STUDY PROTOCOL

Development of advanced double intravenous vasopressor automated (ADIVA)system with improved hemodynamic trend control during spinal anaesthesia for Caesarean section

PROTOCOL NUMBER: SHF/CTG061/2017

CIRB NUMBER: 2018/2213

PROTOCOL VERSION: 1.0

PROTOCOL DATE: 2 Aug 2018

PRINCIPAL INVESTIGATOR:
Dr Singaraselvan Nagarajan, Consultant, Women's Anaesthesia, KK Women's And Children's Hospital, 100 Bukit Timah Road, Singapore 229899

*Refer to Section 9 for determination of sample size, analytical and statistical plan.

Table of Contents

PROTOCOL SIGNATURE PAGE

Protocol Title: Development of advanced double intravenous vasopressor automated (ADIVA) system with improved hemodynamic trend control during spinal anaesthesia for Caesarean section

Protocol Number: SHF/CTG061/2017

Protocol Version/ Date: Version 1, 2 Aug 2018

Sponsor Name: Singhealth Foundation Grant Clinical Trials Grant

Declaration of Investigator

I confirm that I have read the above-mentioned protocol and its attachments. I agree to conduct the described trial in compliance with all stipulations of the protocol, regulations and ICH E6 Guideline for Good Clinical Practice (GCP)

Principal Investigator Name: Dr Singaraselvan Nagarajan

Principal Investigator Signature: _____

Date: _____

1 BACKGROUND AND RATIONALE

Spinal anaesthesia has become more popular in recent years as the efficacy and safety of this anaesthetic technique is being established. Based a recent report, the total global volume of surgery procedure was estimated to be 312.9 million in year 2012, in which 7% are Caesarean sections (1, 2). Over 95% of planned Caesarean sections in the United States used spinal anaesthesia (3). KK Hospital performs more than 6000 spinal anaesthesia procedure every year and 85% of Caesarean section is performed under regional anaesthesia with a majority being spinal anaesthesia.

Spinal anaesthesia is a widely performed anaesthetic technique for surgery to the abdomen, pelvis and lower limbs. The advantages of this technique are reduction of airway complications associated with general anaesthesia, reduction in surgical bleeding and reduction in post-operative nausea and vomiting when compared with general anaesthesia (4, 5). However, this procedure is frequently associated with adverse hemodynamic changes and remains a common clinical problem. The most important severe side effects are hypotension (up to 33%) and bradycardia (up to 13%) in general surgical procedures (6, 7). During spinal anaesthesia for Caesarean section, maternal hypotension is even more common ranging from 70-90% incidence (8).

Sympathetic autonomic blockade from spinal anaesthesia results in decreased perfusion to the cardiac, neurological and renal systems with potential organ dysfunction. The potential adverse effects resulted from maternal hypotension are maternal nausea, vomiting, cardiac dysfunction and foetal acidosis and hypoxia(9-11). Patients with autonomic dysfunction such as diabetes mellitus and elderly are at higher risk of hypotension and bradycardia that constitute national importance (12-14).

Hypotension or bradycardia could be treated with manual bolus of vasopressors (15). Ephedrine increases the blood pressure and heart rate, whilst phenylephrine increases the blood pressure only. Volume expansion using fluids and during surgical bleeding, blood transfusion may be required. Severe and rapid progressing bradycardia and hypotension can become life threatening requiring rapid detection and treatment (16-17). The anaesthetists face the vigilant challenge to prevent mild variations in haemodynamic responses from spiralling into major hemodynamic compromise.

Blood pressure fluctuations especially hypotension during spinal anaesthesia is currently detected using an intermittent blood pressure monitor cycling every 2 to 5 minutes and reactive administration of vasopressors upon detection of hypotension when the blood pressure reading is displayed intermittently (18).Additionally, the use of conventional non-invasive BP monitoring (based on the principle of oscillometry) is limited by the time required to inflate and subsequently to deflate the cuffs commonly applied to the arm. The lag period and lack of a 'real-time' measurement of BP may lead to a failure to react in a timely manner to the BP changes when they occur. During spinal anaesthesia for Caesarean delivery, haemodynamic instability could occur rapidly and suddenly – possibly leading to maternal and foetal complications (19).Stabilizing the hemodynamic status, being alert to downward trends in heart rate and blood pressure, and timely interventions to these changes are the critical steps in order to prevent catastrophic consequences such as cardiac collapse.

Therefore, we developed a double intravenous vasopressor automated (DIVA) system in our institution to treat maternal hypotension during spinal anaesthesia for Caesarean delivery. We performed a randomised, double-blinded controlled trial which involved 226 healthy pregnant women who received spinal anaesthesia during elective Caesarean delivery. The results showed that

DIVA system dramatically decreased the incidence of maternal hypotension (39.3%, 46/117) compared to manual vasopressor bolus group (57.5%,65/113)(p=0.008). The DIVA system achieved less incidence of maternal hypotension and less wobble compared to Manual Vasopressor Bolus (MVB). However, the incidence of reactive hypertension, total vasopressor requirements, maternal nausea and vomiting, neonatal acid-base status and Apgar scores were similar.

The DIVA system built in our centre renders a potentially cost-effective and efficacious way of providing individualised medicine. The algorithm has been improved during its development and shown to be superior to manual vasopressor bolus by the anaesthetist. . Although there was a significant reduction in the incidence of hypotension, the maternal and neonatal adverse effects were still not fully eliminated (20). A rapid bolus of vasopressor used in previous work was efficacious in treating hypotension, however this may lead to over treatment leading to higher risk of reactive hypertension. On the corollary, an infusion method may result in a slower but gentler response leading to lesser risk of reactive hypertension.

We propose to improve the algorithm to achieve much stable haemodynamic outcomes. The analysis of 236 subjects in the most recent randomised controlled trial suggested that improvements can be made by refining the haemodynamic trend control and delivery of vasopressors looking at positive and negative trends in systolic blood pressure (21).For example, if a negative trend in systolic blood pressure is detected, a rapid bolus dose of vasopressor would be delivered to prevent further drop in blood pressure. On the other hand, with a positive trend in systolic blood pressure, an infusion method of vasopressor delivery may reduce the risk of reactive hypertension. Hypertensive response may be detrimental in high risk patients as this increases the risk of cardiac failure and stroke (9-11). This technology would lead to more stable haemodynamic profiles and improve patient outcomes by reducing maternal-foetal morbidity during caesarean section.

In this proposed study we will develop a new algorithm for the advanced double intravenous vasopressor automated (ADIVA) system to control the blood pressure more rigorously by detecting the trend of blood pressure. Vasopressor dose will be adjusted as per the trend of the blood pressure recorded. We aim to improve on the stability of the systolic blood pressure by early proactive treatment of hypotension. This will be achieved by varying the amount of the vasopressor and varying the decision-making steps on whether a bolus or infusion delivery of vasopressor would be administered depending on presence of a negative or positive trend of systolic blood pressure, respectively. For example，when hypotension is detected and if the SBP trend is downward the pump will deliver the appropriate vasopressor as a bolus over 5 seconds (faster response, risk of reactive hypertension less as SBP trend is downward). On the other hand if hypotension is detected with an upward trend of SBP then the appropriate vasopressor dose is delivered as an infusion over 30 seconds (gentle and smooth response, slower response time accepted as SBP trend is upward). We believe this proactive management of hypotension based on the SBP trend and the speed of injection will improve on the stability of systolic blood pressure and decrease the incidence of reactive hypertension.

1.1 General Introduction

We will set up ADIVA system by exporting BP and heart rate data measured by non-invasive blood pressure cardiac monitoring system to a computer that integrates the data every 10 seconds. We propose to improve the algorithm so that a stable blood pressure can be maintained. We plan to achieve this by varying the amount of the vasopressor and determining whether a

bolus or infusion delivery of vasopressor would be administered depending on a negative or positive trend of systolic blood pressure respectively. Commands will be sent to activate either one of the pumps or neither based on the ADIVA algorithm described below.

The investigators and delegated research personnel will assist to prepare the vasopressor drugs including phenylephrine and ephedrine in syringes and to place the medications on the 2 syringe pumps used in the study.

A computer algorithm will deliver the vasopressors according to the set threshold of blood pressure and heart rate.

1.2 Rationale and Justification for the Study

Phenylephrine is a selective alpha 1 receptor agonist that results in vasoconstriction, increased systemic vascular resistance, bradycardia and may result in iatrogenic reactive hypertension in overdose which may be not be innocuous especially in high-risk patients (preeclampsia, cardiac disease). Ephedrine is an alpha and beta receptor agonist that results in vasoconstriction, increased systemic vascular resistance, increased heart rate and contractility. We propose to use two drugs (phenylephrine and ephedrine) to optimise the function of this highly novel closed-loop feedback system to modulate the effects of iatrogenic reactive hypertension, bradycardia and reduction of uteroplacental blood flow due to high doses of phenylephrine alone, as well as controlled fluid administration to address any deficiencies in intravascular volume. Furthermore, our target-controlled system could identify patients who are at risk of developing hypotension and hence, need more vasopressors to maintain normal hemodynamic status. We would also be able to identify (and appropriately treat) patients who may develop bradycardia by the use of ephedrine rather than phenylephrine based on heart rate criteria. The presence of such an innovation to provide an individualised approach based on a closed loop feedback system to maintain hemodynamic stability will assist anaesthetists in the perioperative and intensive care settings.

1.2.1 Rationale for the Study Purpose

The DIVA system built in our centre renders a potentially cost-effective and efficacious way of providing individualised medicine. The algorithm has been improved during its development and shown to be superior to manual vasopressor bolus by the anaesthetist. . Although there was a significant reduction in the incidence of hypotension, the maternal and neonatal adverse effects were still not fully eliminated (20). A rapid bolus of vasopressor used in previous work was efficacious in treating hypotension, however this may lead to over treatment leading to higher risk of reactive hypertension. On the corollary, an infusion method may result in a slower but gentler response leading to lesser risk of reactive hypertension.

We propose to improve the algorithm to improve the stability of haemodynamic outcomes. The analysis of 236 subjects in the most recent randomised controlled trial suggested that improvements can be made by refining the haemodynamic trend control and delivery of vasopressors looking at positive and negative trends in systolic blood pressure (21). For example, if a negative trend in systolic blood pressure is detected, a rapid bolus dose of vasopressor would be delivered to prevent further drop in blood pressure. On the other hand, with a positive trend in systolic blood pressure, an infusion method of vasopressor delivery may reduce the risk of reactive hypertension. Hypertensive response may be detrimental in high risk

patients as this increases the risk of cardiac failure and stroke (9-11). This technology would lead to more stable haemodynamic profiles and improve patient outcomes by reducing maternal-fetal morbidity during caesarean section.

In this proposed study we will develop an improved algorithm for the advanced double intravenous vasopressor automated (ADIVA) system to control the blood pressure more rigorously by detecting the trend of blood pressure. Vasopressor dose will be adjusted as per the trend of the blood pressure recorded. We aim to improve on the stability of the systolic blood pressure by early proactive treatment of hypotension. This will be achieved by varying the amount of the vasopressor and varying the decision-making steps on whether a bolus or infusion delivery of vasopressor would be administered depending on presence of a negative or positive trend of systolic blood pressure, respectively. For example when hypotension is detected and if the SBP trend is downward the pump will deliver the appropriate vasopressor as a bolus over 5 seconds (faster response, risk of reactive hypertension less as SBP trend is downward). On the other hand if hypotension is detected with an upward trend of SBP then the appropriate vasopressor dose is delivered as an infusion over 30 seconds (gentle and smooth response, slower response time accepted as SBP trend is upward). We believe this proactive management of hypotension based on the SBP trend and the speed of injection will improve on the stability of systolic blood pressure and decrease the incidence of reactive hypertension.

1.2.2 Rationale for Doses Selected

Our new ADIVA algorithm is significantly different from DIVA algorism. The DIVA algorithm used a two-step decision process for vasopressor administration based on the percentage drop of systolic blood pressure (SBP) with two different dose regimen for the vasopressors (Phenylephrine 50mcg or 25 mcg (with heart rate > 60), ephedrine 4 mg or 2mg (with heart rate <60) when SBP is below 90% or between 90-100% respectively.

In the ADIVA algorithm in addition to the percentage drop in SBP from baseline, the SBP trend plays a key role in the way the vasopressor is being administered. Hypotension in the presence of up trending SBP is treated by administering the vasopressor as an infusion over 30 seconds. Hypotension in the presence of down trending SBP is treated by administering the vasopressor as a bolus given over 5 seconds. The dose of vasopressor administered is graded in response to the degree of hypotension (phenylephrine 25 mcg, 25 mcg, 50 mcg or 75 mcg (with heart rate >60) or ephedrine 2 mg, 2 mg, 4mg or 6 mg (with heart rate < 60) when SBP is 100%-110%, 90%-100%, 80-90% or <90% respectively).

During hypotension with a down trending SBP, a rapid bolus dose of vasopressor would prevent further drop in blood pressure. On the other hand, hypotension with an up trending SBP treated with vasopressor infusion may prevent the risk of reactive hypertension.

We believe this proactive management of hypotension based on the SBP trend and the speed of injection will improve on the stability of systolic blood pressure and decrease the incidence of reactive hypertension.

1.2.3 Rationale for Study Population

We are investigating the improved algorithm to manage blood pressure during spinal anaesthesia for Caesarean delivery. Hence, our study population must be the parturients who undergo spinal anaesthesia for Caesarean delivery.

This study will be conducted with the approval of the Centralised Institutional Review Board (CIRB) from SingHealth, Health Sciences Authority and clinical trials registration. Informed written consent will be obtained from every patient who participated in the study. The healthy women with singleton pregnancy scheduled for elective Caesarean section at term and who requested for spinal anaesthesia will be recruited.

The inclusion criteria are:

- The indication for an elective Caesarean section.
- The use of spinal anaesthesia for Caesarean section.
- Anthropometric profile within the following range: age 21-45 years old, weight 40-90 kg and height of 145-170 cm.

The exclusion criteria are:

- The presence of at least one medical condition e.g. hypertension, diabetes mellitus and other cardiovascular disease, which is not well controlled.
- Contraindication to spinal anaesthesia and/or allergy to opioids.

1.2.4 Rationale for Study Design

There are two phases in this study.

Phase 1 is a pilot study to recruit 60 healthy pregnant women to investigate the efficacy and safety of the ADIVA algorithm.

Phase 2 is a double-blinded, randomized (1:1 allocation ratio) trial design. This is to investigate the use of ADIVA system in comparison to the existing DIVA system.
The experimental group will be using the ADIVA system and the comparator control group will be using the DIVA system. There is no placebo control in this trial design.

Women will be randomly assigned to the experimental and control groups in a 1:1 allocation ratio based on a computer-generated code that will be prepared at a remote site and sealed in opaque, sequentially-numbered envelopes by the 'unblinded' CRC. The women will be allocated to one of the two groups:
(a) Group ADIVA (experimental) will receive treatment as per the new advanced algorithm;
(b) Group DIVA (control) will be managed as per the DIVA algorithm

Both the patients and the anaesthetist responsible for collecting and analysing the study parameters are 'blinded' to the allocation.

2 HYPOTHESIS AND OBJECTIVES

2.1 Hypothesis

Refer to section 2.2.

2.2 Primary Objective

Primary Objective

To determine the incidence of maternal hypotension between the new ADIVA system and the DIVA system in term women with singleton pregnancy who undergo elective caesarean section under standardized spinal anaesthesia.

- **Primary Hypothesis**
  The incidence^ of maternal hypotension* in the ADIVA system will be less than or equal to 18% compared to the DIVA system.

^Incidence of maternal hypotension of DIVA system: 39%; derived from previous studies by the research team.

*Hypotension is defined as any reading of systolic blood pressure below 80% of the baseline systolic blood pressure. Blood pressure monitoring is done using continuous non-invasive blood pressure monitoring device (continuous non-invasive arterial pressure (CNAP) cardiac monitoring.

2.3 Secondary Objectives

Secondary Objectives

1. To determine the incidence of reactive hypertension, nausea and vomiting, amount of vasopressor use and foetal outcomes (cord pH, APGAR scores) of the ADIVA system.

2. To determine the cardiac output (reflection of cardiac function) and systemic vascular resistance (resistance to blood flow in the circulation) using cardiac monitoring of ADIVA system.

- **Secondary Hypotheses**

  1) The incidence of reactive hypertension using the ADVIA system will be lesser than DIVA system.
  2) The incidence of nausea and vomiting using the ADIVA system will be less than DIVA system.
  3) The amount of vasopressor use using the ADIVA system will be similar to the DIVA system.
  4) The cord pH and APGAR scores (foetal outcomes) using the ADVIA system will be similar to the DIVA system.
  5) The cardiac output and systemic vascular resistance using cardiac monitoring of ADIVA system will be similar to the DIVA system.

2.4 Potential Risks and Benefits:

2.4.1 Potential Risks

There is no additional risk to the patient or her baby by participating in this study. If there are any side effects during the spinal anaesthesia, this would be expeditiously and effectively treated. Rare side effects include respiratory difficulty, nerve injury and post dural puncture headache that are not increased by this study, and are risks associated with spinal anaesthesia as listed in anaesthesia consent form. The drugs (phenylephrine and ephedrine) and the dosage used are the same as standard of care, so there is no additional risk to the patients. However, there may have changes during surgery that may lead to low blood pressure or high blood pressure from the administration of medications.

The attending anaesthetist will treat these side effects accordingly. The proposed double-

vasopressor system does not pose additional clinical risks when compared to other commercial syringe driver pumps. Not only does the pump contain the necessary safety checks and controls, it includes an additional safety feature which prevents infusion from exceeding an hourly dosage limit set by the investigators. There is a rare chance that the ADIVA system may malfunction. If this occurs, the blood pressure control will be taken.

2.4.2 Potential Benefits

Our hypothesis is that the proposed ADIVA system would further stable patients' haemodynamic outcomes and reduce maternal-fetal adverse events during caesarean section, which subsequently provide better maternal satisfaction. This will translate into a more comfortable delivery experience for parturients with greater patient safety in anaesthesia. In addition, preliminary data has shown the need to develop this technology so as reduce perioperative haemodynamic instability during anaesthesia and prevent cardiac and neurological adverse events. By participating in this study, patients may help to contribute to the development roadmap by allowing us to test on the algorithm to further improve haemodynamic stability and reduce maternal-fetal morbidity during caesarean section as well as extend the application of this technology to other anaesthetic settings.

3 STUDY POPULATION

3.1 List The Number and Nature of Subjects to be enrolled.

Phase 1: 70 healthy pregnant women
Phase 2: 230 healthy pregnant women
All patients to be recruited will be from KK Women's and Children's Hospital.

3.2 Criteria for Recruitment and Recruitment Process

This study will be advertised on study brochures. Patients who are undergoing elective caesarean surgery will receive study information either at pre-anaesthetic clinic or upon admission for surgery if they have not attended the pre-anaesthetic clinic. They will be screened for eligibility using the inclusion and exclusion criteria. If eligible for recruitment, the patients will be approached by the investigators for recruitment. Recruitment will be performed in the preanaesthetic clinic or on the same day of surgery if they have not attended pre-anaesthetic clinic. Research personnel will conduct all discussions about the study and answer any questions in a private manner in the consultation rooms. They will be counselled regarding the alternatives and given an opportunity to ask questions and clarify doubts. Ample time will be given to the potential patients for consent taking. Consent will be obtained in writing upon their willingness and agreement to participate in the study. With the activation of HBRA, informed consent will be obtained in the presence of a prescribed witness.

3.3 Inclusion Criteria

The inclusion criteria are:

- Anthropometric profile within the following range: age 21-50 years old, weight 40-90 kg and height of 145-170 cm.
- Healthy adult (American Society of Anesthesiologists physical status 1 and 2) parturients;
- With singleton full-term pregnancy;
- The indication for an elective cesarean delivery;

- The use of spinal anaesthesia for cesarean delivery;

3.4 Exclusion Criteria

The exclusion criteria are:

- Obstetric (e.g. pre-eclampsia, premature rupture of amniotic membranes for more than 48 hours, gestational diabetes on insulin, pregnancy-induced hypertension on medication) and uncontrolled medical(e.g. cardiac disease) complications;
- Contraindication to spinal anaesthesia and/or allergy to opioids.

3.5 Subject Replacement

No subject replacement will be performed.

4 STUDY DESIGN

There are two phases involved in this study.

Phase 1 is an open-labelled pilot study to assess the efficacy and safety of the ADIVA algorithm.

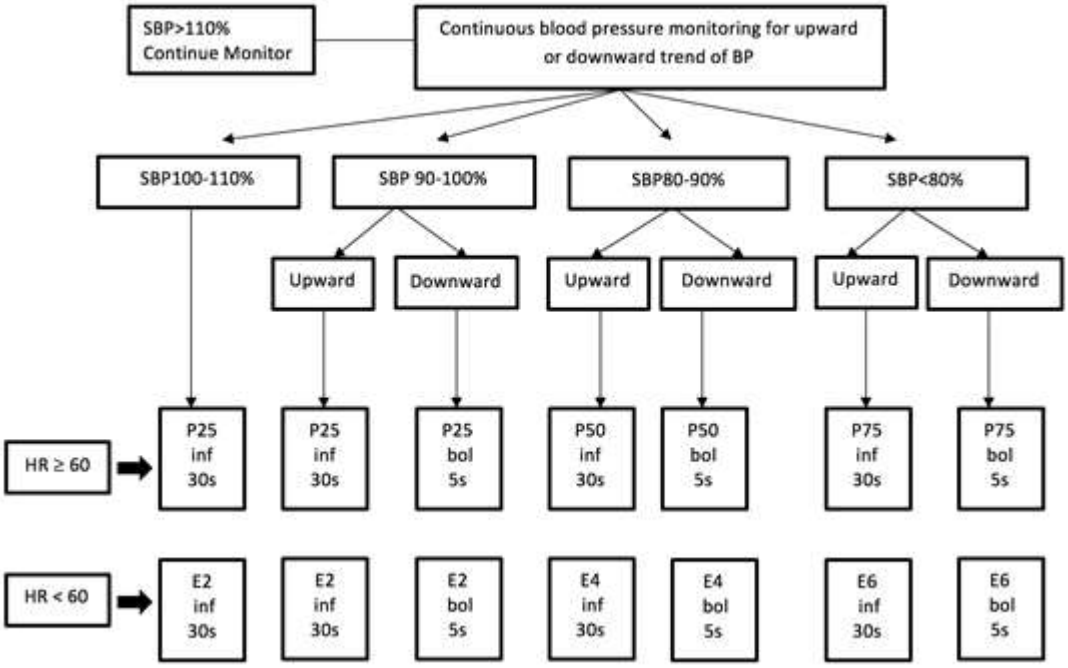
Phase 2 is a double-blinded, randomized (1:1 allocation ratio) trial design. The experimental group will be using the ADIVA system and the comparator control group will be using the DIVA system.

There is no placebo control in this trial design. Women will be randomly assigned to the experimental and control groups in a 1:1 allocation ratio based on a computer-generated code that will be prepared at a remote site and sealed in opaque, sequentially-numbered envelopes by the 'unblinded' CRC. The women will be allocated to one of the two groups:

a) Group ADIVA (experimental) will receive treatment as per the new advanced algorithm. (Refer to Figure 1, Schematic diagram of the algorithm used in the ADIVA system).
Our new ADIVA algorithm is significantly different from DIVA algorism.

The DIVA algorithm used a two-step decision process for vasopressor administration based on the percentage drop of systolic blood pressure (SBP) with two different dose regimen for the vasopressors (Phenylephrine 50mcg or 25 mcg (with heart rate > 60), ephedrine 4 mg or 2 mg (with heart rate <60) when SBP is below 90% or between 90-100% respectively)

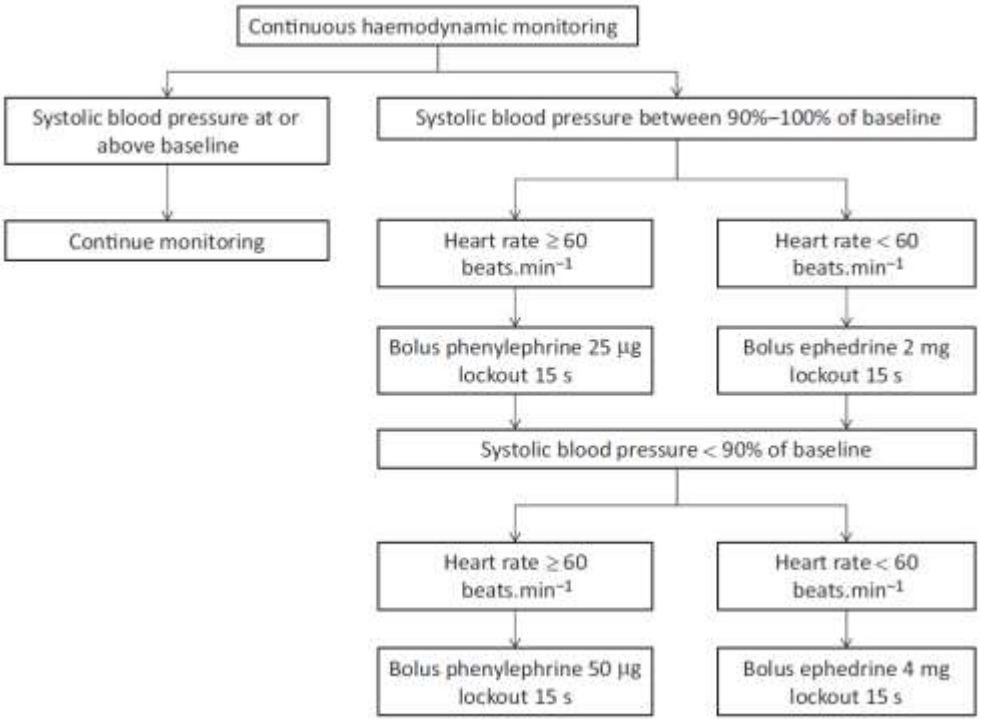
In the ADIVA algorithm in addition to the percentage drop in SBP from baseline, the SBP trend plays a key role in the way the vasopressor is being administered. Hypotension in the presence of up trending SBP is treated by administering the vasopressor as an infusion over 30 seconds. Hypotension in the presence of down trending SBP is treated by administering the vasopressor as a bolus given over 5 seconds. The dose of vasopressor administered is graded in response to the degree of hypotension (phenylephrine 25 mcg, 25 mcg, 50 mcg or 75 mcg (with heart rate >60) or ephedrine 2 mg, 2 mg, 4mg or 6 mg (with heart rate < 60) when SBP is 100%-110%, 90%-100%, 80-90% or <90% respectively).



(inf – Infusion; bol – Bolus; P – Phenylephrine; E – Ephedrine)
Figure 1: Schematic diagram of the algorithm used in the ADIVA system

b) Group DIVA (control) will be managed as per the DIVA algorithm. (Please refer to figure 2. Schematic diagram of the algorithm used in the DIVA system).The DIVA system will infuse vasopressors of phenylephrine of 25mcg (SBP 90-100% of baseline and HR ≥60/min) or ephedrine 2 mg (SBP 90-100% of baseline and HR <60/min) every 30 seconds based on Nexfin cardiac monitoring BP measurements and if the blood pressure is lower, phenylephrine of 50mcg (SBP <90% of baseline and HR >60/min) or ephedrine 4mg (SBP <90% of baseline and HR <60/min) every 30 seconds based on Nexfin cardiac monitoring BP measurements.

Rescue phenylephrine 100mcg boluses, ephedrine 3mg boluses and atropine 0.6mg boluses will be made available for both groups if systolic BP remains less than 70% baseline values or HR remains <60/min for more than 3 minutes by the clinician.



4.1 Randomisation and Blinding

Computer generated code are preprared preoperatively in a 1:1 ratio by the statistician from Duke-NUS Medical School using a computer generated random number sequence and will be allocated to one of two groups using sealed opaque envelopes.

Women will be randomly assigned to the experimental and control groups in a 1:1 allocation ratio based on a computer-generated code that will be prepared at a remote site and sealed in opaque, sequentially-numbered envelopes by the 'unblinded' CRC. The women will be allocated to one of the two groups:

(a) Group ADIVA (experimental) will receive treatment as per the new advanced algorithm;
(b) Group DIVA (control) will be managed as per the DIVA algorithm.

Unblinded team: The designated clinical research coordinators will perform randomization after consent taken. System will be set up by them according to the treatment group allocated. The monitor screen will not show the treatment group.

Blinded team: Both the patients and the anaesthetist who are responsible for collecting and analysing the study parameters are 'blinded' to the allocation.

Study drug preparation will be performed by any delegated study members in view that no unblinding issue is involved.

4.2 Contraception and Pregnancy Testing

Not applicable.

4.3 Study Visits and Procedures

4.3.1 Screening Visits and Procedures

Eligible subjects will be screened for their eligibility and recruited at the antenatal pre-admission caesarean section clinics or in the same day admission ward. The study will be terminated when the patient is discharged from the recovery room after surgery.

The study is conducted in the operating theatre room where the subject has her Caesarean section under spinal anaesthesia.

Subjects may withdraw voluntarily from participation in the study at any time. Subjects may also withdraw voluntarily from receiving the study intervention for any reason. If voluntary withdrawal occurs, the subject will be given spinal anaesthesia for Caesarean section and postoperative analgesia as per routine hospital practice

Patients who have consented to participate in the study will have their case notes/medical records reviewed to confirm their eligibility for the study. The relevant data from the case notes will be recorded in the data collection form.

4.3.2 Study Visits and Procedures

Visit 1 (Before surgery)

- Patient recruitment before the surgery
- Randomization (only for Phase 2 patients)
- Baseline Demographic data collection
- Setting up spinal anaesthesia and connection to ADIVA system

- Medical Procedures during this visit are the following:

1) Intravenous access before surgery will be established using an 18G cannula.
2) Continuous non-invasive blood pressure and cardiac output system have finger cuffs will be placed on the right or left second or middle finger. The average value of 3 readings after the patient has rested for 15 minutes will be taken as the baseline systolic BP value. Every patient will receive a spinal anaesthesia in the sitting position. After ensuring a free flow of cerebrospinal fluid (CSF), 2.3mls of 0.5% heavy bupivacaine 15 mg fentanyl and 100 mg of morphine will be injected intrathecally over 15 sec with the orifice of the spinal needle facing in the cephalad direction which is the routine dose of spinal medications.
3) Each patient will receive IV 1000ml of Hartmann's for coloading fast. Antiemetics (ondansetron 4 mg and dexamethasone 4mg) will be routinely given after the delivery of the foetus.

- Data collection

The following data regarding the patients will be collected: ethnic group, age, weight, height, gestational age. In addition, the following clinical data of the patients will be recorded:
Systolic and diastolic blood pressure; Heart rate; Cardiac output and systemic vascular resistance; Total amount of vasopressors (ephedrine and phenylephrine) used.

The presence of the following data will be recorded by the research coordinator who is not

involved in the clinical care of the patient at 5 min intervals:
Motor block (modified Bromage scale: 0 = no block, 1 = unable to flex either hip joint but able to move knee and ankle joints, 2 = unable to move hip and knee of either limb but able to move either ankle, 3= unable to move hip, knee or ankle joint of either lower limb);
Sensory block level; Presence of shivering (0 = no, 1 = yes), nausea (0 = no, 1 = yes), vomiting (0 = no, 1 = yes).

Visit 2 (After surgery)
Data collection:

- Neonatal APGAR scores at 0 and 5 minutes;
- Neonatal arterial and venous cord pH;
- Maternal satisfaction and intraoperative pain scores with the anaesthesia technique at the end of the surgery (0-100 numerical rating scale);
- Adverse events.

Please refer to Appendix 1 for Study Schedule, appendix 2 for data collection form used in the study.

4.3.3 Final Study Visit:

The study will be terminated after discharge from the recovery room. No further follow-up will be required.

4.3.4 Post Study Follow up and Procedures

No post study follow up and procedures will be performed.

4.4 Discontinuation/Withdrawal

4.4.1 Discontinuation Criteria

The stopping criteria for the research study will be based on safety criteria. The review of serious adverse effects will be performed.

4.4.2 Discontinuation Visit and Procedures

Hourly postoperative monitoring and routine follow up of all patients for 24 hours is carried out in our current practice following any regional anaesthetic for caesarean section. This will also be performed for those patients who withdraw from the study and undergo caesarean section under regional anaesthesia.

4.5 Discontinuation/Withdrawal

4.5.1 Discontinuation Criteria

The stopping criteria for the research study will be based on safety criteria. The review of serious adverse effects will be performed.

4.5.2 Discontinuation Visit and Procedures

Hourly postoperative monitoring and routine follow up of all patients for 24 hours is carried out in our current practice following any regional anaesthetic for caesarean section. This will also be performed for those patients who withdraw from the study and undergo caesarean section under regional anaesthesia.

5 TRIAL MATERIALS

5.1 Trial Product (s)

Phenylephrine is a selective alpha 1 receptor agonist that results in vasoconstriction, increased systemic vascular resistance, bradycardia and may result in iatrogenic reactive hypertension in overdose which may be not be innocuous especially in high-risk patients (preeclampsia, cardiac disease). Ephedrine is an alpha and beta receptor agonist that results in vasoconstriction, increased systemic vascular resistance, increased heart rate and contractility. We propose to use two drugs (phenylephrine and ephedrine) to optimise the function of this highly novel closed-loop feedback system to modulate the effects of iatrogenic reactive hypertension, bradycardia and reduction of uteroplacental blood flow due to high doses of phenylephrine alone, as well as controlled fluid administration to addressany deficiencies in intravascular volume. Furthermore, our target-controlled DIVA & ADIVA system could identify patients who are at risk of developing hypotension and hence, need more vasopressors to maintain normal hemodynamic status. We would also be able to identify (and appropriately treat) patients who may develop bradycardia by the use of ephedrine rather than phenylephrine based on heart rate criteria. The presence of such an innovation to provide an individualised approach based on a closed loop feedback system to maintain hemodynamic stability will assist anaesthetists in the perioperative and intensive care settings.

5.2 Storage and Drug Accountability

Phenylephrine is available as a 1mg/10mL ampoule. It is stored at room temperature.

Ephedrine is available as a 1ml 30mg ampoule. Ephedrine will be diluted to 8mg/ml with normal saline. It is stored at room temperature.

6 TREATMENT

6.1 Rationale for Selection of Dose

Doses selected are based on previous studies done by our research team. Previous studies have shown equivalent vasopressor activity of 100mcg of phenylephrine and 8mg ephedrine. The vasopressors are administered in the intravenous route.

6.2 Study Drug Formulations

Phenylephrine is available as a 1 mg/10 ml ampoule. 2 vials of Phenylephrine will be used to prepare into 50 mls syringe (total volume 15 ml).

Ephedrine is available as a 1ml 30mg ampoule. It is stored at room temperature. 2 vials of ephedrine 30mg/ml (1 ml each) will be diluted to 8mg/ml with 5.5 ml of normal saline (total volume 7.5mls). 2x ephedrine 30mg/ml (1mls each) + 5.5 mls N/S into 10ml syringe (total volume 7.5mls)

6.3 Study Drug Administration

Drug administration is through the DIVA or ADIVA algorithm as shown in Section 4 Figure 1&2.

6.4 Specific Restrictions / Requirements

Not applicable.

6.5 Blinding

Patients will be randomised preoperatively in a 1:1 ratio by the statistician from Duke-NUS School using a computer generated random number sequence and will be allocated to one of two groups using sealed opaque envelopes.

The patients and anaesthetists who are involved in data collection are blinded in this study. The designated research coordinators in this study are in the unblinded group and will perform randomization as well as pump setting up.

Drugs preparation will be performed by delegated study team members.

6.6 Concomitant therapy

Not Applicable.

7 SAFETY MEASUREMENTS

7.1 Definitions

An adverse event (AE) is any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment.

A serious adverse event (SAE) or reaction is any untoward medical occurrence that at any dose:

- results in death
- is life-threatening
- requires inpatient hospitalisation or prolongation of existing hospitalisation
- results in persistent or significant disability/incapacity or
- is a congenital anomaly/birth defect

- is a medical event that may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed above.

Phenylephrine and ephedrine are indirect acting vasopressors. Possible side effects of phenylephrine and ephedrine (based on previous studies) include:

- Tachyphylaxis
- Reactive hypertension

Patients will be monitored for these side effects and given symptomatic relief accordingly by the principal investigator or co-investigator. In the unlikely situation that these symptoms result in prolonged hospital stay, this will be reported to the HSA and CIRB.

In this study, the following adverse event will be collected and reported:

- Hypotention (less than 70% of baseline for >5 mins)
- Persistent maternal severe bradycardia (less than 50 beats per minute for > 5 mins, before delivery

A serious adverse event (SAE) or reaction is any untoward medical occurrence that at any dose:

- results in or contributes to death
- is life-threatening
- requires inpatient hospitalisation or prolongation of existing hospitalisation
- results in or contributes to persistent or significant disability/incapacity or
- results in or contributes to a congenital anomaly/birth defect
- results in such other events as may be prescribed

7.2 Collecting, Recording and Reporting of Adverse Events and Serious Adverse Events to CIRB

Reporting of adverse events involves the PI submitting to the approving CIRB the completed SAE Reporting Form within the stipulated timeframe. PI is responsible for informing the institution representative (local SAE resulting in death), sponsor or regulatory bodies as required and appropriate.

Reporting timeline to CIRB:

- SAE that result in death, regardless of causality, should be reported immediately - within 24 hours of the PI becoming aware of the event.
- Local life-threatening (unexpected/ expected) SAE should be reported no later than 7 calendar days after the Investigator is aware of the event, followed by a complete report within 8 additional calendar days.
- Local unexpected SAE that are related events, but not life-threatening, should be reported no later than 15 calendar days after the investigator is aware of the event.
- An increase in the rate of occurrence of local expected SAE, which is judged to be clinically important, should be reported within 15 calendar days after the PI is aware of the event.
- Local expected SAE should be reported annually (together with Study Status Report for annual review).

- Local unexpected and unlikely related SAE that are not life-threatening should also be reported annually (together with Study Status Report for annual review).
- Local unexpected AE that are related events should be reported at least annually (together with Study Status Report for annual review).
- Non-local unexpected SAE that are fatal or life threatening and definitely/probably/possibly related should be reported not later than 30 calendar days after the PI is aware of the event.

7.3 Collecting, Recording and Reporting of Serious Adverse Events (SAEs) to the Health Science Authority (HSA)

All SAEs that are unexpected and related to the study drug will be reported to HSA. All SAEs will be reported to HSA. Please refer to the HSA website for more information on Safety Reporting Requirements for Clinical Trials.

The investigator is responsible for informing HSA no later than 15 calendar days after first knowledge that the case qualifies for expedited reporting. Follow-up information will be actively sought and submitted as it becomes available. For fatal or life-threatening cases, HSA will be notified as soon as possible but no later than 7 calendar days after first knowledge that a case qualifies, followed by a complete report within 8 additional calendar days.

7.4 Safety Monitoring Plan

The plan for adverse effect monitoring, severe adverse effect monitoring and unforeseen reactions would include reporting of adverse effects to the Health Sciences Authority and Central Institutional Review Board.

Safety data is monitored at all times by the principal investigator, co-investigators and attending anaesthetists in the operating theatres. The study drug would only be available in the operating theatres. The principal investigator and co-investigators would institute medical treatment, e.g. anti-emetics for nausea and vomiting, intravenous fluid loading and vasopressors for hypotension, analgesics for pain during caesarean delivery.

There is no interim analysis. Approval from the Health Sciences Authority would be sought before the trial commences.

7.5 Complaint Handling

Any complaints arising from the conduct of the study will be reviewed and the patient interviewed by the principal investigator. Any serious or potentially litigious complaints will be reported to the Health Sciences Authority and Institutional Review Board.

The data will be kept locked by the principal investigator and by the use of computer security of Singhealth. The data will be accessible only the investigators and for analysis purposes only. The data and computer will be under locked in the office of the principal investigator.

8 DATA ANALYSIS

8.1 Data Quality Assurance

Data obtained from this research that has been keyed into the appropriate computer software programme will be counter-checked by a second investigator to ensure that it is accurate, complete and reliable.

8.2 Data Entry and Storage

The subjects would be de-identified and only the study number would be communicated through in electronic softcopy format. Data entry will be in softcopy format and The soft copy of research data will be stored in a password protected PC. Hard copies of data collection forms are kept by the Principal Investigator under lock and key. The data is accessible only by Investigators for analysis purposes only. The research data will be kept under lock and key and using computer security of Singhealth. The data will be destroyed after keeping for 6 years upon completion of the study.

9 SAMPLE SIZE AND STATISTICAL METHODS

9.1 Determination of Sample Size

Our primary outcome of this study is the incidence of hypotension. A sample size of 204 (102 X 2) is required to show that the incidence of maternal hypotension in the experimental group 18% and the control group 39%, based on the following assumptions: proportion of hypotension in DIVA group =0.39, proportion of hypotension in ADIVA group = 0.18, 1:1 allocation ratio, α = 0.05 and power = 80%. Sample size calculations accounted for a conservative 20% dropout rate due to spinal anaesthesia placement failure. Two hundred and four patients are required to adequately power the study.

9.2 Statistical and Analytical Plans

a. General Considerations

b. Safety Analyses

c. Interim Analyses

d. Describe the types of statistical interim analyses, including their timing.

The primary specific aims will be addressed by estimating the incidence of hypotension in the experimental and control groups, together with their corresponding 95% confidence interval CI). A univariate analyses will be performed with possible logistic regression modelling to adjust for unbalanced potential baseline confounders.

Our secondary outcomes include the incidence of reactive hypertension, nausea or vomiting, the amount of vasopressor, cardiac output and systemic vascular, umbilical cord blood pH and APGAR scores with anaesthesia technique. Student's t-test will be used to compare the data that are normally distributed. Otherwise, the Mann Whitney test will be used. For nominal data and proportions, the c2 test with Yates correction when appropriate, will be used.

We will also assess the reliability of ADIVA system by calculating the percentage performance error (the percentage difference between measured BP and baseline BP), median performance error (median of percentage performance error, a measure of bias), median absolute performance error (median of the absolute values of performance error, a measure of inaccuracy), wobble (median of the absolute difference between percentage performance error and median performance error at every time point) and divergence (measures the trend of changes in percentage performance error) (21).

10 DIRECT ACCESS TO SOURCE DATA/DOCUMENTS

The investigator(s)/institution(s) will permit study-related monitoring, audits and/or IRB review and regulatory inspection(s), providing direct access to source data/document.

11 QUALITY CONTROL AND QUALITY ASSURANCE

Data is extracted from data collection forms and random audits will be performed to make sure it is authentic, accurate and complete.

12 ETHICAL CONSIDERATIONS

This study will be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki and that are consistent with the Good Clinical Practice and the applicable regulatory requirements.

This final study protocol, including the final version of the Patient Information and Informed Consent Form, must be approved in writing by the Centralised Institutional Review Board (CIRB) and regulatory approval from Health Sciences Authority (HSA), prior to enrolment of any patient into the study.

The principle investigator is responsible for informing the CIRB and HSA of any amendments to the protocol or other study-related documents, as per local requirement.

12.1 Informed Consent

The informed consent process will be conducted by a trained study team member as shown in the delegation log. The informed consent process will be conducted in compliance with ICH-GCP.

12.2 Confidentiality of Data and Patient Records

The subjects would be de-identified and only the study number would be communicated through in electronic softcopy format. Data entry will be in softcopy format and the data will be kept under lock and key using the computer security of Singhealth. The data will be destroyed after keeping for up to 6-years after completion of the study.

13 PUBLICATIONS

Study findings will be published in indexed journals (at least two publications expected).

14 RETENTION OF TRIAL DOCUMENTS

Records for all participants, patient informed consent forms, IRB records and other regulatory documentation will be retained by the PI and locked securely in a storage cupboard. The records will be accessible for inspection and copying by authorized authorities.

(1) The holder of a certificate shall keep adequate clinical records of each subject for the duration of the clinical trial.

(2) The holder of a certificate shall ensure that such records are —
- (a) kept up to date at all times;
- (b) available at all times for inspection by the licensing authority or any person authorised by him in that behalf;
- (c) kept at least for whichever of the following periods expires later:
  - (i) until there are no pending or contemplated marketing applications of the test material in Singapore;
  - (ii) 2 years after the last approval of a marketing application for the test material in Singapore;
  - (iii) where the clinical trial is discontinued, 2 years after the licensing authority has been informed of the discontinuation of the clinical trial under regulation 9;
  - (iv) 6 years after the completion of the clinical trial; or
  - (v) such other period as the licensing authority may direct.

(3) The holder of a certificate shall maintain a record containing the names and such other particulars of every person assisting or participating in a clinical trial.

(4) In this regulation, "marketing application" means an application for a product licence under the Act in respect of the test material.

15 FUNDING and INSURANCE

Singhealth Foundation Grant Clinical Trials Grant has been awarded to support this study.
Study is covered by the National Clinical Trial Insurance.

List of Attachments

Appendix 1 Study Schedule

Appendix 2 Data Collection Form

Appendix 3 List of References

Appendix 1. Study Schedule (Version 1, dated 23 Feb 2018)

Study Title: Development of advanced double intravenous vasopressor automated (ADIVA) system with improved hemodynamic trend control during spinal anaesthesia for Caesarean section	PI: Dr Singaraselvan Nagarajan

Study Schedule

Procedures	Pre-operative period		During surgical operation	Post-operative period
	Pre-anaesthetic clinic	Admission for surgery (Preoperative area/ward)		Before discharge to ward (if patient needs hospitalization); or before discharge from hospital
Informed consent	x			
Randomization (only for Phase 2 patients)	x			
Baseline Demographic data collection	x			
Setting up spinal anaesthesia and connection to ADIVA or DIVA system	x (Right before surgery)			
Data collection	(pain score, pain data, etc.)			
Vasopressor administration			x	
Vital sign Monitoring			x	x
Data collection				(Neonate outcomes, maternal satisfaction, pain scores, adverse events etc.)

Version 1, dated 23 Feb 2018

Appendix 2: Data Collection Form (Version 1, dated 28 Feb 2018)

KK Women's and Children's Hospital
SingHealth

DATA COLLECTION FORM

Subject Number: ☐☐☐ Subject Initials: _____ Date: ☐☐/☐☐/☐☐

DEVELOPMENT OF ADVANCED DOUBLE INTRAVENOUS VASOPRESSOR AUTOMATED (ADIVA) SYSTEM WITH IMPROVED HEMODYNAMIC TREND CONTROL DURING SPINAL ANAESTHESIA FOR CAESAREAN SECTION

Please complete the following details appropriately prior to data analysis.

Notes:

- **Sitting position 27G Whitacre needle with 20G introducer needle**
- **Intrathecal bupivacaine 0.5% 2.2ml, 15mcg fentanyl, 100mcg morphine**
- **Hartmann's fast 1000mls as coload via 18G intravenous cannula, 3mls of venous blood**

0. Screening Form

No.	Inclusion Criteria	Yes	No
1	Between 21-50 years old?		
2	Healthy adult (ASA physical status 1 and 2) parturients?		
3	Weight 40-90 kg?		
4	Height of 145-170 cm?		
5	With a singleton fetus, and full-term?		
6	Indication for an elective cesarean delivery?		
7	Use of spinal anaesthesia for cesarean delivery?		
	Checking of inclusive criteria 'All Yes'		
No.	**Exclusion Criteria**	**Yes**	**No**
1	Obstetric (e.g. pre-eclampsia, premature rupture of amniotic membranes for more than 48 hours, gestational diabetes on insulin, pregnancy-induced hypertension on medication) and uncontrolled medical (e.g. cardiac disease) complications;		
2	Contraindication to spinal anaesthesia and/or allergy to opioids?		
	Checking of exclusion criteria "all No"		
Check done by (Name and signature):		**Date:**	

1. Patient Demographics

Age			
Race	☐ 1 Chinese ☐ 2 Malay ☐ 3 Indian ☐ 4 Others _____		
Weight (kg)		Height (cm)	
ASA Grade (1-4)		Gestation Age (wks)	
LSCS start time (HH:MM)		LSCS end time (HH:MM)	
Bolus oxytocin (U)		Oxytocin infusion	☐ 0 No ☐ 1 Yes
Fetal Weight (g)			
APGAR score (1min)		APGAR score (5min)	
Cord venous pH		Cord arterial pH	
Core venous lactate		Cord arterial lactate	
Pain score (before surgery; 0-10)			

2. Intraoperative Information

Baseline BP (mmHg)	
Time of Spinal Anaesthesia (HH:MM)	
Duration of surgery (minutes)	
Sensory block to cold sensation at 5min	
Bromage score at 5min	
Total amount of fluid given	
Pain score (delivery; 0-10)	

3. Postoperative Analgesic Information

Side effects and Complications	☐ Hypotension (>20% below baseline SBP) ◯ Before Delivery ◯ After Delivery ☐ Bradycardia (<60 beats per min) ☐ Reactive Hypertension (>20% above baseline SBP) **Total Phenylephrine _____mcg** **Total Ephedrine _____ mg** ☐ Nausea ◯ Before Delivery ◯ After Delivery ☐ Vomiting ◯ Before Delivery ◯ After Delivery ☐ Shivering ◯ Before Delivery ◯ After Delivery ☐ High block (>T1 block) ☐ Inadequate block (<T6) ☐ Supplemental medications ◯ **IV Fentanyl _____ mcg** ◯ **IV Midazolam _____ mcg** ◯ **Entonox _____ min** ◯ **Others: _____**
Technical problems	
Maternal Satisfaction with the anesthesia technique in recovery (0-100)	
Pain score (end of surgery; 0-10)	
Remarks	

DATA ENTERED & VERIFIED BY:

NAME:	**ROLE IN STUDY:**
SIGNATURE:	**DATE:**

T after RA (min)	Systolic blood pressure (SBP)	Diastolic blood pressure (DBP)	Cardiac output (CO)	Systemic vascular resistance (SVR)	Heart rate (HR)	Phenyle-phrine (mcg)	Ephedrine (mg)	Phenyle-phrine (mcg) Manual	Ephedrine (mg) Manual	Volume Hartman Solution (pint 500ml complete)	Other Comments
0											
1											
2											
3											
4											
5											
6											
7											
8											
9											
10											
11											
12											
13											
14											
15											
16											
17											
18											
19											
20											
21											
22											
23											
24											
25											
26											
27											

28											
29											
30											
35											
40											
45											
50											
55											
60											
70											
80											
90											
100											
110											
120											

Notes:

1. Start anaes, Supine position, start op, delivery, end op,
2. Events: H (Hartmann's solution 500mL), N (nausea), V (vomiting), S (shivering). Rescue Phenylephrine (mcg), Rescue Ephedrine (mg), Rescue Atropine (mg).

Appendix 3. List of References

1. Weiser TG, Haynes AB, Molina G, Lipsitz SR, Esquivel MM, Uribe-Leitz T, Fu R, Azad T, Chao TE, Berry WR, Gawande AA. Size and distribution of the global volume of surgery in 2012. Bull World Health Organ. 2016 Mar 1;94(3):201-209F.

2. Weiser TG, Haynes AB, Molina G, Lipsitz SR, Esquivel MM, Uribe-Leitz T, Fu R, Azad T, Chao TE, Berry WR, Gawande AA. Estimate of the global volume of surgery in 2012: an assessment supporting improved health outcomes. Lancet. 2015 Apr 27;385 Suppl 2:S11.

3. Bucklin BA, Hawkins JL, Anderson JR, Ullrich FA. Obstetric anesthesia workforce survey: twenty-year update. Anesthesiology. 2005 Sep;103(3):645-53.

4. Attari MA, Mirhosseini SA, Honarmand A, Safavi MR. Spinal Anesthesia Versus General Anesthesia for Elective Lumbar Spine Surgery: A Randomized Clinical Trial. J Res Med Sci 2011;16:524-529.

5. Goeller JK, Bhalla T, Tobias JD. Combined Use of Neuraxial and General Anesthesia During Major Abdominal Procedures in Neonates and Infants. Paediatr Anaesth 2014;24:553-560.

6. Carpenter RL, Caplan RA, Brown DL, Stephenson C, Wu R: Incidence and risk factors for side effects of spinal anesthesia. ANESTHESIOLOGY 1992; 76:906–16

7. Arndt JO, Bomer W, Krauth J, Marquardt B: Incidence and time course of cardiovascular side effects during spinal anesthesia after prophylactic administration of intravenous fluids or vasoconstrictors. Anesth Analg 1998; 87:347–54

8. Roofthooft E, Van de Velde M. Low-dose spinal anaesthesia for Caesarean section to prevent spinal-induced hypotension. Curr Opin Anaesthesiol. 2008 Jun;21(3):259-62.

9. Smiley RM, Blouin JL, Negron M, Landau R. beta2-adrenoceptor genotype affects vasopressor requirements during spinal anesthesia for cesarean delivery. Anesthesiology. 2006 Apr;104(4):644-50.

10. Greiss FC Jr. Pressure-flow relationship in the gravid uterine vascular bed. American Journal of Obstetrics and Gynecology 1966; 96: 41–7.

11. Hawthorne, L. & Lyons G.Cardiac arrest complicating spinal anaesthesia for caesarean section. Int J Obstet Anesth, 1997. 6(2):126-9.

12. Crites J, Ramanathan J. Acute hypoglycemia following combined spinal-epidural anesthesia (CSE) in a parturient with diabetes mellitus. Anesthesiology. 2000 Aug;93(2):591-2.

13. Buggy DJ, Power CK, Meeke R, O'Callaghan S, Moran C, O'Brien GT. Prevention of spinal anaesthesia-induced hypotension in the elderly: i.m. methoxamine or combined hetastarch and crystalloid. Br J Anaesth. 1998 Feb;80(2):199-203.

14. Kyokong O, Charuluxananan S, Sriprajittichai P, Poomseetong T, Naksin P. The incidence and risk factors of hypotension and bradycardia associated with spinal anesthesia. J Med Assoc Thai. 2006 Sep;89 Suppl 3:S58-64.

15. Ngan Kee WD. Prevention of maternal hypotension after regional anaesthesia for caesarean section. Current Opinion in Anesthesiology 2010; 23: 304–9.

16. Lewinsky RM, Riskin-Mashiah S. Autonomic imbalance in preeclampsia: evidence for increased sympathetic tone in response to the supine-pressor test. Obstetrics and Gynecology 1998; 91: 935–9.

17. Li P, Tong C, Eisenach JC. Pregnancy and ephedrine increase the release of nitric oxide in ovine uterine arteries. Anesthesia and Analgesia 1996; 82: 288–93.

18. Sia AT, Tan HS, Sng BL. Closed-loop double-vasopressor automated system to treat hypotension during spinal anaesthesia for caesarean section: a preliminary study. Anaesthesia. 2012 Dec;67(12):1348-55. doi: 10.1111/anae.12000. Epub 2012 Sep 28.

19. Ilies C, Kiskalt H, Siedenhans D, et al. Detection of hypotension during Caesarean section with continuous non-invasive arterial pressure device or intermittent oscillometric arterial pressure measurement. Br J Anaesth 2012;109:413–9.

20. Sng BL, Wang H, Assam PN, Sia AT. Assessment of an updated double-vasopressor automated system using Nexfin for the maintenance of haemodynamic stability to improve peri-operative outcome during spinal anaesthesia for caesarean section. Anaesthesia. 2015 Jun;70(6):691-8. doi: 10.1111/anae.13008. Epub 2015 Jan 28.

21. Sng BL, Du W, Lee MX, Ithnin F, Mathur D, Leong WL, Sultana R, Han NLR, Sia ATH. Comparison of double intravenous vasopressor automated system using Nexfin versus manual vasopressor bolus administration for maintenance of haemodynamic stability during spinal anaesthesia for caesarean delivery: A randomised double-blind controlled trial. Eur J Anaesthesiol. 2018 May;35(5):390-397.

22. Struys MM, De Smet T, Greenwald S, Absalom AR, Bingé S, Mortier EP. Performance evaluation of two published closed-loop control systems using bispectral index monitoring: a simulation study. Anesthesiology. 2004 Mar;100(3):640-7.