CLINICAL UPDATE

Recipes for obstetric spinal hypotension: The clinical context counts

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Hypotension following obstetric spinal anaesthesia remains a common and important problem. While recent research advances have brought us closer to the perfect recipe for the obstetric spinal anaesthetic, these advances have not been translated into practical guidelines able to reduce the unacceptable number of fatalities that occur in environments where resources are limited. In South Africa, more than half of anaesthetic deaths are still related to spinal hypotension. A gap exists between the 'perfect recipe', developed from a clinical context rooted in resource-rich research environments, and its application and performance in real-world resource-poor environments – conditions experienced by more than 75% of the world's population. This review attempts to define this knowledge gap and proposes a research agenda to address the deficiencies.

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Hypotension following obstetric spinal anaesthesia remains a common and important problem. Recent advances, including better incidence delineation,[1] improved understanding of haemodynamics[2,3] and growing clarity on vasopressor choice,[4] have brought us closer to the recipe for the perfect obstetric spinal anaesthetic – the elusive 'Holy Grail'.[5] Unfortunately, in many resource-limited environments these advances have not been adopted. This may be related to concerns about generalisability, in part due to known anatomical and physiological differences in populations and minor differences in the studied recipes, and in part to the context in which they are applied. Research advances have not been translated into practical guidelines able to reduce the unacceptable number of fatalities that occur in resource-limited environments. In South Africa (SA) the 2011 - 2013 National Committee for Confidential Enquiry into Maternal Deaths (NCCEMD)[6] reported that more than half of all anaesthetic deaths were still related to spinal hypotension. A gap exists between the 'perfect recipe', developed from a clinical context rooted in resource-rich research environments, and its application and performance in real-world resource-poor environments – conditions experienced by more than 75% of the world's population.[7] This review attempts to define this knowledge gap and proposes a research agenda to address the deficiencies.

Context is king – the importance of the clinical environment

Why is it necessary to distinguish between differing clinical contexts? There are marked differences in the availability of staff, equipment, drugs and infrastructure across different levels of the health sector. This is tacitly acknowledged by the reluctance to implement some research findings in resource-poor environments. Management strategies need to be adapted to match available clinical skill, drug availability, monitoring capabilities and patient profile. To frame further discussion, we propose a classification of three contexts that potentially require different clinical approaches (Table 1).

Resource-poor clinical contexts are limited on multiple fronts. For example, poorer staffing ratios are compounded by a lack of

Table 1. Suggested definitions of clinical context in obstetric anaesthesia

Clinical context	Personnel	Equipment	Health system
Resource rich	Dedicated senior anaesthetist with obstetric expertise	Invasive monitoring, full anaesthetic facilities and infusion pumps	Well-assessed and triaged, hydrated and optimised patients. Modern theatres, recovery facilities and good staffing ratios
Resource constrained	Dedicated junior anaesthetist, lacks experience, slower reaction times	Basic monitoring (NIBP/ECG/SpO_2) in all cases, anaesthesia machine, infusion pumps usually available	Intermittent-level care – may be dehydrated patients, unrecognised comorbidity. Overloaded systems with delays in accessing theatres
Resource poor	Part-timer/nurse, lack of experience, slower reaction times, divided attention	NIBP, SPO_2 in most cases, Ambu bag and oxygen available. No infusion pumps. Inconsistent drug and sundry supply	Not reliably assessed and managed preoperatively. Undetected pathology more likely. Poor theatre design and no recovery facility

NIBP = non-invasive blood pressure; ECG = electrocardiogram; SpO_2 = peripheral capillary oxygen saturation.

expertise and training. The responsible doctor does not necessarily have an understanding of the principles of anaesthesia, and the job is often allocated by default to the doctor or nurse who is unable to perform the surgery. This is further complicated by a lack of available equipment (such as electrocardiographic monitoring) and inconsistent drug supplies. Vasopressor choice is often dictated by availability rather than preference. In addition, the attending doctor is frequently required to perform more than one function, often as both obstetrician and anaesthetist, and will be making rapid assessments of patients in multiple locations in the lead-up to surgery. This increases the likelihood of missing significant obstetric and medical comorbidities and significant dehydration in patients presenting to theatre. Attending doctors may need to administer the initial anaesthetic and also conduct the surgery, being required to monitor the anaesthetic either directly while operating or via a nurse. This scenario applied in 7% of the anaesthetic deaths analysed in a recent national report.[8] The anaesthetist may have very limited experience of general anaesthesia for caesarean section (CS) and therefore inappropriately administer spinal anaesthesia in cases where general anaesthesia is indicated. Management strategies must therefore be tailored to a low-expertise environment with poorly prepared patients and a lack of anaesthetic vigilance. Theoretically, simple preventive strategies such as fixed, low-dose vasopressor infusions may minimise the need for rapid clinician intervention and therefore hold an advantage over strategies highly reliant on clinician intervention.

The SA context

The SA health system includes hospitals from all three contexts. Tertiary hospitals are often well staffed and well equipped, while district-level hospitals, especially in the rural setting, suffer from staffing and equipment deficiencies. Even at regional level, the number of CSs performed outstrips the number of trained anaesthesia providers, creating a relatively resource-constrained environment.[6] In the *Saving Mothers* report for 2011 - 2013,[6] three out of every four mothers who died as a result of direct anaesthetic causes received spinal anaesthesia, with 'small district hospitals contributing disproportionately to anaesthetic related maternal deaths'. This pattern is unusual, as mortality rates generally tend to increase in more specialised centres owing to greater case complexity. In SA this pattern is reversed, with 56% of all deaths occurring in district hospitals, 35% in the regional centres and 8% in the tertiary centres.[6] The majority of women who died in district-level hospitals received a spinal anaesthetic. This pattern has been noted in previous reports,[8] where 64% of all spinal deaths were related to severe uncorrected hypotension. Although the exact case fatality rate for spinal v. general anaesthesia is unknown because denominator data are incomplete, the total number of anaesthetic deaths in SA is increasing, particularly in the group who receive spinal anaesthesia.[6] This represents an area where relatively simple interventions may result in significant changes.

The clinical context and current obstetric evidence

Research on obstetric spinal hypotension has largely been performed under highly standardised research conditions, which do not reflect the broader SA context. There is an intense focus on management of patients by senior clinicians, usually in elective rather than emergency cases and often incorporating highly specialised invasive monitoring. This is a requirement for high-quality research, where sophisticated methods elucidate an underlying mechanism and are then translated into simple clinical interventions. However, given that these interventions will be applied in a significantly different context, they must still be tested in the real-world setting. While SA has continued to produce internationally recognised research, a gap exists between the research context and the reality of the SA public health sector. There is a need to translate critical research into pragmatic management strategies that target a specific clinical context, and then test these strategies in that environment.

Relevant current literature

Over the past 10 years, significant progress has been made in defining and predicting hypotension, and describing haemodynamic changes during spinal anaesthesia for CS. These insights have all contributed to the development of the current state-of-the-art recipe. We will discuss each of these aspects in turn, focusing on clinical context gaps.

Incidence and definition

The incidence of obstetric spinal hypotension varies according to the definition applied.[1] Klohr *et al.*[1] found across 63 publications that the incidence of spinal hypotension was 27% when defined as a systolic blood pressure (SBP) <70% of baseline, but that it increased to 39% using an SBP of <75% of baseline. Up to 80% of spinal anaesthetics in obstetrics require the use of a vasopressor to treat hypotension.[9] Most of these studies came from resource-rich environments, and there are few studies that look at this incidence in resource-constrained environments. It is reasonable to assume that the incidence and severity of hypotension could be significantly higher in the latter setting. This is important because the NCCEMD process does not address the 'near-misses', and therefore does not quantify the true extent of the problem.

Prediction of obstetric spinal hypotension

Avoiding spinal hypotension is important for maternal and fetal safety as well as for maternal comfort, since even minor degrees of hypotension are associated with an increased incidence of intraoperative nausea and vomiting.[10] The prediction of obstetric spinal hypotension has received considerable attention and has recently been the subject of review in a local journal.[11] While a number of practical predictors such as body mass index, maternal age and baseline heart rate have shown potential, results have been conflicting and applied predominantly to elective patients. Autonomic indices such as heart rate variability have also shown promise,[12] but have yet to be translated into a practical clinical tool. Given the high incidence of hypotension,[1,9] research in this area should focus on predicting which patients will have *severe* hypotension, where outcomes relating to maternal and fetal safety are more likely to be affected. We need simple clinical parameters that identify high-risk patients and can be coupled to preventive strategies or earlier referral to specialist centres. There are no scoring systems in daily use addressing this need.

Haemodynamic changes under spinal anaesthesia

The dominant mechanism behind obstetric spinal hypotension is a reduction in arterial sympathetic tone,[2,3,13,14] although venodilatation probably also plays a role. This hypotension results in an increased heart rate,[3] although a small proportion of patients may respond with hypotension and bradycardia.[15] Better understanding of the

mechanism of hypotension has led to clinical management moving from a fluid-based strategy towards a vasopressor-based prophylactic strategy supported by fluid co-loading.[16] One study proposed that heart rate may be 'the best surrogate indicator of cardiac output during spinal anesthesia for cesarean delivery'.[2] This is of particular relevance to the resource-poor setting, where targeting simple surrogate outcomes such as heart rate could be explored for practical implementation in clinical guidelines.

The choice of vasopressor

In recent years there has been a move towards using phenylephrine as the agent of choice in treating obstetric spinal hypotension.[4] Despite prevailing evidence, practice has been slow to change even in settings with similar resources to those in which the research was conducted.[17] In an excellent editorial, Smiley[17] questioned the reluctance of anaesthetists to embrace the use of phenylephrine and offered several explanations for this. One reason put forward was that the choice is not perceived as 'being quite a life and death issue'. This argument could be advanced in resource-rich settings where a dedicated anaesthetist is available to respond quickly and appropriately to a decrease in blood pressure, but it may not apply to a less ideal context. Experienced anaesthetists potentially respond more rapidly to signals such as patient symptoms and heart rate, but this cannot be relied upon in settings where there is no dedicated anaesthetist. Preventive strategies that reduce the need for rapid intervention should have important advantages in this context. Prophylactic strategies have not been adopted in SA because of concerns about feasibility in resource-constrained hospitals and about safety in the hands of inexperienced clinical staff, a concern echoed in international guidelines.[18] This concern may be unfounded, given that simple strategies such as fixed-rate, low-dose phenylephrine infusions have a low complication rate and provide improved haemodynamic stability and are therefore particularly suited to the inexperienced anaesthetist. Also, it is only by effective prophylactic use of vasopressors that maternal symptoms due to spinal hypotension can be prevented.

Vasopressor management strategies

Modern strategies for combating obstetric spinal hypotension employ a combination of fluid and a vasopressor. The recommended first-line agent is phenylephrine,[4] with the notable exceptions being the patient who responds to spinal anaesthesia with bradycardia and hypotension, or has undiagnosed cardiac disease and unexpectedly requires positive inotropy. Recent literature has moved the debate from the choice between ephedrine and phenylephrine to the manner in which phenylephrine should be given. This reflects an acceptance of phenylephrine as the drug of choice. Initial work using high phenylephrine infusion rates (100 μg/min) and aggressive fluid co-loading showed that hypotension could be almost eliminated, but at the cost of reactive hypertension.[10,19] Subsequent work with lower-dose phenylephrine infusions supported prophylactic infusions as part of routine CS.[14] Further dose-finding studies suggested that a range of 25 - 50 μg/min seemed to give the most benefit with the fewest side-effects.[20,21] Haemodynamic studies also suggested that targeting the baseline heart rate may be the best way to maintain cardiac output during phenylephrine administration.[2]

A recent systematic review concluded that prophylactic phenylephrine infusions reduced maternal hypotension, nausea and vomiting without altering other relevant maternal or neonatal outcomes.[22] The setting of this work is elective CS in healthy patients, in ideal clinical conditions. In a recent editorial, Butwick *et al.*[16] noted that the potential impact of phenylephrine infusions in a number of higher-risk groups, including women undergoing unplanned CS, has not been well elucidated. They went on to state that 'titrated phenylephrine infusions co-administered with crystalloid should now be recommended for prophylaxis against spinal hypotension'.[16] However, because the context of the research is very specific, it is not clear how to implement this in differing environments.

Current guidelines

Strategies to combat hypotension on a pharmacological basis can be divided into 'reactive' or 'preventive' approaches. Reactive approaches generally involve early and aggressive treatment with fluid and a vasopressor bolus in response to a significant decrease in blood pressure. Implicit in these strategies is a vigilant anaesthetist with adequate experience in the field. Many guidelines offer the choice of ephedrine or phenylephrine as the vasopressor, including the National Institute for Health and Care Excellence (NICE)[23] and SA guidelines.[24] These recommendations reflect caution in applying conclusions drawn from research on elective CS in healthy women to the urgent CS in women with comorbidity in different clinical environments.

The NICE clinical guidelines for CS[23] state that 'Women who are having a CS under regional anaesthesia should be offered intravenous ephedrine or phenylephrine, and volume pre-loading with crystalloid or colloid to reduce the risk of hypotension occurring during CS.' They further recommend that 'intravenous ephedrine or phenylephrine should be used in the management of hypotension during CS'. One guideline in the UK recommends that anaesthetists should 'only consider phenylephrine infusion for elective CS and if they have received training in equipment and the technique'. For emergency cases, a bolus technique is recommended.[18] 2004 SA recommendations[24] state that 'the standard first line and very safe vasopressor is ephedrine', although later Essential Steps in the Management of Obstetric Emergencies (ESMOE) informal recommendations allow for either ephedrine or phenylephrine to be used. No mention is made of prophylactic vasopressor infusions. It is evident that despite overwhelming evidence for the benefit of prophylactic phenylephrine infusions in elective patients, clinicians are reluctant to implement these findings even in the resource-rich setting in which the research was performed. This was highlighted more than 6 years ago, but continues to be a concern.[17]

Closing the gap

It is clear that there is a gap between the research clinical context and the application of research to the resource-poor context. In order to close this gap, we need to develop and test models in a broader context and acknowledge the need for context-sensitive management strategies. Table 2 offers some hypothetical context-sensitive guidelines and the rationale for these approaches.

These recipes need to be refined and tested with pragmatic studies that evaluate the ability of institutions in differing contexts to achieve success with differing guidelines in resource-limited areas, by conducting well-designed, multicentre studies. In SA this could be accomplished through the establishment of an obstetric anaesthesia research group focused on large pragmatic clinical trials aimed at improving maternal safety during CS. Such a network could be established rapidly by making use of existing structures such as the South African Obstetric Anaesthesia Special Interest Society, the ESMOE and the South African Perioperative Research Group. This network should set national priorities for obstetric anaesthesia research and focus on the SA context. Research centres could be established in resource-limited areas, where potential interventions could be tested in small pilot trials preceding large national pragmatic

Table 2. Suggested vasopressor recipes based on clinical context

Context	Presumption	Fluids	Vasopressor	Notes
Resource rich	Patients hydrated and well assessed, vigilant senior anaesthetist	Co-load	Phenylephrine infusion (start at 50 µg/min), titrate to effect	Good evidence-based research Target near-normal baseline heart rate and blood pressure
Resource constrained	May be fluid deficit, unrecognised pathology, junior anaesthetist	Consider preload, administer co-load	Phenylephrine infusion (25 µg/min) Titrate if experienced, otherwise run at fixed rate: bolus intermittently and discontinue if reactive hypertension	Applied from research-setting data Good theoretical basis, requires testing in real-world setting
Resource poor	May be fluid deficit and unrecognised pathology, junior anaesthetist, divided attention	Preload/ rehydrate and co-load	Phenylephrine (500 µg) or ephedrine (50 mg) in first litre of crystalloid – run freely then convert to bolus strategy	Lack of evidence for this approach Requires study prior to application

Table 3. Proposed perioperative research agenda for obstetric spinal hypotension

Need	Rationale
Validate traditional predictors of spinal hypotension in context and continue to explore novel predictors with practical applicability	Early identification of high-risk patients a priority, enabling appropriate resource allocation via referral and potentially different management strategies
Develop a robust scoring system to identify mothers at risk of hypotension following spinal anaesthesia for CS, using these predictors	
Develop easily available novel scoring tools (such as the obstetrics shock index)	
Comparison of a prophylactic vasopressor infusion with a treatment bolus strategy for the management of hypotension following spinal anaesthesia for CS	Safe practical ways to utilise the current knowledge base in resource-poor settings should be tested
Develop simple methods of applying prophylactic vasopressor infusion strategies in resource-poor environments	
Research the principle of targeting heart rate for the prevention and treatment of hypotension: initially in the academic setting, and then apply to regional centres	Newer techniques first studied in controlled, strictly protocol-driven studies before testing in other contexts
Develop an obstetric research network in SA and agree on a research framework and pathway	Co-ordinating research will enable bigger, multicentre trials, while drawing on experience from established centres

trials. A proposed research agenda for such a programme is outlined in Table 3.

Conclusion

In recent years there have been significant advances in the field of obstetric anaesthesia. High-quality research has outlined the mechanism, described the haemodynamic changes and refined the management of obstetric spinal hypotension. However, there is a gap between this knowledge base and its implementation in real-world settings outside the research environment. We need to acknowledge this gap, and focus on contextualising research findings in a pragmatic fashion. This is best achieved through innovative, collaborative research, starting in academic centres, and applying the findings in the context of limited-resource environments.

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