Title:

Closed-loop feedback computer-controlled phenylephrine for maintenance of blood pressure during spinal anesthesia for cesarean delivery: a randomized trial comparing automated boluses versus infusion

Authors:

Warwick D. NGAN KEE, MD, FANZCA, FHKCA
Department of Anaesthesia and Intensive Care, The Chinese University of Hong Kong, Hong Kong, China.

Yuk-Ho TAM, BSc, MPhil
Department of Anaesthesia and Intensive Care, The Chinese University of Hong Kong, Hong Kong, China.

Kim S. KHAW, MD, FRCA, FHKCA
Department of Anaesthesia and Intensive Care, The Chinese University of Hong Kong, Hong Kong, China.

Floria F. NG, RN, BASc
Department of Anaesthesia and Intensive Care, The Chinese University of Hong Kong, Hong Kong, China.

Shara W.Y. LEE, PhD
Department of Health Technology and Informatics, The Hong Kong Polytechnic University

Corresponding author:
Warwick D. NGAN KEE, MBChB, MD, FANZCA
Department of Anaesthesia and Intensive Care
The Chinese University of Hong Kong
Prince of Wales Hospital
Shatin
Hong Kong, China.
Tel: +852 2632 2735
Fax: +852 2637 2422
Email: warwick@cuhk.edu.hk

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Abstract

Background:

We previously described the use of closed-loop feedback computer-controlled infusion of phenylephrine for maintaining blood pressure (BP) during spinal anesthesia for cesarean delivery. In this study we report a modified system in which phenylephrine is delivered by intermittent boluses rather than infusion. We hypothesized that the use of computer-controlled boluses would result in more precise control of BP compared with infusions.

Methods:

Two hundred and fourteen healthy patients having spinal anesthesia for elective cesarean delivery were randomized to have their BP maintained by phenylephrine administered by computer-controlled continuous infusion or computer-controlled intermittent boluses. From induction of anesthesia until the time of uterine incision, a non-invasive BP monitor was set to cycle at 1-min intervals. In the infusion group, the infusion rate was automatically adjusted after each BP measurement using a previously described algorithm. In the bolus group, the algorithm was modified so that the mass of drug that would have been delivered over 1 min was instead injected as a rapid intravenous bolus after each BP measurement. The precision of BP control was assessed using performance error calculations and compared between groups.

Results:

The precision of BP control was greater, as shown by smaller values for median absolute performance error (MDAPE), in the bolus group (median 4.38 [interquartile range 3.22 – 6.25] %) versus the infusion group (5.39 [4.12 – 7.04] %, $P = 0.008$). In the bolus group,

phenylephrine consumption was smaller and this was associated with maintenance of BP on average at a slightly lower level as indicated by smaller values for median performance error (MDPE) compared with the continuous infusion group ($P < 0.001$). There were no differences in cardiac output, nausea or vomiting or neonatal outcome between groups.

Conclusions:

We confirmed the hypothesis that BP control was more precise when computer-controlled phenylephrine was delivered using intermittent boluses rather than continuous infusion. However, the difference between groups was small and was not associated with any difference in clinical outcomes. In the infusion group, greater doses of phenylephrine were delivered which was related to the time taken for the non-invasive BP monitor to complete measurements. The use of intermittent boluses is an incremental improvement to a system that already performs well.

Introduction

We have previously described the maintenance of blood pressure (BP) during spinal anesthesia for cesarean delivery the using closed-loop feedback computer-controlled infusion of phenylephrine.[1,2] This method of drug administration enables BP to be controlled automatically with precision that is equal to or better than manually-controlled infusion.[1] Our system was designed to operating using a standard non-invasive BP monitor. However, this results in an imperfect match because although the rate of a continuous vasopressor infusion can be adjusted on a second-by-second basis, non-invasively BP measurement is only performed intermittently, usually no more frequently than every one minute.

We postulated that delivery of calculated doses of vasopressor by rapid boluses given immediately after the completion of each BP measurement would result in a faster response and therefore could improve control compared with adjustment of a continuous infusion rate. According, we hypothesized that computer-controlled administration of phenylephrine by intermittent boluses would result in greater precision of BP control compared with computer-controlled continuous infusion. This hypothesis was tested in the present study in which patients having spinal anesthesia for elective cesarean section were randomly assigned to have their BP controlled by one of two computer-controlled systems with performance of the two systems compared using performance error calculations.

Methods

This was a randomized, two-arm parallel single-blinded controlled trial. Approval for the study was obtained from the Joint Chinese University of Hong Kong – New Territories East Cluster Clinical Research Ethics Committee, Shatin, Hong Kong, China, and the study was registered in the Chinese Clinical Trial Registry (registration no. ChiCTR-TRC-12002418). All patients included gave written, informed consent. A total of 214 patients scheduled for elective cesarean delivery under spinal anesthesia at the Prince of Wales Hospital, Shatin, Hong Kong, China, were enrolled. Inclusion criteria were: singleton pregnancy, age ≥18 yr, weight ≥ 50 kg, height 140 - 180 cm, ability to give informed consent. Exclusion criteria were: American Society of Anesthesiologists physical status ≥ 3, pre-existing or pregnancy-induced hypertension, cardiovascular or cerebrovascular disease, known fetal abnormality, any signs of onset of labor.

Standard antacid premedication was given. On arrival in the operating room, patients were allowed to rest in the left-tilted supine position and standard monitoring was attached (Infinity C500, Dräger Medical AG & Co. KG, Germany). BP was measured non-invasively at 1-min intervals and after a brief stabilizing period, baseline values were recorded as the mean of three consecutive measurements with a difference of no more than 10%. A wide-bore intravenous cannula was then inserted into a forearm vein under local anesthesia but no prehydration was given. Spinal anesthesia was induced with the patient in the right lateral position. After skin disinfection and skin infiltration with lidocaine 1% w/v, a 25-gaugeWhitacre spinal needle was inserted via an introducer at the estimated L3-4 or L4-5 vertebral interspace. After confirmation of free-flow of cerebrospinal fluid, 2.2 mL of hyperbaric bupivacaine 0.5% w/v and fentanyl 15

μg were injected intrathecally. The patient was then returned to the left-tilted supine position. Supplemental oxygen was not given unless the pulse oximeter reading was <95%.

Immediately after intrathecal injection, intravenous cohydration of up to 2 L of warmed Hartmann's solution was started by fully opening the clamp of the infusion set. The non-invasive BP monitor was set to measure at 1-min intervals starting 1 min after the completion of intrathecal injection.

BP was maintained using phenylephrine administered by closed-loop feedback computer-control that was started immediately after induction of spinal anesthesia. A standardized preparation of phenylephrine 100 μg/mL[1] was prepared in a 50 mL syringe that was connected via narrow bore tubing to a three-way stopcock attached to the intravenous cannula through which intravenous fluid was continuously administered. The phenylephrine was delivered by a syringe pump (Graseby 3500 Anaesthesia Pump, Graseby Medical Ltd, Watford, Herts, UK) that was controlled by laptop computer running one of two algorithms. The computer programs were developed by one of the authors (YHT) using Microsoft Visual Studio 6.0 using Visual C++. The general basis of the system has been described previously.[1,2]

Patients were randomly assigned by the principal investigator (WN) at a 1:1 ratio to one of two groups according to a computer-generated random number code that had been prepared by one of the secretarial staff. In both groups, the calculated dose of phenylephrine per minute (*I*) was determined according to the following algorithm:

$$I \text{ (mL)} = (10 - \text{error\%}) /20$$

where error% = (measured systolic BP – baseline systolic BP)/baseline systolic BP × 100 and the value of *I* was constrained to be within the limits 0 – 1 mL. This regimen has previously been shown to be effective for maintaining systolic BP near baseline.[1]

In the infusion group, the syringe pump was controlled to deliver phenylephrine at the rate of *I* mL/min. The infusion rate was adjusted following the completion of each automated BP measurement. In the bolus group, the syringe pump was controlled to deliver a rapid bolus of *I* mL of phenylephrine given at a rate of 1200 mL/h started following the completion of each automated BP measurement. The principal investigator was continuously present during operation and had discretion to inactivate or override the system if deemed necessary. The senior investigator was aware of the group to which patients were assigned but patients were blinded.

BP and heart rate (HR) were recorded after each automated measurement. In addition, cardiac output (CO) was measured non-invasively using a suprasternal Doppler technique (USCOM 1A cardiac output monitor, USCOM Ltd, Sydney, NSW, Australia) as we have previously described.[3,4] These measurements were made by the same investigator (SL) who was blinded to the patient's group at baseline and at 5-min intervals after induction of anesthesia until delivery. The incidences of hypotension (defined as systolic BP < 80% of baseline), hypertension (defined as systolic BP > 120% of baseline), bradycardia (defined as HR < 50 beats/min) and nausea or vomiting were recorded.

Computer-controlled administration of phenylephrine was continued until the time of uterine incision after which the study was terminated and further hemodynamic management was at the discretion of the attending anesthesiologist. Apgar scores and umbilical cord blood gases were measured according to usual practice.

Statistical analysis

The performance of the two systems for controlling BP was assessed using performance error calculations as we have previously described.[1,2] The following parameters were calculated: 1) *percentage performance error* (*PE*) (defined as the difference between each measured value of systolic SBP and the baseline value, expressed as a percentage of the baseline value; 2) *median performance error* (*MDPE*) (defined as the median of all values of *PE* for each patient); 3) *median absolute performance error* (*MDAPE*) (defined as the median of the absolute values of *PE* ($\left|PE\right|$) for each patient; 4) *wobble* (a measure of the variability of *PE* around *MDPE* for each patient); and 5) *divergence* (a measure of the trend of change in $\left|PE\right|$ with time for each patient. Derivation of these parameters has been described previously.[5] These calculations were performed using Microsoft Office Excel 2010 (Microsoft Corporation, Redmond, WA).

Data for CO values were normalized to percentage of baseline values. For each patient, the area under the curve (AUC) for these values plotted against time were calculated using the trapezium rule.[6] Because the number of data points recorded was variable among patients because of varying surgical times, standardized values were derived by dividing the values for AUC by the

number of data points recorded for each patient.[7] Standardized values were then compared between groups as a measure of overall change in CO.

The objective of the study was to determine differences in the precision of control of BP between groups. Accordingly the primary outcome was defined as *MDAPE*. An *a priori* power analysis was performed based on data from our previous study in which closed-loop feedback computer-controlled phenylephrine infusion resulted in mean (SD) values for *MDAPE* of 4.82 (2.01)%.[1] In order to determine a difference of 20% in *MDAPE* between groups with 80% power at an alpha level of 0.05 it was calculated that a sample size of 103 patients per group was required. To allow for an estimated dropout rate of 5%, the sample size was increased to 107 patients per group.

Continuous data were checked for normal distribution using the Kolmogorov-Smirnov test and intergroup comparisons were performed using Student's t-test or the Mann-Whitney U test as appropriate. Nominal data were compared using the Chi-square test. Statistical comparisons were made using IBM SPSS Statistics version 20 (IBM SPSS Inc., Chicago, IL). Values of $P < 0.05$ were considered statistically significant.

Results

Patient recruitment and flow is shown in Figure 1. A total of 214 patients were enrolled into the study between August 2012 and September 2014. Ten patients were excluded from analysis for the following reasons: fault with syringe pump or tubing connections (4), severe shivering preventing accurate BP measurement (3), inadequate spinal anesthesia (2) and fault in BP monitor (1). Following exclusions, 102 patients in the bolus group and 102 patients in the infusion group completed the study and had data analyzed for the primary outcome. In no case was it necessary for the senior investigator to inactivate or override the computer-controlled system. Because the investigator responsible for CO measurements had a change in employment status during the study, she was only able to be present and make measurements for 43 patients in the bolus group and 39 patients in the infusion group. As CO was a secondary outcome of the study it was considered acceptable to continue the study with this limitation.

Patient characteristics are shown in Table 1. Anesthetic details and surgical times are shown in Table 2. The total dose of phenylephrine and the rate of phenylephrine administration up to the time of uterine incision were greater in the infusion group versus the bolus group (both $P < 0.001$).

Changes in systolic BP over time for all patients are shown in Figure 2. Results for performance error calculations are shown in Table 3. The primary outcome *MDAPE* was smaller in the bolus group (median 4.38 [interquartile range 3.22 – 6.25] % versus the infusion group (5.39[4.12 – 7.04] %, P <0 001, Figure 3). *MDPE* was smaller in the bolus group (-0.21 [-2.82 – 1.95] %

versus the infusion group (3.72[0.43 – 5.84] %, *P* = 0.008). Wobble and divergence were similar between groups.

Changes in CO over time, normalized to percentage of baseline, are shown in Figure 4. The standardized AUC was similar in the bolus group (median 586.7 [interquartile range 549.1 – 621.8] %.min versus the infusion group (552.4[524.5 – 596.3] %.min, *P* =0.16).

The incidences of hypotension, hypertension, bradycardia and nausea or vomiting are shown in Table 4. More patients in the infusion group had one or more episodes of hypertension (*P* = 0.007).

Neonatal outcome is summarized in Table 5. Insufficient umbilical arterial blood was obtained for blood gas analysis in nine patients in the bolus group and four patients in the infusion group. Insufficient umbilical venous blood was obtained for blood gas analysis in three patients in the bolus group and five patients in the infusion group. The UA PO_2 was less than the lower limit of detection of the blood gas analyzer (10 mmHg) in eight patients in the bolus group and five patients in the infusion group; for these analyses the data values were entered as constant values equal to the lower limit of detection divided by $\sqrt{2}$ [6] and the values were then analyzed by ranks. There was no difference between groups.

Discussion

The results of this study showed that when using closed-loop feedback computer-control to administer phenylephrine to maintain BP during spinal anesthesia for cesarean delivery, use of

intermittent boluses resulted in more precise control of BP compared with continuous infusion. This was evidenced by smaller values for *MDAPE*, a standard parameter used for assessing inaccuracy of closed-loop systems,[5] in the bolus group compared with the infusion group. However, the difference between groups was modest and there was no difference in clinical outcomes between groups; therefore the use of closed-loop administration of intermittent boluses rather than continuous infusion can be viewed as an incremental improvement of a system that already performs well.

The reason why the computer-controlled system performed better using intermittent boluses compared with continuous infusion probably relates to the method of BP measurement. We used a standard non-invasive monitor set to cycle at 1-min intervals which was the highest frequency we considered practical. Administering the calculated vasopressor dose by a rapid bolus after the completion of each BP measurement may have resulted in a more rapid response compared with adjustment of the rate of infusion. Closed-loop administration of the vasopressor by intermittent boluses may thus be a better match to intermittent measurement of BP, which is the usual method of BP management in normal clinical practice. Although Sia and Sng et al. recently described the use of a continuous non-invasive BP monitor in a computer-controlled double-vasopressor system,[8-10] continuous non-invasive monitors are not generally used in routine practice. Further investigation to determine the relative performance of vasopressor administration by boluses versus infusion in computer-controlled systems when continuous BP monitoring is used would be of interest.

Our results showed that *MDPE* was greater in the infusion group compared with the bolus group. *MDPE* is a measure of bias[5] and our results indicate that BP on average was maintained at a higher level in the infusion group (3.72% above baseline) compared with the bolus group (0.21% below baseline). Of note this was associated with a greater rate of phenylephrine consumption in the infusion group compared with the bolus group. Although the two computer-control algorithms were designed to deliver the same amount of phenylephrine per minute, the algorithms did not account for the time required to complete each BP measurement. Each cycled measurement required a finite and variable period to complete. In addition, there were occasional further delays to measurement because of motion artifacts or other interferences that required the monitor to recycle. As a result, the average actual time between BP measurements was usually greater than 1 min. This biased towards a higher rate of phenylephrine administration in the infusion group since in this group the rate of infusion was continuous and independent of the BP measurement time whereas in the bolus group the equivalent of a 1-min dose was only delivered after each BP measurement regardless of the actual time taken.

Intermittent failures of measurement often occur in awake patients and this is especially important for obstetric patients because of the high incidence of intraoperative shivering during neuraxial anesthesia.[11] Because in a bolus system each dose of vasopressor is only administered after a BP measurement is successfully completed, whereas in a continuous infusion system vasopressor administration continues regardless of any delays in BP measurement, unnecessary or overly large doses are less likely to be administered using a bolus system; this suggests a potential safety advantage of systems using boluses. Although it would be possible to modify the

infusion system by incorporating a time limit for the infusion period, the simplicity of the bolus system remains attractive.

Previously, it has been shown that administration of phenylephrine in high doses during spinal anesthesia was associated with dose-dependent decreases in CO, which is thought to be related primarily to baroreceptor-mediated decreases in HR.[12] In our study, phenylephrine consumption was greater in the infusion group compared with the bolus group and this was associated with maintenance of BP at a higher average level. Furthermore, the incidence of hypertension was greater in the infusion group compared with the bolus group. However, despite this, no difference in CO changes was found between groups. This suggests that the mean rate of phenylephrine administration in the infusion group (36.9 μg/min) was not excessive. However, because logistic reasons prevented CO measurement in all patients, a type II statistical error for this outcome cannot be excluded.

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Legend for Figures

Figure 1.

CONSORT diagram showing patient recruitment and flow.

Figure 2.

Systolic blood pressure for all patients plotted against time in the bolus group (upper panel) and infusion group (lower panel). Values on the x-axis correspond to the number of each consecutive blood pressure measurement made with the monitor set to record at 1-min intervals and are not exactly equal to chronological time.

Figure 3.

Median absolute performance error (*MDAPE*) for all patients plotted against time in the bolus group (upper panel) and infusion group (lower panel). Values on the x-axis correspond to the number of each consecutive blood pressure measurement made with the monitor set to record at 1-min intervals and are not exactly equal to chronological time.

Figure 4.

Serial changes in cardiac output after induction of spinal anesthesia. Values were normalized to percentage of baseline values and are shown for the first 30 min. Comparison of standardized area under the curve showed no difference between groups ($P = 0.16$).

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Figure

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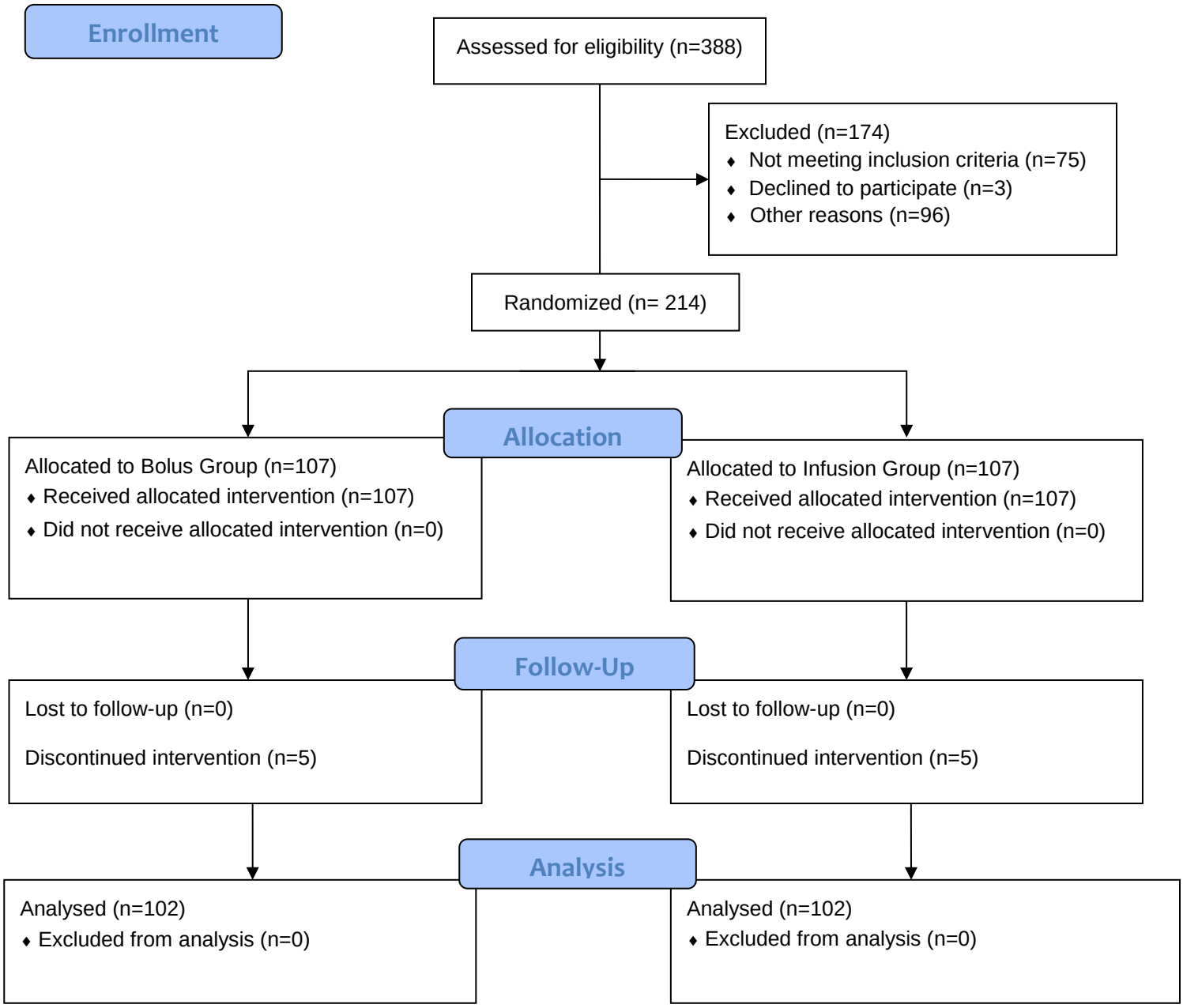

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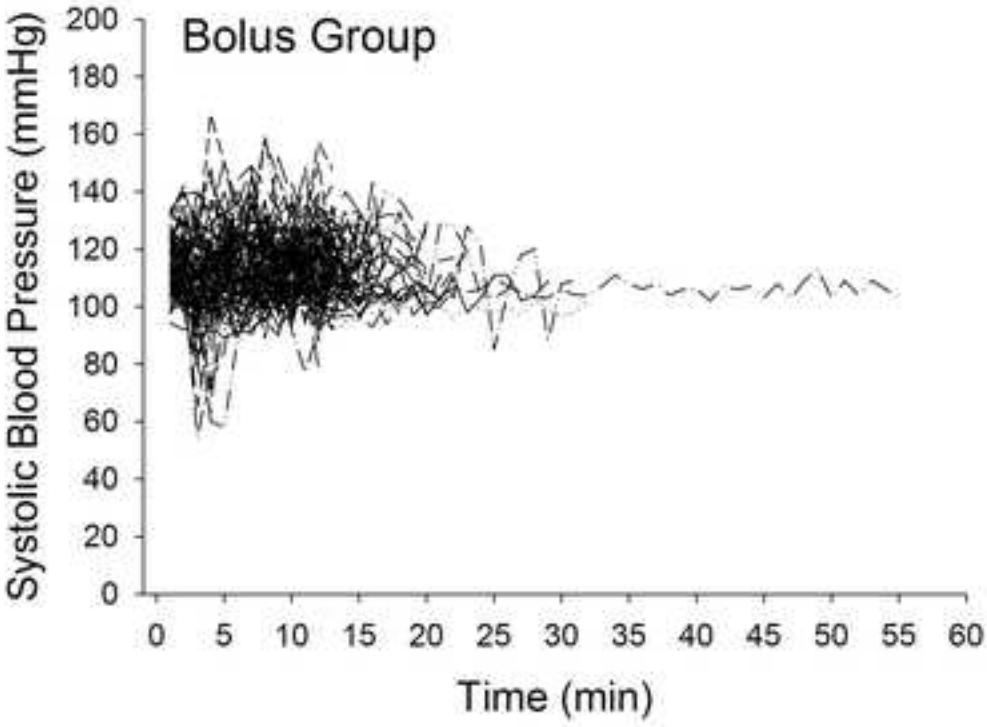

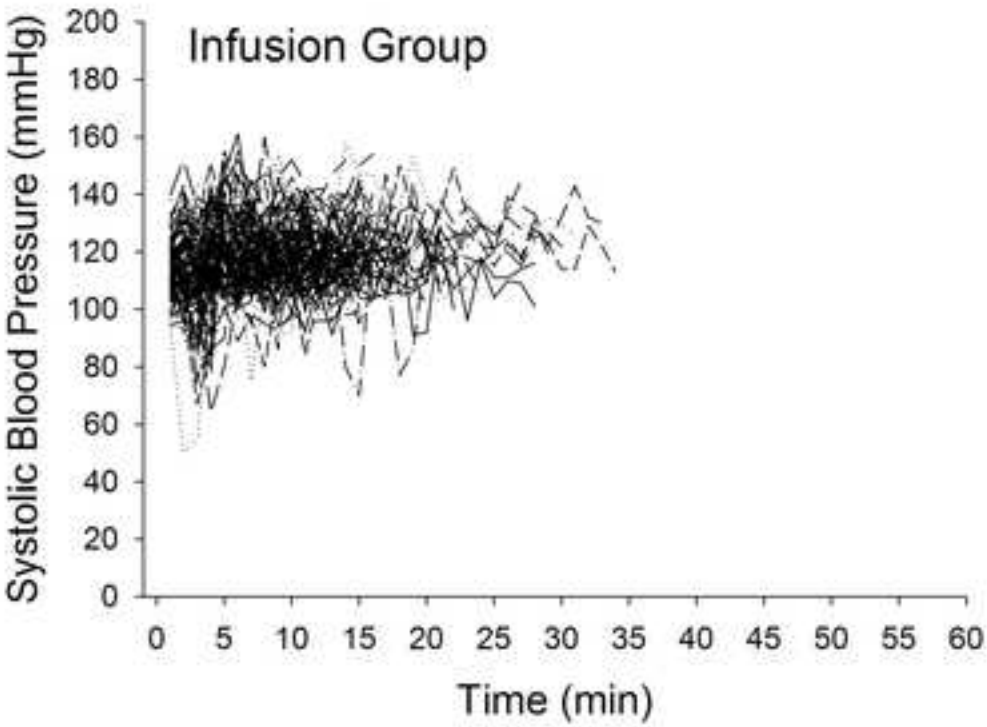

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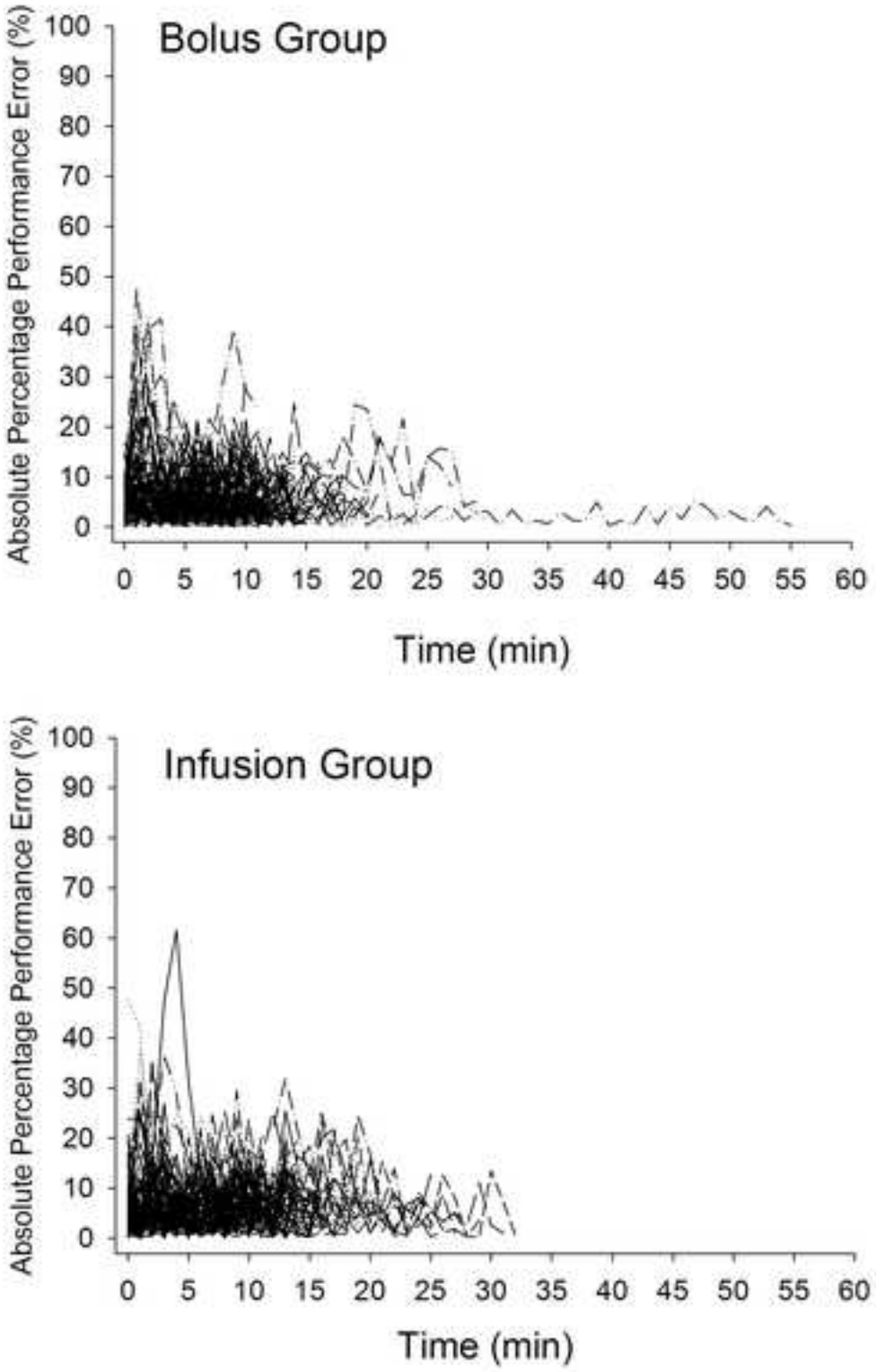

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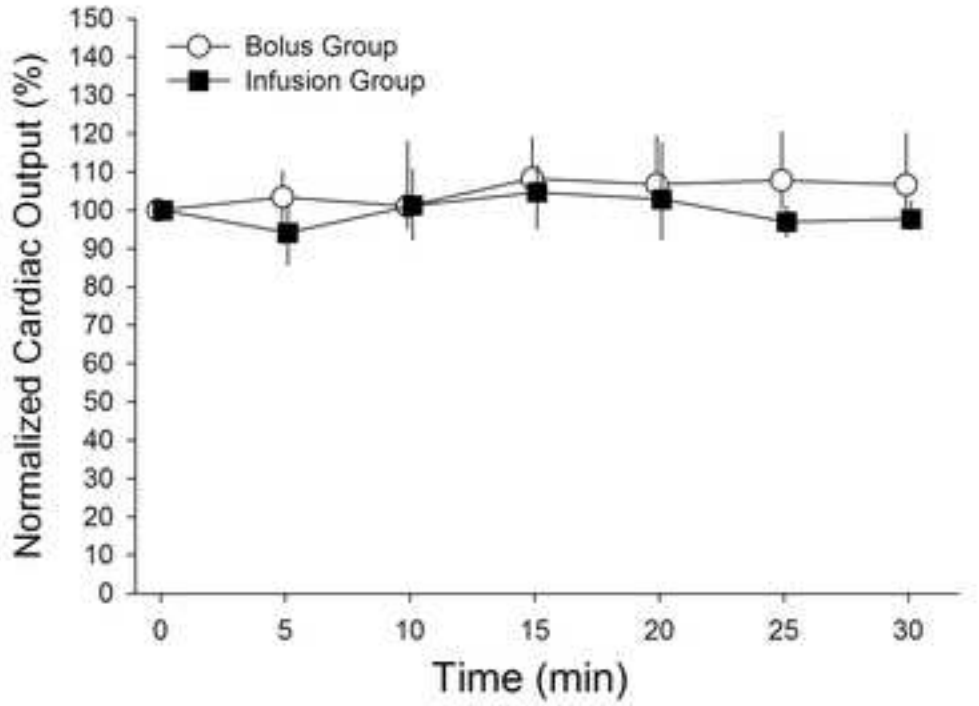

Table 1. Patient Characteristics. Values are mean (standard deviation).

	Bolus Group (*n* = 102)	**Infusion Group (*n* = 102)**
Age (yr)	32.8 (4.4)	33.4 (4.6)
Weight (kg)	66.3 (8.9)	68.5 (9.7)
Height (m)	1.57 (0.06)	1.58 (0.05)

Table 2. Anesthesia details and surgical times. Data are mean (standard deviation) or median (interquartile range). Data recorded up to the time of uterine incision.

	Bolus Group	Infusion Group	*P*-value
Block height (dermatome)	T4 [T3 – T5]	T3.5 [T3 – T5]	0.71
Total phenylephrine dose (µg)	852 (487)	1189 (626)	< 0.001
Rate of phenylephrine administration (µg/min)	27.2 (8.6)	36.9 (13.4)	< 0.001
Total intravenous fluid given (mL)	1586 (455)	1594 (479)	0.90
Block height (dermatome)	T4 [T3 – T5]	T4 [T3 – T6]	0.27
Induction-to-delivery interval (min)	30.9 [26.6 – 34.7]	31.1 [27.4 – 36.5]	0.56
Uterine incision-to-delivery interval (s)	87 [59 – 137]	87 [54 – 124]	0.41

Table 3. Performance error calculations. Data are median (interquartile range).

	Bolus group	Infusion group	*P*-value
Median performance error (MDPE)(%)	-0.21 [-2.82 – 1.95]	3.72 [0.43 – 5.84]	< 0.001
Median absolute performance error (MDAPE) (%)	4.38 [3.22 – 6.25]	5.39 [4.12 – 7.04]	0.008
Wobble (%)	3.35 [2.59 – 4.61]	3.71 [2.63 – 4.65]	0.38
Divergence (%/min)	-0.05 [-0.29 – 0.27]	0 [-0.22 – 0.22]	0.93

Table 4. Incidences of hypotension, hypertension, bradycardia and nausea or vomiting. Values are number (%).

	Bolus group (n = 102)	Infusion group (n = 102)	P-value
Patients with one or more episode of hypotension (systolic blood pressure < 80% of baseline)	19 (18.6%)	13 (12.7%)	0.25
Patients with one or more episode of hypertension (systolic blood pressure > 120% of baseline)	7 (6.9%)	20 (19.6%)	0.007
Patients with one or more episode of bradycardia (heart rate < 50 beats/min)	6 (5.9%)	10 (9.8%)	0.30
Nausea or vomiting	6 (5.9%)	7 (6.9%)	0.72

Table 5. Neonatal outcome. Values are mean (standard deviation), median (interquartile range) or number (%).

	Bolus group	Infusion group	*P*-value
Birthweight (kg)	3.13 (0.44)	3.15 (0.40)	0.80
Umbilical arterial blood gases			
pH	7.30 [7.27 – 7.32]	7.30 [7.28 – 7.32]	0.56
PCO_2 (mmHg)	48 [44 – 53]	45 [41 – 51]	0.18
PO_2 (kPa)	15 [13 – 17]	16 [13 – 18]	0.12
Base excess (mmol/L)	-4.0 [-5.8 – -2.0]	-4.4 [-5.9 – -2.6]	0.32
Umbilical venous blood gases			
pH	7.35 [7.33 – 7.36]	7.35 [7.33 – 7.37]	0.23
PCO_2 (mmHg)	41[38 – 45]	41 [36 – 45]	0.35
PO_2 (mmHg)	26 [21 – 29]	26 [23 – 30]	0.17
Base excess (mmol/L)	-3.5 [-4.7 – -2.0]	-3.3 [-5.0 – -2.1]	0.87
1 min Apgar score < 7	1	2	0.56
5 min Apgar score <9	2	1	0.56