It may be that propofol is a suitable agent for obstetric use but available data do not support this assertion nor do 75% of obstetric anesthetists (Sneyd 2004).

We recommend more clinical studies to compare propofol outcomes on neonate and mothers.

More data is required to conclude if propofol is 100% suitable for cesarean sections.

References

[1]. Arzu Mercan et al. A prospective, randomized comparison of the effects of thiopental and propofol on bispectral index during caesarean section till delivery of new-born. 2012.

[2]. Celleno D1 et al.1993 J Clin Anesth. 1993 Jul-Aug; 5(4):284-8.

[3]. Dr Tom Lupton &Dr Oliver Pratt. Tutorial on: Intravenous drugs used for the induction of anesthesia. Salford Royal Hospitals NHS Foundation Trust, Salford, UK (2003).

[4]. Dadras MM, Mahjoobifard M, Panahipoor A, &Dadras MA. Comparing propofol with sodium thiopental on neonatal Apgar score after elective cesarean section. Zahedan J Res Med Sci (ZJRMS) 2013; 15(4): 21-24.

[5]. Heather McKenzie et al. The pregnant patient: assessment and perioperative management...2015.

[6]. Mahjoobifard M et al. The comparison of propofol with thiopental as induction drug on neonatal Apgar during elective cesarean section. Zahedan J Res Med Sci (Zahedan Journal of Research in medical sciences) 2011; 13(4):35-39.

[7]. **M. Valtonen et al.** Comparison of propofol and thiopentone for induction of anesthesia for elective Caesarean section. 1989.

[8]. M. Mamidi, Shiva Prasad D. Propofol and Thiopentone as induction agents in obstetric anesthesia – A comparative study. IAIM, 2016; 3(4): 111-117.

[9]. Michael A et al. Propofol infusion for cesarean section. 1990; 37:5 pp514-20.

[10]. Perisa Golfam et al. The effect of propofol and thiopental on apgar score during caesarean section. 2009.

[11]. Rob Dyer. Update on general anesthesia for C/S. South African Journal of Anesthesia Analgesia 2011; 17(1).

[12]. South African guidelines for safe use of procedural sedation and analgesia for diagnostic and therapeutic procedures in adults: 2010.

[13]. Tiffany Sun Moon &Joshua Sappenfield Anaesthesia management and challenges in the pregnant patient. 2016; 6:89-94.

[14]. Tumukunde et al. The effect of propofol versus thiopental on Apgar scores in newborns and peri-operative outcomes of women undergoing emergency caesarean section: a randomized clinical trial. 2015.

[15]. Update on use of propofol and thiopental 2016.

[16]. Which induction drug for cesarean section? A comparison of thiopental sodium, propofol, and midazolam.

[17]. Vedat et al. Comparison of the effect of thiopental sodium and propofol on haemodynamics, awareness and newborns during caesarean section under general anaesthesia 2015. Turk Journal of anaesthesia reanimation.

[18]. xJR Sneyd. Recent advances in intravenous anesthesia. British Journal of Anesthesiology 2004; 93: 725–36