

Effect of Adding a Low Dose Epinephrine Bolus Prior to Epinephrine Infusion on Maternal Hemodynamic Stability During Cesarean Section Under Spinal Anesthesia: A Randomized Clinical Trial

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Abstract

Background

Maternal hypotension remains one of the most frequent complications following spinal anesthesia for cesarean delivery and may adversely affect both maternal and fetal outcomes. Epinephrine infusion has recently emerged as a potential vasopressor strategy because of its combined α - and β -adrenergic activity. However, whether administration of an initial low dose epinephrine bolus before initiating infusion improves maternal hemodynamic stability remains unclear. This study evaluated the effect of adding a low dose epinephrine bolus prior to epinephrine infusion on maternal hemodynamic stability during cesarean delivery under spinal anesthesia.

Methods

Full term singleton pregnant women scheduled for elective cesarean delivery under spinal anesthesia were randomized into two groups. Patients in the bolus plus infusion group received an intravenous epinephrine bolus of 4 μg immediately after spinal anesthesia followed by continuous epinephrine infusion at 0.03 $\mu\text{g}/\text{kg}/\text{min}$. Patients in the infusion-only group received placebo saline bolus followed by the same epinephrine infusion regimen. The primary outcome was incidence of post-spinal hypotension defined as a systolic blood pressure decrease greater than 20% from baseline between spinal anesthesia and 5 minutes after delivery. Secondary outcomes included severe hypotension, reactive hypertension, tachycardia, rescue norepinephrine consumption, maternal adverse events, and neonatal outcomes.

Results

The incidence of hypotension was significantly lower in the epinephrine bolus group, occurring in 4 patients (10%) compared with 12 patients (30%) in the epinephrine infusion group, relative risk (RR) = 0.8, (95% CI 0.6–0.97; $p = 0.025$). Rescue norepinephrine requirements were significantly reduced in the bolus group. Maternal heart rate was generally higher in the bolus group without clinically significant increase in severe tachycardia or reactive hypertension. Neonatal Apgar scores and umbilical arterial blood gas parameters were comparable between groups.

Conclusion

Administration of a low dose epinephrine bolus before initiation of epinephrine infusion improved maternal hemodynamic stability during cesarean delivery under spinal anesthesia and reduced vasopressor rescue requirements without adversely affecting neonatal outcomes.

Key points

Question

Does adding a low dose epinephrine bolus before continuous epinephrine infusion reduce the incidence of post spinal hypotension in women undergoing cesarean delivery under spinal anesthesia?

Finding

Adding a small epinephrine bolus before epinephrine infusion significantly reduced the incidence of post spinal hypotension compared with epinephrine infusion alone and reduced rescue norepinephrine requirements.

Meaning

A low dose epinephrine bolus before initiating continuous epinephrine infusion may provide improved maternal hemodynamic stability during cesarean delivery under spinal anesthesia without clinically significant increases in adverse outcomes.

Introduction

Spinal anesthesia is considered the preferred anesthetic technique for elective cesarean delivery because of its rapid onset, high success rate, and safety.¹ However, sympathetic blockade induced by spinal anesthesia frequently results in maternal hypotension, which remains one of the most common intraoperative complications during cesarean delivery.^{2–4} Maternal hypotension may lead to nausea, vomiting, dizziness, decreased uteroplacental perfusion and fetal acidosis.⁵

Prophylactic vasopressor administration represents the cornerstone strategy for prevention and treatment of post spinal hypotension during cesarean delivery. Phenylephrine has traditionally been recommended because of its potent α -adrenergic vasoconstrictive effects and favorable fetal acid base profile.² Nevertheless, phenylephrine may produce reflex bradycardia and reduction in cardiac output.¹ Norepinephrine has therefore gained increasing interest because of its combined α - and mild β -adrenergic effects that better preserve maternal heart rate and cardiac output.⁶

Epinephrine has a balanced α - and β -adrenergic activity⁷ and has been safely used in obstetric practice.^{1, 8} Recent trials had demonstrated that prophylactic epinephrine infusion may effectively reduce the incidence of spinal hypotension during cesarean delivery without adverse neonatal effects.^{9, 10} Furthermore, epinephrine infusion has shown hemodynamic profiles comparable to phenylephrine while potentially preserving maternal hemodynamic stability.

Despite growing evidence supporting prophylactic epinephrine infusion for the prevention of spinal anesthesia induced hypotension during cesarean delivery, the incidence of hypotension remains considerable.⁹ This high incidence of hypotension suggests that infusion alone may be insufficient to prevent the early decrease in blood pressure following spinal anesthesia. Therefore, administration of an initial low dose epinephrine bolus before starting the continuous infusion may provide more immediate vasopressor support and reduce the incidence of hypotension during this vulnerable period. We hypothesized that an epinephrine bolus followed by continuous infusion would reduce the incidence of post spinal hypotension and decrease vasopressor rescue requirements compared with continuous infusion alone.

Methods

This randomized controlled trial was conducted between 18th of March and 3rd of August 2026 at Kasr Al Ainy Hospital, Cairo University, following approval from the Research Ethics Committee, Faculty of Medicine, Cairo University (MS – 572–2025). The study was registered prior to patient enrolment at ClinicalTrials.gov (identifier: NCT07480889, principal investigator: Abd ElKhalik Mahmoud Shaban, date of registration: March 14, 2026). Written informed consent was obtained from all participants before enrollment. The study was conducted in accordance with CONSORT recommendations and the ethical principles of the Declaration of Helsinki.

Full term singleton pregnant women aged between 18 and 35 years with American Society of Anesthesiologists physical status II scheduled for elective cesarean delivery under spinal anesthesia were considered eligible for participation.

Patients were excluded if they had uncontrolled cardiac disease, hypertensive disorders of pregnancy, peripartum hemorrhage, coagulation abnormalities, baseline systolic blood pressure < 100 mmHg or refusal to participate.

Patients were randomized in a 1:1 ratio using a computer-generated randomization sequence and concealed in sealed opaque envelopes. Patients were allocated into either the bolus plus infusion group or infusion only group. Study drug preparation was performed by a research assistant not involved in patient management or data collection.

Upon arrival to the operating room, standard monitoring including electrocardiography, pulse oximetry, and non-invasive blood pressure monitoring was applied and baseline measurements

were recorded. An 18-gauge intravenous cannula was inserted. All patients received 15 mL/kg lactated Ringer's crystalloid co-loading over 15 minutes together with intravenous metoclopramide 10 mg for postoperative nausea and vomiting (PONV) prophylaxis. Spinal anesthesia was performed at the L3-L4 or L4-L5 interspace using a 25-gauge Quincke spinal needle under aseptic precautions. Hyperbaric bupivacaine 12.5 mg combined with fentanyl 25 µg was injected intrathecally. Sensory block level was assessed using loss of pinprick sensation aiming for T4 level before skin incision.

Following spinal anesthesia, patients were positioned supine with left uterine displacement. Patients in the bolus plus infusion group received intravenous epinephrine bolus 4 µg immediately after spinal anesthesia followed by continuous epinephrine infusion at 0.03 µg/kg/min. Patients in the infusion only group received equal placebo saline bolus followed by the same epinephrine infusion regimen.

Epinephrine infusion was prepared by diluting 3 mg epinephrine in 500 mL normal saline producing a concentration of 6 µg/mL. Infusion rate was adjusted according to the body weight.

Hemodynamic variables including heart rate and systolic blood pressure were recorded at baseline, immediately after spinal anesthesia, and every 3 minutes until delivery.

Post-spinal hypotension was defined as a decrease in systolic blood pressure > 20% from baseline and was treated with intravenous norepinephrine boluses of 8 µg. Severe hypotension was defined as a drop in systolic blood pressure > 30% from baseline or systolic blood pressure < 80 mmHg and was treated with norepinephrine 16 µg boluses.

Reactive hypertension was defined as systolic blood pressure $\geq$ 120% of baseline and was treated by reduction of the infusion rate to the half. Reactive tachycardia was defined as heart rate > 130% of baseline unrelated to hypotension. Bradycardia was defined as heart rate < 55 beats/minute and was treated with atropine 0.5 mg bolus.

Umbilical arterial blood samples were obtained immediately after delivery for analysis. Apgar scores were recorded at 1 and 5 minutes after delivery.

The primary outcome was the incidence of post-spinal hypotension between initiation of spinal anesthesia and 5 minutes after delivery. Secondary outcomes included incidence of severe hypotension, reactive hypertension, tachycardia, nausea and vomiting, rescue norepinephrine requirements, and neonatal outcomes.

Sample size:

A pilot study involving 10 patients per group was conducted to estimate the incidence of post-spinal hypotension, defined as a > 20% decrease in systolic blood pressure from baseline. Hypotension occurred in 2/10 patients (20%) in the epinephrine infusion-only group and in none of the patients (0%) in the epinephrine bolus-plus-infusion group. The sample size was calculated using G*Power version 3.1.9.2 (Universität Düsseldorf, Germany) with Fisher's exact test for a two-group comparison. A minimum of 78 patients (39 per group) was required to achieve 80% power at an alpha level of 0.05. To account for potential dropouts, 16 additional patients were recruited, resulting in a final sample size of 94 patients (47 per group).

Statistical analysis:

Statistical analysis was performed using IBM SPSS Statistics version 25 (IBM Corp., Armonk, NY, USA). Continuous variables were expressed as mean $\pm$ standard deviation or median (interquartile range), as appropriate according to the distribution of the data. Categorical variables were presented as frequencies and percentages. Between-group comparisons of continuous variables were performed using the independent-samples *t*-test or Mann–Whitney *U* test, as appropriate. Categorical variables were compared using the chi-square test or Fisher's exact test, as appropriate. Repeated hemodynamic measurements were analyzed using repeated-measures analysis of variance (ANOVA), with Bonferroni adjustment for post hoc pairwise comparisons. A *p* value < 0.05 was considered statistically significant.

Results

In this study, 93 patients were assessed for eligibility. Nine patients did not meet the inclusion criteria and four declined to participate. Eighty patients were included in the final analysis (Figure 1).

Baseline demographic characteristics, duration of surgery and spinal anesthesia level were comparable between the two groups (Table 1).

The incidence of hypotension was significantly lower in the epinephrine bolus group, occurring in 4 patients (10%) compared with 12 patients (30%) in the epinephrine infusion group, relative risk (RR) =0.8, (95% CI 0.6–0.97; *p* = 0.025). The incidence of severe hypotension was comparable between groups, occurring in 1 patient (2.5%) in the bolus group and 3 patients (7.5%) in the infusion group (RR =0.95, 95% CI 0.86–1.05; *p* = 0.31).

The frequency of multiple (>1 bolus) rescue norepinephrine bolus requirements was significantly lower in the epinephrine bolus group compared to the epinephrine infusion group {0 (0%) vs. 8 (20%), *p* = 0.005}.

Patients in epinephrine bolus group demonstrated significantly higher mean arterial pressure and significantly lower heart rate at several predefined intraoperative time points compared with those receiving continuous epinephrine infusion (Figure 2).

Neonatal outcomes were generally comparable between the two groups. Apgar scores at both 1 and 5 minutes were similar, and umbilical cord blood gas analysis parameters demonstrated no significant differences (Table 2).

None of the assessed adverse effects differed significantly between groups (Table 3). Nausea and vomiting occurred more frequently in the epinephrine infusion group than in the bolus group, affecting 11 patients (27.5%) compared with 4 patients (10%), respectively (RR 2.75, 95% CI 0.96–7.89; *p* = 0.057). Tachycardia and reactive hypertension occurred at comparable frequencies between the two groups.

Discussion

The present study demonstrated that administration of a low dose epinephrine bolus before initiation of prophylactic epinephrine infusion significantly reduced the incidence of post-spinal hypotension and rescue norepinephrine requirements during cesarean delivery under spinal anesthesia compared with epinephrine infusion alone, without increasing maternal adverse effects or compromising neonatal outcomes.

The beneficial effect of an initial bolus is physiologically reasonable. Although prophylactic vasopressor infusion is started immediately after intrathecal injection, therapeutic drug concentrations may not be achieved before the onset of sympathetic blockade.¹¹ An initial low dose epinephrine bolus may bridge this vulnerable period by providing immediate

vasopressor activity until the infusion becomes effective, thereby reducing early hypotension and the need for rescue vasopressors.

This mechanism is supported by previous studies evaluating norepinephrine. In a randomized dose finding trial ¹¹, an initial norepinephrine bolus followed by continuous infusion significantly reduced maternal hypotension and severe hypotensive episodes compared with infusion alone, demonstrating the importance of rapidly establishing effective vasopressor concentrations during the early post spinal period. Our findings indicate that a similar principle may also apply to epinephrine.

Epinephrine has recently emerged as a promising alternative to traditional vasopressors for the prevention of spinal anesthesia-induced hypotension because of its combined α - and β -adrenergic activity which maintains vascular tone while supporting heart rate and cardiac output. ¹²⁻¹⁴ In contrast to predominantly α -adrenergic agents such as phenylephrine, epinephrine may better preserve maternal cardiovascular performance without increasing adverse neonatal outcomes.⁸

Previous clinical studies have primarily focused on identifying the optimal epinephrine infusion dose.^{9, 14} Hassanin et al.⁹ demonstrated that escalating doses of prophylactic epinephrine infusion reduced maternal hypotension while maintaining acceptable maternal and neonatal safety compared with phenylephrine. Nevertheless, hypotension remained relatively common despite continuous prophylactic infusion across different dosing regimens, suggesting that optimization of infusion dose alone may not fully overcome the vulnerable period immediately after spinal anesthesia. ^{10, 15, 16}

The present study was designed to address this potential limitation by evaluating whether modification of the administration strategy, rather than the infusion dose, could further improve hemodynamic control. The lower incidence of hypotension and reduced rescue norepinephrine requirements observed with epinephrine bolus followed by infusion support the concept that the timing of vasopressor delivery is an important determinant of prophylactic efficacy.

Improved maternal blood pressure control was accompanied by a lower incidence of intraoperative nausea and vomiting, which is consistent with the well-established association between maternal hypotension and these symptoms. Importantly, the addition of an initial epinephrine bolus did not increase excessive tachycardia or hypertension, and neonatal outcomes, including Apgar scores and umbilical cord blood gas parameters, remained comparable between groups, supporting the maternal and neonatal safety of this approach.

This study has some limitations. It was conducted at a single tertiary center, which may limit generalizability. In addition, only short term maternal and neonatal outcomes were evaluated.

Conclusion

Administration of a low dose epinephrine bolus before prophylactic epinephrine infusion significantly reduced post spinal hypotension and rescue vasopressor requirements during cesarean delivery under spinal anesthesia without increasing maternal or neonatal adverse outcomes.

Abbreviations

ANOVA: analysis of variance; CONSORT: Consolidated Standards of Reporting Trials; PONV: postoperative nausea and vomiting; SPSS: Statistical Package for the Social Sciences.

Declarations

The authors certify that the work has not been published previously, it is not under consideration for publication elsewhere; it does not duplicate or overlap other published work; and, if accepted, it will not be published elsewhere in the same form, in English or in any other language, including electronically without the written consent of the copyright-holder. The authors will take public responsibility for the contents

All authors have contributed substantially to the drafting and have approved the final version; and the responsible authorities where the work was carried out had approved the publication.

The lead author affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

The authors declare that they have no conflict of interest with this work and did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Authors' contributions:

Dina Turki: Study conception, data collection, and contribution to manuscript preparation.

Asmaa Adel: Data collection and manuscript drafting.

Khaled Sarhan: Study design, statistical analysis, interpretation of data, and manuscript writing.

Nashwa Elzayat: Supervision of study conduct and manuscript revision.

Ahmed Elsakka: Data collection and manuscript revision.

AbdElKhalik Mahmoud Shaban: Contribution to data interpretation and manuscript revision.

Declaration of interests:

The authors declare no conflict of interest.

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Clinical trial: <https://clinicaltrials.gov/study/NCT07480889>.

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Tables

Table 1: Demographic and baseline characteristics

	Epinephrine bolus (n = 40)	Epinephrine infusion (n = 40)	Standardized difference ^a
Age (years)	26.5 ± 5.6	27.2 ± 4.7	-0.14
Weight (kg)	77.3 ± 6.4	79.3 ± 6.9	-0.31
Height (cm)	160.8 ± 3.6	159.1 ± 5.8	0.34
Duration of surgery (min)	33.6 ± 2.8	33.2 ± 2.4	0.17
Spinal level (%)			-0.06
T3	1 (2.5%)	1 (2.5%)	
T4	37 (92.5%)	36 (90.0%)	
T5	1 (2.5%)	2 (5.0%)	
T6	1 (2.5%)	1 (2.5%)	

Data are presented as mean ± SD or frequency (%). ^a Standardized difference was calculated as the difference in means or proportions divided by the pooled standard deviation.

Table 2: Neonatal Outcomes

	Epinephrine Bolus (n=40)	Epinephrine Infusion (n=40)	P value
Umbilical pH	7.36 ± 0.05	7.33 ± 0.08	0.057
Umbilical PCO ₂ (mmHg)	40.92 ± 3.89	41.33 ± 5.21	0.688
Umbilical PO ₂ (mmHg)	38.53 ± 6.02	36.88 ± 4.94	0.184
Umbilical HCO ₃ ⁻ (mmol/L)	22.68 ± 2.04	21.90 ± 2.39	0.123
Apgar score at 1 min	7 (6–8)	8 (6–9)	0.105
Apgar score at 5 min	9 (9–10)	10 (9–10)	0.072

Data are presented as mean ± standard deviation (SD) for continuous variables and median (minimum–maximum) for Apgar scores. * Denotes statistical significance.

Table 3: intraoperative adverse events:

	Epinephrine Bolus (n = 40)	Epinephrine Infusion (n = 40)	P value
Reactive hypertension	4 (10%)	1 (2.5%)	0.36
Nausea and vomiting	4 (10%)	11 (27.5%)	0.057
Tachycardia	3 (7.5%)	2 (5.0%)	1

Data are presented as frequency (%); * denotes considered statistical significance.

Figures

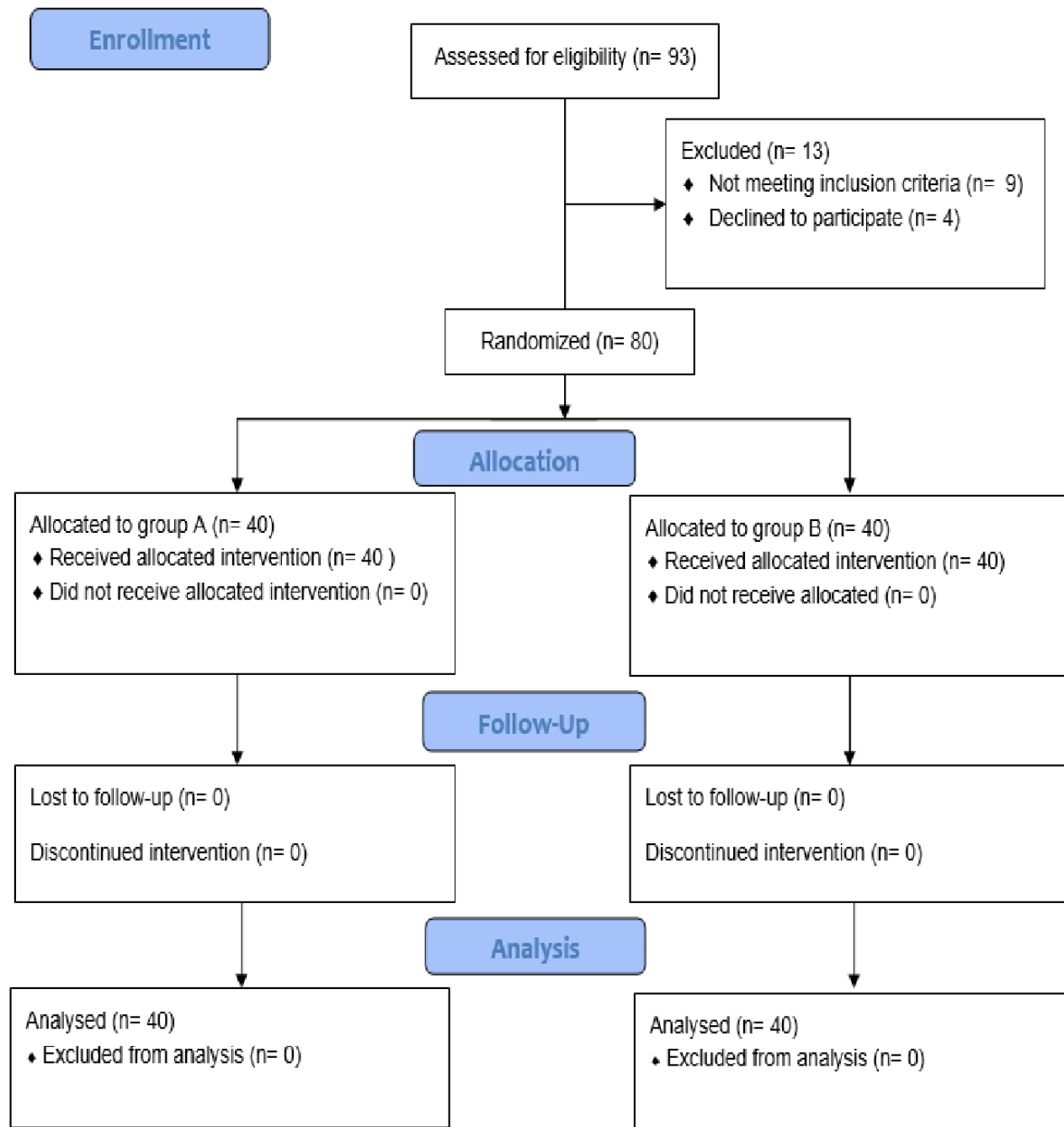


Figure 1

Flow diagram showing patient enrolment and analysis.

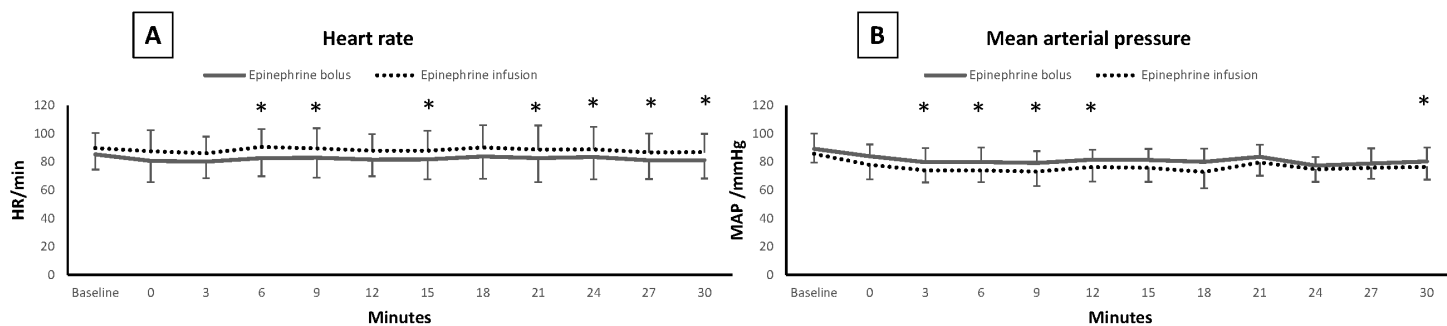


Figure 2

Intraoperative hemodynamics in both groups. A: heart rate (HR), B: mean arterial pressure (MAP), * Denotes significance between the two groups.

Supplementary Files

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- [CONSORT2010Checklist1.doc](#)