PROPHYLACTIC PHENYLEPHRINE INFUSION VERSUS RESCUE BOLUSES: EFFECT ON THE PHYSICIAN INTERVENTION AND FLUID ADMINISTRATION

Saira Mahboob, Ahmed Mujadid Burki

Combined Military Hospital/ National University of Medical Sciences (NUMS) Rawalpindi Pakistan

ABSTRACT

Objective: To compare the effect of prophylactic phenylephrine infusion on the fluid management and physician intervention as compared with rescue boluses of phenylephrine alone.

Study Design: Randomized controlled trial.

Place and Duration of Study: Anesthesiology department, Combined Military Hospital, Rawalpindi; from Feb to Jul 2016.

Material and Methods: A total of 70 patients were randomly divided into two groups, 35 in each. After a preload of 10ml/kg of ringer lactate; spinal anesthesia was given with 12 mg 0.75% hyperbaric bupivacaine. Group A given prophylactic phenylephrine infusion at the rate of 0.75ug/kg/minute for 5minutes after initiation of spinal anesthesia. Group B was given 50ug rescue bolus of phenylephrine when hypotension occurred.

Results: The two groups did not differ in their demographic profile and mean fluid pre-load. The mean preload was 691.4ml (±110.1) in group A versus 721.4ml (±89.3) in group B, *p*-value 0.215. The total fluid administered in group A was lower than group B, 1634.2ml (±232.5) versus 1777.1 ml (±328.1); *p*-value 0.039. An average of 0.23 (±0.49) number of physician interventions were done in hypotensive patients in group A versus 1.26 (±1.29 in group B; *p*-value 0.06, which is statistically insignificant. The groupA received a much higher dose of phenylephrine, mean dose 287.2ug ± 48.8 versus 64.2ug ± 64.8; *p* value<0.001. The mean rescue phenylephrine bolus dose in group A was 15.7ug (±31.5) in group A versus 64.2 ± 64.8ug, *p*-value<0.001; which is statistically insignificant.

Conclusion: Prophylactic phenylephrine infusion with crystalloid preload was found associated with reduced number of rescue boluses and rescue phenylephrine dose and lesser total intraoperative fluid administration, when compared to preload with rescue boluses.

Keywords: Elective cesarean section, Fluid preload, Prophylactic phenylephrine infusion, Rescue boluses, Spinal anesthesia.

INTRODUCTION

Maternal hypotension is one of the most common complication of spinal anesthesia for cesarean section. The incidence is as high as 70-80% when pharmacological prophylaxis is not used[1]. Various techniques have been used for prevention and treatment of hypotension. These include IV crystalloid and colloid fluid pre-load and co-load, lateral uterine displacement, gravity (Trendelenburg or leg raising), compression devices on the legs and prophylactic vasopressors[2]. No single method has been shown to completely prevent maternal hypotension. Jacob *et al* showed that the incidence of hypotension (60 versus 46%, *p*-value 0.1607) was similar whether crystalloid preload or co-load was done[3]. Recent research has shown that phenylephrine is as effective as ephedrine in prevention of maternal hypotension, nausea and vomiting and it is associated with higher umbilical blood pH with no difference in APGAR scores or neonatal outcome[4-6]. Prophylactic phenylephrine given as infusion provides better hemodynamic stability than rescue boluses. In normal pregnancy, the overall venous tone is low and spinal anesthesia further reduces venous tone, often unmasking the effects of caval compression, by blocking the compensatory sympathetic response. Increasing the venous

Correspondence: Dr Ahmed Mujadid Burki, Classified Anaesthetist, Combined Military Hospital Rawalpindi Pakistan
Email:ahmedburki@yahoo.com
Received: 25 Feb 2018; revised received: 06 Apr 2018; accepted: 09 Apr 2018

tone with an alphaagonist can be effective at countering the effects of spinal anesthesia and caval compression. Alkaissi *et al* reported lower number of patients that required rescue boluses when preventative phenylephrine was used as compared to ephedrine. However, the total fluid given, total blood loss and anesthesia were comparable in both groups[7]. According to the authors' knowledge, limited data is available on the intraoperative fluid therapy, the dose administered for effectively preventing maternal hypotension or the number of rescue boluses required when prophylactic phenylephrine infusion is used. The aim of our study was to compare the effect of prophylactic phenylephrine infusion and rescue boluses on the fluid management, rescue bolus and physician intervention to maintain hemodynamic stability.

MATERIAL AND METHODS

This randomized controlled trial was conducted at Anesthesiology department, Combined Military Hospital, Rawalpindi from Feb to Jul 2016. WHO sample size calculator was used to calculate a sample size of 70 (n=35 in each group) with power of test 80% and level of significance 5%. The anticipated population proportion was 20% and 90% hypotension in the two groups[8]. The patients were divided into two equal groups (n=35 in each group) randomly by battery method. After the approval of hospital ethical committee, the preanesthesia assessment was done as per institute protocol. Patients with American Society of Anesthesiology physical status I, II, age 18-35 years with full term, singleton pregnancy undergoing elective lower segment cesarean delivery were included in our study by non-probability, consecutive sampling. Patients with pre-existing or pregnancy induced hypertension, gestational or pre-existing diabetes mellitus, cardio respiratory or peripheral vascular disease; and any contraindication to spinal anesthesia were excluded from the study. On the day of surgery, 18 G intravenous cannula was inserted. All the patients were premedicated with intravenous metoclopramide 10mg and dexamethasone 8mg. Patient were preload with 10ml/kg Ringers lactate over 20 minutes, and same fluid was used for maintenance during surgery. Under complete aseptic measures, spinal anesthesia was initiated with 12 mg bupivacaine (0.75% hyperbaric) was given by using 25 G Quincke needle at L3-4 level. Surgery was allowed when sensory block level of T4 was achieved and at least 10 minutes after initiation of subarachnoid block. If spinal block failed completely general anesthesia or reinjection were offered and patient were excluded from study and more females were included to complete the sample size. Group A received phenylephrine infusion at 0.75ug/kg/min for five minutes once intrathecal bupivacaine was given; whereas group B received phenylephrine rescue boluses if maternal hypotension occurred. The infusion was made in syringe pump with a strength of 50microgram/ml and weight dependent dose was calculated according to measured weight in kilograms. The number of physician interventions was recorded; 50microgram phenylephrine rescue bolus in case of maternal hypotension (maternal systolic blood pressure less than 100 mm Hg). The fluid given as preload and total intraoperative fluid were also recorded.

All collected data was analyzed using SPSS version 25. Descriptive statistics were calculated for both quantitative and qualitative variables. Mean and standard deviation were calculated for quantitative variables like age, weight, fluid administered. Independent t-test was used for normal quantitative values (pre-load, total fluid and weight) and Mann Whitney U test for non-normal quantitative values (number of bolus, bolus dose and total phenylephrine dose). Chi square test and Fisher's exact test to compare the qualitative values (ASA status) between the two groups. A *p*-value of less than or equal to 0.05 was considered as statistically significant.

RESULTS

A total of 70 parturient were included in my study. The demographic profile is tabulated as table. The mean preload was 691.4ml (±110.1) in group A versus 721.4ml (±89.3) in group B,

p-value 0.215. The total fluid administered in group A was lower than group B, 1634.2ml (±232.5) versus 1777.1 ml (±328.1); *p*-value 0.039. An average of 0.23 (±0.49) number of physician interventions were done in hypotensive patients in group A versus 1.26 (±1.29 in group B; *p*-value 0.06, which is statistically insignificant. The group A received a much higher dose of phenylephrine, mean dose 287.2ug ± 48.8 versus 64.2ug ± 64.8; *p*-value<0.001. The mean rescue phenylephrine bolus dose in group A was 15.7ug (±31.5) in group A versus 64.2 ± 64.8 ug, *p*-value<0.001; which is statistically significant.

DISCUSSION

Prophylactic phenylephrine has been shown to reduce the incidence of maternal hypotension by various authors[8-11]. It is considered as vasopressor of choice by many obstetric anesthetists. Phenylephrine infusion has been shown to maintain the blood pressure near the baseline without potentially harmful extremes of hypotension or hypertension that may be associated with phenylephrine boluses. According to the authors' knowledge, limited data is available regarding the effect of phenylephrine infusion on the physician intervention. In our study, the prophylactic phenylephrine infusion was associated with reduced number of rescue bolus number as well as rescue dose; total fluid administered intraoperatively as compared to phenylephrine rescue boluses alone. Sayyid *et al* compared variable rate phenylephrine infusion with rescue boluses with crystalloid co-load. They reported a reduced number of physician intervention in the infusion group, median 0 vs 3 in either group; difference in median=3, 95% confidence interval. They also reported the number to treat was 1.4 women to prevent hypotension[8]. A study by Allen *et al* reported reduction in the number of physician intervention when 25 and 50 microgram/ minutes were compared with 100 microgram/ minutes infusion *p*=0.004 and *p*=0.02 respectively. However, there was no difference in number of physician intervention when the prophylactic infusion was compared with placebo[13]. Although the number of physician interventions required to maintain maternal hemodynamics may not matter in institute with 1:1 anesthetist to patient ratio or where the obstetric workload is comparatively light. Our institute caters to ten surgical specialties, including obstetrics with upto 150 cases in 18 operation theaters every day. When the physician intervention are reduced in addition to providing better hemodynamics, the workload on the anesthetist may be reduced with improved patient care. We studied a weight based infusion which may not always be the most appropriate dose for all the hospital. Further study is required to prove the safety of fixed dose, weight independent prophylactic phenylephrine infusion and the optimal dose in Asian population. According to authors knowledge, no single method has been shown to completely prevent maternal hypotension. Some studies have shown superiority of colloids over crystalloids[2,4,14]. Intravenous crystalloid combination with vasopressor has been shown to reduce the frequency of maternal hypotension[15,16]. A study by Loubert *et al* reported the minimum effective fluid volume of hydroxyethyl starch to be 733ml (95% CI, 388-917ml) for prevention of maternal hypotension in 50% of the parturient[17]. Limited research has been done regarding the fluid administered intraoperatively when phenylephrine prophylactic infusion is used. Ngan *et al* studied a combination of phenylephrine infusion with crystalloid co-

Table: Demographic profile of study population.

	Group-A (n=35)	Group-B (n=35)	*p*-value
	Mean ± SD	Mean ± SD	
Age (years)	27.2 ± 3.43	28.7 ± 3.33	0.09
ASA I	n=30 (85.7%)	n=34 (97.1%)	0.198
Weight (kg)	73.6 ± 7.24	74.8 ± 11.4	0.605

hydration. They infused phenylephrine infusion at 100ug/minute with one group receiving maintenance dose of crystalloid versus high flow of crystalloid. They reported a much higher crystalloid infusion rate in second group; 63.5ml/minute versus 1.7ml/minutes, *p*-value <0.0001[15,10]. In our study the fluid was given as weight calculated preload over 20 minutes. The preload given was comparable, whereas the total intraoperative fluid was significantly lower in prophylactic phenylephrine group. In healthy parturient, the total fluid administration may not make a difference in their outcome; however, patients with limited cardiac reserve may be better managed with fluid restriction. The safety of phenylephrine infusion has not been proven in parturient suffering from cardiovascular disease and its use is not recommended at present. In our study, the total phenylephrine given as rescue bolus was significantly higher in the prophylactic infusion group. Similar results have been reported by Doherty *et al* who reported increased phenylephrine administration in infusion group; 1740 versus 964 microgram in bolus group, *p*-value <0.001[18]. They had used a much higher infusion rate of 120ug/min post initiation of spinal anesthesia versus 0.75ug/kg/min for 05 minutes in our study. Ngan *et al* also reported a higher dose of 1260microgram in infusion group versus 450ug in rescue bolus group. They used an infusion of 100ug/min for 03 minutes after spinal anesthesia and bolus of 100ug; while we used a prophylactic infusion for 5 mintues and rescue bolus of 50 ug. We have safely given a prophylactic phenylephrine infusion in our study with reduced number of physician interventions required to maintain hemodynamic stability.

CONCLUSION

Prophylactic phenylephrine infusion with crystalloid preload was found associated with reduced number of rescue boluses and rescue phenylephrine dose and lesser total intra-operative fluid administration, when compared to preload with rescue boluses. The weight based phenylephrine infusion can be safely given for prevention of maternal hypotension during cesarean section under spinal anesthesia. It can not only improve patient outcome by improving hemodynamics but also reduces anesthetist workload.

CONFLICT OF INTEREST

This study has no conflict of interest to declare by any author.

REFERENCES

1. Mercier FJ, Augè M, Hoffmann C, Fischer C, Le Gouez A. Maternal hypotension during spinal anesthesia for caesarean delivery. Minerva Anestesiol 2013; 79: 62-73.
2. Cyna AM, Andrew M, Effect RS, Middleton P, Simmons SW. Techniques for preventing hypotension during spinal anesthesia for caesarean section. Cochrane Database Syst Rev 2006; (4): CD002251.
3. Jacob JJ, Williams A, Verghese M, Afzal L. Crystalloid preload versus crystalloid coload for parturients undergoing cesarean section under spinal anesthesia. J Obstet Anaesth Crit Care 2012; 2: 10-5
4. Lin FQ, Qui MT, ding XX, Fu Sk, Li Q. ephedrine versus phenylephrine for the management of hypotension during spinal anesthesia for cesarean section: an updated meta-analysis. CNS Neurosci Ther 2012; 18(7): 591-7.
5. Afshari A, Moller AM, Hangaard N. Comparison of prophylactic infusion of ephedrine and phenylephrine during caesarean section under spinal anesthesia. Ugeskr Laeger 2006; 168: 1428-31.
6. Loubert C. Fluid and vasopressor management for Cesarean delivery under spinal anesthesia: continuing professional development. Can J Anaesth 2012; 59: 604-19.
7. Alkaissi A, Ussbah Q, Al-Bargouthi A. Prophylactic Ephedrine Versus Phenylephrine for Maternal Hypotension in Women Undergoing Spinal Anesthesia for Caesarean Section-A Randomized Double Blind Clinical Trial. J Biomedical Sci 2017; 6: 1-6.
8. Sahar M SiddikSayyid, Taha SK, Kanazi GE, Aouad MT. A randomized controlled trail of variable rate phenylephrine infusion with rescue boluses versus rescue boluses alone on physician interventions during spinal anesthesia for elective cesarean delivery. Anesth Analg 2014; 118(3): 611-8.
9. Neves JF, Monterio GA, Almeida JR, Anna RS, Bonin HB, Macedo CF. Phenylephrine for blood pressure control in elective cesarean section. Therapeutic versus prophylactic dose. Rev Bras Anestehsiol 2010; 60: 391-8.
10. Ngan Kee WD, Khaw KS, Ng FF, Lee BB. Prophyalctic Phenylephrine infusion for preventing hypotension during spinal anesthesia for cesarean delivery. Anesth Anlg 2004; 98(3): 815-21.
11. Stewart A, Fernando R, McDonald S, Hignett R, Jones T, Columb M. The dose-dependent effects of phenylephrine for elective cesarean delivery under spinal anesthesia. Anesth Analg 2010; 111: 1230-7.
12. Ngan Kee, warwick d. Phenylephrine infusion for maintaining blood pressure during spinal anesthesia for cesarean delivery: finding the shoe that fits. Anesth Analg 2014; 118(3): 496-8.
13. Allen TK, White WD, George RB, Habib A. A Double-Blind, Placebo-Controlled Trial of Four Fixed Rate Infusion Regimens of Phenylephrine for Hemodynamic Support during Spinal

Anesthesia for Cesarean Delivery. Anesthesia and analgesia 2010; 1111: 221-9.
14. Bottiger BA, Bezinover DS, Mets B, Dalal PG, Prozesky J, Ural S, et al. Phenylephrine infusion for spinal induced hypotension in elective delivery: does pre-load make a difference? J Anaestehsiol. Clin Pharmacol 2016; 32(3): 319-24.
15. Lee A, Ngan Kee WD, Gin T: Prophylactic ephedrine prevents hypotension during spinal anesthesia for cesarean delivery but does not improve neonatal outcome: A quantitative systematic review. Can J Anesth 2002; 49: 588–99.
16. Ngan Kee WD, Khaw KS, Ng FF. Prevention of hypotension during spinal anesthesia for cesarean delivery: an effective technique using combination phenylephrine infusion and crystalloid cohydration. Anesthesiology 2005; 103: 744-50.
17. Loubert C, Gagnon PO, Fernando R. Minimum effective fluid volume of colloid to prevent hypotension during cesarean section under spinal anesthesia using a prophylactic phenylephrine infusion; an up-down sequential allocation study. J Clin Anesth 2017; 36: 194-200.
18. Doherty A, Ohashi Y, Downey K, Carvelho JC. Phenylephrine infusion versus bolus regimens during cesarean delivery under spinal anesthesia: A double blind randomized clinical trial to assess hemodynamic changes. Anesth Analg 2012; 115(6): 1343-50.