

A prospective interventional study of the efficacy of a protocol for prevention and treatment of hypotension following spinal anaesthesia for Caesarean section at Pelonomi Hospital

**JL Esterhuizen*, G Lamacraft
2005076647**

Department of Anaesthesiology, University of the Free State, Universitas Academic Hospital, Bloemfontein, South Africa

**Corresponding author, email: jovan2607@gmail.com*

A research report submitted to the Faculty of Health Sciences, University of the Free State, Bloemfontein, in partial fulfilment of the requirements for the degree Masters of Medicine in the branch of Anaesthesia.

Bloemfontein 2019

Index

Acknowledgements	iv
List of Figures	v
List of Tables.....	v
List of Appendices.....	v
• Ethics approval letter.....	v
• Permission from department.....	v
• Permission from Province	v
• Consent in Sotho, English and Afrikaans.....	v
• Patient information sheet in Sotho, English and Afrikaans.....	v
• Data Collection sheets Baseline and Intervention Group	v
Abbreviations	vi
Chapter 1	1
Protocol	1
1.1 Introduction	1
1.2 Aim.....	3
1.3 Methods.....	3
1.3.1 Study design	3
1.3.2 Sample	3
1.3.3 Consent.....	4
1.3.4 Measurement	4
1.3.5 PROTOCOL TO BE USED FOR STUDY	8
1.3.6 Algorithm	16
1.3.7 Pilot study.....	17
1.3.8 Limitations.....	17
1.3.9 Ethical considerations.....	18
Chapter 2	19
2.1 Abstract	19
2.2 Introduction	20
2.3 Methodology	21
2.3.1 Introduction	21
2.3.2 Study design	22
2.3.3 Study Site	22

2.3.4 Study Population	22
2.3.5 Ethical considerations.....	22
2.3.5.1 Authorization.....	22
2.3.5.2 Participation and Informed Consent.....	23
2.3.5.3 Confidentiality.....	23
2.3.6 Inclusion and exclusion criteria.....	23
2.3.6.1 Inclusion criteria.....	23
2.3.6.2 Exclusion criteria.....	23
2.3.7 Construction of the Study.....	24
2.3.8 Data Management/Analysis.....	35
2.4 Results	35
2.....	46
5.....	46
Discussion	46
2.6 Discussion of potential limitations and shortcomings of the study	50
2.7 Conclusion.....	51
2.8 Declaration of interest	51
2.9 Funding.....	51
2.10 References	51
Chapter 3	54
Suggestions for practice and further research.....	54
Appendices	54
Appendix A: Ethics approval letter	55
Appendix B: Permission from department.....	56
Appendix C: Permission from province	57
Appendix D: Consent in Sotho, English and Afrikaans	58
Appendix E: Patient information sheet in Sotho, English and Afrikaans.....	61
Appendix F: Data collection sheet	65
<i>(Baseline Group)</i>	65
<i>(Intervention Group)</i>	66

Declaration of own work

I, Jovan Esterhuizen, declare that this research report is my own work. It is being submitted for the degree of Master of Medicine in the branch of Anaesthesia at the Faculty of Health Sciences, University of the Free State, Bloemfontein. It has not been submitted before for any degree or examination at this or any other University.

Acknowledgements

I am grateful to the following people:

- Prof G Lamacraft; my mentor, supervisor and study leader, for her advice, encouragement and support during the supervision of this project.
- The Department of Anaesthesia, Universitas Hospital complex, for the countless hours of research time given for data collection and for the costs of the consent and data collection forms.
- Mr. Cornel van Rooyen, Department Biostatistics for the data analysis and graphs.
- Prof Gina Joubert, Department of Biostatistics for all her teaching on how to write a protocol and a MMed report.
- Dr. Lemmer (Obstetric Anaesthesia Specialist at Universitas Academic Hospital), for her advice on the compilation of the algorithm.
- Dr. David Bishop (Specialist in Anaesthesia, Pietermaritzburg), a South African Obstetric Anaesthesia expert for reviewing the algorithm.
- The consultants in the Department of Anaesthesiology, Universitas Hospital.

List of Figures

- Figure 1: Infusion setup with flow control device and PEP infusion connected to patient
- Figure 2: CONSORT flow chart
- Figure 3: Number of patients expressed as % who required boluses of phenylephrine (PEP), ephedrine, atropine or adrenaline.
- Figure 4: Median Systolic BP before and after delivery.
- Figure 5: Heart Rates before and after delivery
- Figure 6. Distribution of patients with hypotension and/or bradycardia

List of Tables

- Table 1: Baseline patient characteristics.
- Table 2: Blood pressures in Baseline and Intervention Groups.
- Table 3: Maternal Complications.
- Table 4: Summary of the differences found between Group B and Group I.

List of Appendices

- Ethics approval letter
- Permission from department
- Permission from Province
- Consent in Sotho, English and Afrikaans
- Patient information sheet in Sotho, English and Afrikaans
- Data Collection sheets Baseline and Intervention Group

Abbreviations

Baseline group: Group B

Beats per minute: bpm

Blood pressure: BP

Caesarean Section: CS

Cardiac Pulmonary Resuscitation: CPR

Cerebral Spinal Fluid: CSF

Degree: °

Electrocardiogram: ECG

Example: e.g.

Gauge: G

Gram: g

Gravidity: G

Heart rate: HR

International units: IU

Intervention group: Group I

Intravenous: IV

Kilogram: kg

Micrograms: mcg

Milligram: mg

Milliliters: mL

Millimeters mercury: mmHg

Minute: min

Non-Invasive Blood Pressure: NIBP

Percentage: %

Phenylephrine: PEP

Thoracic: T

Chapter 1

Protocol

1.1 Introduction

Hypotension after spinal anaesthesia for Caesarean section (CS) is common with an incidence of up to 71%.⁽¹⁾ To prevent this hypotension, a number of approaches have been investigated, notably fluid loading, vasopressors, or both.⁽²⁾⁽³⁾ Spinal hypotension can occur precipitously and, if severe, can result in important perinatal adverse outcomes, such as maternal nausea and vomiting, hypo perfusion of vital organs and fetal acidosis. Hypotension is an important contributory factor for maternal deaths related to regional anaesthesia.^(4,5)

There are multiple definitions for hypotension and different methods of determining hypotension. Using an absolute value is more practical although a percentage decrease is probably more accurate.⁽⁶⁾

The effect of spinal anaesthesia in a healthy woman is a decrease in systemic vascular resistance due to small artery vasodilation with a modest degree of venodilation. There is a compensatory baroreceptor-mediated increase in heart rate and stroke volume, which increases cardiac output⁽⁷⁾. The incidence of hypotension during CS is high due to compression of the gravid uterus on the inferior vena cava reducing venous return. In addition, collateral venous plexus circulation in the epidural space leads to a decreased volume of cerebral spinal fluid within the lumbosacral area and a higher cephalad spread of local anaesthetic.⁽⁸⁾

The main aim of treatment with vasopressor treatment should be to restore the reduced systematic vascular treatment caused by the spinal anaesthesia. This is best achieved by alpha 1 agonist treatment with phenylephrine.⁽⁷⁾

The causes of this hypotension have been investigated; hypovolemia, fixed cardiac output and aortocaval compression have been established as major risk factors. The 15° lateral tilt position or obstetric wedge are now almost universally used to relieve aortocaval compression by displacement of uterus away from the inferior vena cava. However, in some patients this maneuver is ineffective and unexpected profound hypotension develops in patients with none of

these risk factors. Further research is therefore needed to determine if other risk factors for this hypotension exist.

Inappropriate selection of spinal anaesthesia for a hemodynamically unstable patient may result in hypotension with a possible fatal outcome and spinal anaesthesia must be avoided in such circumstances. (4) A greater degree of left lateral tilt, or even a right tilt, may be needed to relieve aortocaval compression in some patients. The challenge is to identify these patients before administering spinal anaesthesia.

Traditionally, fluid loading regimens were seen as the gold standard for preventing hypotension.(9) More recently vasopressors, including phenylephrine and ephedrine, have been found to be more beneficial for the treatment of spinal hypotension.(10) Timing of fluid administration does play a role in preventing spinal induced hypotension. Colloid preload is more effective than crystalloid preload and crystalloid coload is more effective than crystalloid pre-loading. In general, a 500mL colloid preload is as effective as a 1000mL crystalloid coload. Thus both fluid loading techniques can be used to improve the hemodynamic status of the patient during spinal anaesthesia.(7)

The use of prophylactic phenylephrine infusion for preventing hypotension during spinal anaesthesia for CS delivery has been investigated; a randomized, double-blinded, controlled trial found a significant decrease in hypotension can be achieved with a simple technique involving a constant infusion rate. There were no adverse outcomes demonstrated measuring fetal Apgar scores.(11) The authors of this study suggested that a more flexible algorithm was needed to completely prevent hypotension as some women still experienced hypotension with their regime. (12) Phenylephrine infusions that are titrated and initiated immediately after the induction of spinal anaesthesia appears to be less labour intensive and safe.(13) Based on current evidence, phenylephrine infusion is still the standard of care in many institutions.

Automated closed loop target controlled infusions with phenylephrine have also been shown to have superior results to maintain blood pressure(BP) compared to manual administration (14) but this technology is not widely used or available in most South African hospitals.

1.2 Aim

Primary outcome:

The aim of this study was to determine the incidence of hypotension after spinal anaesthesia for CS at Pelonomi Hospital and assess the effect of a protocol aimed to lower this incidence.

Secondary outcomes:

- To determine the safety of implementing this newly developed spinal hypotension protocol in clinical practice.
- To determine any problems using this protocol.

1.3 Methods

1.3.1 Study design

Prospective interventional study

1.3.2 Sample

Institutional Ethics Committee and Free State Department of Health approval for this study was obtained (Ethics approval number UFS-HSD2017/0798). All women scheduled to receive spinal anaesthesia over a period of three months for elective or emergency CS at Pelonomi Hospital, a tertiary hospital in Bloemfontein, were invited to be included in this study and consent for this study obtained. The department of Biostatistics at the University of the Free State determined that 100 patients in each of the two groups would be needed to have significant power to determine the primary outcome. After they had their operation, their anaesthetic records were collected and analyzed for the incidence of hypotension. The newly developed protocol for hypotension was presented to doctors in the Department of Anaesthesia at a meeting and then it was implemented

for the following three months. Anaesthesia records were then used to investigate the incidence of hypotension in this second three-month time period. The results of the first three-month time period were then compared to the second three-month time period.

Exclusion criteria were explained to the anaesthesia registrars recruiting patients for this study and were then checked before data analysis started. The exclusion criteria were: patients under the age of 18 years old, patient refusal to participate in the study, any contraindications to spinal anaesthesia, multiple births, local or generalized sepsis, gestation less than 28 weeks, pre-eclampsia, chronic hypertension, conversion to general anaesthesia prior to delivery of the fetus and a non-standard anaesthetic technique.

Conveniently the first 100 patients were selected in each group.

1.3.3 Consent

The anaesthesia registrar on duty for obstetric anaesthesia obtained written consent for this study from each patient whilst obtaining standard pre-operative anaesthesia consent.

1.3.4 Measurement

The protocol was devised by the main researcher in conjunction with Professor Lamacraft and Dr Lemmer (Obstetric Anaesthesia Specialist at Universitas Academic Hospital). The protocol was also reviewed by Dr David Bishop (Specialist in Anaesthesia, Pietermaritzburg), a South African Obstetric Anaesthesia expert. The final protocol was agreed upon by the consultants in the Department of Anaesthesiology, Universitas Hospital.

The following information was recorded on the patients' anaesthesia record forms:

1. The indication for CS and any co-morbid conditions.
2. Gravidity and parity
3. The hydration status of the patient (recorded as: well hydrated, moderately hydrated or poorly hydrated).
4. The baseline noninvasive blood pressure (NIBP) reading with an appropriate sized cuff was obtained in the left lateral position.

5. An electrocardiogram was placed and the HR and pulse oximetry were recorded prior to spinal anaesthesia.

(All the above are standard pre-operative measurements and are recorded on the anaesthetic chart as routine)

If not previously in situ, an 18gauge (or 16G) IV cannula was inserted peripherally. An intravenous (IV) infusion of IV modified Ringers lactate or Normal Saline was commenced, via an infusion set delivering at least 20 drops per min.

The patient sat upright for administration of the spinal anaesthesia.

6. Spinal anaesthesia was administered according to the standard regime of this hospital. Spinal anaesthesia was administered at level L3/L4 or below, in the sitting position, using a spinal needle no wider than 22G. A sterile technique was used, including the use of a face mask and sterile gloves. On visualization of cerebrospinal fluid, 9 mg of 0.5% hyperbaric bupivacaine (1.8 mL) plus 10 mcg (0.2 mL) of fentanyl were injected intrathecally over approximately over 30 seconds and modified Ringers lactate or Normal Saline 10 mL/kg was administered rapidly intravenously (the “co-load”).
7. The patient was then immediately positioned supine with 15-30° left lateral tilt and a pillow placed under the shoulders and head for thoracic curvature. The maternal HR was continually monitored using the ECG and NIBP was measured at 1-minute (min) intervals for the first 10 min and then, if stable, measured every 3 min. If the patient was unstable, the BP was checked every min.
8. The height of the block was checked after 5 min or sooner if a high motor block was suspected.
9. At delivery, 2.5(international units) IU of oxytocin was given slowly IV over 30 to 60 seconds and the BP were checked again.

This was followed by an oxytocin infusion consisting of 20 IU of oxytocin in 1000 mL of Ringer’s Lactate or Normal Saline, infusing over 8 hours (125 mL/hour).

After the co-load, the crystalloid infusion was continued at 2 mL/kg/hour. Blood loss was replaced with crystalloids, colloids and blood products as required.

Although hypotension is clearly defined as “subnormal arterial BP”, the definition of subnormal arterial BP remains controversial. However, previous studies support the criteria of 30% decrease in systolic BP as the definition of hypotension in obstetric anesthesia.(15) Bradycardia was defined as a heart rate (HR) of less than 70 beats per minute (bpm).

Phenylephrine is the preferred vasopressor of choice but the optimal fluid volume, timing and type of fluid remains controversial.(16)

Following routine institutional practice, phenylephrine is used for hypotension as it is an alpha-adrenergic agonist and its action directly addresses the decrease in peripheral vascular resistance following spinal anaesthesia. The onset of action of phenylephrine is faster than ephedrine.

The following routine important information was documented on the anaesthetic record and then captured on the data collection form by the researcher:

- estimated blood loss
- total amount of intravenous fluids (crystalloids/ colloids/ blood products)
- if it was necessary to convert to general anaesthesia and the reason for the conversion
- gravidity and parity
- weight
- previous CS
- other chronic-illnesses or pregnancy related e.g. pre -eclampsia
- age of the patient
- tocolytic received in last six hours
- dose of oxytocin
- indication for CS
- duration of labor
- if patient was in labor
- duration of surgery
- the time of delivery
- adverse events such as cardiac arrest
- Apgars at birth

In addition to the above routine anaesthetic monitoring data, the 1 and 5 min APGAR scores were also recorded on the anaesthesia record forms. This information is relevant to gather and was included in the data collection as it can be influenced by the incidence of maternal hypotension before delivery.

The anaesthetic registrar on duty for obstetric anaesthesia obtained consent for anaesthesia and the study.

Spinal anaesthesia for each patient was administered if indicated and the data collected on the usual anaesthesia record forms. The copy of the anaesthesia records which are routinely kept by the anaesthesia registrars for medico-legal purposes (the originals remain in the patient's file), with the study consent forms, was submitted on a weekly base to the researcher at the department's academic meeting and was photocopied. The anaesthetic form was returned to the individual registrar the following week.

The researcher then extracted the relevant data from these anaesthesia record forms, and record the data on a specific data collection form. He also stored the study consent forms with the data collection forms.

This data included: the age and weight of the patient, the number of previous CS and whether the patient was pre-eclamptic. The systolic BP immediately prior to administration of spinal anaesthesia was recorded in the left lateral position.

The total IV dosage (amount of times and total amount) of phenylephrine, adrenaline, ephedrine and atropine given to manage hypotension and bradycardia was recorded, up until oxytocin is administered and then until the end of surgery.

Data collection was over a three-month period.

The following month, the Prevention and Treatment of Hypotension Protocol (see Appendix) was introduced to all members of the Department Anaesthesia, over a one-month period.

In the following three-month period, following this implementation of the hypotension protocol, the data collection was the same as for the first three-month period. On the routine anaesthetic form in the "other notes" section, it was indicated if the hypotension protocol was followed. It also stated a reason why it was not followed, e.g. drugs not available (specify), equipment not

available (specify) or the reason could be stated if not included as above. These forms were distributed weekly to the anaesthesia registrars and handed in when they hand in their anaesthesia record forms weekly to the investigators.

1.3.5 PROTOCOL TO BE USED FOR STUDY

The following protocol has been developed for spinal anaesthesia for CS and was implemented for the second three-month study period, to determine the efficacy of the protocol introduced after the first three-month study period.

Spinal Anaesthesia for Caesarean Section

PROTOCOL

(“Blood pressure” = SYSTOLIC BP)

CONTRAINDICATIONS:

These include but are not limited to the following:

Absolute

1. *Blood clotting problems* which predispose patient to high risk of paralysis after spinal needle inserted intrathecally e.g. severe coagulation abnormality (e.g. INR ≥ 1.5 or platelets $< 75 \times 10^9$).
2. *Cardiac conditions* which would result in significant hypotension as a result of the sympathetic blockade from spinal anaesthesia e.g. fixed cardiac output valvular lesions such as aortic stenosis or mitral stenosis.

3. *Hemodynamically unstable* patients who would become severely hypotensive as a result of the sympathetic blockade from spinal anaesthesia e.g. patients who are intravascularly depleted as a result of dehydration, sepsis or haemorrhage.

The pre-operative maternal HR can give an indication of potential hemodynamic instability following spinal anaesthesia. The following table was used as a guideline:

<i>Heart rate</i>	<i>Guideline</i>
> 140 bpm	Spinal inadvisable. Discuss with senior anaesthetist.
120-140	Spinal may be inadvisable. Discuss with senior anaesthetist.
100-120	Consider causes of tachycardia. If not related to potential hemodynamic instability, proceed with spinal.
<100 and ≥ 55	Proceed with spinal
<55	Investigate cause of bradycardia and discuss with senior anaesthetist.

4. *Infections* which associated with high risk of meningitis as a result of introducing the spinal needle into the subarachnoid space e.g. untreated systemic infection or skin infection at site of spinal needle insertion.
5. *Allergy* to amide local anaesthetics.
6. *Patient refusal*.

Relative

1. Fetal distress such that a general anaesthesia is considered indicated as a quicker technique (however, if the mother is a possible difficult intubation, a spinal anaesthesia may still be preferable).
2. Conditions which predispose patients to risk of meningitis (but lower than above) e.g. systemic infection treated with antibiotics.

3. Pre-existing neurological condition: these should be clearly documented pre-operatively – the evidence that they may worsen with spinal anaesthesia is controversial.
4. Respiratory failure – this may be worsened with the motor blockade from spinal anaesthesia.

PREOPERATIVE PREPARATION

1. Check drugs and equipment to induce general anaesthesia, intubate and resuscitate the patient, are immediately available in theatre; a cardiac defibrillator must be available in the theatre complex.
2. Emergency drugs that are drawn up standard for every patient are: Adrenaline, atropine, phenylephrine and ephedrine and if they are not used for a patient it will be used for the following patient.
3. Attach ECG and BP cuff (right arm). Obtain baseline systolic BP and HR readings with the patient lying in the full left lateral position.
4. A. Make up a **phenylephrine** infusion of 50 mcg/mL (e.g. 200 mL 0.9% Saline with 10 mg phenylephrine). Take a 10 mL syringe and put 10mL of this solution into it for BOLUS use.
 B. Make up an **ephedrine** solution of 5 mg/mL (draw up 50 mg ephedrine in 10 ml saline).
 C. Make up a **STRONG adrenaline** solution of 1:10 000 (1 mg in 9mL saline, thus 100mcg/mL) and a **WEAK adrenaline** 1: 100 000 (1 mL of 1:10 000 diluted in 9 mL saline, thus 10mcg/mL).
5. If not already in situ, insert an IV cannula, 18G or 16G into the patient's arm. This must be connected to a short extension with a three way tap connected on one side to an infusion set with Ringer's lactate or Normal Saline, which can run at least 20 drops per min, and on the other side to a flow control device which should already be in place from labour ward or ante natal ward (for the post-operative oxytocin infusion) which is

connected to the 50 mcg/mL of phenylephrine infusion via the flow control device. The flow control device is able to be dialed to a millimeter per hour setting and will ensure a constant one directional flow of the fluid (PEP 50mcg/mL) in to the patient. Great care will be taken to prevent an erroneously selected setting. Please see the schematic presentation of the prescribed setup for the flow control device and PEP infusion connected to the patient.

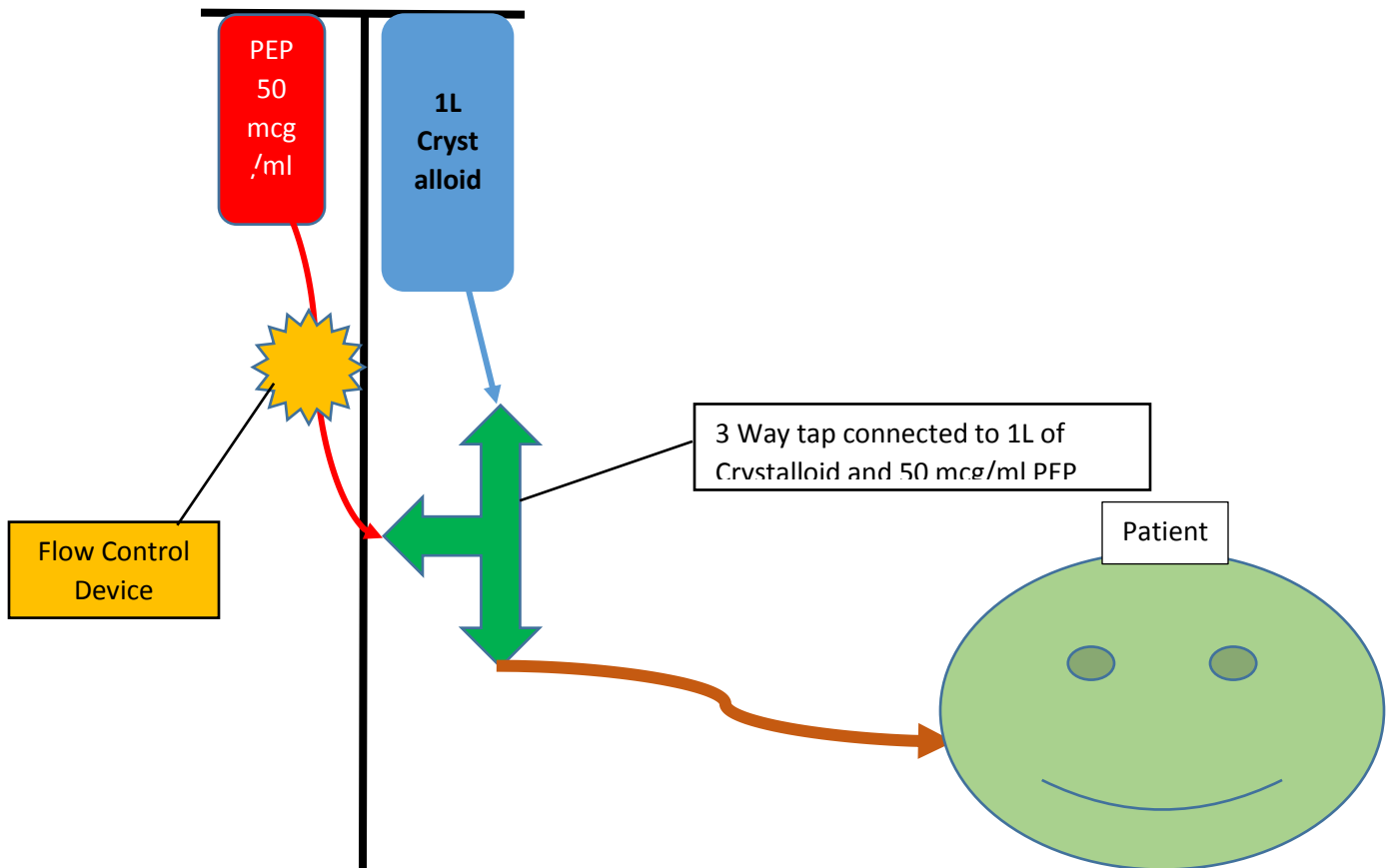


Figure 1 Infusion setup with flow control device and PEP infusion connected to patient

6. Attach pulse oximeter.
7. Sit the patient up, clean the lumbar region with antiseptic solution and drape with sterile towels.

8. Insert the spinal needle at the level of L 3/4 or lower, using a spinal needle no wider than 22G and a sterile technique including the use of a face mask and sterile gloves.
9. On visualizing cerebrospinal fluid through the needle hub, inject 1.8 mL 0.5% heavy bupivacaine with 0.2 mL (10 mcg) of fentanyl over 30 seconds.
10. Then open up the IV infusions:
 - a. Infuse 10 mL/kg Ringer's lactate or Normal Saline stat (the "co-load")
 - b. At the same time, start the phenylephrine infusion at a rate of 50 mcg/min (i.e. 60 mL/hour of infusion containing 50 mcg/min). NB DO NOT START THE PHENYLEPHRINE INFUSION IF THE BASELINE SYSTOLIC BP WAS \geq 140 mmHg. ONLY START THE PHENYLEPHRINE INFUSION WHEN THE SYSTOLIC BP DROPS BELOW 140 mmHg.
11. After *commencing* these infusions (but do not wait for the *completion* of the co-load), position the patient supine with a 15-30° left lateral tilt and a pillow under the shoulders.
12. Check the BP every one min and continually monitor the HR. After 10 min, if BP is stable, continue to check BP every 3 min. If unstable, continue to check every 1 min.
13. If the systolic BP falls below 110 mmHg, take the following actions:

A. SYSTOLIC HYPOTENSION WITHOUT BRADYCARDIA

(HEART RATE \geq 70bpm)

SYSTOLIC BP	ACTION
100-110 mmHg	Increase phenylephrine infusion to 100 mcg/min (120 mL/hour)

90-99 mmHg	Increase phenylephrine infusion to 100 mcg/min (120 mL/hour) AND give 1 mL phenylephrine bolus (50mcg)
80-89 mmHg	Increase phenylephrine infusion to 100 mcg/min (120 mL/hour) AND give 2 mL phenylephrine bolus (100 mcg)
70-79 mmHg	Increase phenylephrine infusion to 100 mcg/min (120 mL/hour) AND give 2mL phenylephrine bolus (100 mcg) AND give 1mL ephedrine bolus (5mg)
<70 mmHg	Increase phenylephrine infusion to 100 mcg/min (120 mL/hour) AND give 1mL WEAK adrenaline (1: 100 000) AND give 200 mL fluid bolus* Also: - increase relief of aortocaval obstruction (e.g. more lateral tilt, lift uterus or deliver baby) - if loss of conscious level –intubate patient** - if central pulse lost – institute cardiac pulmonary resuscitation (CPR)

B. SYSTOLIC HYPOTENSION WITH BRADYCARDIA

(HEART RATE <70 bpm)

SYSTOLIC BP	ACTION – Reduce phenylephrine infusion to 25 mcg/min AND do the following:
100-110 mmHg	Give 5 mg ephedrine (1 mL) stat
90-99 mmHg	Give 7.5 mg ephedrine (1.5 mL) stat
80-89 mmHg	Give 10 mg ephedrine (2 mL) stat

70-79 mmHg	Give 15 mg ephedrine (3 mL) stat
<70 mmHg	Give 1 mL WEAK adrenaline (1: 100 000). Repeat every 30 seconds until BP returned to baseline AND give 200 mL fluid bolus* Also: - increase relief of aortocaval obstruction (e.g. more lateral tilt, lift uterus or deliver baby) - if loss of conscious level or respiratory problems – intubate patient ±GA** - if central pulse lost – institute CPR

C. BRADYCARDIA (HEART RATE <70 bpm) WITH NO HYPOTENSION

Heart Rate	ACTION
Heart rate < 70 bpm	Reduce phenylephrine rate to 25 mcg/min
Heart rate < 60 bpm	Stop phenylephrine infusion and administer 0.5 mg atropine.

**Fluids bolus can be of 0.9% Saline, Ringers lactate, Gelofusine® or Voluven®*

*** If the patient is still conscious, give IV etomidate or ketamine before giving a muscle relaxant for intubation*

14. If BP rises to 140 mmHg or higher, stop the phenylephrine. If the BP falls below 140 mmHg, restart the phenylephrine infusion.

15. After every change of phenylephrine infusion rate or bolus of vasopressor given, re-check the BP after 1 min.

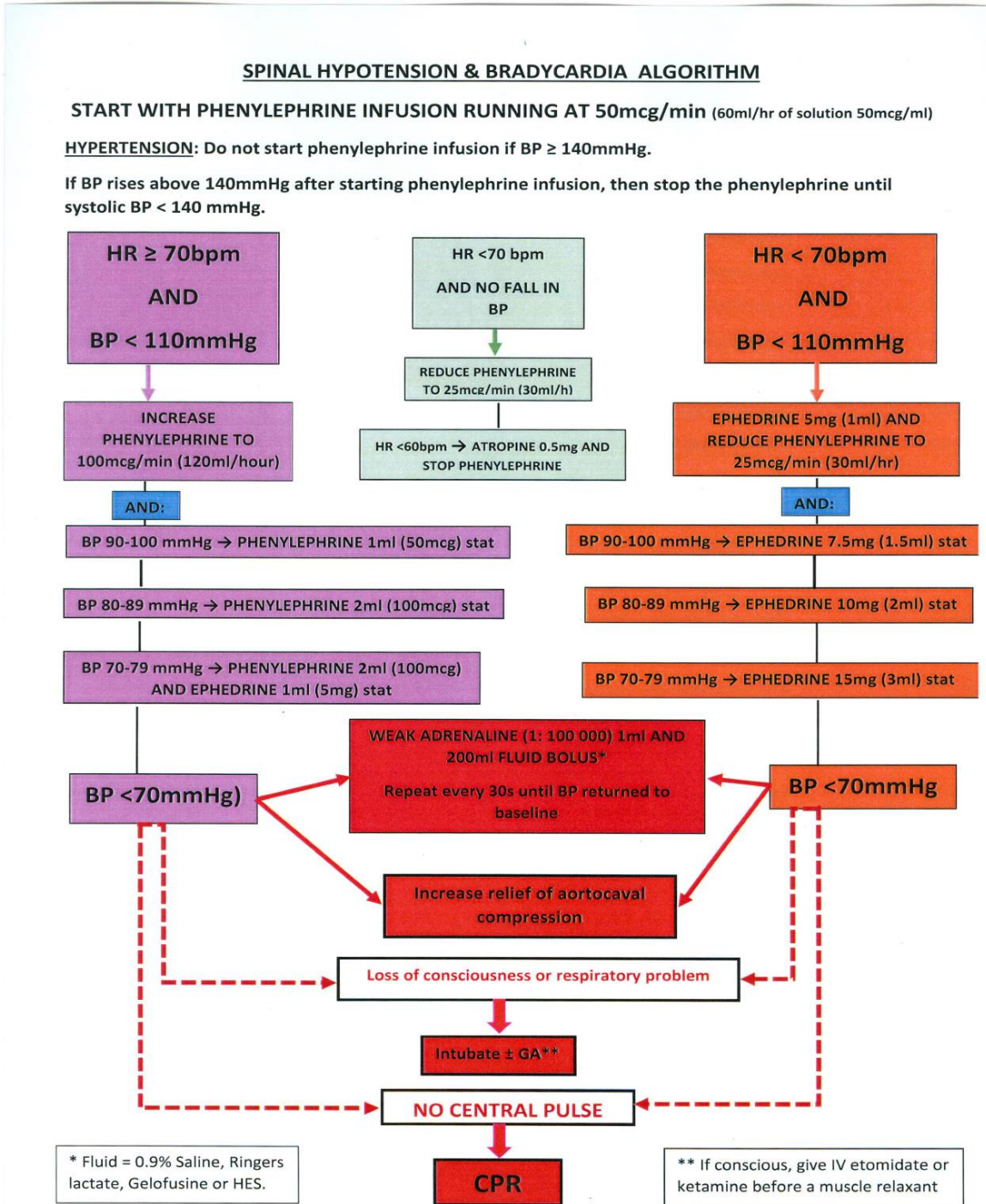
16. Check the height of the block after 5 min or sooner if suspect high motor block.

17. At delivery give oxytocin 2.5 (IU). Give slowly, over 30 seconds and then check BP.

18. Fluids: after the co-load, continue crystalloid infusion at 2 mL/kg/hour. If blood loss occurs then replace with crystalloids, colloids and blood products, as required.

1.3.6 Algorithm

An algorithm has been developed that will be implemented in conjunction with the protocol for spinal anaesthesia:



1.3.7 Pilot study

A pilot study will be performed following the procedures as outlined above. All the patients that in a 24-hour period receiving spinal anaesthesia for caesarean sections will be included. If there is no need to deviate from the protocol for subsequent data collection, the pilot study group data will be included in the final analysis.

If any adverse events were noted regarding the BP and or HR, the anaesthetic registrar would have contacted the investigator within 48 hours. The algorithm would have been reviewed and modified as needed and ethics committee permission would be sought before implementing the new algorithm.

1.3.8 Limitations

Variation will be prevented as far as possible by limiting the number of researchers involved to those at Pelonomi Hospital.

Recorded blood pressures and heart rates can possibly be recorded more thoroughly after the implementation of the protocol due to greater awareness of the risks of hypotension and bradycardia.

Baseline cardiovascular recordings can possibly be inaccurate due to external factors such as stress, pain and tocolytic usage.

The condition can change after the initial baseline readings, such as bleeding intra operatively. The effect of factors such as bleeding on haemodynamic status, will be minimized by only including haemodynamic readings up until 5 minutes after delivery for the data collection purposes of this study.

Pre-operative assessment can be influenced by drugs given to patient before arriving in theatre, for example tocolytics such as salbutamol that can cause a substantial tachycardia.

The skill of the surgeon can influence the duration of the surgery with prolonged surgery leading to increased blood loss before delivery.

Inter-observer variation must be avoided especially at determining the blood pressure technique pre-operatively, and researchers must be trained well in the methodology of the study as a whole as well as the different measurements that will be performed. Regular checks must be done of the data collection.

Specific terminology, in- and exclusion criteria and measurement procedures will be clearly defined in advance and applied consistently and precisely in this study.

Repeating communication and continuously encouraging staff will help to prevent mislaying of data forms.

1.3.9 Ethical considerations

Only patients 18 years and older were included as additional ethical permission would have been required to include minors in the study

Chapter 2

2.1 Abstract

Abstract

Background

Hypotension after spinal anaesthesia for Caesarean section is common with an incidence of up to 71%. To prevent this hypotension, a number of approaches have been investigated, notably fluid loading, vasopressors, or both. The aim of this study was to determine the incidence of hypotension after spinal anaesthesia for Caesarean section at Pelonomi Hospital and assess the effect of a protocol aimed to lower this incidence.

Methods

This was a Prospective interventional Study with 91 patients in the Baseline Group and 99 in the Intervention Group. The data was recorded for the incidence of hypotension and bradycardia for 3 months. A newly developed algorithm to prevent and treat bradycardia and hypotension was introduced and data was recorded again. The intervention group received a background phenylephrine infusion with a flow control device starting at 50 mcg/min and was titrated to maintain a blood pressure above 110 mmHg with an increase or decrease in phenylephrine and boluses of phenylephrine, atropine, ephedrine and adrenaline. The primary outcome was to determine the efficacy of a protocol for prevention and treatment of hypotension following spinal anaesthesia for Caesarean section.

Results

This study showed that the introduction of an algorithm, to prevent and treat hypotension and bradycardia following spinal anaesthesia for caesarean section, did not result in any significant differences in systolic hypotension before or after delivery ($p = 0.1427$). Use of the algorithm in patients, did result in fewer patients requiring phenylephrine boluses (vs Group B, 57% vs Group I, 35%).

Conclusion

This study showed that the introduction of an algorithm, to prevent and treat hypotension and bradycardia following spinal anaesthesia for caesarean section, did not result in any significant differences in systolic hypotension before or after delivery.

2.2 Introduction

Hypotension after spinal anaesthesia for Caesarean section (CS) is common with an incidence of up to 71%.⁽¹⁾ To prevent this hypotension, a number of approaches have been investigated, notably fluid loading, vasopressors, or both.⁽²⁾⁽³⁾ Spinal hypotension can occur precipitously and, if severe, can result in important perinatal adverse outcomes, such as maternal nausea and vomiting, hypo perfusion of vital organs and fetal acidosis. Hypotension is an important contributory factor for maternal deaths related to regional anaesthesia.^(4,5)

Hypotension occurs due to sympathetic blockade leading to a decrease in systemic vascular resistance causing peripheral pooling of blood and decreased cardiac output. The incidence of hypotension during CS is high due to compression of the gravid uterus on the inferior vena cava reducing venous return. In addition, collateral venous plexus circulation in the epidural space leads to a decreased volume of cerebral spinal fluid within the lumbosacral area and a higher cephalad spread of local anaesthetic.⁽⁸⁾

The causes of this hypotension have been investigated; hypovolemia, fixed cardiac output and aortocaval compression have been established as major risk factors. The 15° lateral tilt position or obstetric wedge are now almost universally used to relieve aortocaval compression by displacement of uterus away from the inferior vena cava. However, in some patients this maneuver is ineffective and unexpected profound hypotension develops in patients with none of these risk factors. Further research is therefore needed to determine if other risk factors for this hypotension exist.

Inappropriate selection of spinal anaesthesia for a hemodynamically unstable patient may result in hypotension with a possible fatal outcome and spinal anaesthesia must be avoided in such circumstances. ⁽⁴⁾ A greater degree of left lateral tilt, or even a right tilt, may be needed to relieve aortocaval compression in some patients. The challenge is to identify these patients before administering spinal anaesthesia.

Traditionally, fluid loading regimens were seen as the gold standard for preventing hypotension.(9) More recently vasopressors, including phenylephrine and ephedrine, have been found to be more beneficial for the treatment of spinal hypotension.(10) Timing of fluid administration does not play a major role in preventing hypotension but rather the type of fluid, in effect crystalloid vs colloid.(5)

The use of prophylactic phenylephrine infusion for preventing hypotension during spinal anesthesia for CS delivery has been investigated; a randomized, double-blinded, controlled trial found a significant decrease in hypotension can be achieved with a simple technique involving a constant infusion rate. There were no adverse outcomes demonstrated measuring fetal Apgar scores.(11) The authors of this study suggested that a more flexible algorithm was needed to completely prevent hypotension as some women still experienced hypotension with their regime. (12) Phenylephrine infusions that are titrated and initiated immediately after the induction of spinal anaesthesia appears to be less labour intensive and safe.(13) Based on current evidence, phenylephrine infusion is still the standard of care in many institutions.

Automated closed loop target controlled infusions with phenylephrine have also been shown to have superior results to maintain blood pressure(BP) compared to manual administration (14) but this technology is not widely used or available in most South African hospitals.

2.3 Methodology

2.3.1 Introduction

Approval from the institutional ethics committee was obtained. Informed written consent for this study was obtained from the patients. All women scheduled to receive spinal anaesthesia over a period of three months for elective or emergency CS at Pelonomi Hospital, a tertiary hospital in Bloemfontein, were invited to be included in this study and consent for this study obtained. After they had their operation, their anaesthetic records were collected and analyzed for the incidence of hypotension. The newly developed protocol for hypotension was presented to doctors in the Department of Anaesthesia at a meeting and then it was implemented for the following three months.

2.3.2 Study design

Prospective interventional study

2.3.3 Study Site

The study was conducted at Pelonomi Hospital in Bloemfontein, in the maternity theatre.

2.3.4 Study Population

The study population was woman for caesarean section divided into 2 samples. The two groups was group B (baseline group) and group I (intervention group). Screening of the patients in terms of inclusion and exclusion criteria, was performed during the preoperative visit by the registrar on duty in the maternity theatre. A thorough history was taken during the preoperative examination, whereby it was determined if a patient qualified for the trial and if any exclusion criteria existed, which would exclude the patient from the trial. Informed consent was obtained.

2.3.5 Ethical considerations

Institutional Ethics Committee and Free State Department of Health approval for this study was obtained (Ethics approval number UFS-HSD2017/0798).

2.3.5.1 Authorization

Consent for the conductance of the study was obtained from the Free State Department of Health and the Department of Anaesthesiology in Bloemfontein.

Informed consent was obtained from the patients involved in the study.

2.3.5.2 Participation and Informed Consent

All women scheduled to receive spinal anaesthesia over two periods of three months for elective or emergency CS at Pelonomi Hospital, a tertiary hospital in Bloemfontein, were invited to be included in this study and consent for this study obtained.

The anaesthetic registrar on duty for obstetric anaesthesia obtained consent for anaesthesia and the study.

2.3.5.3 Confidentiality

Efforts was made to keep personal information confidential. All the data captured was kept safe in a dedicated area by the investigator. Only hospital numbers were used after data collection and no names and surnames.

2.3.6 Inclusion and exclusion criteria

2.3.6.1 Inclusion criteria

All women scheduled to receive spinal anaesthesia over two periods of three months for elective or emergency CS at Pelonomi Hospital, a tertiary hospital in Bloemfontein, were invited to be included in this study and consent for this study obtained.

2.3.6.2 Exclusion criteria

Exclusion criteria were explained to the anaesthesia registrars recruiting patients for this study and were then checked before data analysis started. The exclusion criteria were: patients under the age of 18 years old, patient refusal to participate in the study, any contraindications to spinal anaesthesia, multiple births, local or generalized sepsis, gestation less than 28 weeks, pre-

eclampsia, chronic hypertension, conversion to general anaesthesia prior to delivery of the fetus and a non-standard anaesthetic technique.

The department of biostatistics determined that 100 patients in each group will be needed.

Conveniently the first 100 patients were selected in each group after which exclusion criteria was applied.

2.3.7 Construction of the Study

The following information was recorded on the patients' anaesthesia record forms:

1. The indication for CS and any co-morbid conditions.
2. Gravidity and parity
3. The hydration status of the patient (recorded as: well hydrated, moderately hydrated or poorly hydrated).
4. The baseline noninvasive blood pressure (NIBP) reading with an appropriately sized cuff was obtained in the left lateral position.
5. An electrocardiogram was placed and the HR and pulse oximetry were recorded prior to spinal anaesthesia.
 - a. (All the above are standard pre-operative measurements and are recorded on the anaesthetic chart as routine)
 - b. If not previously in situ, an 18gauge (or 16G) IV cannula was inserted peripherally. An intravenous (IV) infusion of IV modified Ringers lactate or Normal Saline was commenced, via an infusion set delivering at least 20 drops per min.
 - c. The patient was sat up for administration of the spinal anaesthesia.
6. Spinal anaesthesia was administered according to the standard regime of this hospital.
 - a. Spinal anaesthesia was administered at level L3/L4 or below, in the sitting position, using a spinal needle no wider than 22G. A sterile technique was used, including the use of a face mask and sterile gloves. On visualization of cerebrospinal fluid, 9 mg of 0.5% hyperbaric bupivacaine (1.8 mL) and 10 mcg (0.2 mL) of fentanyl injected were injected intrathecally over approximately over

30 seconds and modified Ringers lactate or Normal Saline 10 mL/kg was administered rapidly intravenously (the “co-load”).

7. The patient was then immediately positioned supine with 15-30° left lateral tilt and a pillow placed under the shoulders and head for thoracic curvature. The maternal HR was continually monitored using the ECG and NIBP was measured at 1-minute (min) intervals for the first 10 min and then, if stable, measured every 3 min. If the patient was unstable, the BP was checked every min.
8. The height of the block was checked after 5 min or sooner if a high motor block was suspected.
9. At delivery, 2.5(international units) IU of oxytocin was given slowly IV over 30 to 60 seconds and the BP were checked again.
 - a. This was followed by an oxytocin infusion consisting of 20 IU of oxytocin in 1000 mL of Ringer’s Lactate or Normal Saline, infusing over 8 hours (125 mL/hour).

After the co-load, the crystalloid infusion was continued at 2 mL/kg/hour. Blood loss was replaced with crystalloids, colloids and blood products as required.

Although hypotension is clearly defined as “subnormal arterial BP”, the definition of subnormal arterial BP remains controversial. However, previous studies support the criteria of 30% decrease in systolic BP as the definition of hypotension in obstetric anaesthesia.(15) Bradycardia was defined as a heart rate (HR) of less than 70 beats per minute (bpm).

Phenylephrine is the preferred vasopressor of choice but the optimal fluid volume, timing and type of fluid remains controversial.(16)

Following routine institutional practice, phenylephrine is used for hypotension as it is an alpha-adrenergic agonist and its action directly addresses the decrease in peripheral vascular resistance following spinal anaesthesia. The onset of action of phenylephrine is faster than ephedrine.

The following routine important information was documented on the anaesthetic record and then captured on the data collection form by the researcher:

- estimated blood loss
- total amount of intravenous fluids (crystalloids/ colloids/ blood products)
- if it was necessary to convert to general anaesthesia and the reason for the conversion

- gravidity and parity
- weight
- previous CS
- other chronic-illnesses or pregnancy related e.g. pre -eclampsia
- age of the patient
- tocolytic received in last six hours
- dose of oxytocin
- indication for CS
- duration of labor
- if patient was in labor
- duration of surgery
- the time of delivery
- adverse events such as cardiac arrest
- APGARS at birth

In addition to the above routine anaesthetic monitoring data, the 1- and 5-min APGAR scores was also recorded on the anaesthesia record forms. This information is relevant to gather and was included in the data collection as it can be influenced by the incidence of maternal hypotension before delivery.

The anaesthetic registrar on duty for obstetric anaesthesia obtained consent for anaesthesia and the study.

Spinal anaesthesia for each patient was administered if indicated and the data collected on the usual anaesthesia record forms. The copy of the anaesthesia records which are routinely kept by the anaesthesia registrars for medico-legal purposes (the originals remain in the patient's file), with the study consent forms, was submitted on a weekly base to the researcher at the department's academic meeting and was photocopied. The anaesthetic form was returned to the individual registrar the following week.

The researcher then extracted the relevant data from these anaesthesia record forms, and record the data on a specific data collection form. He also stored the study consent forms with the data collection forms.

This data included: the age and weight of the patient, the number of previous CS and whether the patient was pre-eclamptic. The systolic BP immediately prior to administration of spinal anaesthesia was recorded in the left lateral position.

The total IV dosage (amount of times and total amount) of phenylephrine, adrenaline, ephedrine and atropine given to manage hypotension and bradycardia was recorded, up until oxytocin is administered and then until the end of surgery.

Data collection was over a three-month period.

The following month, the Prevention and Treatment of Hypotension Protocol (see Appendix) was introduced to all members of the Department Anaesthesia, over a one-month period.

In the following three-month period, following this implementation of the hypotension protocol, the data collection was the same as for the first three-month period. On the routine anaesthetic form in the “other notes” section, it was indicated if the hypotension protocol was followed. It also stated a reason why it was not followed, e.g. drugs not available (specify), equipment not available (specify) or the reason could be stated if not included as above. These forms were distributed weekly to the anaesthesia registrars and handed in when they hand in their anaesthesia record forms weekly to the investigators.

PROTOCOL TO BE USED FOR STUDY

The following protocol has been developed for spinal anaesthesia for CS and was implemented for the second three-month study period, to determine the efficacy of the protocol introduced after the first three-month study period.

Spinal Anaesthesia for Caesarean Section

PROTOCOL

CONTRAINDICATIONS:

These include but are not limited to the following:

Absolute

1. *Blood clotting problems* which predispose patient to high risk of paralysis after spinal needle inserted intrathecally e.g. severe coagulation abnormality (e.g. INR \geq 1.5 or platelets $< 75 \times 10^9$).
2. *Cardiac conditions* which would result in significant hypotension as a result of the sympathetic blockade from spinal anaesthesia e.g. fixed cardiac output valvular lesions such as aortic stenosis or mitral stenosis.
3. *Hemodynamically unstable* patients who would become severely hypotensive as a result of the sympathetic blockade from spinal anaesthesia e.g. patients who are intravascularly depleted as a result of dehydration, sepsis or haemorrhage.
4. The pre-operative maternal HR can give an indication of potential hemodynamic instability following spinal anaesthesia. The following table was used as a guideline:

Heart rate	Guideline
> 140 bpm	Spinal inadvisable. Discuss with senior anaesthetist.
120-140	Spinal may be inadvisable. Discuss with senior anaesthetist.
100-120	Consider causes of tachycardia. If not related to potential hemodynamic instability, proceed with spinal.
<100 and \geq 55	Proceed with spinal
<55	Investigate cause of bradycardia and discuss with senior anaesthetist.

("Blood pressure" = SYSTOLIC BP)

5. *Infections* which associated with high risk of meningitis as a result of introducing the spinal needle into the subarachnoid space e.g. untreated systemic infection or skin infection at site of spinal needle insertion.
6. *Allergy* to amide local anaesthetics.
7. *Patient refusal*.

Relative

1. Fetal distress such that a general anaesthesia is considered indicated as a quicker technique (however, if the mother is a possible difficult intubation, a spinal anaesthesia may still be preferable).
2. Conditions which predispose patients to risk of meningitis (but lower than above) e.g. systemic infection treated with antibiotics.
3. Pre-existing neurological condition: these should be clearly documented pre-operatively – the evidence that they may worsen with spinal anaesthesia is controversial.
4. Respiratory failure – this may be worsened with the motor blockade from spinal anaesthesia.

PRE-OPERATIVE PREPARATION

1. Check drugs and equipment to induce general anaesthesia, intubate and resuscitate the patient, are immediately available in theatre; a cardiac defibrillator must be available in the theatre complex.
2. Emergency drugs that are drawn up standard for every patient are: Adrenaline, atropine, phenylephrine and ephedrine and if they are not used for a patient it will be used for the following patient.
3. Attach ECG and BP cuff (right arm). Obtain baseline systolic BP and HR readings with the patient lying in the full left lateral position.
4. A. Make up a **phenylephrine** infusion of 50 mcg/mL (e.g. 200 mL 0.9% Saline with 10 mg phenylephrine). Take a 10 mL syringe and put 10mL of this solution into it for BOLUS use.

5. B. Make up an **ephedrine** solution of 5 mg/mL (draw up 50 mg ephedrine in 10 ml saline).
6. Make up a **STRONG adrenaline** solution of 1:10 000 (1 mg in 10mL saline) and a **WEAK adrenaline** 1: 100 000 (1 mL of 1:10 000 diluted to 10 mL with saline).
7. If not already in situ, insert an IV cannula, 18G or 16G into the patient's arm. This must be connected to a short extension with a three way tap connected on one side to an infusion set with Ringer's lactate or Normal Saline, which can run at least 20 drops per min, and on the other side to a flow control device which should already be in place from labour ward or ante natal ward (for the post-operative oxytocin infusion) which is connected to the 50 mcg/mL of phenylephrine infusion via the flow control device.
8. Attach pulse oximeter.
9. Sit the patient up, clean the lumbar region with antiseptic solution and drape with sterile towels.
10. Insert the spinal needle at the level of L 3/4 or lower, using a spinal needle no wider than 22G and a sterile technique including the use of a face mask and sterile gloves.
11. On visualizing cerebrospinal fluid through the needle hub, inject 1.8 mL 0.5% heavy bupivacaine with 0.2 mL (10 mcg) of fentanyl over 30 seconds.
12. Then open up the IV infusions:
13. Infuse 10 mL/kg Ringer's lactate or Normal Saline stat (the "co-load")
14. At the same time, start the phenylephrine infusion at a rate of 50 mcg/min (i.e. 60 mL/hour of infusion containing 50 mcg/min). **NB DO NOT START THE PHENYLEPHRINE INFUSION IF THE BASELINE SYSTOLIC BP WAS \geq 140 mmHg. ONLY START THE PHENYLEPHRINE INFUSION WHEN THE SYSTOLIC BP DROPS BELOW 140 mmHg.**
15. After *commencing* these infusions (but do not wait for the *completion* of the co-load), position the patient supine with a 15-30° left lateral tilt and a pillow under the shoulders.
16. Check the BP every one min and continually monitor the HR. After 10 min, if BP is stable, continue to check BP every 3 min. If unstable, continue to check every 1 min.
17. If the systolic BP falls below 110 mmHg, take the following actions:

D. SYSTOLIC HYPOTENSION WITHOUT BRADYCARDIA**(HEART RATE \geq 70bpm)**

SYSTOLIC BP	ACTION
100-110 mmHg	Increase phenylephrine infusion to 100 mcg/min (120 mL/hour)
90-99 mmHg	Increase phenylephrine infusion to 100 mcg/min (120 mL/hour) AND give 1 mL phenylephrine bolus (50mcg)
80-89 mmHg	Increase phenylephrine infusion to 100 mcg/min (120 mL/hour) AND give 2 mL phenylephrine bolus (100 mcg)
70-79 mmHg	Increase phenylephrine infusion to 100 mcg/min (120 mL/hour) AND give 2mL phenylephrine bolus (100 mcg) AND give 1mL ephedrine bolus (5mg)
<70 mmHg	Increase phenylephrine infusion to 100 mcg/min (120 mL/hour) AND give 1mL WEAK adrenaline (1: 100 000) AND give 200 mL fluid bolus* Also: - increase relief of aortocaval obstruction (e.g. more lateral tilt, lift uterus or deliver baby) - if loss of conscious level –intubate patient** - if central pulse lost – institute CPR

E. SYSTOLIC HYPOTENSION WITH BRADYCARDIA**(HEART RATE <70 bpm)**

SYSTOLIC BP	ACTION – Reduce phenylephrine infusion to 25 mcg/min AND do the following:
100-110 mmHg	Give 5 mg ephedrine (1 mL) stat
90-99 mmHg	Give 7.5 mg ephedrine (1.5 mL) stat
80-89 mmHg	Give 10 mg ephedrine (2 mL) stat
70-79 mmHg	Give 15 mg ephedrine (3 mL) stat
<70 mmHg	Give 1 mL WEAK adrenaline (1: 100 000). Repeat every 30 seconds until BP returned to baseline AND give 200 mL fluid bolus* Also: - increase relief of aortocaval obstruction (e.g. more lateral tilt, lift uterus or deliver baby) - if loss of conscious level or respiratory problems – intubate patient ±GA** - if central pulse lost – institute CPR

F. BRADYCARDIA (HEART RATE <70 bpm) WITH NO HYPOTENSION

Heart Rate	ACTION
Heart rate < 70 bpm	Reduce phenylephrine rate to 25 mcg/min
Heart rate < 60 bpm	Stop phenylephrine infusion and administer 0.5 mg atropine.

**Fluids bolus can be of 0.9% Saline, Ringers lactate, Gelofusine® or Voluven®*

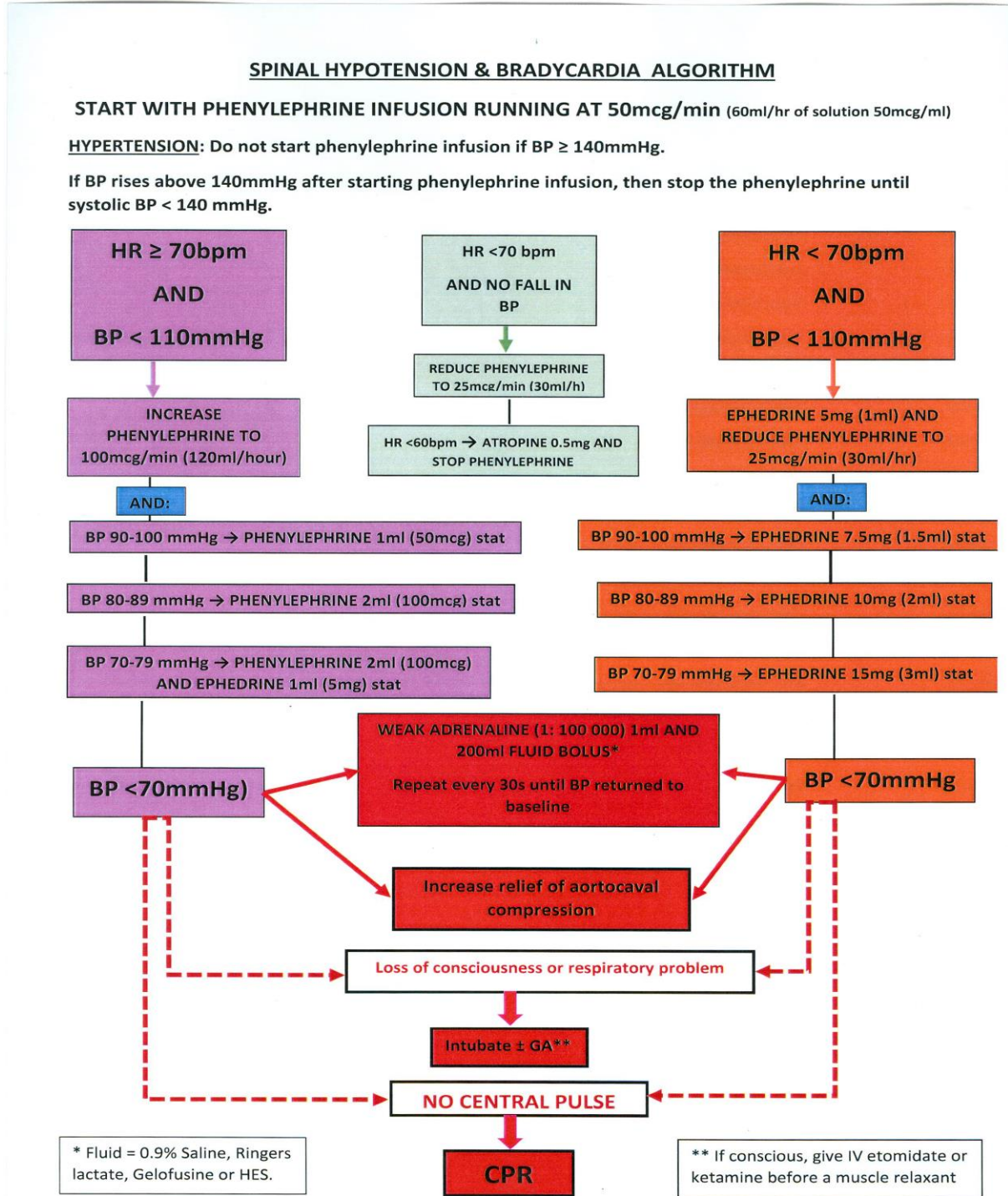
*** If the patient is still conscious, give IV etomidate or ketamine before giving a muscle relaxant for intubation*

19. If BP rises to 140 mmHg or higher, stop the phenylephrine. If the BP falls below 140 mmHg, restart the phenylephrine infusion.

20. After every change of phenylephrine infusion rate or bolus of vasopressor given, re-check the BP after 1 min.
21. Check the height of the block after 5 min or sooner if suspect high motor block.
22. At delivery give oxytocin 2.5 (IU). Give slowly, over 30 seconds and then check BP.
23. Fluids: after the co-load, continue crystalloid infusion at 2 mL/kg/hour. If blood loss occurs then replace with crystalloids, colloids and blood products, as required.

Algorithm

An algorithm has been developed that will be implemented in conjunction with the protocol for spinal anaesthesia



2.3.8 Data Management/Analysis

Continuous variables were summarized by medians, minimum, maximum or percentiles.

Categorical variables were summarized by frequencies and percentages. Differences between groups were evaluated using the Wilcoxon Two-Sample test for unpaired data. The analysis was done by the Department of Biostatistics, University of the Free State using Statistical Analysis Software. (SAS 9.4)

The first 3 months of data capturing in the baseline group were from 1 April to 30 June 2018. The second three-month period for the intervention group was from 9 July 2018 to 8 October 2018.

2.4 Results

There were 91 patients in the baseline group (Group B) and 99 patients in the intervention group (Group I), after data collection, exclusion criteria were reapplied, due to some patients being erroneously included in the study.

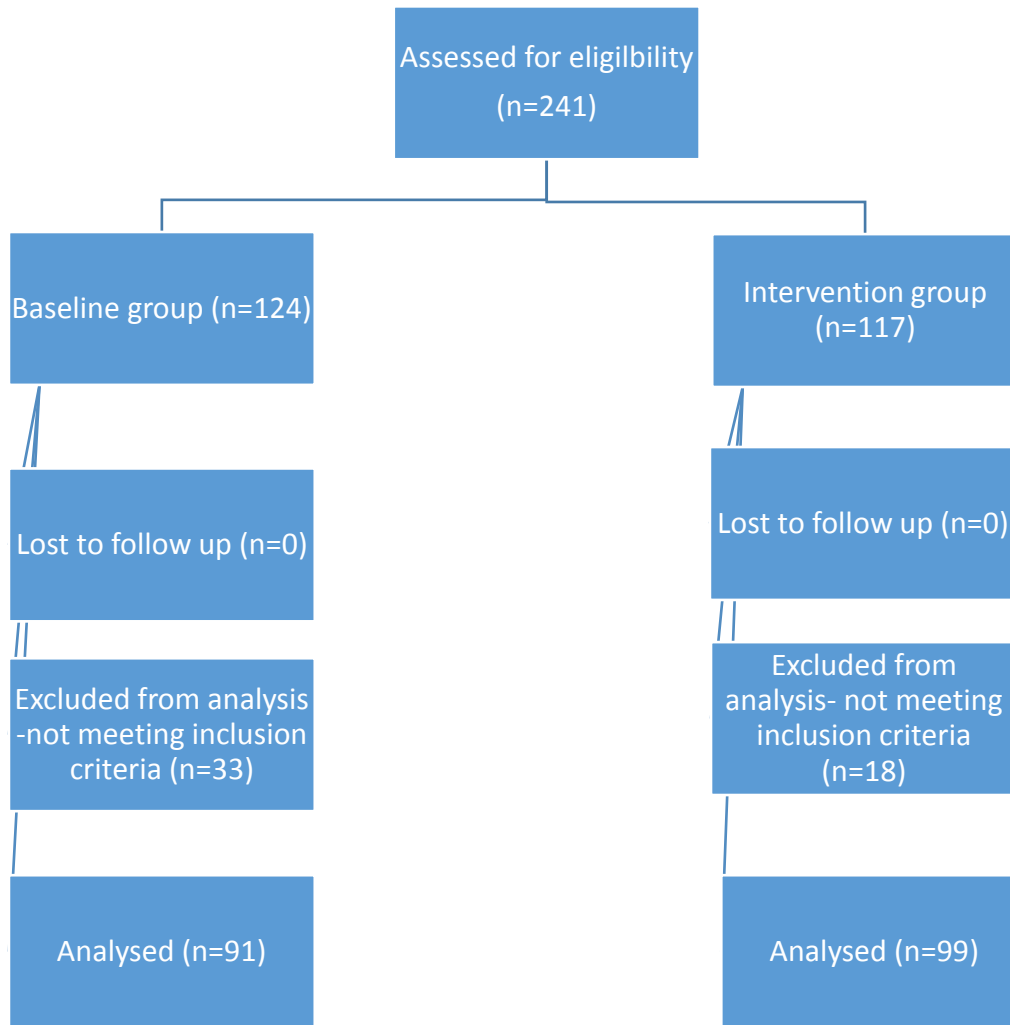


Figure 2 Flow diagram of patient recruitment

As regards to characteristics of the patients included in the study, the only significant difference between the two groups was that there were significantly more patients in labour in Group B compared to Group I (Group B, 60% vs Group I, 42%; $p = 0.0131$). (Table 1)

The median age in both Group B and Group I was 30 years. The mean weight in Group B was 82 kg and in Group I was 81kg. The indications for the CS were mostly previous CS (Group B 46 %, Group I 56%) and fetal distress (Group B 23% vs Group I 18%). In both groups, the most frequent gravidity was G₃, (Group B 30% and Group I 38%), followed by primigravidas (Group

B, 25% vs Group I 20%). The median gestation in both groups were also similar (Group B, 38 weeks vs Group I, 39 weeks). The hydration status in both groups were similar (Group B – 74% were well hydrated vs Group I, 68%; $p=0.4403$). The baseline, pre-spinal systolic BP in both groups were similar (Group B, 130 mmHg vs Group I, 128 mmHg). Diastolic BP was also very similar in both groups, (Group B, 72 mmHg vs Group I, 74 mmHg). In both groups the median HR pre-spinal was 93 bpm. The height of the sensory block was similar in both groups: in Group B, the level was T 6 or higher in 50% of patients and T6 or higher in 57% of patients in Group I, which was not significantly different. ($p=0.3315$).

Baseline maternal characteristics	Group B (n=91)	Group I (n=99)	P value
	Median (Range)	Median (Range)	
Age (years)	28 (18-46)	30 (18-44)	0.127
Weight (kilogram)	82 (55-119)	81 (51-159)	0.561
Primigravidas (% of total)	25	20	
Labour	60	42	0.013*
Hydration status (% well hydrated)	74	68	0.440
Hydration status (% moderately hydrated)	19	26	0.440
Hydration status (% poorly hydrated)	7	5	0.440
Baseline systolic BP (mmHg)	130 (100-178)	128 (70-156)	0.214
Baseline HR (bpm)	93 (66-136)	93 (56-133)	0.303
T 6 or higher block (% of total)	50	57	0.332

Table 1. Baseline patient characteristics. Values are medians unless otherwise specified

Significantly more patients were administered phenylephrine boluses in Group B, 57% vs Group I, 35% ($p=0.0005$). (Figure 2)

The patients who received phenylephrine boluses, received a significantly higher dose in total in Group B compared to Group I, (median total dose of phenylephrine in boluses per patient: Group B, 300 mcg vs Group I, 150 mcg; $p = 0.0016$).

The phenylephrine infusion rate was increased in Group I from 50 mcg/min to 100 mcg/min for 47% patients and decreased for 25% patients to 25 mcg/min. In 24% of patients the phenylephrine infusion was stopped.

Atropine was given more often in the intervention group than the baseline group (Group B, 0% vs Group I, 3%) but this was not significant ($p= 0.2474$).

Significantly less total ephedrine in boluses were given in the baseline compared to the intervention group (Group B, 7% of patients: total of 45 mg vs Group I, 16% of patients: total 80 mg; $p=0.0029$).

Adrenaline was given in 4% of the patients in Group B (total dose 35 mcg) and in 1% of the patients in group I (total dose 30 mcg); the difference between the two groups was not significant ($p=0.1955$).

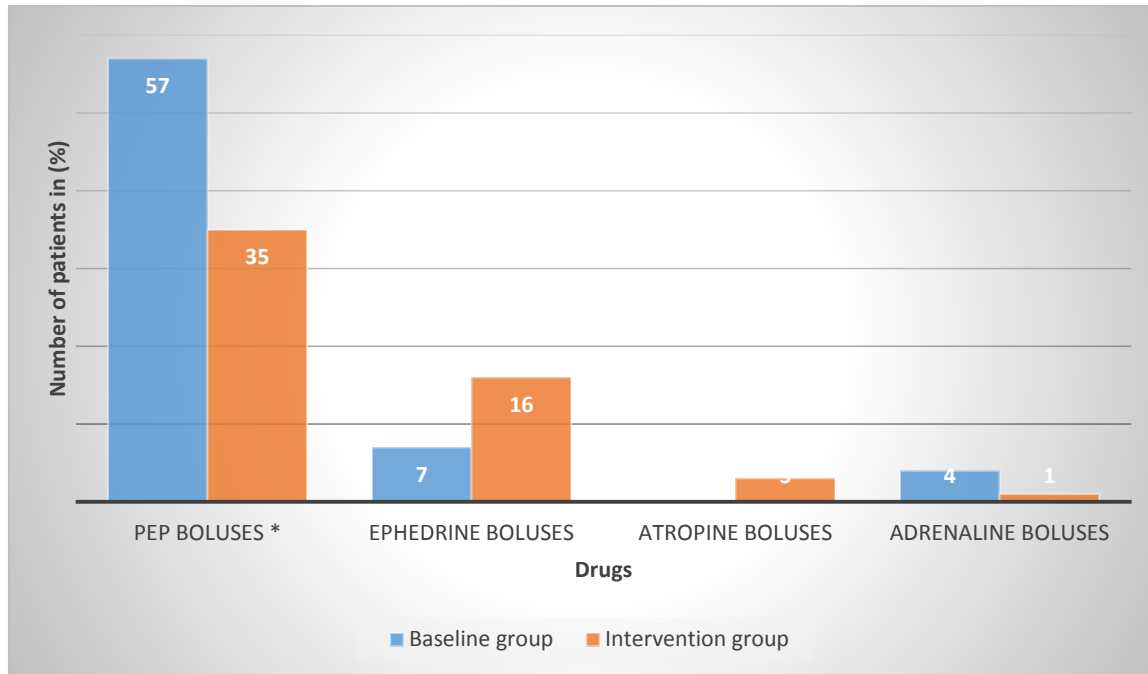


Figure 3 Number of patients expressed as % who required boluses of phenylephrine (PEP), ephedrine, atropine or adrenaline. * = significantly different in Group B and I.

In both groups, similar amounts of crystalloids were administered with a median of 1000 mL (IQR 800-1000).

Significantly more patients received colloids clinically in the baseline group vs the intervention group (Group B, 34% vs group I, 15%) although the amount they received were similar (mean 500 mL) and was not statistically significant ($p=0.3423$).

The median estimated blood loss in both groups was similar, 400 mL. Only one patient received a blood transfusion (500 mL) and that patient was in Group B.

Both groups received a 2.5 IU oxytocin bolus after delivery of the fetus.

<u>Variable</u>	<u>Group B :</u> <u>Median</u> <u>(IQR)</u> <u>n = 91</u>	<u>Group I :</u> <u>Median</u> <u>(IQR)</u> <u>n = 99</u>	<u>Group B :</u> <u>Minimum -</u> <u>Maximum</u>	<u>Group I :</u> <u>Minimum -</u> <u>Maximum</u>	<u>P - value</u>
<i>Before delivery</i> <i>(Blood pressure in</i> <i>mmHg)</i>					
Lowest Systolic	108 (96-120)	105 (90-117)	68-152	54-92	0.089
Lowest Diastolic	52 (42-70)	53 (43-65)	27-93	28-189	0.965
Highest Systolic *	133 (125- 150)	140 (130- 150)	99-194	108-130	0.04*
Highest Diastolic *	68 (60-82)	77 (68-88)	30-153	32-140	0.002*
<i>After delivery</i> <i>(Blood pressure in</i> <i>mmHg)</i>					
Lowest Systolic	110 (99-118)	109 (100- 115)	80-143	79-82	0.675
Lowest Diastolic	50 (41-62)	54 (45-62)	30-95	32-170	0.099
Highest Systolic	127 (119- 137)	127 (120- 137)	102-163	105-139	0.699
Highest Diastolic *	60 (48-71)	64 (57-73)	32-123	40-119	0.009*

Table 2 Blood pressures in Baseline and Intervention Groups. Median and Interquartile ranges (IQR).

**= Statistically significant difference between Group B and Group I.*

<u>Variable</u>	<u>Group B :</u> <u>Median</u> <u>(IQR)</u> <u>n = 91</u>	<u>Group I :</u> <u>Median</u> <u>(IQR)</u> <u>n = 99</u>	<u>Group B :</u> <u>Minimum -</u> <u>Maximum</u>	<u>Group I : Minimum</u> <u>-Maximum</u>	<u>P - value</u>
<i>Before delivery</i> <i>(HR in bpm)</i>					
Lowest	82 (68-95)	70 (63-84)	40-136	50-165	<i>0.001*</i>
Highest	112 (98-124)	108 (98-120)	74-155	73-115	0.325
<i>After delivery</i> <i>(HR in bpm)</i>					
Lowest	83 (69-95)	72 (63-88)	50-128	49-160	<i>0.001*</i>
Highest	100 (91-111)	99 (88-110)	65-165	60-137	0.364

Table 3 Heart Rates in Baseline and Intervention Groups. Median and Interquartile ranges (IQR).

** = Statistically significant difference between Group B and Group I.*

The highest readings of systolic BP before delivery were on average, significantly greater in the intervention group compared to the baseline group (Group B, 133 mmHg vs Group I, 140 mmHg ($p = 0.0409$)).

According to the range of BP readings, the highest BP recording before delivery was 194 mmHg in Group B. Similarly, the highest BP recording after delivery was 163 mmHg in the Group B. The lowest systolic BP recording was in Group B before delivery of 54 mmHg.

The diastolic BP were also, on average, significantly higher in Group I, both before and after delivery; there were no significant differences in the lowest systolic or diastolic BP's, both before and after delivery (Table 1).

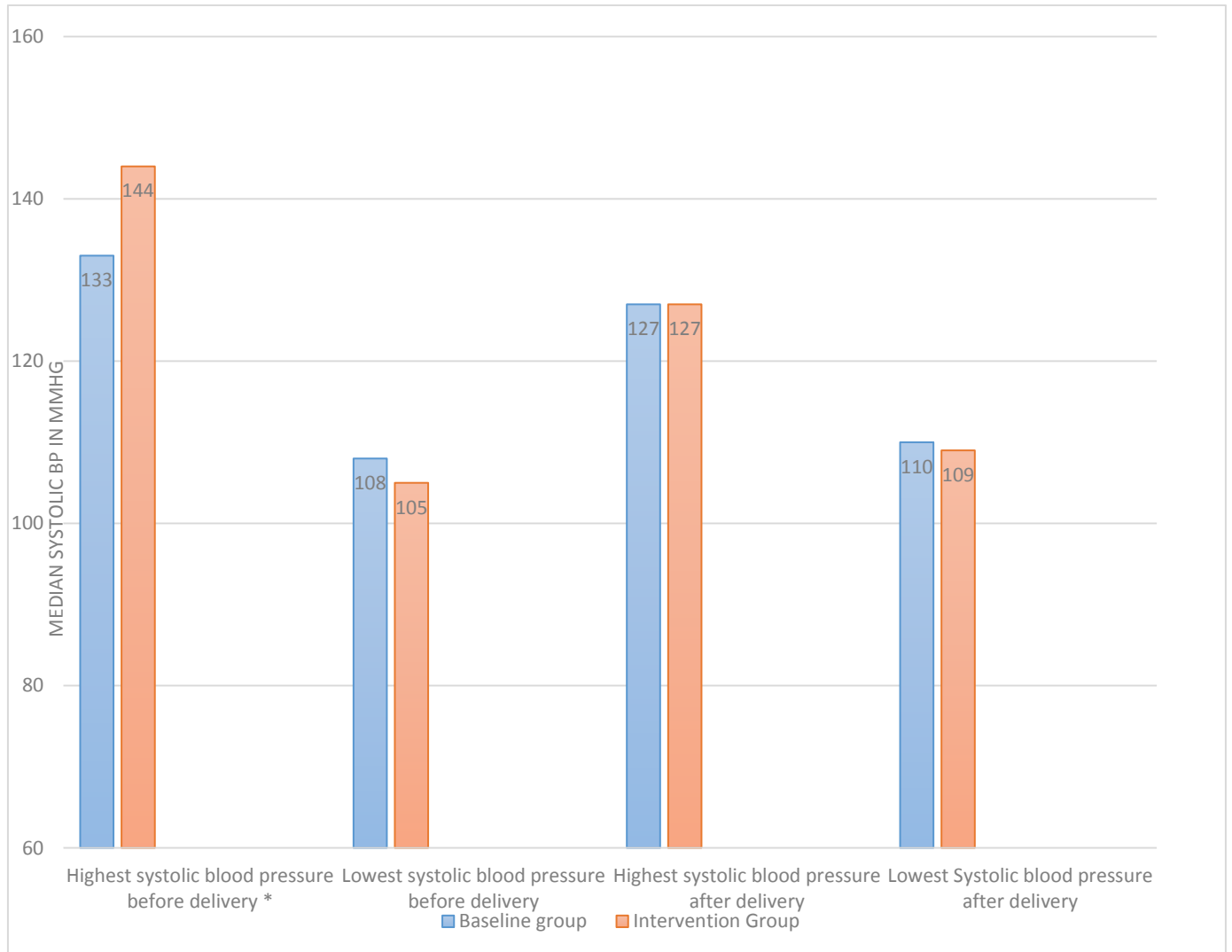


Figure 4 Median Systolic BP Before and after Delivery.

* = Statistically significant difference between Group B and Group I.

The HR's of the patients were significantly lower in the intervention group both before and after delivery; median values before delivery: Group B = 82 bpm vs Group I = 70 bpm ($p=0.001$) and median values after delivery, Group B = 83 bpm vs Group I = 72 bpm ($p=0.001$). The lowest HR reading was 40 bpm and this occurred in Group B, before delivery. The lowest HR's recorded in Group I were 49 bpm before delivery and 50 bpm after delivery (Table 2).

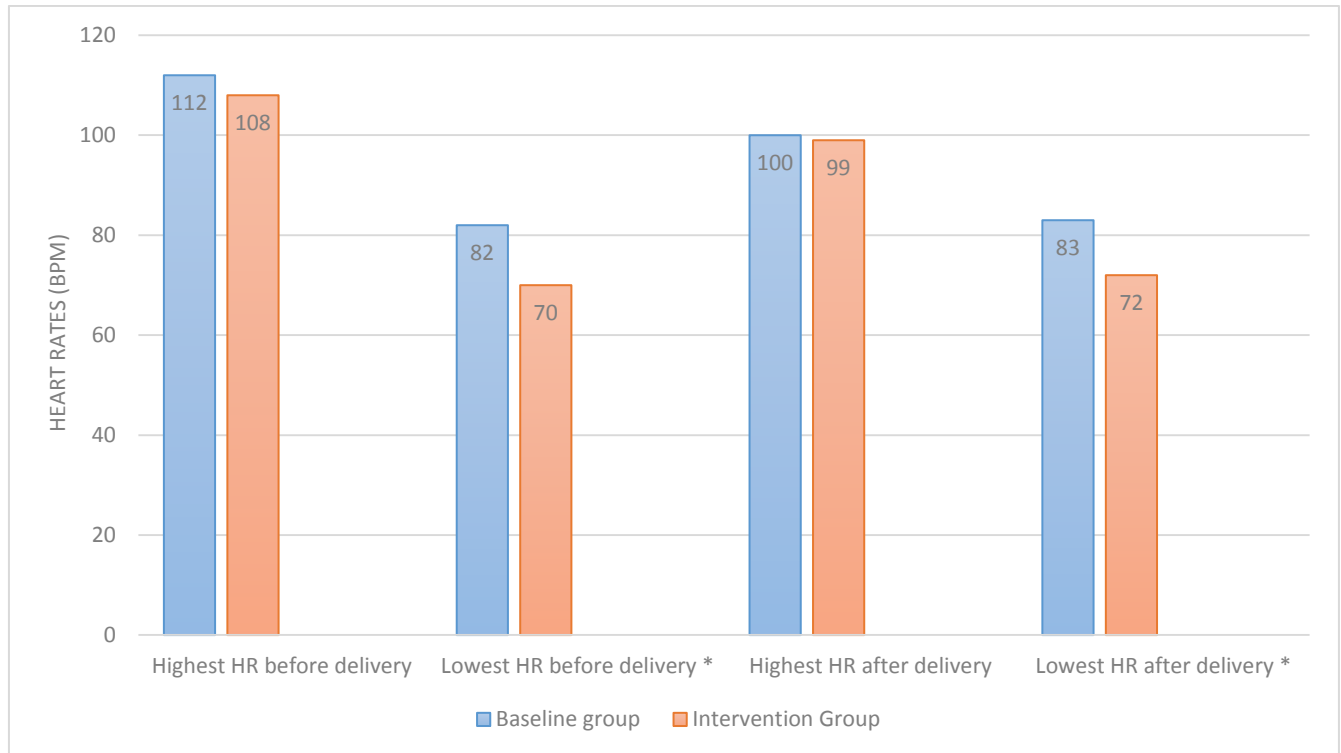


Figure 5. Heart Rates before and after delivery (Median values in beats per minute = bpm)

* = Statistically significant difference between Group B and Group I.

As regards peri-operative episodes of hypotension (i.e. systolic BP <110 mmHg) and bradycardia (HR <70 bpm), there was no significant difference between the two groups in the number of patients who had episodes of “Hypotension **or** Bradycardia”; Group B, 70% vs Group I, 76% ($p = 0.2507$).

There was also no significant differences between the two groups in the number of patients who had episodes of “Hypotension **without** Bradycardia”; group B, 40% vs Group I, 49% ($p = 0.1427$).

Similarly, there was no significant difference between the two groups in the number of patients who experienced “Bradycardia **and** Hypotension”; Group B, 23% vs Group I, 13% ($p = 0.3117$). Significantly more patients experienced “Bradycardia **without** Hypotension” in the intervention group; Group B, 7% vs Group I, 14% ($p=0.007$).

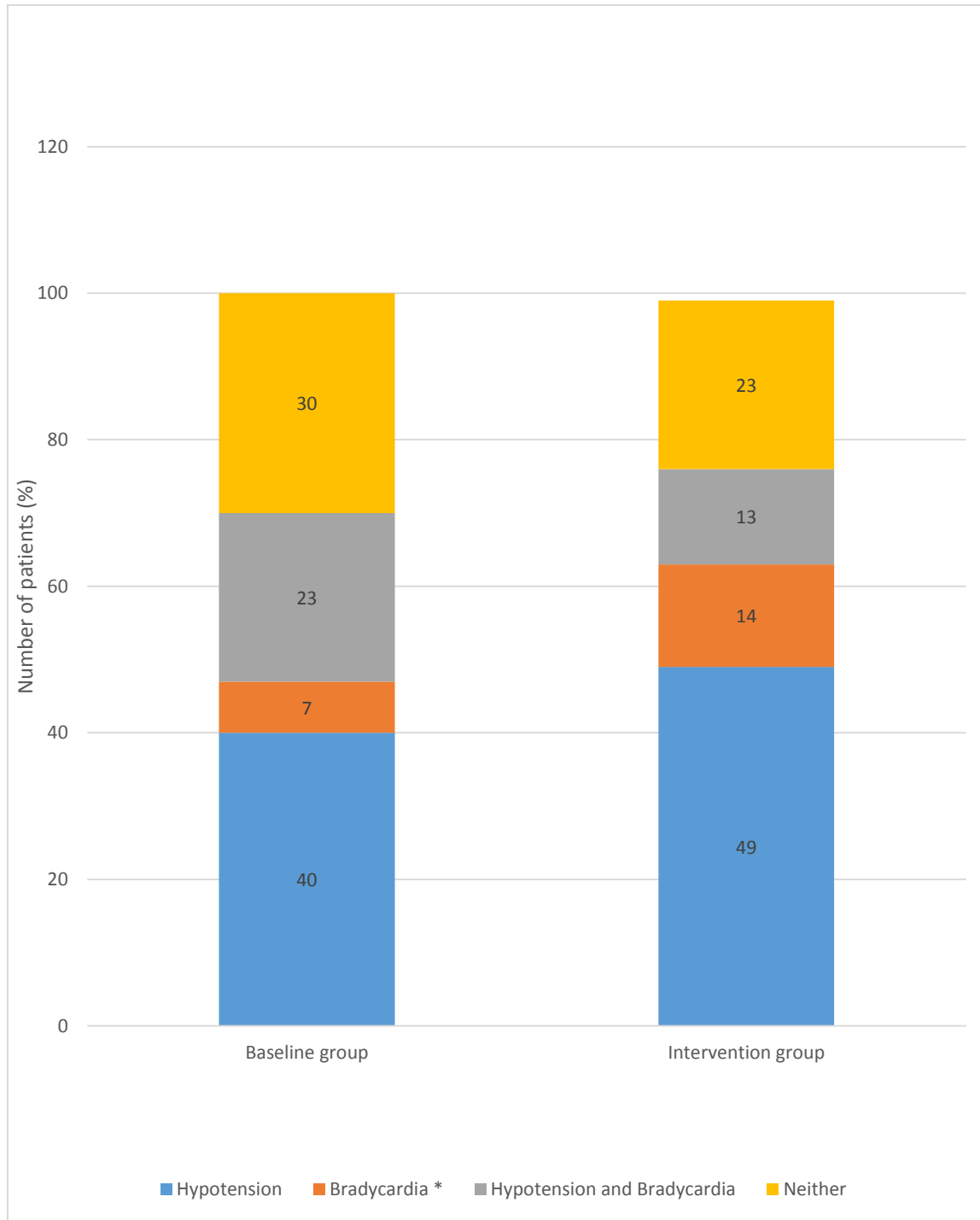


Figure 6. Distribution of patients with hypotension and/or bradycardia

* = Statistically significant difference between Group B and Group I.

Only 1 patient required conversion to general anaesthetic in Group B (after the delivery of the fetus) due to pain experienced by the patient; no patients needed conversion to general anaesthesia in Group I.

No patients in either group needed cardio-pulmonary resuscitation.

However, there were several other significant differences in maternal peri-operative HR and BP, vasopressors and fluid usage compared to before the algorithm was introduced. These differences are summarized in Table 4.

Difference Found <i>(italics = higher in baseline group)</i>	Baseline Group (Group B)	Intervention Group (Group I)	P value
Patients in labour	60%	42%	0.013
Number of patients who required phenylephrine boluses	57%	35%	0.0005
Median dose of phenylephrine per patient	300 mcg	150 mcg	0.0016
Number of patients who required ephedrine boluses	7%	16%	0.002
Total dose ephedrine	45 mg	80 mg	0.003
Number of patients who received colloid	34%	15%	0.342
Highest systolic blood pressure before delivery	133 mm Hg	140 mmHg	0.04

Highest diastolic BP's before delivery	68	77	0.002
Highest diastolic BP's after delivery	60	64	0.009
Heart rates lowest before delivery	82 bpm	70 bpm	0.001
Heart rates lowest after delivery	83 bpm	72 bpm	0.004
Patients who experienced bradycardia without hypotension	7%	14%	0.007

Table 4. Summary of the differences found between Group B and Group I.

The 1 min APGAR scores were similar in both groups; the APGAR scores were 6 or lower in 12% of neonates born to mothers in Group B vs 10% in Group I. The 5 min APGAR scores were 7 or higher in all neonates in both groups.

<u>Group B</u>	<u>Group I</u>
Pain	Vomiting
Shivering	Nausea
Cardiac Palpitations	Nausea and vomiting
Vomiting	Feeling anxious
	Abdominal Pain

Table 4. Maternal Complications. No patient had more than one of the above complications.

2.5 Discussion

This study showed that the introduction of an algorithm, to prevent and treat hypotension and bradycardia following spinal anaesthesia for CS, did not result in any significant differences in

systolic hypotension before or after delivery. This was in contrary to other recently published results that showed a decrease in hypotensive episodes with a infusion technique vs a bolus technique of phenylephrine and we could unfortunately not replicate these results.(17)

The optimal dosage of phenylephrine infusion is still controversial, but recent evidence has showed that a 50 mcg/min is close to the perfect dosage as higher (75-100 mcg/min) shows an increase in hypertensive episodes and lower dosages (25 mcg/min) had increase episodes of hypotension.(18) We started a 50 mcg/min baseline phenylephrine infusion.

We used a flow control device to deliver the phenylephrine and could not find similar techniques used in the literature. Using a infusion with a syringe driver is a well-known technique that works very well but is not applicable in a poor socio economic environment (19) . The patients in the group treated using the algorithm (Group I) did experience more episodes of bradycardia, as defined by a HR less than 70 bpm, but these episodes of bradycardia were not all clinically significant as the number of patients who required atropine boluses (for a HR of 60 bpm or less) was not significantly different between the two groups.

Significantly more patients were in labour in the Group B vs Group I (60% vs 42%, $p=0.013$) and this could cause an increase in Group B BP and HR.

Use of the algorithm in patients, did result in fewer patients requiring phenylephrine boluses (Group B, 57% vs Group I, 35%).This is clinically relevant as it suggests that use of the algorithm with a background phenylephrine infusion, is less labour intensive for the anaesthetist providing anaesthesia and enables the anaesthetist to perform other activities instead of giving repeated phenylephrine boluses.

The phenylephrine infusion did need adjusting in most patients, in 47% of patient it was increased from 50 mcg/min to 100 mcg/min and 25% of patients the infusion was decreased or stopped respectively. Unfortunately, it was not recorded how often the infusion speed needed

titration. Only 4% of the patients did not require adjustment of the rate of phenylephrine infusion. We tried to simplify the algorithm to increase compliance with the algorithm.

In addition, use of the algorithm resulted in lower total doses of phenylephrine, given as boluses (Group B, 135 mcg vs Group I, 88 mcg). However, as the intervention group also received a background infusion of phenylephrine, it is possible that the total perioperative dose of phenylephrine used per patient was higher in Group I.

Atropine was never given in the baseline group but was given 3 times in Group I, this could possibly be explained due to the algorithm compliance.

Ephedrine was given much more in the intervention group, 7 times in the baseline vs 16 times in the intervention group ($p=0.0029$). This could possibly be explained by the lower phenylephrine boluses that was needed in the intervention group and according to the algorithm needed rather ephedrine due to low BP and HR.

As expected, the median age and weight in both groups were very similar. Significantly more patients were in labour in group B vs group I, 60% vs 42 ($p=0.0131$). It could possibly contribute to an increase in baseline BP before spinal anaesthesia due to pain induced by labour.

There was a slight increase in the percentage of patients who had a spinal block of T6 and higher in group I (50 vs 57%) but not statistically significant ($p=0.3315$).

In the Group B, 4 patients received adrenaline boluses and 1 patient received adrenaline in the intervention group, possibly due to more ephedrine given in the Group I vs the Group B. Possibly due to the small size of the study, it could not show any significance in the adrenaline usage in the groups.

More than double the number of patients received colloids in Group B, but when they received colloids in either group it was the same amount, 500 mL. Possibly hypotension was treated more with fluids (i.e. colloids) in the Group B instead of using vasopressors.

Both groups had similar estimated blood loss, well in the accepted range of 400 mL.

The median (lower, upper quartile) lowest systolic BP in Group B before delivery was 108 mmHg (96-120 mmHg) and 105 mmHg (90-117 mmHg) in Group I ($p=0.0894$).

The highest systolic median BP before delivery increased from 133 mmHg to 140 mmHg ($p=0.0409$) making it a significant increase in BP. The range is also narrower (20 mmHg vs 25 mmHg) in Group I.

The lowest systolic median BP decreased non-significantly before delivery from 108mmHg to 105 mmHg ($p=0.0894$).

There was no statistically significant difference in the lowest median systolic BP before delivery.

The highest diastolic BP pre-delivery increased significantly from 68-77 mmHg ($p=0.002$).

The highest median systolic BP after delivery had no change, 127 mmHg in both groups. The lowest median systolic BP decreased non-significantly from 110 mmHg in Group B to 109 mmHg ($p=0.6754$).

The highest diastolic BP after delivery increased from 60-64 mmHg after delivery significantly although not clinically relevant ($p=0.009$).

As expected, the median lowest HR before delivery decreased significantly from 82 to 70 bpm ($p=0.0018$) although not clinically significant. The median HR did not change significantly before delivery from 112-108 bpm.

After delivery, once again there was a significant decrease in median HR from 83-72 bpm. The median highest HR after delivery showed a similar pattern as before delivery with no significant change, from 100 to 99 bpm.

We can thus see that the lower HR before and after delivery both has a statistically significant difference but in clinical practice not truly significant.

Isolated hypotensive episodes increased in Group I from 75% to 63% in Group B ($p=0.1427$).

Patients having bradycardias and hypotensive episodes improved from 36% in Group B to 25% in Group I although not statistically significant ($p=0.3117$).

There was an increase in the number of patients having bradycardia episodes, 7% in Group B to 14% in Group I ($p=0.007$). This can possibly be explained by the dead space that contains phenylephrine between the injection port and the patient and thus delivers a bolus effect of

phenylephrine after each injection via the injection port of the intravenous set. This was not clinically important bradycardia episodes as the amount of atropine needed to treat the hypotensive episodes was only in 3% of Group I.

Although one patient needed conversion to a general anaesthetic, it is unrelated to the hypotensive and bradycardia management as this patient experienced pain after delivering of the baby.

Scores were slightly better in the 1 min APGAR scores, although not clinically significant. APGAR scores of 6 and lower was recorded in 12% of Group B and 10% in Group I. In both groups there was no 5 min APGAR scores recorded below 7. Although there is not a dramatic improvement in the APGAR scores, it is reassuring to see that there was not a worsening in the APGAR scores.

There was an increase in nausea and vomiting episodes in Group I, 3 in the intervention group and only 1 in Group B, although not significant. It is difficult to describe these complications due to the hypotensive and bradycardia episodes.

2.6 Discussion of potential limitations and shortcomings of the study

Our study had several limitations. Firstly, the infusion with phenylephrine was done with a flow control device. This could possibly affect the accuracy of the infusion. Secondly, there was a prolonged dead space between the injection port and the intravenous cannula entering the vein with subsequently causing a phenylephrine bolus effect with each drug administered at the injection port and could explain the increase in bradycardias recorded in the Group I. There were several reports of difficulty using the drop counter infusions with the anaesthetist needing to increase the height of the phenylephrine bag to make sure the infusion infuses adequately. We were aware of this possible influence before we initiated the study but wanted to make use of an infusion setup that could possibly be used in the rural areas and hospitals without access to infusion pumps. Thirdly, we aimed for 100 patients per group but due to patients that was erroneously included not meeting the inclusion criteria, they had to be excluded and we only had 91 and 99 patients respectively in Group B and Group I. Fourthly, our study was underpowered to detect if there was a statistically significant difference for example in the adrenaline usage.

Fifthly, we postulate that our registrars treat hypotension very effectively during spinal anaesthesia with boluses due to the fact that they already have good experience with CS anaesthetics when they start the registrar program. This could explain why there was not a significant difference between Group B and group I with hypotension episodes. Sixthly, at the time of writing, phenylephrine is low in stock country wide and using an ampule of phenylephrine per patient for an infusion and using additional phenylephrine boluses could possibly influence the available stock in a high-volume center.

2.7 Conclusion

This study showed that the introduction of an algorithm with a phenylephrine infusion via a flow control device, to prevent and treat hypotension and bradycardia following spinal anaesthesia for CS, did not result in any significant differences in systolic hypotension before or after delivery. Every patient still needs to be individualized and it is important to choose the best method that is appropriate for the patient's condition. The skill and experience of the operator can determine if a phenylephrine infusion or a bolus technique will be best suited(13). In an environment with experienced personnel under supervision, the algorithm did not significantly influence outcome, but in a resource poor environment with inexperienced personnel it will at least be safe and may actually improve outcomes. This needs further testing.

2.8 Declaration of interest

None declared.

2.9 Funding

R500 Was granted to pay for the stationary and printing of data sheets.

2.10 References

1. Klöhr S, Roth R, Hofmann T, Rossaint R, Heesen M. Definitions of hypotension after

- spinal anaesthesia for caesarean section: Literature search and application to parturients. *Acta Anaesthesiol Scand*. 2010;54(8):909–21.
2. Dyer RA., Rout CC., Kruger AM., van der Vyver M., Lamacraft G., James MF. Prevention and treatment of cardiovascular instability during spinal anaesthesia for caesarean section. *South African Med J [Internet]*. 2004;94(5):367–72. Available from: <http://www.scopus.com/inward/record.url?eid=2-s2.0-2642555453&partnerID=40&md5=20246d09de5199b136127460b8f13b74>
 3. Hawkins JL, Chang J, Palmer SK, Gibbs CP, Callaghan WM. Anesthesia-related maternal mortality in the United States: 1979-2002. *Obstet Gynecol*. 2011;117(1):69–74.
 4. Auroy Y, Benhamou D, Bargues L, Ecoffey C, Falissard B, Mercier F, et al. Major Complications of Regional Anesthesia in France The SOS Regional Anesthesia Hotline Service. *Anesthesiology*. 2002;97(5):1274–80.
 5. Butwick AJ, Columb MO, Carvalho B. Preventing spinal hypotension during Caesarean delivery: What is the latest? *Br J Anaesth*. 2015;114(2):183–6.
 6. Zwane S, Bishop D, Rodseth R. Hypotension during spinal anaesthesia for Caesarean section in a resource-limited setting: towards a consensus definition. *South African J Anaesth Analg*. 2018;25(1):1–5.
 7. Kinsella SM, Carvalho B, Dyer RA, Fernando R, McDonnell N, Mercier FJ, et al. International consensus statement on the management of hypotension with vasopressors during caesarean section under spinal anaesthesia. *Anaesthesia [Internet]*. 2018;73(1):71–92. Available from: <http://doi.wiley.com/10.1111/anae.14080>
 8. Ahmed HO, Hossam M, Adel A. Volume Preload versus Ephedrine Infusion for Prevention of Hypotension Due to Spinal Anesthesia for Cesarean Section. 2016;(March):37–44.
 9. Mercier FJ. Fluid loading for cesarean delivery under spinal anesthesia: have we studied all the options? *Anesth Analg*. LWW; 2011;113(4):677–80.
 10. Cooper DW. Caesarean delivery vasopressor management. *Curr Opin Anesthesiol*. LWW; 2012;25(3):300–8.

11. Kee WDN, Khaw KS, Ng FF, Lee BB. Prophylactic Phenylephrine Infusion for Preventing Hypotension During Spinal Anesthesia for Cesarean Delivery. 2004;(6).
12. Kee N, Kong H, Kee N, Kee N. More perfect ? 2017;1–4.
13. Gibbs MW, Van Dyk D, Dyer RA. Managing spinal hypotension during caesarean section: An update. South African Med J [Internet]. 2018;108(6):460. Available from: <http://www.samj.org.za/index.php/samj/article/view/12317>
14. Kuizenga MH, Vereecke HEM, Struys MMRF. Model-based drug administration: current status of target-controlled infusion and closed-loop control. Curr Opin Anesthesiol [Internet]. 2016;29(4). Available from: http://journals.lww.com/co-anesthesiology/Fulltext/2016/08000/Model_based_drug_administration___current_status.6.aspx
15. Somboonviboon W, Kyokong O, Charuluxananan S, Narasethakamol A. Incidence and risk factors of hypotension and bradycardia after spinal anesthesia for cesarean section. J Med Assoc Thai. 2008;91(2):181–7.
16. McDonald S, Fernando R, Ashpole K. Maternal Cardiac Output Changes After Crystalloid or Colloid Coload Following Spinal Anesthesia for Elective Cesarean Delivery: A Randomized Controlled Trial. 2011;113(4):3–8.
17. Lee JE, George RB, Habib AS. Spinal-induced hypotension: Incidence, mechanisms, prophylaxis, and management: Summarizing 20 years of research. Best Pract Res Clin Anaesthesiol [Internet]. Elsevier Ltd; 2017;31(1):57–68. Available from: <http://dx.doi.org/10.1016/j.bpa.2017.01.001>
18. Hasanin A, Mokhtar AM, Badawy AA, Fouad R. Post-spinal anesthesia hypotension during cesarean delivery, a review article. Egypt J Anaesth [Internet]. Egyptian Society of Anesthesiologists; 2017;33(2):189–93. Available from: <http://dx.doi.org/10.1016/j.egja.2017.03.003>
19. Ngan Kee WD, Khaw KS, Ng FF, Lee BB. Prophylactic Phenylephrine Infusion for Preventing Hypotension During Spinal Anesthesia for Cesarean Delivery. Anesth Analg [Internet]. 2004;(6):815–21. Available from:

<http://content.wkhealth.com/linkback/openurl?sid=WKPTLP:landingpage&an=00000539-200403000-00046>

Chapter 3

Suggestions for practice and further research

As our study showed that the newly developed algorithm with a phenylephrine infusion with a flow control device did not result in a significant improvement in spinal hypotension, we suggest that an area of future research could aim at developing an algorithm with phenylephrine boluses. This could possibly be of an advantage as at the writing of the study, phenylephrine is short in stock country wide.

We showed that significantly less colloids were used in the Group I, but we did not follow the patients up post-operative. This has a cost implication as colloids are more expensive than crystalloids. In future, we could follow these patients up and determine if they had fewer complications possibly related to less colloid usage.

We suggest that the protocol should be tested with less experienced rural personnel.

Appendices

Appendix A: Ethics approval letter



Health Sciences Research Ethics Committee

29-Mar-2018

Dear Mr Jovan Esterhuizen

Ethics Clearance: A prospective interventional study of the efficacy of a protocol for prevention and treatment of hypotension following spinal anaesthesia for Caesarean section at Pelonomi Hospital.

Principal Investigator: Mr Jovan Esterhuizen

Department: Anaesthesiology (Bloemfontein Campus)

APPLICATION APPROVED

Please ensure that you read the whole document

With reference to your application for ethical clearance with the Faculty of Health Sciences, I am pleased to inform you on behalf of the Health Sciences Research Ethics Committee that you have been granted ethical clearance for your project.

Your ethical clearance number, to be used in all correspondence is: **UFS-HSD2017/0798**

The ethical clearance number is valid for research conducted for one year from issuance. Should you require more time to complete this research, please apply for an extension.

We request that any changes that may take place during the course of your research project be submitted to the HSREC for approval to ensure we are kept up to date with your progress and any ethical implications that may arise. This includes any serious adverse events and/or termination of the study.

A progress report should be submitted within one year of approval, and annually for long term studies. A final report should be submitted at the completion of the study.

The HSREC functions in compliance with, but not limited to, the following documents and guidelines: The SA National Health Act. No. 61 of 2003; Ethics in Health Research: Principles, Structures and Processes (2015); SA GCP(2006); Declaration of Helsinki; The Belmont Report; The US Office of Human Research Protections 45 CFR 461 (for non-exempt research with human participants conducted or supported by the US Department of Health and Human Services- (HHS), 21 CFR 50, 21 CFR 56; CIOMS; ICH-GCP-E6 Sections 1-4; The International Conference on Harmonization and Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH Tripartite), Guidelines of the SA Medicines Control Council as well as Laws and Regulations with regard to the Control of Medicines, Constitution of the HSREC of the Faculty of Health Sciences.

For any questions or concerns, please feel free to contact HSREC Administration: 051-4017794/5 or email EthicsFHS@ufs.ac.za.

Thank you for submitting this proposal for ethical clearance and we wish you every success with your research.

Yours Sincerely

Dr. SM Le Grange
Chair : Health Sciences Research Ethics Committee



Appendix B: Permission from department



Department of Anaesthesiology
Faculty of Health Sciences
University of the Free State
Bloemfontein
9321
Tel 051 4053071
Cell 0722803828
Email: jovan2607@gmail.com

Dear Prof Diedericks

Analytical audit of a protocol for prevention and treatment of hypotension following spinal anaesthesia for Caesarean section at Pelonomi Hospital.

All women scheduled to receive spinal anaesthesia over a period of three months for elective or emergency Caesarean section at Pelonomi Hospital, will be invited to be included in this study and their anaesthetic records will be collected and analyzed for the incidence of hypotension.

Informed consent will be obtained prior to evaluation of each study candidate.

With your permission I would like to initiate the study on the

If you have any further queries regarding any aspect of the study please do not hesitate to contact me.

Sincerely yours,

Dr JL Esterhuizen
Registrar
Department of Anaesthesiology
University of the Free State

Handwritten signature: Permission Granted
Diedericks
2017 10 06



Appendix C: Permission from province



health

Department of
Health
FREE STATE PROVINCE

20 February 2018

Mr. J Esterhuizen
Dept. of Anaesthesiology
University of the Free State

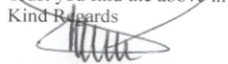
Dear Mr. J Esterhuizen

Subject: A prospective interventional study of the efficacy of a protocol for prevention and treatment of hypotension following spinal anaesthesia for Caesarean section at Pelonomi Hospital

- Please ensure that you read the whole document, Permission is hereby granted for the above – mentioned research on the following conditions:
- Serious Adverse events to be reported to the Free State department of health and/ or termination of the study
- Ascertain that your data collection exercise neither interferes with the day to day running of Pelonomi Hospital nor the performance of duties by the respondents or health care workers.
- Confidentiality of information will be ensured and please do not obtain information regarding the identity of the participants.
- **Research results and a complete report should be made available to the Free State Department of Health on completion of the study (a hard copy plus a soft copy).**
- Progress report must be presented not later than one year after approval of the project to the Ethics Committee of the University of Free State and to Free State Department of Health.
- Any amendments, extension or other modifications to the protocol or investigators must be submitted to the Ethics Committee of the University of Free State and to Free State Department of Health.
- **Conditions stated in your Ethical Approval letter should be adhered to and a final copy of the Ethics Clearance Certificate should be submitted to sebeelats@fshealth.gov.za before you commence with the study**
- No financial liability will be placed on the Free State Department of Health
- Please discuss your study with the institution manager/CEOs on commencement for logistical arrangements
- Department of Health to be fully indemnified from any harm that participants and staff experiences in the study
- Researchers will be required to enter in to a formal agreement with the Free State department of health regulating and formalizing the research relationship (document will follow)
- You are encouraged to present your study findings/results at the Free State Provincial health research day
- Future research will only be granted permission if correct procedures are followed see <http://nhrd.hst.org.za>

Trust you find the above in order.

Kind Regards


Dr D Motau
HEAD: HEALTH
Date: 21/3/2018

Appendix D: Consent in Sotho, English and Afrikaans

TŠEBELETSO EA BOPHELO

Tlhahlobo ea ho kenella ka lipuisano tsa ho thibela phekolo ea phekolo ea thibelo le kalafo ea hypotension ho latela sehlabelo sa mokokotlo bakeng sa karolo ea Kesarena lipetleleng tsa Pelonomi

U 'nile ua kōpuoa hore u kopanele thuputsong ea lipatlisiso.

U tsebisitsoe ka thuto ena ke ngaka ea sebetsang setsing sa liketsahalo tsa lik'hemik'hale sepetleleng sa Pelonomi.

U ka ikopanya le Dr JL Esterhuizen ka 051 4017795 neng kapa neng haeba o e-na le lipotso ka lipatlisiso.

Ho kenya letsoho phuputsong ena ke ka boithatelo, 'me u ke ke ua fuaa phoso kapa ua felloa ke melemo haeba u hana ho nka karolo kapa u etsa qeto ea ho khaotsa ho nka karolo.

Haeba u lumellana ho kenya letsoho, u tla fuaa kopi e saenneng ea tokomane ena hammoho le lethathamo la boitsebiso ba ho kenya letsoho, e leng kakaretso e ngotsoeng ea lipatlisiso.

Liphello tsa lipatlisiso li ka hatisoa koranteng ea bongaka.

Phuputso ea lipatlisiso, ho kenyelletsa le boitsebiso bo ka holimo e hlaloso ka mantsoe. Kea utloisisa hore na karolo ea ka ea thuto e bolela'ng 'me ke ithaopela ho lumela ho nka karolo.

Pontšo ea Mohoeletsi Letsatsi

Pontšo ea Paki Letsatsi

Letšoao la Mofetoleli Letsatsi

Consent**A prospective interventional study of the efficacy of a protocol for prevention and treatment of hypotension following spinal anaesthesia for Caesarean section at Pelonomi Hospital**

You have been asked to participate in a research study.

You have been informed about this study by the doctor working in the caesarean section theatre at Pelonomi Hospital.

You may contact Dr JL Esterhuizen at 051 4017795 at any time if you have questions about the research.

Your participation in this research is voluntary, and you will not be penalized or lose benefits if you refuse to participate or decide to terminate participation.

If you agree to participate, you will be given a signed copy of this document as well as the participation information sheet, which is a written summary of the research.

The results of the research can be published in a medical journal.

The research study, including the above information has been verbally described to me. I understand what my involvement in the study means and I voluntarily agree to participate.

_____	_____
Signature of Participant	Date

_____	_____
Signature of Witness	Date

_____	_____
Signature of Translator	Date

Toestemming**‘n Prospektiewe intervensionele studie van die effektiwiteit van n protokol en behandeling van lae bloeddruk na spinale narkose vir ‘n keisersnit by Pelonomi Hospitaal.**

U word vriendelik uitgenooi om deel te neem in die studie.

U is ingelig deur die mediese dokter wat in die keiser teater werk in Pelonomi Hospitaal.

U mag vir Dr JL Esterhuizen kontak by 051 4017795 enige tyd indien daar enige vrae is oor die studie.

U deelname in die navorsing is u eie keuse en u sal nie gepenaliseer word of oor enige voordele weerhou word as u weier om deel te neem of u deelname staak nie.

As u instem, sal u ‘n getekende kopie van die document ontvang asook die deelname informasie blad wat n geskrewe opsomming is van die navorsing.

Die uitslae van die navorsing kan gepubliseer word in n mediese joernaal.

Die navorsings studie, insluitend die bogenoemde informasie was verbaal verduidelik aan my. Ek verstaan wat by betrokkenheid in die studie betekin en ek stem vrywillig in om deel te neem.

_____ Datum
Handtekening van deelnemer

_____ Datum
Handtekening van getuie

_____ Datum
Handtekening van tolk

Appendix E: Patient information sheet in Sotho, English and Afrikaans

Tokomane ea tlhahisoleseding ea baithuti

Tlhahlobo ea ho kenella ka lipuisano tsa ho thibela phekolo ea phekolo ea thibelo le kalafo ea hypotension ho latela sehlabelo sa mokokotlo bakeng sa karolo ea Kesarena lipetleleng tsa Pelonomi.

Moratuo ea Ratehang

'Na, Dr JL Esterhuizen, ke etsa lipatlisiso mabapi le katleho ea protocol bakeng sa taolo le phekolo ea khatello e tlaase ea mali nakong ea likarolo ka morao ho anesthesia ea mokokotlo. Lipatlisiso ke mokhoa oo re ithutang likarabo tsa lipotso tsa rona. Phuputsong ena re lakatsa ho ithuta hore na e tla atleha ho sebelisa le ho kenya ts'ebetso ea tsamaiso ea tsamaiso ea khatello e tlaase ea mali nakong ea likarolo tsa lijo.

Re u botsa / re mema hore u kenye letsoho thuputsong ena ea lipatlisiso

Ke thuto ea ho kena-kenana le batho ba ka kenang ts'ebetsong eo re lakatsang ho elelloa hore na bakuli ba tla ba le khatello ea mali e tlaase hakae ka mor'a lefu la sepalesa bakeng sa karolo ea Kesarena lipetleleng tsa Pelonomi le ho hlahlola phello ea protocol e reretsoeng ho fokotsa ketsahalo ena.

Ho ke ke ha e-ba le moputso kapa litšenyehelo bakeng sa barupeluo ba kenang thutong ena.

Ho nka karolo ka boithatelo le ho hana ho nka karolo ho ke ke ha e-ba le kotlo kapa tahlehelo ea melemo ea hau. U ka khaotsa ho kenya letsoho nako efe kapa efe ntle le kotlo kapa tahlehelo ea melemo eo u seng u e-na le eona. Ha ho na likotsi tsa ho kopanela thutong ena.

Liphello tsa thuto li ka phatlalatsoa. Barupeluo ba ka ikopanya le mofuputsi oa tlhahisoleseding mabapi le liphuputso tsa lithuto.

Lekunutu: Ho bokelloa ha tlhahisoleseding le boitsebiso bohle ba data ho tla etsoa ka lekunutu.

Lintlha tsa boitsebiso ba mofuputsi (s) - Dr JL Esterhuizen 051 4053307; Prof G Lamacraft 051 4053613

Lintlha tsa boitsebiso tsa Sechaba le Sehlooho: Boitšoarō \ Komiti ea Setsebi sa Setsebi sa Bophelo, Univesithing ea Free State - bakeng sa ho tlaleha litlelebo: Nomoro ea mohala 051 4017795

Patient information

Dear Participant

I, Dr JL Esterhuizen, am doing a research project on the efficacy of a protocol for the management and treatment of low blood pressure during a caesarean section after spinal anaesthesia. Research is the process by which we learn the answers to our questions. In this study we wish to learn if it will be effective to use and implement a protocol for the management of low blood pressure during a caesarean section.

We are asking/inviting you to participate in this research study.

It is a prospective interventional study in which we wish to determine the number of patients that will develop low after spinal anaesthesia for Caesarean section at Pelonomi Hospital and assess the effect of a protocol aimed to lower this incidence.

There will be no remuneration or cost for participants taking part in this study.

Participation is voluntary and refusal to participate will involve no penalty or loss of your benefits. You may discontinue participation at any time without penalty or loss of benefits to which you are otherwise entitled. There are no risks for participating in this study.

The results of the study may be published. Participants may contact the researcher for information regarding study findings.

Confidentiality: Collection of all information and data capturing will be done confidentially.

Contact details of researcher(s) - Dr JL Esterhuizen 051 4053307; Prof G Lamacraft 051 4053613

Contact details of Secretariat and Chair: Ethics \committee of the Faculty of Health Sciences,
University of the Free State – for reporting of complaints: Telephone number 051 4017795

Pasient deelname informasie dokument

‘n Prospektiewe intervensionele studie van die effektiwiteit van ’n protokol vir die voorkoming en behandeling van hipotensie na spinale narkose vir ‘n keisersnit by Pelonomi Hospitaal.

Geagte Deelnemer

Ek, Dr JL Esterhuizen, doen ‘n navorsings projek oor die effektiwiteit van ‘n protokol vir die hantering en behandeling van lae bloeddruk gedurende ‘n keisersnit onder spinal narkose.

Navorsing is ‘n proses waarby ons antwoorde leer vir ons vrae. In die studie, wil ons graag leer of dit effektief sal wees om ‘n protokol te implementeer vir die behandeling van lae bloeddruk gedurende ‘n keiser snit onder spinal narkose.

Ons nooi u vriendelik/vra asb om deel te neem in ons navorsing studie.

Dit is ‘n prospektiewe intervensionele studie wees waarin ons graag wil bepaal die hoeveelheid pasiente wat lae bloeddruk ontwikkel na spinal narkose vir ‘n keisersnit by Pelonomi Hospitaal en bepaal hoe effektief ‘n protokol sal wees om die insidensie te verlaag.

Daar sal geen vergoeding wees of enige uitgawes vir die deelnemers aan die studie nie.

Deelname is vrywillig en indien deelname geweier word sal daar geen straf of voordele weerhou word nie. U mag teen enige tyd deelname staak en verlies van voordele of behandeling sal nie plaasvind nie. Daar is geen gevare/risikos tydens deelname in die studie.

Die resultate van die studie kan gepubliseer word. Deelnemers kan die navorser enige tyd bel vir navrae oor die studie.

Vertroulikheid: Versameling van alle data en informasie sal streng vertroulik plaasvind.

Kontak besonderhede van navorsers: - Dr JL Esterhuizen 051 4053307; Prof G Lamacraft 051 4053613

Appendix F: Data collection sheet(Baseline Group)

Patients Hospital number.....

Date (DD/MM/YY).....

Age of patient.....years

Weight of patient.....kg

Consent for study

Please send photo of
chart

1) Circle the appropriate number or fill in the details in the space provided:

1. Indication for casaerean section
2. G.....P.....
3. Gestation
4. Labour: Yes/No
5. Hydration status (Well, moderately or poor hydrated) (please encircle)
6. Baseline BP
7. Baseline HR
8. Standard Spinal Anaesthesia dose and technique?
9. Co-load given?
10. Correctly positioned
11. Height of block after 5 minutes
12. Phenylephrine boluses (dose and times)
13. Atropine given? (amount of times and total dose)
14. Ephedrine given? (amount of times and dose)
15. Adrenaline given? Amount of times and dose)
16. Fluids Total volume crystalloid
 Total volume colloids
 Total volume blood products
17. Estimated blood loss up to 5 minutes post-delivery.
18. Dose of oxytocin

- 19. BP – Lowest and highest level before delivery
 - Lowest and highest after oxytocin
- HR- lowest and highest before delivery
 - lowest and highest after oxytocin
- 20. Hypotension – with no bradycardia
 - With bradycardia
- Bradycardia alone (yes /no)
- 21. Converted to General anaesthesia and the reason
- 22. CPR?
- 23. APGARS scores 1 & 5
- 24. Other maternal and neonatal problems e.g. Vomiting, anti-emetics needed etc.

Please send photo of ANAESTHETIC CHART to 072 280 3828

(Intervention Group)

2) Patient information

Patients Hospital number.....

Date (DD/MM/YY).....

Age of patient.....years

Weight of patient.....kg

Did you use the protocol? If no, please select one of the following:

- a) Drugs not available
 - i. Phenylephrine
 - ii. Adrenaline
 - iii. Ephedrine
 - iv. Atropine
 - v. Other (Specify)
- b) Equipment not available
 - i. Dial a flow
 - ii. Three-way drip connector
 - iii. Other equipment-please specify:.....

c) Other:

- i. Forgot
- ii. General anaesthesia
- iii. Protocol not found
- iv. Other (please specify)

Consent for study

Exclusion criteria

3) Circle the appropriate number or fill in the details in the space provided:

1. Indication for caesarean section
2. G.....P.....
3. Gestation
4. Labour: Yes/No
5. Hydration status (well/moderate/poor)
6. Baseline BP
7. Baseline HR
8. Standard Spinal Anaesthesia dose and technique?
9. Co-load given? (yes/no?)
10. Correctly positioned (yes /no?)
11. Height of block after 5 minutes
12. Phenylephrine
 - i. Phenylephrine infusion commenced on cerebral spinal fluid (CSF)?
(Yes/No- if No, was BP > 140mmHg? Exclude if not.
 - ii. Was phenylephrine infusion increased to 100mcg/min? (time when increased)
 - iii. Was phenylephrine infusion stopped? (time please)
 - iv. Was phenylephrine decreased to 25mcg/min?
 - v. Phenylephrine boluses (dose and times)
13. Atropine given? (amount of times and total dose)
14. Ephedrine given? (amount of times and dose)

15. Adrenaline given? Amount of times and dose)

16. Fluids

- i. Total volume crystalloid
- ii. Total volume colloids
- iii. Total volume blood products

17. Estimated blood loss up to 5 minutes post-delivery.

18. Dose of oxytocin

19. BP - Lowest and highest level before delivery L- H-

- Lowest and highest after oxytocin L- H-

20. HR - lowest and highest before delivery L- H-

-lowest and highest after oxytocin L- H-

21. Hypotension (encircle if hypotension, if no hypotension- leave out) -no bradycardia

- with bradycardia

22. Bradycardia alone (yes/no?)

23. Converted to General anaesthesia and the reason

24. CPR?

25. APGARS scores 1 & 5

26. Other maternal and neonatal problems e.g. Vomiting, anti-emetics needed etc.