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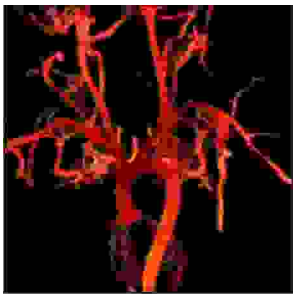

EPHEDRINE FOR PREVENTION HYPOTENSION;

COMPARISON BETWEEN INTRAVENOUS, INTRAMUSCULAR AND ORAL ADMINISTRATION DURING SPINAL ANESTHESIA FOR ELECTIVE CESAREAN SECTION

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ABSTRACT... hameedchohedri@yahoo.com. **Background/Aim:.** To ameliorate post spinal anesthesia hypotension in patients undergoing cesarean section. To compare the incidence of maternal hypotension associated with spinal anesthesia for cesarean section when intravenous (IV), intramuscular (IM) or oral prophylactic boluses of ephedrine were used. **Design:** Prospective randomized double blind study. **Setting:** Department of anesthesiology, Zainibiae Hospital, Shiraz University, Iran. **Period:** From: June 2004 to November 2005. **Materials and Methods**: 60 ASA grade I-II pregnant mothers were enrolled. Spinal anesthesia was performed using 60-70 mg of 5% solution of lidocaine. The patients were divided into three equal groups (n=20). Oral and IM ephedrine (25 mg) was administered to the first two groups 30 to 60 minutes before induction of anesthesia (Group A and B, respectively). In the last 20 patients, IV Ephedrine (25 mg) was administered immediately after induction of spinal anesthesia (Group C). Maternal blood pressure and pulse rate was checked every 2 minutes. Hypotension was promptly treated with 10-mg ephedrine boluses. **Results**: Both IM and IV prophylactic doses of ephedrine significantly decreased the incidence of hypotension, compared to oral prophylactic dose of ephedrine [4/20 and 0/20 in the IM and IV ephedrine groups, respectively vs. 9/20 in the oral ephedrine group ($p < 0.05$)]. **Conclusion**: Oral prophylactic dose of ephedrine is not effective in preventing hypotension in pregnant women undergoing cesarean section with spinal anesthesia. Therefore, we only recommend a single bolus of IV ephedrine with a dose of 25mg.

Key words: Spinal Anesthesia; Ephedrine; Hypotension; Obstetrical; Cesarean Section; Route of Administration

INTRODUCTION

The incidence of hypotension during spinal anesthesia for cesarean section is reported to be as high as 80%, despite fluid preload, and use of vasopressors[1].

Hypotension following spinal anesthesia for cesarean section may result in maternal nausea and vomiting and decreased uteroplacental blood flow with possible fetal acidemia[2]. Numerous methods have been tried to minimize hypotension. For example, prophylactic administration of ephedrine has been advocated to avoid hypotension associated with spinal anesthesia for cesarean section[1].

The appropriate route and dose of ephedrine that should be used to prevent spinal associated hypotension during cesarean section still remains controversial. Simon et al showed that a singlebolus of IV ephedrine with doses of either 15 or 20 mg decreased significantly the incidence of maternal hypotension associated with spinal anesthesia for cesarean section[3]. Kee et al reported that the lowest effective dose of ephedrine to reduce the incidence of hypotension was 30 mg[4]. Some authors recommend intravenous bolus injection, some intravenous continuous infusion and some recommend intramuscular route[1,5,6]. However, to our knowledge there has not been any study administering oral ephedrine. Neither has there been any study comparing these different routes of administration.

We designed this prospective study to evaluate the efficiency of three prophylactic route of administration of ephedrine, IV, IM and oral.

MATERIALS AND METHODS

In a prospective randomized double-blind clinical trial, from June 2004 to November 2005, 60 ASA grade I-II ambulatory pregnant mothers in whom elective cesarean section with spinal anesthesia was planned for them enrolled in this study. The study was conducted in educational hospitals of Shiraz University of Medical Sciences enrolled. A written informed consent was obtained from each patient and Shiraz University of Medical Sciences Research Committee had approved the study. None of the mothers' fetus had fetal distress. The mothers were randomly divided into three equal groups of 20. A 16-gauge IV cannula was inserted into a peripheral vein and a 20 mL/kg preload of Ringer's lactate solution was given to all patients.

The women were placed in the sitting position and a 23-gauge pencil point needle (Pencan™, Braun, Melsungen, Germany) was inserted at the L3-L4 or L4-L5 space. Five mL of a solution containing 60 mg lidocaine 5% was injected intrathecally, with the needle hole directed cephalad. If the woman's height was more than 160 cm then 70 mg of lidocaine 5% was injected. All women were positioned in the sitting position during the injection time and then immediately transferred to the left 15˚ lateral tilt. Heart rate, blood pressure (BP) [systolic (SBP), mean (MAP), and diastolic (DBP)], and oxygen saturation via pulse oximetry (SpO2) were recorded in the modified supine position with at least 15˚ of left lateral tilt. These parameters were recorded during fluid preloading 30, 15, 10, and 5 minutes before the dural puncture, and repeated every 2 minutes for 30 minutes after the end of the injection. Hypotension was defined as a decrease of 30% or more below baseline BP value or SBP below 100 mm Hg. Hypertension and tachycardia were defined as an increase of 30% from baseline in SBP and HR.

The first 20 mothers received 25 mg of ephedrine, orally administered, 60 minutes before the spinal anesthesia induction (Group A). Group B (n = 20) received intramuscular injection of 25 mg of ephedrine, 30 minutes before induction and group C received 25 mg of ephedrine in 2-mL IV bolus injected over a 1-minute period. In all groups, hypotension was treated immediately with 10 -mg ephedrine IV bolus increments every minute until SBP returned to normal values (> 100 mmHg and > 70% of baseline value). The volume of Ringer's lactate solution and the total dose requirements of ephedrine administered were recorded. Apgar scores were determined at 1 minute by a pediatrician. The primary endpoints of this study were maternal hypotension and ephedrine requirements. All data were analyzed and computed by SPSS (Chicago, IL) software, version 10.0, and Microsoft EXCEL (Microsoft, Redmond, WA) software. Data are expressed as mean ± standard deviation (SD) and 95% confidence interval (CI) are also given when essential. The association between variables was assessed with Student's t-test; Fisher's exact, χ^2 test and Mann Whitney U-test when

appropriate. p values less than 0.05 were considered statistically significant.

RESULTS

Twenty patients were studied in each group. Maternal demographic and clinical data were similar in the three groups (Table I). Median level of block, mean spinal injection to delivery time, mean uterine incision to delivery time and total intravenous fluid administered before delivery was the same in the three groups (Table II). Preoperative mean systolic pressures were similar between groups. These pressures decreased significantly in all three groups within 5 minutes after spinal anesthesia was administered ($p < 0.005$). The incidence of hypotension was 45% (9 patients) in the oral ephedrine group, 20% (3 patients) in the IM group and 0% in the IV ephedrine group. This occurred most frequently at 5 min in the oral group but at 15 min in the IM ephedrine group. The incidence of hypotension was significantly lower in the IV ephedrine group compared with the oral and IM groups ($p < 0.05$). No patients developed hypertension (MAP > 25% increase from the baseline blood pressure). Figure 1 shows the mean±SD of decrease in the MAP. The greatest drop in mean systolic pressure was 25.4±18.2 mm Hg, observed in group A, who received oral ephedrine and occurred at 5 min after spinal anesthesia while that in the IM group was 6.25±16.3 mm Hg which occurred at 15 min.

Table-I. Demographic characteristics (age, weight, height and parity) and hemodynamic data (Mean arterial pressure and heart rate) of 60 patients enrolled in the study. MAP = mean arterial pressure. NS: not significant; *p* > 0.05. IDT = Induction delivery time. Data are shown as n (SD).

	Oral therapy (n=20)	IM Therapy (n=20)	IV Therapy (n=20)	P value
Age (years)	27.6±7.7	26.9±6.4	27.65±7.4	NS
Weight (Kg)	821±12.2	83.2±13.2	81.9±13.3	NS
Height (cm)	159.7±4.5	160.4±5.5	159.5±5.5	NS
Parity	2(0-5)	1 (0-6)	2 (0-6)	NS
IDT (min)	20.8 ±4.1	22.3±4.1	20.7±3.5	NS
Baseline MAP (mm Hg)	85.5 (9.5)	81.5(10.4)	89.4(13.3)	NS
Baseline heart rate	101.1 (14.1)	105.2(13.2)	102.4(15.3)	NS
ASA grade I/II	15/5	16/4	16/4	NS
NS: Not significant				

Table-II. Baseline and Decrease in mean arterial blood pressure in the three groups after induction of spinal anesthesia. Oral Eph: Oral ephedrine group; IM Eph: IM Ephedrine group; IV Eph: IV ephedrine group

	Oral Ep	IM Eph	IV Eph	P value
Baseline blood pressure (mm Hg)	85.5±10	81.5±11	89.4±13	NS
Decrease rate at 5 min post induction	25±18	6.5±18	6.5±18	<0.05
Decrease rate at 10 min post induction	6±22	6±17	1.7±12	NS
NS: Not significant				

Fig-1. Systolic blood pressure variations in the three groups from 30 minutes before induction of spinal anesthesia up to 60 minutes after induction.

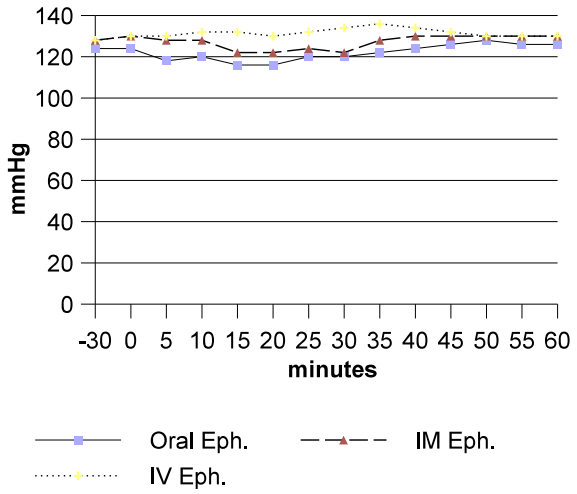
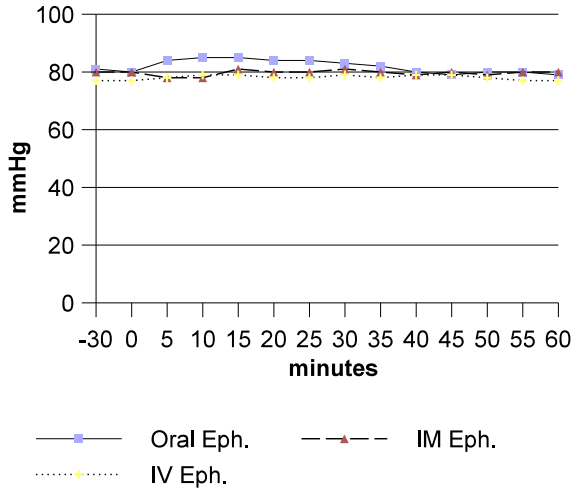


Figure 2. Pulse rate variations in the three groups from 30 minutes before induction of spinal anesthesia up to 60 minutes after induction.



Patients in the IV and IM group maintained higher blood pressure compared to the oral group ($p < 0.05$). Fig. 2 shows that a significant difference in heart rate existed between IV and IM or oral groups only at 10 and 15 min then remained similar for the rest of the study. The incidence other than side effects of hypotension was similar in the two groups of oral and IM ephedrine. Nausea occurred in four hypotensive patients in group 1(20%) and three in group (15%), while none of the patients in group 3 developed nausea. Neonatal status at delivery did not differ between groups (Table III). There was no difference in Apgar scores between groups at 1 or 5 min.

Table-III. Neonatal Apgar scores as mean ± SD. No statistically significant different existed between the three groups. Oral Eph: Oral ephedrine group; IM Eph: IM Ephedrine group; IV Eph: IV ephedrine group

	Oral Ep	IM Eph	IV Eph
Apgar Score (1 min)	8.6±1.6	8.4±1.6	8.8±1.3
Apgar Score (5 min)	10	10	10

DISCUSSION

This is the first report to our knowledge that oral ephedrine 25 mg has been given pre-emptively at induction of spinal anesthesia for Cesarean section in order to reduce the incidence of hypotension. In this study, oral ephedrine has been compared with IM and IV route of administration. Oral route of administering drugs is the most safest and cost effective method. Unfortunately, we didn't obtain satisfactory results to recommend oral adnisitration of ephedrine and oral ephedrine could not significantly reduce the incidence of hypotension.

The prevention and treatment of maternal hypotension associated with spinal anesthesia for cesarean section remains a difficult problem. The ideal prophylactic sympathomimetic drug has not been identified, but ephedrine seems to be the most commonly used[7]. Phenylephrine has been investigated and has showed to have equivalent efficacy to ephedrine in preventing hypotension after spinal anesthesia for Caesarean section[9]. Angiotensin II has been successfully used in prevention of maternal hypotension[10]. It is accompanied with higher mean fetal umbilical artery blood pH and less

fetal acidosis than patients who had received ephedrine[11]. Ramin et al concluded that in the healthy term fetus there was an advantage in using angiotensin II to maintain maternal blood pressure during regional anesthesia[11].

In the present study we investigated the effect of ephedrine, given before the onset of hypotension, and observed that in the IM and IV form it has therapeutic effect. Desalu and Kushimo compared standard infusion of ephedrine 30 mg IV, with traditional prehydration in preventing spinal hypotension in sixty patients for elective caesarean section. They concluded that prophylactic ephedrine given by standard infusion set was more effective than crystalloid prehydration in the prevention of hypotension during spinal anesthesia for elective caesarean section[1]. Previous studies have revealed that the best way of administering ephedrine is by infusion pump and that this be started during spinal anesthesia and maintained at least at 2 mg/min[8]. Desalu and Kushimo administered ephedrine by a carefully controlled standard IV infusion set as facilities for use of an infusion pump were not available for them[1].

Similarly in our setting infusion pump are less uniformly available therefore we used single bolus injection. We obtained similar results with centers in which ephedrine had been injected using infusion pump or controlled IV infusion. Desalu and Kushimo who used controlled standard infusion administered mean rescue dose of 9 mg of ephedrine. Chan *et al* used prophylactic ephedrine using an infusion pump at a dose of 0.25 mg/kg and required a mean rescue bolus dose of 14 mg to treat hypotension[12]. In our study, despite the use of a bolus IV injection we required a smaller mean rescue dose of ephedrine (5 mg) to treat our patients in the IV ephedrine group. However, in the IM ephedrine group mean rescue dose was 15 mg. We didn't observe no hypertension or other side effects of ephedrine.

Ephedrine is popularly given by the IV route which is simple and cheap. In our study, we investigated whether bolus IV administration of ephedrine would be simpler and cheaper in our environment. Our results showed that IV bolus ephedrine has comparable results to infusion pump or standard continuous IV injection and so we recommend it in centers with limitation in infusion pump.

Ephedrine has been administered through Intramuscular route. Webb and Shipton assessed the safety and efficacy of 37.5 mg ephedrine IM in preventing hypotension associated with spinal anesthesia for Caesarean section[6]. They concluded that 37.5 mg ephedrine IM prior to spinal anesthesia was not associated with reactive hypertension or tachycardia and that IM ephedrine provides more sustained cardiovascular support than intravenous ephedrine[6]. In our study, we observed more hypotensive patients in the IM group when compared to the IV group. This may be due to the lower dose of ephedrine (25 mg) that we administered to our patients.

The best dose of ephedrine in which the best effect is obtained along with minimum side effect and complication has been studied previously. Simon et al showed that a single bolus of IV ephedrine with doses of either 15 or 20 mg decreased significantly the incidence of maternal hypotension associated with spinal anesthesia for cesarean section[3]. In a recent study, Kee et al. found that the lowest effective dose of ephedrine to reduce the incidence of hypotension was 30 mg[4]. However, Kee et al reported that 45% of the patients developed reactive hypertension[4]. Ephedrine may cause tachycardia and hypertension in the mother and has also been suggested to cause fetal acidemia and electroencephalographic (EEG) abnormalities in the newborns. In a study performed by Lee *et al* all available studies on IV prophylactic ephedrine administration was systematically reviewed in order to determine the dose-response characteristics of prophylactic IV ephedrine for the prevention of hypotension during spinal anesthesia for cesarean delivery[13]. In this dose respond meta-analysis they concluded that prophylactic ephedrine cannot be recommended. They observed that the efficacy of ephedrine was poor at smaller doses (14 mg or less), whereas at larger doses (30 mg or more), the likelihood of causing hypertension is actually more than that of preventing hypotension[13]. The dose we used in

our study (25 mg) was an average of different studies and our results show that it is a safe and effective dose, sufficient to prevent hypotension, and cause no side effects of nausea, vomiting or hypertension.

Nausea and vomiting, which are the most frequent side effects of maternal hypotension, occurred in the oral and IM ephedrine group. They promptly resolved by restoration of maternal blood pressure.

In conclusion, we observed that IV bolus infusion of ephedrine is an effective method of administering ephedrine and can be used in setting were infusion pump is not available. Additionally, we observed that oral route of administering ephedrine can not be recommended.

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