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Literature Review

Compare Thiopental and Propofol Effect on Neonatal and Maternal Outcomes after Caesarean Section: A Non-Systematic Review

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Abstract

Background: Current study in obstetric anaesthesia recommends caesarean section to perform under neuraxial anaesthesia either spinal or epidural anaesthesia, but some conditions contraindicate neuraxial anaesthesia, and general anaesthesia is an alternative choice for these conditions. Thiopental 4 - 5 mg/kg and Propofol 2 mg/kg are used for general anaesthesia induction during caesarean section.

Methods: The study articles from 1989 up to 2016 comparing thiopental to Propofol in caesarean section have been reviewed.

Result: About 20 published articles and abstracts from 1989 up to 2016 were reviewed, these articles show that Propofol was an alternative induction agent for general anaesthesia in caesarean section and have few disadvantages on Apgar score of the neonate at one minute.

Conclusion: The reviewed articles show that Propofol is currently the most commonly used as induction drug for general anaesthesia and have good maternal and neonatal outcomes post caesarean section compare to thiopental.

Keywords: *Propofol; Obstetric Anaesthesia; Thiopental; Caesarean Section*

Introduction

Currently most caesarean section are done under regional anaesthesia than general anaesthesia, the use of regional anaesthesia is increasing because of fail intubation [1] and it has good post-operative analgesia. Currently the use of general anaesthesia in caesarean section is less than 5% of caesarean deliveries in the united states and United Kingdom [2].

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 outcome, when used during general anaesthesia induction for Caesarean Section and find which one is best induction drug for caesarean section procedure.

Literature Review

A study done comparing the effect of thiopental and Propofol on Apgar score done in Uganda at Mulago national referral hospital concluded that there was not significant difference between the two drugs used for induction in women undergoing general anaesthesia for a caesarean section [3].

Another study done on pregnant women show that there is some evidence that Propofol may exert neurodevelopmental effects in animals but the effect on a developing human foetus is not clear [4] although many anaesthetists use Propofol for Caesarean Section, a dose of 2.8 mg/kg but a study done before show that there is no advantage to neonate in using Propofol [1].

Thiopental is no longer available in many western countries, Propofol is the alternative and in china thiopental is not available and ketamine was recommended as drug of choice for induction for caesarean section by obstetric anaesthesia society (Jeffrey Huang and Huan Gao 2016).

Thiopental have been routinely used for caesarean section since 1930 as anaesthetic induction agent, it has disadvantages as hypotension and can reduce Apgar score. Propofol is widely used for induction and maintenance of anaesthesia for other surgeries, not for caesarean section it has also hypotension as side effect.

Agents used during general anaesthesia

Intravenous agents

These are agents that, when intravenously given produce a rapid loss of consciousness. Is described as "one arm-brain circulation time" that is the travelling time taken for the drug to go from the site of injection (usually the arm) to the brain, where they have their effect.

They are used:

- For induction of anesthesia prior to other drugs being given to maintain anesthesia.
- As the total intravenous anaesthesia for short procedures.
- Intravenous infusion for maintenance of anesthesia for longer procedures. For sedation in short procedure.

Intravenous anesthesia concept was born in 1932, the first rapidly acting intravenous drug used was phenobarbitone published in a report by Wesse and Schrapff. In 1934 two years later, sodium thiopental was introduced into clinical practice by Waters and Lundy, and this is still widely used today. Many other drugs came after. The drugs commonly use currently can be classified according to their chemical structure and include:

- Barbiturates
- Phenols
- Imidazole
- Phencyclidines
- Benzodiazepines.

Barbiturates and phenols class will be discussed below for our study.

Pharmacokinetic

In the blood stream a percentage of the drug binds to the plasma proteins and the rest remaining unbound or free. The degree of binding on the protein depend of the physical characteristics of the drug in question.

Such as lipid solubility and degree of ionization. The drug is transported in the venous blood to the right side of the heart, through the pulmonary circulation and pass 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 bolus is 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.

The lipid soluble, unionized, unbound molecules cross the blood brain barrier the fastest. The drug exerts its effects in the CNS tissue once it has penetrated it. for most anesthetic 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 potential sites of action.

Following the initial flooding of the Central Nervous System and other vessel rich tissues with non-ionized molecules, the drug starts to diffuse into other tissues that do not have such a rich blood supply. This secondary tissue uptake, predominantly by skeletal muscle, causes the plasma concentration to reduce, allowing drug to diffuse out of the central nervous system down the resulting reverse concentration gradient. It is this initial drug redistribution into other tissues that leads to the rapid wake up seen after a single dose of an induction drug. Plasma clearance and metabolism have a much less important role following a single bolus but are more important following infusions and repeat doses of a drug.

Fat makes little contribution to the early redistribution of free drug following a bolus due to its poor blood supply (vessel poor tissues), as is seen on the diagram below. However, after repeat doses or infusions of the drug, equilibration with adipose tissue forms a drug reservoir, and often lead to a delayed wake up, is observed mostly with obese patients.

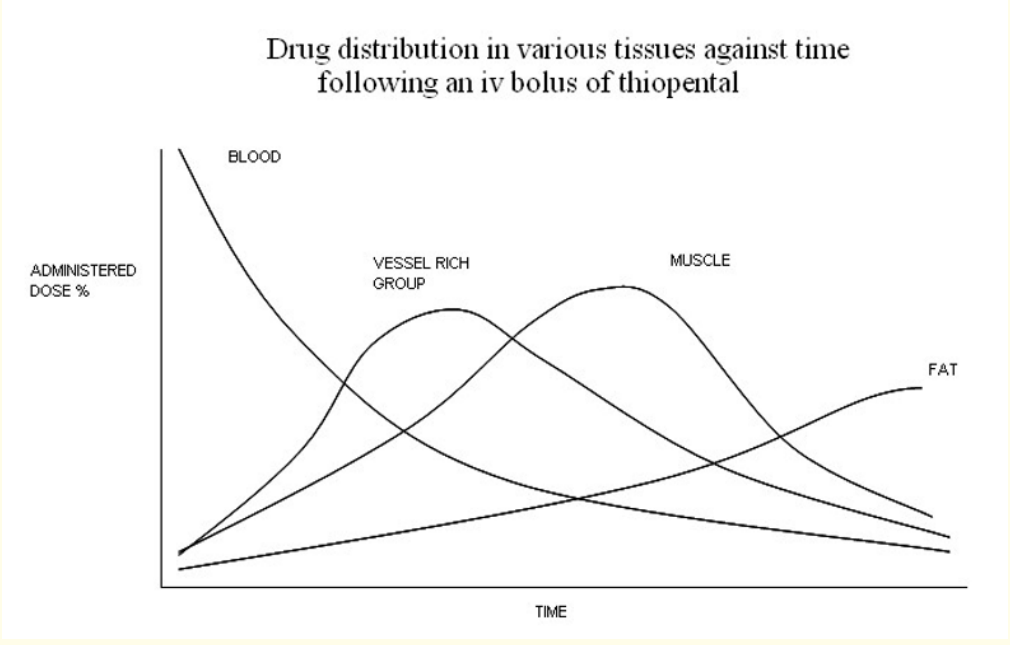

Figure 1

Effect on the cardiac output

In case of shocked patients, cesarean section (due to physiologic changes).

Elderly the cardiac output is reduced and the body compensates by diverting an increased proportion of the cardiac output to the cerebral circulation, as preservation of cerebral blood flow. So great proportion of any drug given will enter the cerebral circulation. In these situations where cardiac output is reduce, the dose of induction drug must be reduced. Furthermore, as global cardiac output is reduced, the induction time taken to reach the brain and exert its effect is prolonged. The titration of a reduced dose of drug in this situation is the key to a safe induction.

The properties of intravenous induction drug

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 into an artery
    - Non-irritant when injected subcutaneously
    - Low incidence of thrombophlebitis
    - Cheap
2. **Pharmacokinetic properties**
    - Rapid onset in one arm-brain circulation time
    - Rapid redistribution to vessel rich tissue
    - Rapid clearance and metabolism
    - No active metabolites
3. **Pharmacodynamic properties**
    - High therapeutic ratio (ratio of toxic dose: minimally effective dose)
    - Minimal cardiovascular and respiratory effects
    - No histamine release/hypersensitivity reactions

- No emetic effects
- No involuntary movements
- No emergence nightmares
- No hang over effect
- No adrenocortical suppression
- Safe to use in porphyria.

Sodium thiopental

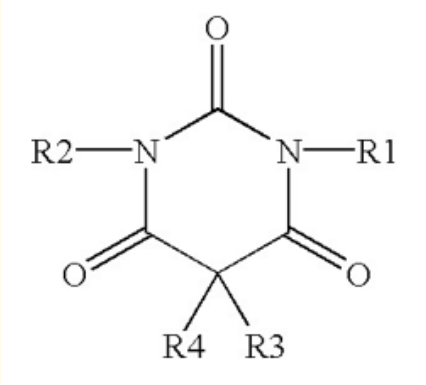

Figure 2

Thiopental is a barbiturate, is also called thiopentone and Pentothal, it supplied as a hygroscopic (attracts moisture from the atmosphere), thiopental is a powder in pale yellow color. The ampoules of thiopental contain 500 mg of sodium thiopental with 6% sodium carbonate in an inert atmosphere of nitrogen. Reconstitution is done with 20 ml of water this yields a 2.5% solution (25 mg/ml) with a pH of 10.8. The mixed solution is alkaline and bacteriostatic and should be keep for 48 hours. The thiopental molecular structure is based upon the barbiturate ring - as structure above. The short duration of action is due to a Sulphur atom at the carbon R2 position.

Thiopental at a dose of 4 - 5 mg/kg produces a smooth onset of hypnosis with good definitive endpoints within 30 seconds of intravenous injection. After a single dose there is rapid recovery due to redistribution and there is a low incidence of restlessness and nausea and vomiting.

Thiopental is protein bound in plasma about 65 - 85%. The metabolism occurs in the liver and is slow. The excretion of the metabolites occurs in the urine mainly. After infusion or repeated doses of thiopental, metabolism follows zero order kinetics; its means that a constant amount of drug is being eliminated per unit time, irrespective of the concentration of drug in the plasma. Drugs metabolized by first order kinetics have a constant fraction of drug elimination per unit time, means dependent on plasma concentration. The zero-order kinetics happen when the metabolic pathways are saturated and will leading to an accumulation of the active drug and delay the recovery.

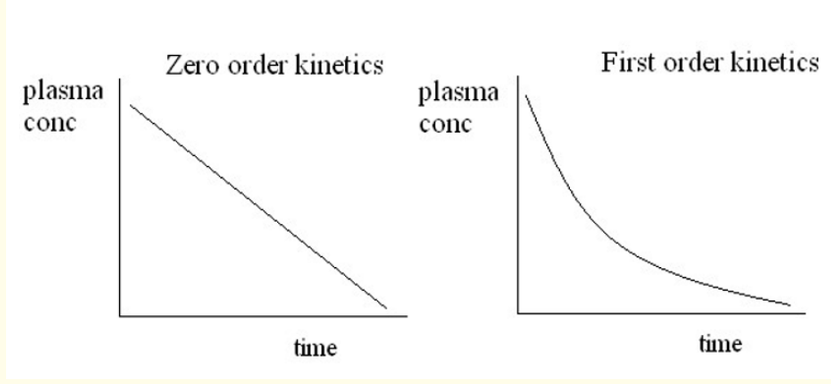

Figure 3

Thiopental depresses the heart contractility, leading to cardiac output and blood pressure reducing. There is a compensatory increase heart rate due to depression of the myocardial contractility. Decreases also the venous tone, causing pooling of blood in the peripheral veins; causing severe degree of hypotension, particularly in patients who are hypovolemic (e.g. following hemorrhage).

Thiopental induces respiratory depression and a period of apnea is usually following a bolus dose. Airway reflexes are preserved when compare with Propofol; therefore, it is unsuitable for use when inserting a laryngeal mask airway (LMA) which because it may cause coughing and laryngospasm. Thiopental induce Histamine release which may precipitate bronchospasm.

The cerebral blood flow, cerebral metabolic rate and oxygen demand are reduced by thiopental. It has also potent anticonvulsant properties. In traumatic brain injury, infusion of thiopental to produce a "barbiturate coma" it lowers intracranial pressure and may improve neurological outcome. The infusion of thiopental is however associated with significant accumulation of the drug, causing a prolonged effect with multiple complications.

Porphyria is disease characterized by overproduction and excretion of porphyrins (the intermediate compounds produced during hemoprotein synthesis). Acute attacks of porphyria may be precipitated by drugs, stress, infection, alcohol, pregnancy and starvation. Thiopental is among the drug contraindicated in this condition because it may precipitate porphyria due to hepatic enzyme induction in susceptible patients, so it

should be avoided.

Propofol (2,6 di-isopropylphenol)

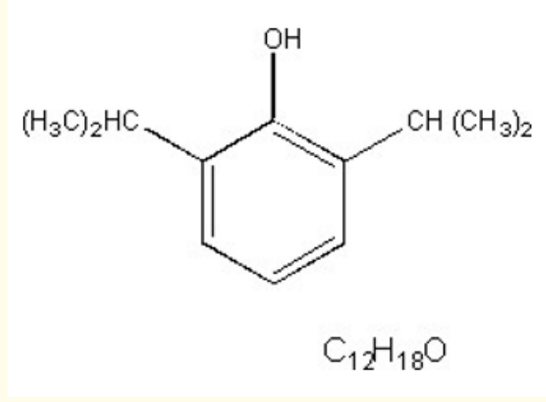

Figure 4

Usually Propofol is presented as a 1 or 2% aqueous emulsion (tiny fat droplets in suspension, white color) containing soya oil, egg phosphatide and glycerol. The PH is 7.0 - 8.5 and is isotonic to plasma. Propofol cause pain on injection into small veins.

For general anaesthesia propofol is a short-acting drug, with an onset of action of approximately 30 seconds. During anesthesia the recovery is usually rapid. A dose of 2 - 2.5 mg/kg, Propofol induce a smooth anaesthesia. The titration of Propofol should be done against the response of the patient until the clinical signs show the onset of anesthesia. The verbal contact loss with the patient is the best endpoint.

After an intravenous bolus injection, there is rapid equilibration between the plasma and the highly perfused 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 half-life is between 2 and 4 minutes. Mild and moderate renal or hepatic impairment does not affect the pharmacokinetics of propofol.

Propofol bolus causes the marked reduction of blood pressure of all the induction drugs. This reduction of blood pression is mainly due to systemic vasodilatation. slight increase in heart rate may accompanying this blood pression reduction. The reduction of blood pressure is dose dependent and is most marked in the elderly and in shocked patients. Slow induction can minimize this, overdose should be avoiding.

All induction drugs act on the respiratory center to cause respiratory depression except ketamine. The respiratory depression effect is the most profound with Propofol and a period of apnea is usually seen.

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

Propofol has been associated with epileptiform movements, that must not be confused with true seizure activity, on induction and recovery, but it is anticonvulsant in normal doses. Propofol reduce the cerebral blood flow, metabolic rate and intra-cranial pressure.

Commonly Propofol infusion is used to provide sedation for adult patients undergoing minor procedures and on the intensive care unit, is also used as sole drug to provide total intravenous anesthesia.

Propofol is safe to be use in patients susceptible to porphyria and those who are pregnancy.

Inhalation agents

The inhalation agents used for maintenance of GA were analysed and fund that sevoflurane and desflurane have been with no adverse maternal or neonatal effects and sevoflurane was associated with rapid recovery than isoflurane [1], sevoflurane has been successfully used for anaesthesia induction in patients with needle phobia.

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Muscle relaxant

Suxamethonium have been used for rapid sequence of intubation, it use have shown success, but in the case of anaphylactic reaction rocuronium can be use as alternative.

Opioids

A study done show that remifentanil is effective for intubation in healthy patient but they may require neonatal respiratory support most in preterm.

100% oxygen in general anaesthesia lead to about 50% and more umbilical venous oxygenation, the intubation in general anaesthesia for Caesarean Section is a goal standard, but a study show that laryngeal mask airway is an alternative to tracheal intubation during elective Caesarean Section, fail intubation delay the surgery and lead top poor oxygenation of the unborn baby which may deliver with poor Apgar score.

Propofol cross the placenta and can depress the neonatal respiration.

Tables of articles reviewed

Study: Jeffrey Huang, Huan Gao 2016

Methods	Survey of current obstetric anaesthesia practice in china.
Participants	78000 registered anaesthesiologists members in new youth anaesthesia forum, respond by WeChat, the questionnaire was about agent use in General anaesthesia for caesarean section .and their opinion about manufactures 'the statement that Propofol is not licensed for use in obstetric anaesthesia.
Interventions	No
Outcomes	The author concluded that anaesthesiologist strongly supported the use of propofol to replace ketamine as the induction agent of choice for caesarean section, manufacture should change their statement in their package insert about the use of Propofol in obstetric anaesthesia.
Notes	This survey was done in china other anaesthetist did not support the replacement of ketamine by Propofol.

Study: Munender Mamidi., *et al.* [5]

Methods	Comparative study randomized study.
Participants	103 healthy patients randomized in two group of ,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.

Study: Tumukunde., *et al. BMC Anaesthesiology* [3]

Methods	Randomised single blinded clinical trial at Mulago hospital, in Uganda, ASA1 and 2 included term pregnant women.
Participants	150 term pregnant women, form November 2013 to April 2014.
Interventions	Premedication done with: cimetidine 200 mg IV, metoclopramide 10 mg IV 1 - 2 hours before operation, preoxygenate for 3 - 5 minutes general group with thiopental 4 mg/kg iv, succinylcholine, oxygen, isoflurane inhalation, then atracurium, nalbuphine 10 mg was given then halothane was discontinued, reversal was given: neostigmine 0.05 mg/kg of body weight plus atropine 0.02 mg/kg GA group with Propofol had 2 mg/kg administered in one minute iv, succinylcholine 1,5 mg/kg, oxygen, isoflurane inhalation, then atracurium, nalbuphine 10mg was given then halothane was discontinued, reversal was given: neostigmine 0.05 mg/kg of body weight plus atropine 0.02 mg/kg. both intubated. All received 1.5l of crystalloid.
Outcomes	The author concluded that Maternal recovery was shorter in the Propofol group than in 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 of Propofol used as induction.

Study: Vedat., *et al*. [6]

Methods	Patients were selected by randomized.
Participants	70 women term pregnant, divided in two group T (N = 35) and P (N = 35), undergoing C/S for any indication.
Interventions	Premedication done with: cimetidine 200 mg IV, metoclopramide 10 mg IV 1 - 2 hours before operation, preoxygenate for 3 - 5 minutes general group had thiopental 5 mg/kg iv and for Propofol was 2,5 mg/kg then, 0,6 mg/kg of rocuronium, oxygen, sevoflurane inhalation for maintenance, 15 unit of oxytocin infusion then 10unit bolus, reversal was given: neostigmine 0.05 mg/kg of body weight plus atropine 0.02 mg/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 provides adequate anaesthetic depth and more rapid recovery
Notes	

Study: Dadras MM., *et al*. [7]

Methods	In this double-blind clinical trial.
Participants	230 healthy women who were 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 proper drug to achieve anaesthesia. Moreover, it exerts less impact on caesarean babies Apgar and stimulates lower levels of nausea and vomiting in mothers.

Study: Arzu Mercan., *et al.* [8]

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 were 82 patients divided in two group, Propofol group (N = 42) and thiopental (N = 40), undergoing elective Caesarean Section for any indication.
Interventions	Premedication done with: cimetidine 200 mg IV, metoclopramide 10 mg IV 1 - 2 hours before operation, preoxygenate for 3 - 5 minutes general group had thiopental 5 mg/kg iv, succinylcholine 1 mg/kg, oxygen, isoflurane inhalation, then atracurium0.5 mg/kg, nalbuphine 10 mg was given then isoflurane was discontinued, reversal was given: neostigmine 0.05 mg/kg of body weight plus atropine 0.02 mg/kg, 100% oxygen 5 mg/kg and Propofol 2 mg/kg thiopental.
Outcomes	The author concluded that induction agent for caesarean section could be effective on maintaining adequate BIS levels till the delivery of neonate. Furthermore, Propofol was more effective to keep BIS (bispectral index) values levels till delivery of new-born lower than thiopental when it was used as an induction agent.

Study: Maziar Mahjoobifard., *et al*. [9]

Methods	230 Patients selected by randomized prospective study.
Participants	230 pregnant healthy women, divided in two group thiopental (N = 115) and Propofol (N = 115), undergoing elective Caesarean Section for any indication.
Interventions	General group had Propofol or thiopental succinylcholine, oxygen/nitrous oxide, isoflurane at 0.25 - 0.5% for maintenance, reversal given was neostigmine plus atropine.
Outcomes	The author concluded that in elective caesarean section in which there is no danger to mother and neonate without any contraindication, propofol may be useful as an anesthetic inducing agent. Despite its less effect on the neonatal Apgar score, it induces less post-operative nausea and vomiting for mothers.

Study: Perisa Golfam., *et al*. [10]

Methods	Double blinded clinical trial study, done for patients scheduled for elective caesarean section.
Participants	60 term pregnant women, Sample size were 60 patients divided in two group 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 10 mg IV 1 - 2 hours before operation, preoxygenate for 3 - 5 minutes general group had thiopental 4 mg/kg iv, or Propofol 2.5 mg/kg succinylcholine, oxygen, halothane inhalation, then atracurium, nalbuphine 10 mg was given then halothane was discontinued, reversal was given: neostigmine 0.05 mg/kg of body weight plus atropine 0.02 mg/kg.
Outcomes	The author concluded that has Propofol had not adverse effect on mother's hemodynamic and the clinical status of neonates, it can be used as an alternative drug to induce anaesthesia.

Study: Celleno D., *et al*. [11]

Methods	Randomized, double-blind study.
Participants	90 healthy patients undergoing elective caesarean 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 caesarean 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	

Study: M Valtonen., *et al*. [12]

Methods	Patients were selected by randomized prospective study
Participants	32 term pregnant women, divided in two group A (N = 16) and B (N = 16), undergoing elective C/S for Cephalo Pelvic Disproportion.
Interventions	General group had thiopental 4 mg/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 the neonates. Recovery times after anaesthesia 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 anaesthesia in elective caesarean section.
Notes	

Methods

We have done a non-systematic literature review of articles comparing Propofol to thiopental from 1989 to 2016.

Findings

On all articles read, Celleno D., *et al.* [11] said that thiopental remain the first line choice for C/S and other concluded that Propofol can be use in pregnancy for caesarean section as an alternative.

Conclusion

Most of the study read show that general anaesthesia for caesarean section is a challenge for the modern anaesthesiologist, because the physiological change during pregnant make the general anaesthesia difficult.in case of general anaesthesia Propofol can be used as an alternative, but manufacturers advice not to use in pregnancy.

Recommendations

There is many articles supporting the use of Propofol in pregnant women, this is a practice based rather than research evidence. It's true we are not sure of its safety in obstetric. manufacture still contraindicate it for obstetric use.

Clinical practice shows that Propofol is a suitable agent for obstetric use but available data do not support this assertion nor do 75% of obstetric anesthetists [13].

We recommend more clinical study to compare Propofol outcome on neonate and mothers.

More data is required to conclude if Propofol is 100% suitable for cesarean section.

Conflict of Interest

No conflict of interest.

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