

Type of obstetric anaesthesia administered and complications in women with pre-eclampsia in low and middle-income countries (LMIC): a systematic review

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Abstract:**Background:**

Delivery is often expedited with caesarean section, necessitating anaesthesia, to prevent complications in women with pre-eclampsia. Anaesthesia associated risks in these women from low and middle-income countries (LMIC) is not known.

Methods:

We searched major databases (until Feb 2017), for studies on general vs. with regional anaesthesia in women with pre-eclampsia. We summarised the association between outcomes and type of anaesthesia using a random effects model, and reported as odds ratio (OR) with 95% confidence intervals.

Findings:

We included 14 studies (10,411 pregnancies). General anaesthesia, was associated with an increase in the odds of maternal death seven-fold (OR 7.70, 95% CI 1.9 to 31.0, $I^2=58%$) than regional anaesthesia. The odds of pulmonary oedema (OR 5.16, 95% CI 2.5 to 10.4, $I^2=0%$), maternal intensive care unit admissions (OR 16.25, 95% CI 9.0 to 29.5, $I^2=65%$), and perinatal death (OR 3.01, 95% CI 1.4 to 6.5, $I^2=56%$) were increased with general vs. regional anaesthesia.

Conclusion:

General anaesthesia is associated with increased complications in women with pre-eclampsia undergoing caesarean section in LMIC.

Key words: pre-eclampsia, anaesthesia, maternal mortality

Introduction

Pre-eclampsia, a condition unique to pregnancy with hypertension and proteinuria is often associated with other maternal organ dysfunction, such as renal insufficiency, liver involvement, neurological or haematological complications, uteroplacental dysfunction, or fetal growth restriction. ^[1, 2]

Globally 10 million women develop pre-eclampsia every year, with women in low and middle income countries being seven times more likely to develop the condition, of these 76000 women and 500000 babies die yearly with the majority being in low and middle income countries (ref). Pre-eclampsia and eclampsia contributes up to 15% of overall maternal deaths.^[3]

Mothers with pre-eclampsia are more likely to be delivered by caesarean section than those without the condition, since expedited delivery is considered to be the cure (ref). Anaesthetic management of these mothers is a crucial part of intrapartum care. The challenges are profound in a LMIC setting with limitations in resources, training and skilled anaesthetists. In countries such as the UK, it is now accepted that regional anaesthesia is safer than general anaesthesia for women with pre-eclampsia, where no contraindications exist.^[4] However the influence of type of anaesthesia on maternal and neonatal outcomes in an LMIC setting is not known, where the findings of high-income environment may not be transferrable. Studies involving mothers from LMIC on type of obstetric anaesthesia provide imprecise and varied estimates of maternal and neonatal risks (ref).

We undertook a systematic review of studies that compared the rates of maternal and perinatal complications in pregnant women who were administered general vs.

regional anaesthesia in LMIC.

Methods

The systematic review was done using a prospective protocol in line with current recommendations, and reported as per the PRISMA guidelines.^[5]

Literature search

We searched Medline, Embase, Scopus, CINAHL, Web of Science and WHO Library and Medicus from inception until June 2016. We used MeSH headings, text words and word variants for "pregnancy" and combined them with terms for low resource countries like "low- income " or "middle income" or " developing country". These were then combined with an(a)esthesia and surgery related terms such as “ an(a)esthesia” or “ an(a)esthetist” or “ nurse an(a)esthetist” or ‘c(a)esarean section” (Appendix 1). There were no language restrictions. Additionally, we searched the reference lists of the included studies, and relevant reviews and articles for eligible papers. All studies that included women with pre-eclampsia and compared type of anaesthesia were included in this review,

Study selection

Studies were selected in a two-stage process. In the first stage, we screened the titles and abstracts of all citations for potentially relevant papers. In the second stage, we did a detailed examination of the full texts of the retrieved papers. Two independent reviewers (SS, KD) selected the papers against pre-specified inclusion criteria. Any discrepancies were resolved after discussion with a third reviewer (ST). Studies were included if they were comparative cohort studies, and assessed maternal and perinatal outcomes in pre-eclamptic women exposed to general or regional anaesthesia in

LMIC as defined by the World Bank.^[6] We excluded studies in high-income countries, those involving women without pre-eclampsia and studies published before 1990.

Maternal death was defined as the death of a woman while pregnant or within 42 days (or 1 year for late maternal deaths) of birth or termination of pregnancy, irrespective of the duration and site of the pregnancy, from any cause related to or aggravated by the pregnancy or its management, but not from accidental or incidental causes.^[7]

Perinatal death included any fetal death that occurred after 28 completed weeks of gestation, stillbirth and early neonatal death until one week after birth.^[8] Apgar scores were classed as low if they were less than or equal to 7 at one and five minutes. We accepted the authors' definitions for other maternal and fetal complications such as postpartum hemorrhage, cardiac arrest and admission to the intensive care unit.

The definitions for mild, moderate, severe pre-eclampsia and eclampsia were taken as defined by the study authors and included in Appendix 2.

Quality assessment of the included studies

We used the Newcastle-Ottawa scale to evaluate the risk of bias in the selection, and comparability of subjects and cohorts and of the outcome.^[9] Studies that scored four stars for selection; two stars for comparability and three stars for ascertainment of the outcome were regarded to have a low risk of bias. Studies with two or three stars for selection, one for comparability and two for outcome ascertainment were considered to have a medium risk of bias. Any study with a score of one for selection or outcome ascertainment, or zero for any of the three domains was deemed to have a high risk of bias.^[9]

Data extraction and analysis

Data were extracted by two independent reviewers (SS and KD). We obtained information on study design, setting, population characteristics, type of anaesthesia, year of publication and maternal and fetal outcomes. We extracted data on the number of events observed amongst women exposed to the different types of anaesthesia, mainly general and regional anaesthesia. We computed individual study odds ratios and pooled them using a random effects model. Heterogeneity was evaluated using I^2 statistic. All analyses were performed using Stata 12.^[10]

Results

From 11,200 citations, we included 14 studies that evaluated the association between type of anaesthesia and pregnancy complications in women diagnosed with pre-eclampsia. (Figure 1)

Characteristics of the included studies

Fourteen studies included 10,411 pregnant women undergoing caesarean section with varying severity of pre-eclampsia. Of these, 37% (3899/10,411) had mild pre-eclampsia, 61% (6304/10,411) had severe pre-eclampsia and 2% (208/10,411) had eclampsia; 16% (1701/10,411) of caesarean sections were performed under general anaesthesia and 84% (8710/10,411) under regional anaesthesia. The studies included women from Nigeria (n=5), South Africa (n=3), India (n=2) and one study from each of the following countries: Iran, Pakistan, Thailand and Taiwan. All women were delivered in tertiary centers. Ten were retrospective observational studies, one was a prospective study and three were randomised studies.

The studies reported the following outcomes: maternal death (n=8), perinatal death (n=7), low Apgar score at 1 minute (n=6), low Apgar score at 5 minutes (n=5), post partum hemorrhage (n=3), intensive care unit admission (n=6), seizures (n=6), pulmonary oedema (n=4), postpartum haemorrhage (n=4), and one reported on the following outcomes, admission to neonatal intensive care unit (NICU), post operative ventilation, blood transfusion and cerebral vascular accidents (CVA). Appendix 1 shows characteristics of included studies.

Quality of the studies

Quality assessment by the Newcastle Ottawa Scale for comparative studies on type of anaesthesia in women with pre-eclampsia showed that a fifth (3/14, 21%) had high risk of overall bias. None of the studies had a high risk of bias for selection or outcome assessment domains, and three quarters (11/14) had high risk of bias for comparability. The risks of bias for individual domains are provided in Fig 2.

Type of anaesthesia administered and maternal outcomes

Administration of general anaesthesia increased the odds of maternal death (OR 7.70, 95% CI 1.9- 31.0, $I^2=58\%$) by seven fold in women with pre-eclampsia compared with regional anaesthesia. There was a significant increase in the odds of maternal admission to intensive care unit (OR 16.25, 95% CI 9.0 to 29.5, $I^2=65\%$), need for post operative ventilation (OR 45.0, 95% CI 8.16 to 248.12), pulmonary oedema (OR 5.16, 95% CI 2.5 to 10.4, $I^2=0\%$) and post partum haemorrhage (OR 6.53, 95% CI 2.3 to 18.9, $I^2=78\%$). There was no significant difference in the risk of eclampsia (Fig 3).

Type of anaesthesia administered and perinatal outcomes

The odds of perinatal death were increased by three-fold (OR 3.01, 95% CI 1.4 to 6.5, $I^2=56\%$) when general anaesthesia was administered to women with pre-eclampsia than regional anaesthesia. There was a significant association between general anaesthesia and low Apgar score at 1 minute (OR 2.50, 95% CI 1.3 to 4.6, $I^2=50\%$), at 5 minutes (OR 4.73, 95% CI 2.4 to 9.5, $I^2=40\%$), and admission to NICU (OR 2.75, 95% CI 1.5 to 5.0) than regional anaesthesia (Fig 4).

Types of anaesthesia and maternal haemodynamic state

General anaesthesia was significantly associated with intraoperative hypertension (OR 17.49, 95% CI 5.43 to 56.36, $I^2=41\%$), postoperative hypertension (OR 13.4, 95% CI 2.46 to 73.46, $I^2=0\%$), and maternal tachycardia (defined as rise of 25% from baseline) than regional anaesthesia (OR 5.50, 95% CI 2.51 to 12.05, $I^2=0\%$) (Figure 5).

We observed a protective effect of general anaesthesia on intraoperative hypotension (OR 0.43, 95% CI 0.21 to 0.85, $I^2=0\%$), vasopressor use (OR 0.45, 95% CI 0.22 to 0.94, $I^2=0\%$), and maternal bradycardia (defined as fall of 25% from baseline) (OR 0.40, 95% CI 0.17 to 0.95, $I^2=0\%$) than regional anaesthesia. There were no differences in postoperative hypotension (OR 0.46, 95% CI 0.13 to 1.63, $I^2=0\%$) (Figure 5).

Discussion

General anaesthesia administration in women with pre-eclampsia undergoing caesarean section is significantly associated with an increase in maternal and perinatal death, and other complications such as maternal intensive care admission, pulmonary oedema and low Apgar scores at one and five minutes. There was also a higher

association of intraoperative and postoperative hypertension following general than regional anaesthesia.

The review was carried out using a prospective protocol, and rigorous methodology. The studies included women across the spectrum of disease, and the findings are generalisable. We were able to perform analysis of comparative data for general and regional anaesthesia, for key clinical outcomes. We were limited by the heterogeneity in definitions of population, intervention and outcome. Individual studies did not provide data on outcomes according to the severity of the disease, and we were unable to look for a differential effect according to disease severity. The methods and drugs used to carry out the regional and general anaesthesia were not the same across the studies, or were not documented.^[11, 12] The majority of the studies were limited to only tertiary centers, with the possibility of worse outcomes in district and rural settings, as well as a higher percentage of general anaesthesia use. We were unable to undertake meta-regression to assess the effects of disease severity, setting, practitioners, study quality and year of publication on outcomes due to paucity of data, and the small numbers of studies.

Existing systematic reviews in pregnant women in LMIC has shown tripling of odds of maternal death with caesarean section.^[13] However, in this review, we found that a diagnosis of pre-eclampsia further doubled the already high maternal mortality rate in these women. Women with pre-eclampsia are at higher risk from general anaesthesia for a variety of reasons. These include difficult or failed intubation from associated airway oedema and from intra operative blood pressure surges precipitating intra-cerebral haemorrhage. This may have been significant in many of these women, as more than half of mothers in this review had severe pre-eclampsia. The adverse effect

on perinatal deaths with general anaesthesia in these women with pre-eclampsia was similar to that of general population in LMIC. ^[13]

We found an increase in intraoperative and post-operative hypertension (rise in 20-25% from baseline) in the general anaesthesia group. This is similar to the findings observed in other studies^[14], and is hypothesised to be due to sympathetic response during intubation. Such a phenomenon could be very serious in women who have severe pre-eclampsia and are already severely hypertensive. UK confidential enquiries have found that in deaths the largest number of deaths following pre-eclampsia are secondary to intracranial haemorrhage, a known complication of severe hypertension.^[15]

The fear of spinal anaesthesia in patients with severe pre-eclampsia is the perceived risk of severe hypotension and low cardiac output resulting in placental hypoperfusion and poor perinatal outcomes, as well as the risk of iatrogenic pulmonary oedema if intravenous fluid bolus is used to treat hypotension.^[16, 17] However studies have shown that patients with severe preeclampsia have less frequent and less severe hypotension in response to spinal anaesthesia than normotensive parturients.^[18] Our findings have shown intraoperative hypotension (fall in 20-25% from baseline) in the spinal group, but this was reported to be easily treated and to have responded well to vasopressors.

In high-income countries it is now accepted that regional anaesthesia for Caesarean delivery is safer where no contraindications exist, and in women with pre-eclampsia spinal anaesthesia is recommended (unless epidural analgesia for labour is already working). However in LMIC, these recommendations do not always filter through and

are sometimes unclear or not always easy to follow. Anaesthetic care providers in LMIC are restricted in their ability to perform regional anaesthesia due to the high cost and unavailability of epidural and spinal sets, lack of personnel with the skills to administer regional anaesthesia, and moribund condition of the presenting patients, and little time and resources to optimise the condition prior to anaesthesia. Our systematic review has highlighted the potential harm of using general anaesthesia in this group of very high-risk women. The haemodynamic effects and feto-maternal consequences of spinal anaesthesia need to be also compared with epidural anaesthesia and newer combined spinal epidural (CSE) techniques.

There is a need for well conducted large studies evaluating the risks of general and regional anaesthesia in LMIC, and compare the effects of administering anaesthesia between physician anaesthetists, and non-physician cadre of trained anaesthetic providers. Health policy makers need to prioritise improvements in the ability of maternity units in LMIC to provide safe anaesthesia and promote good practice guidelines in the management of high-risk patients. On going efforts such as those of LifeBox, which promote safe anaesthesia during surgery^[19], needs to be extended to include high risk women undergoing caesarean section.

Conclusion:

Regional anaesthesia should be considered as the first choice of anaesthesia in women with pre-eclampsia in LMIC necessitating caesarean section if there are no specific contraindications.

Declaration of interest: The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

References

- [1] Tranquilli AL, Dekker G, Magee L, Roberts J, Sibai BM, Steyn W, et al.: The classification, diagnosis and management of the hypertensive disorders of pregnancy: A revised statement from the ISSHP. *Pregnancy Hypertens* 2014;4(2): 97-104.
- [2] Mol BWJ, Roberts CT, Thangaratinam S, Magee LA, de Groot CJM, Hofmeyr GJ: Pre-eclampsia. *The Lancet* 2016;387(10022): 999-1011.
- [3] Say L, Chou D, Gemmill A, Tunçalp Ö, Moller A-B, Daniels J, et al.: Global causes of maternal death: a WHO systematic analysis. *The Lancet Global Health* 2014;2(6): e323-e333.
- [4] Gogarten W: Preeclampsia and anaesthesia. *Current opinion in anaesthesiology* 2009;22(3): 347-351.
- [5] Moher D, Liberati A, Tetzlaff J, Altman DG, Group P: Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *PLoS medicine* 2009;6(7): e1000097.
- [6] world bank. <http://data.worldbank.org/>.
- [7] Organization WH: ICD-10, International statistical classification of diseases and related health problems, 10th revision. 2010.
- [8] WHO. http://www.who.int/maternal_child_adolescent/topics/maternal/maternal_perinatal/en/ Accessed 10/08/14 2014.
- [9] Wells GA SB, O'Connell D, Peterson J, Welch V, Losos M, Tugwell P, . http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp. Accessed 10/08/14.
- [10] StataCorp.: Stata Statistical Software: Release 12. *College Station, TX: StataCorp LP* 2015.
- [11] Ul-Haq MA: Analysis of outcome of general versus spinal anaesthesia for caesarean delivery in severe pre-eclampsia with foetal compromise. . *Biomedica* 2005;20-27.
- [12] Keerath K, Cronje L: Observational study of choice of anaesthesia and outcome in patients with severe pre-eclampsia who present for emergency Caesarean section. *Southern African Journal of Anaesthesia and Analgesia* 2014;18(4): 206-212.
- [13] Sobhy S, Zamora J, Dharmarajah K, Arroyo-Manzano D, Wilson M, Navaratnarajah R, et al.: Anaesthesia-related maternal mortality in low-income and middle-income countries: a systematic review and meta-analysis. *The Lancet Global Health* 2016;4(5): e320-e327.
- [14] Connell H, Dalgleish JG, Downing JW: General anaesthesia in mothers with severe pre-eclampsia/eclampsia. *British journal of anaesthesia* 1987;59(11): 1375-1380.
- [15] Neilson J: Centre for Maternal and Child Enquiries- Saving mothers' lives: reviewing maternal deaths to make motherhood safer: 2006-8: a review. *British journal of anaesthesia* 2011;107(2): 66-70.
- [16] Hood DD, Curry R: Spinal versus epidural anesthesia for cesarean section in severely preeclamptic patients: a retrospective survey. *Anesthesiology* 1999;90(5): 1276-1282.
- [17] Howell P: Spinal anaesthesia in severe preeclampsia: time for reappraisal, or time for caution? *International Journal of Obstetric Anesthesia* 1998;7(4): 217-219.

- [18] Henke VG, Bateman BT, Leffert LR: Spinal Anesthesia in Severe Preeclampsia. *Anesthesia & Analgesia* 2013;117(3): 686-693.
- [19] Walker IA, Reshamwalla S, Wilson IH: Surgical safety checklists: do they improve outcomes? *British journal of anaesthesia* 2012;109(1): 47-54.