Closed-loop Double-pump Automated System versus Manual Boluses to treat Hypotension during Spinal Anaesthesia for Caesarean Section: randomised controlled trial

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Introduction

- Hypotension is a common adverse effect of spinal anaesthesia during Caesarean section
- Occurs in up to 90% of cases\(^1\)
- Requires vasopressor administration
- **Phenylephrine** is a potent alpha-1 agonist used to treat hypotension but may cause reactive hypertension and bradycardia
- **Ephedrine** is a mixed alpha and beta agonist used to treat hypotension and bradycardia
- Optimal regimen is still unclear

1. Ngan Kee et al 2004 BJA Comparison of phenylephrine infusion regimens for Maintaining maternal blood pressure during spinal anaesthesia for Caesarean section
Closed-loop double pump automated system (CLDPAS)

- Continuous Noninvasive Arterial Pressure (CNAP) device monitors beat-to-beat systolic BP
- Laptop integrates novel customised algorithm
- Controls syringe pumps that deliver Phenylephrine and Ephedrine boluses
- Efficacy shown in preliminary study\(^2\)

\(^2\) Sia et al 2012 Anaesthesia Closed-loop double-vasopressor automated system to treat hypotension during spinal anaesthesia for caesarean section: a preliminary study

A. T. H. Sia,\(^1\) H. S. Tan\(^2\) and B. L. Sng\(^3\)
Infinity CNAP Smartpod Monitor with 2 alternating finger cuffs

B Braun Syringe Pumps:
(1) phenylephrine 100mcg/ml
(2) ephedrine 8mg/ml

Laptop Computer with RS232 interface
**Methodology:** Ethics Approval (CIRB:2010/365/D)

Patient, Attending Anaesthetist → Blinded to Group Allocation
Investigator → Open Sealed Envelopes, Prepared Study Drugs

Inclusion Criteria: ASA I and II Term Singleton Pregnancy, 21 to 45 years old, Weight 50 to 99kg, Height 145 to 170cm, Elective Caesarean Section, Spinal Anaesthesia

Resting Baseline BP 3 readings
IV cannula 18G in Forearm

Spinal Anaesthesia in Sitting Position
27G pencil point needle (Espocan, Germany) with introducer
11mg heavy bupivacaine, 15mcg fentanyl, 100mcg morphine
L2/3 or L3/4 interspace
Left lateral tilt
Coload 10 to 15ml/kg Ringer’s Lactate solution

Exclusion Criteria: Allergy to study agents, In Labour, Contraindication to Spinal, Obstetric complications, Preeclampsia
CLDPAS vs Manual Boluses

Experimental Group
- CLDPAS
  - VASOPRESSORS
- Manual Boluses
  - SALINE
  - PLACEBO

Control Group
- CLDPAS
  - SALINE
  - PLACEBO
- Manual Boluses
  - VASOPRESSORS
CNAP continuously monitors systolic blood pressure and heart rate

Data integrated every 10 seconds

Systolic blood pressure within 90% of baseline
- Continue CNAP monitoring

Systolic blood pressure below 90% of baseline
- Heart rate above 60 bpm
  - Infuse phenylephrine 50µg over 10s; lockout 10s
- Heart rate 60 bpm or lower
  - Infuse ephedrine 4mg over 10s; lockout 10s

Experimental Group
Systolic blood pressure and heart rate displayed at 1 minute intervals

Systolic blood pressure within 90% of baseline
- Continue monitoring

Systolic blood pressure below 90% of baseline
- Heart rate above 60 bpm
  - Infuse phenylephrine 100µg manual bolus
- Heart rate 60 bpm or lower
  - Infuse ephedrine 8mg manual bolus

Control Group
OUTCOME DEFINITIONS

Hypertension $\rightarrow>120\%$ above Baseline SBP

Hypotension $\rightarrow<80\%$ below Baseline SBP

CNAP readings every 2 seconds $\rightarrow$ averaged over 1 minute
Statistical Analysis
Categorical data: N (%), Chi-squared test
Ordinal data: Median [IQR], Mann Whitney U test
Parametric data: Mean (SD), Student’s T test

Sample Size Calculation
Target Cohort of 200
20% reduction of 47% incidence of reactive hypertension
Reported by Ngan Kee 2005 Anesthesiology[^3]
Alpha Error 0.05, Power of Study 0.8
10% drop out rate

[^3]: Ngee Kee 2005 Anesthesiology Prevention of Hypotension during Spinal Anaesthesia for Cessarean Delivery
Consecutive screening of women admitted under our research team of anaesthetists for elective caesarean section, from Oct 2011 to Jul 2012

221 women met inclusion criteria

Excluded

5 refused consent
3 excluded due to failed spinal anaesthesia

213 patients recruited for study

106 patients in experimental group
107 patients in control group
### Baseline Data are Comparable

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Experimental Group</th>
<th>Control Group</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>32.4 (5.4)</td>
<td>33.5 (4.6)</td>
<td>0.096</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>72.4 (12.3)</td>
<td>70.9 (11.7)</td>
<td>0.357</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>158.5 (6.7)</td>
<td>158.2 (5.6)</td>
<td>0.744</td>
</tr>
<tr>
<td>SBP baseline (mmHg)</td>
<td><strong>122.7 (10.6)</strong></td>
<td><strong>124.4 (11.1)</strong></td>
<td>0.244</td>
</tr>
<tr>
<td>Heart rate baseline (bpm)</td>
<td><strong>89.1 (12.8)</strong></td>
<td><strong>88.9 (13.6)</strong></td>
<td>0.929</td>
</tr>
<tr>
<td>Anaesthetic block (dermatome)</td>
<td>T4 [T4 to T4]</td>
<td>T4 [T4 to T4]</td>
<td>0.527</td>
</tr>
<tr>
<td>Spinal to delivery time (min)</td>
<td>19 [14 to 23]</td>
<td>18 [14 to 24]</td>
<td>0.786</td>
</tr>
<tr>
<td>Total fluids given (L)</td>
<td>1.0 [1.0 to 1.0]</td>
<td>1.0 [1.0 to 1.0]</td>
<td>0.973</td>
</tr>
<tr>
<td>Parameter</td>
<td>Experimental Group</td>
<td>Control Group</td>
<td>p</td>
</tr>
<tr>
<td>-------------------------------------------------------</td>
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</tr>
<tr>
<td>Number of patients with Hypertension</td>
<td>8 (7.6%)</td>
<td>14 (13.1%)</td>
<td>0.260</td>
</tr>
<tr>
<td>Number of patients with Hypotension</td>
<td>37 (34.9%)</td>
<td>63 (58.9%)</td>
<td>0.001</td>
</tr>
<tr>
<td>Highest blood pressure (mmHg)</td>
<td>139.0 [130 to 149]</td>
<td>142.0 [132 to 153]</td>
<td>0.081</td>
</tr>
<tr>
<td>Lowest blood pressure (mmHg)</td>
<td>90.0 [79 to 98]</td>
<td>86.0 [75 to 98]</td>
<td>0.471</td>
</tr>
<tr>
<td>Highest heart rate (bpm)</td>
<td>110.0 [99 to 121]</td>
<td>109.0 [98 to 120]</td>
<td>0.415</td>
</tr>
<tr>
<td>Lowest heart rate (bpm)</td>
<td>59.0 [54 to 64]</td>
<td>60.0 [54 to 68]</td>
<td>0.340</td>
</tr>
</tbody>
</table>
## Incidence of Maternal Nausea

<table>
<thead>
<tr>
<th>Parameter</th>
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<th>Control Group</th>
<th>$p$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Incidence of Nausea (Self Reported)</td>
<td>1 (0.9%)</td>
<td>11 (10.2%)</td>
<td>0.005</td>
</tr>
<tr>
<td>Incidence of Vomiting</td>
<td>0 (0.0%)</td>
<td>3 (2.8%)</td>
<td>0.246</td>
</tr>
<tr>
<td>Phenylephrine administered (mcg)</td>
<td>400 [250 to 650]</td>
<td>400 [300 to 700]</td>
<td>0.727</td>
</tr>
<tr>
<td>Ephedrine administered (mg)</td>
<td>0 [0 to 0]</td>
<td>0 [0 to 0]</td>
<td>0.947</td>
</tr>
<tr>
<td>Incidence of Ephedrine used</td>
<td>17 (16.0%)</td>
<td>17 (15.9%)</td>
<td>1.000</td>
</tr>
</tbody>
</table>
# Neonatal Outcomes are Comparable

<table>
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<th>Parameter</th>
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<tbody>
<tr>
<td>pH difference (umbilical artery – vein)</td>
<td>0.0715 [0.057 to 0.095]</td>
<td>0.0770 [0.048 to 0.097]</td>
<td>0.813</td>
</tr>
<tr>
<td>Lactate difference (umbilical artery – vein)</td>
<td>0.3400 [0.060 to 0.620]</td>
<td>0.3900 [0.073 to 0.783]</td>
<td>0.389</td>
</tr>
<tr>
<td>APGAR score at 1 minute</td>
<td>9 [9 to 9]</td>
<td>9 [9 to 9]</td>
<td>0.991</td>
</tr>
<tr>
<td>APGAR score at 5 minute</td>
<td>9 [9 to 9]</td>
<td>9 [9 to 9]</td>
<td>1.000</td>
</tr>
<tr>
<td>Neonatal birthweight (g)</td>
<td>3204 (400)</td>
<td>3166 (415)</td>
<td>0.501</td>
</tr>
</tbody>
</table>
Accuracy of CLDPAS to maintain baseline SBP

<table>
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</tr>
</thead>
<tbody>
<tr>
<td>Median absolute performance error (MDAPE) (%)</td>
<td>8.7</td>
<td>9.8</td>
<td>0.013</td>
</tr>
<tr>
<td>Median performance error (MDPE) (%)</td>
<td>-5.4</td>
<td>-5.2</td>
<td>0.264</td>
</tr>
<tr>
<td>Wobble (%)</td>
<td>6.2</td>
<td>6.4</td>
<td>0.684</td>
</tr>
</tbody>
</table>
Discussion

• **Closed-loop Double-pump Automated System** is a superior vasopressor delivery system compared to manual boluses during spinal anaesthesia for Caesarean Section
  
• **Similar Incidence of Reactive Hypertension**

• **Lowered Incidence of Hypotension**

• **Lowered Incidence of Maternal Nausea**

• **Similar Good Neonatal Outcomes**

• **CLDPAS maintains SBP closer to baseline SBP with Higher Accuracy**
Acknowledgements
National Medical Research Council, Singapore (Exploratory Development Grant)
Prof Alex Sia and research team
Equivalent dose of ephedrine and phenylephrine in the prevention of post-spinal hypotension in Caesarean section

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Background. Comparative studies of ephedrine and phenylephrine in prevention of hypotension after spinal anaesthesia for Caesarean section have lacked a consensus on dose equivalence. The aim of this study was to determine the minimum vasopressor dose for each of these drugs to calculate the dose ratio for clinical equivalence in the prevention of hypotension.

Methods. Patients with a normal singleton pregnancy beyond 36 weeks gestation undergoing elective Caesarean section under spinal anaesthesia were randomized into two groups. The first patient in Group A received 50 mg of ephedrine in saline 0.9% w/v, 500 ml at 999 ml h⁻¹, the maximum rate possible on the pump and the first patient in Group B received 500 µg of phenylephrine in saline 0.9% w/v, 500 ml at the same rate. The initial dose for dilution was an arbitrary choice. The dose of vasopressor in the saline bag for every subsequent patient was established by the efficacy of the dose in preventing hypotension in the previous patient according to the technique of up-down sequential allocation. Minimum vasopressor dose for each drug was determined according to the Dixon-Massey formula.

Results. The minimum vasopressor dose in saline 500 ml was 532.9 µg (95% CI 506.0–559.8) for phenylephrine and 43.3 mg (95% CI 39.2–47.3) for ephedrine. The concentration needed for equivalence at an infusion rate of 999 ml h⁻¹ was 1.07 µg ml⁻¹ for phenylephrine and 86.66 µg ml⁻¹ for ephedrine. Mean (SD) dose used for phenylephrine was 496.45 (78.3) µg and for ephedrine 39.64 (6.33) mg.

Conclusion. This study demonstrates a potency ratio of 81.2 (95% CI 73.0–89.7) for equivalence between phenylephrine and ephedrine in prevention of hypotension after spinal anaesthesia for Caesarean section.

Br J Anaesth 2006; 96: 95–9

Equivalent dose of Vasopressor effect
100mcg phenylephrine
8mg ephedrine
To prevent hypotension
After spinal anaesthesia
For caesarean section
Hypotension defined as
Less than 80% below
Baseline SBP

Hypertension defined as
More than 120% above
Baseline BP

Bradycardia defined as
Heart rate less than
50bpm
Phenylephrine Infusion Versus Bolus Regimens During Cesarean Delivery Under Spinal Anesthesia: A Double-Blind Randomized Clinical Trial to Assess Hemodynamic Changes

Anne Doherty, MD,* Yayoi Ohashi, MD, PhD,* Kristi Downey, MSc,* and Jose C. A. Carvalho, MD, PhD*

**INTRODUCTION:** Phenylephrine is used to prevent and treat hypotension during spinal anesthesia for cesarean delivery. The optimal administration regimen is undetermined. We used a non-invasive cardiac output monitor to test the hypothesis that a fixed-rate phenylephrine infusion regimen would cause a smaller reduction in maternal cardiac output, and result in less maternal hypotension, as compared to a phenylephrine bolus regimen.

**METHODS:** This was a double-blind, randomized clinical trial of women undergoing elective cesarean delivery under spinal anesthesia. Patients were randomized to an intermittent bolus (120 μg) or a fixed-rate infusion (120 μg/min) regimen of phenylephrine. Any decrease in systolic blood pressure from baseline was treated. The primary outcome was the maximum change in cardiac output in the predelivery period, assessed using bioreactance technology. Secondary outcomes included the maximum change in heart rate, incidence of hypotension, nausea/vomiting and bradycardia, total dose of phenylephrine, umbilical blood gases, and Apgar scores. The hemodynamic profiles over time in each treatment arm were compared.

**RESULTS:** Sixty patients were studied. There was no significant difference in the maximum change in cardiac output between the 2 treatment arms: mean (SD) maximum change in cardiac output in the bolus group was 1.87 (1.68) L/min versus 1.9 (1.46) L/min in the infusion group (P = 0.94) (95% confidence intervals of difference in means: −0.84 to 0.78 L/min). The infusion group received significantly more phenylephrine (1740 (613) versus 964 (454) μg) (P < 0.001). In the initial 6 min after intrathecal injection, there was a significant decrease in blood pressure in the infusion group compared to the bolus group (P = 0.007). There was no significant difference in the other secondary outcomes.

**CONCLUSION:** There were no clinical benefits to administering phenylephrine as an infusion versus a bolus regimen. The bolus regimen maintained maternal arterial blood pressure closer to baseline in the initial minutes after spinal injection but this had no clinical benefits. The infusion regimen required a higher total dose of phenylephrine to maintain maternal arterial blood pressure at baseline during the predelivery period. *(Anesth Analg 2012;115:1343–50)*
CARDIOVASCULAR

Precision and accuracy of a new device (CNAP\textsuperscript{TM}) for continuous non-invasive arterial pressure monitoring: assessment during general anaesthesia

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**Key points**

- Continuous non-invasive arterial pressure measurement using the finger cuff method has shown comparable precision and accuracy to invasive arterial pressure measurement from radial artery catheter in patients undergoing general anaesthesia.
- It may be a useful alternative to invasive measurements when continuous arterial pressure monitoring is deemed important for patient care.

**Background.** Continuous non-invasive arterial pressure measured with CNAP\textsuperscript{TM} (CNAP) has been shown to be superior to intermittent oscillometric measurements during procedural sedation and spinal anaesthesia. We assessed the performance of CNAP during general anaesthesia by analysis of agreement with invasive measurements of arterial pressure (AP).

**Methods.** Eighty-eight patients undergoing elective abdominal surgery, cardio-, or neurosurgery were included in the study. Systolic, diastolic, and mean AP measured by an intra-arterial catheter in the radial artery (IAP) were compared with those obtained by CNAP from the same arm. Data were analysed to determine the precision (i.e. measurement error) and accuracy (i.e. systematic error) of beat-to-beat CNAP values with respect to IAP. Also, we compared the frequency of fast changes in AP (FCAP) and hypotension (IOH) by both methods.

**Results.** CNAP precision of 4.5, 3.1, and 3.2 mm Hg (systolic, diastolic, and mean AP, respectively) was not significantly different from IAP precision, and CNAP accuracy was \(\pm 6.7, -5.6, \) and \(-1.6 \) mm Hg. The frequency of AP pairs having a difference within the calculated limits of agreement was 81\%, 64\%, and 76\% for systolic, diastolic, and mean AP, respectively. The calculated limits of agreement were \(\pm 17.6, \pm 11.4, \) and \(\pm 12.0 \) mm, Hg, respectively. CNAP and IAP detected simultaneously to 82.1\% FCAP and to 84.6\% IOH.

**Conclusions.** CNAP provides real-time estimates of arterial pressure comparable with those generated by an invasive intra-arterial catheter system during general anaesthesia.

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