Comparison of the effect of intravenous epinephrine and ephedrine in the management of hypotension and bradycardia during cesarean section under spinal anesthesia in Kamali Hospital, Karaj

Comparación del efecto de la epinefrina intravenosa y la efedrina en el tratamiento de la hipotensión y la bradicardia durante la cesárea bajo anestesia espinal en el Hospital Kamali, Karaj

Fatemeh Moradi[1], Seyyed Mohsen Pouryaghobi[2], Mehdi Rezaee[3], Fatemeh Bayat[4], Maryam Hashem Nejad[5], Alireza Montaseri[6], Banafsheh Mashak[7*]

[1]General practitioner from Alborz University of Medical Sciences, Karaj, Iran,
[2]Department of Anesthesiology, Alborz University of Medical Sciences, Karaj, Iran,
[3]Assistant professor of anesthesiology, school of medicine, Alborz university od medical sciences, Karaj, Iran
[4]Department of Anesthesiology, Alborz University of Medical Sciences, Karaj, Iran,
[5]Assistant Professor of Obstetrics and Gynecology, Department of Obstetrics and Gynecology, School of Medicine, Alborz University of Medical Sciences, Karaj, Iran,
[6]Department of Anesthesiology and Intensive Care, Shahid Madani Hospital, Alborz University of Medical Sciences, Alborz, Iran,
[7]Assistant Professor of Anesthesiology, School of Medicine, Alborz University of Medical Sciences, Karaj, Iran,
[*]Corresponding Author: Banafsheh Mashak, Assistant Professor of Anesthesiology, School of Medicine, Alborz University of Medical Sciences, Karaj, Iran. EMAIL: Mashakbanafsheh@yahoo.com
Received/Recibido: 12/28/2020 Accepted/Aceptado: 01/15/2021 Published/Publicado: 03/10/2021 DOI: http://doi.org/10.5281/zenodo.4710978

Abstract

Introduction: hypotension and bradycardia are two underlying and almost common complications caused by spinal anesthesia in cases of elective cesarean section (CS). Suitable treatment of the complications is particularly important to improve the conditions of patients. Hence, the aim of this study is to compare the effect of intravenous administration of epinephrine and ephedrine in the management of hypotension and bradycardia caused by CS spinal anesthesia.

Method: the study was done as a random clinical trial on 126 women under spinal anesthesia for elective CS, hospitalized in Kamali Hospital, Karaj in 2020-21. The statistical samples were classified into two ephedrine and epinephrine. Patients systolic blood pressure, diastolic blood pressure, heart rate and Apgar and VBG of the newborn were analyzed in two study groups.

Results: The results showed that the mean value of diastolic blood pressure, which was the same in the two groups at the beginning, was significantly increased in the ephedrine group compared to the epinephrine group from minute eight. Mean systolic blood pressure, which was the same in the two groups at the beginning, was significantly increased in the ephedrine group compared to the epinephrine group in minutes 8-16. However, they showed no significant difference in the rest of the evaluations. The mean value of heart rate that was the same between the two groups at the beginning was significantly increased in the ephedrine group in minutes 10, 25, 35, and 45; although the two groups showed no significant difference in other times assessed. The mean value of PCO2 and HCO3 showed a significant difference between the two groups, and both were higher in the ephedrine group.

Conclusion: Our results indicate that intravenous ephedrine compared to intravenous epinephrine produces a higher increasing the values blood pressure and heart rate in the management of hypotension and bradycardia caused by spinal anesthesia in the cases of elective cesarean section.

Keywords: epinephrine, ephedrine, hypotension, bradycardia, spinal anesthesia, elective cesarean section (CS).

Resumen

Introducción: la hipotensión y la bradicardia son dos complicaciones subyacentes y casi frecuentes provocadas por la raquianestesia en los casos de cesárea electiva (SC). El tratamiento adecuado de las complicaciones es muy importante para mejorar las condiciones de los pacientes. Por lo tanto, el objetivo de este estudio es comparar el efecto de la administración intravenosa de epinefrina y efedrina en el manejo de la hipotensión y bradicardia causadas por la anestesia espinal con CS.

Método: el estudio se realizó como un ensayo clínico aleatorio en 126 mujeres bajo anestesia espinal para cesárea electiva, hospitalizadas en el Hospital Kamali, Karaj en 2020-21. Las muestras estadísticas se clasificaron en dos efedrina y epinefrina. Se analizaron la presión arterial sistólica, la presión arterial diastólica, la frecuencia cardíaca de las pacientes y el Apgar y VBG del recién nacido en dos grupos de estudio.

Resultados: Los resultados mostraron que la media de la presión arterial diastólica, que fue igual al inicio en los dos grupos primero, aumentó significativamente en el grupo de efedrina en comparación con el grupo de epinefrina desde el minuto ocho. La presión arterial sistólica media, que fue la misma en los dos grupos primero al inicio, aumentó significativamente en el grupo de efedrina en comparación con el grupo de epinefrina en el minuto 8-16. Sin embargo, no mostraron diferencias significativas en el resto de las evaluaciones. El valor medio de la frecuencia cardíaca que fue el mismo entre los dos grupos al inicio y aumentó significativamente en el grupo de efedrina en los minutos 10, 25, 35 y 45; aunque los dos grupos no mostraron diferencias significativas en otros tiempos evaluados. El valor medio de PCO2 y HCO3 mostró una diferencia significativa entre los dos grupos, y ambos fueron más altos en el grupo de efedrina.

Conclusión: nuestros hallazgos indican que la efedrina intravenosa comparada con la epinefrina intravenosa produce incrementos mayores de la presión arterial y frecuencia cardíaca en el manejo de la hipotensión y bradicardia causadas por la raquianestesia en los casos de cesárea electiva.

Palabras clave: epinefrina, efedrina, hipotensión, bradicardia, anestesia espinal, cesárea electiva (CS).

Introduction

Caesarean section is one of the most performed major surgeries in obstetric practice, which now a day is significantly increased compared to last decades. For example, the cesarean rate in America and Australia includes 26.1% of all deliveries[1].

Over the decade, tendencies to use regional anesthesia to do cesarean surgery are increased to reduce the complications of mortality of mothers compared to general anesthesia 2, although such anesthesia can also bring some complications such as hypotension while a surgical operation is the most common complication. The pressure on the Inferior vena cava (IVC) in the pregnant uterus can cause decreased intravenous return and ultimately, hypotension in the mother, which is called sleep-related hypotension syndrome[3]. On the other hand, Spinal anesthesia is the preferred anesthetic method for elective cesarean section in obstetric anesthesia practice. Cesarean sections (C.S.) normally require an anesthetic block at T4 level, so hypotension is reported in up to 80% of spinal anesthesia cases[4].

Other complications caused by spinal anesthesia include headache, nausea and vomiting, urinary retention, postoperative pain, and postoperative shivering[5,6]. As anesthesia in CS is needed to the level of dermatomes T4-T6 and as the majority of roots of sympathetic nerves are inactivated to this level, it is most likely to have hypotension after spinal anesthesia. This is less likely in low-level anesthesia[7]. Although 70 years have passed from the time that four cases of cardiac arrest following undiagnosed hypotension in CS under spinal anesthesia (1930), still no effective method is proposed to meet the problem. Therefore, the ideal vasopressor to reduce the hypotension caused by spinal anesthesia for CS is the subject of this study. The drug should maintain the maternal blood pressure and placental perfusion with the least negative effects on the fetus[8-10].

Ephedrine as a non-catecholamine sympathetic compound, not only has mainly indirect adrenergic receptor activity through the release of norepinephrine, but also exerts weak direct effects, and its sympathomimetic properties, which in turn occur due to its stimulating action on α-, β1-, and β2-adrenergic. This explains the comparatively slow onset and long duration of action. Ephedrine typically increases heart rate and contractility by cardiac β1-adrenergic receptor stimulation. Ephedrine elimination half-life is two and a half hours, and 70-80% of its compound are excreted from the urine with no change. Ephedrine can enhance intravenous blood pressure and has positive (+) inotrope effects. As it never reduces the uterine blood flow, it has been applied in some studies as a vasopressor to treat the hypotension of pregnant women. The stimulating effects of ephedrine on β1 receptor causing increased cardiac output has made the drug a suitable way to treat mid-hypotension, which comes with a heart rate drop. However, there is more evidence showing that ephedrine causes decreased pH in the fetus[11].

However, the mechanism of the action of epinephrine is non-selective stimulation of sympathetic alpha and beta receptors[12,13]. Epinephrine is a sympathomimetic drug, which has high affinity for α1-, β 1- and β2-adrenergic receptors, β2-effects predominate at low doses, while α1-effects are more significant at higher doses. Epinephrine relaxes the bronchus smooth muscles cells through the stimulation of β2-adrenergic receptor and contracts the bronchial arteries through the alpha-adrenergic receptors. As a result, it can eliminate bronchospasm, congestion, and bloating. Epinephrine can affect the alpha-adrenergic receptors of the skin and membranes and causes arterial contraction and ultimately, reduces intake of regional anesthesia drug and increases its

effect. Epinephrine as a cardiac stimulant affects the beta receptors in the heart and causes positive inotropic and chronotropic effects. By this, epinephrine increase cardiac output, increases the myocardia oxygen intake, contractile force, and decreases cardiac adequacy. On the other hand, epinephrine increases blood pressure[14].

In multiple studies, epinephrine has been investigated as a vasopressor to treat hypotension as a result of local anesthesia and spinal anesthesia and its useful effects have been confirmed. Moreover, the long-lasting effect of Lidocaine is due to addition of epinephrine[15,16]. According to the significance of the issue of reducing the complications including bradycardia and hypotension caused by spinal anesthesia in the women under elective CS with its suitable treatment; this study aimed to investigate the effects of intravenous epinephrine and ephedrine for management of hypotension and bradycardia caused by spinal anesthesia of elective CS patients in Kamali Hospital, Karaj in 2020-21.

Materials and method

This study is a double-blind clinical trial. The studied population consists of the CS cases with hypotension and/or bradycardia, who were elective CS cases hospitalized in Kamali Hospital, Karaj in 2020-21. The sample size consisted of 126 people (63 people per group), obtained using G-power software (comparing two mean values in 2 groups) and concerning the type one error, 5% and power of 80% (beta=20%) and equal standard deviation of both groups (SD=2) for the blood pressure of patients. The inclusion criteria were, elective CS candidate, consent to participate in the study, no prohibition for spinal anesthesia, no background of hypertension or cardiovascular disease, lack of allergy to medication, pregnant women in the age range of 20-40 attended in ASA2 class, and gestational age of 36-40 weeks. Exclusion criteria included lack of consent to participate in the study, a contraindication for spinal anesthesia, or blood pressure more than 140/90mm, and diagnosis of placenta diseases. The conscious consent letter was obtained from the patients, and the Ethics Committee of Alborz University of Medical Sciences provided the ethics code and the permission of using intravenous epinephrine and ephedrine. Variables assessed included demographic such as age, education, and body mass index (BMI); and clinical variables included blood pressure, heart rate. In addition, we measured clinical variables such as Apgar, and laboratory variables such as VBG results. Samples were selected using convenience sampling and were divided into two intervention and control groups randomly using randomizing software. The first group received intravenous epinephrine and the second group received intravenous ephedrine. Before beginning the anesthesia process and surgery, the patients were monitored in terms of blood pressure and heart rate. Also, before the infusion of the anesthesia drug, they received 500 cc ringer serum. In sitting position, the anesthesia was applied in L3-L4 or L4-L5 region by spinal needle No. 25 and 15mg hyperbaric Marcain Spinal Heavy anesthesia equivalent to 3cc of 0.5% Marcain in the subarachnoid space by one anesthesiologist and trying once. Patients basal blood pressure and heart rate were measure before anesthesia, and every 2 minutes and up to 20 min, and then every 5 min up to 45min after infusion of an anesthesia drug. The pH ratio and Apgar were also measured for the fetus. In the ephedrine group, after beginning spinal anesthesia, blood pressure dropped more than 20%, and systolic blood pressure was reduced to less than 100 mmHg. 10mg intravenous ephedrine was prescribed until the time that systolic blood pressure of the mother was above 100 mmHg[17]. In the epinephrine group, based on the study conducted in 1997, the blood pressure drop was more than 20% and systolic blood pressure was below 100 mmHg and a 4μg bolus epinephrine was applied until systolic blood pressure of mother reached above 100 mmHg[18].

Data we expressed as mean ± SD, and analyzed using independent t-test, Chi-squared, and Mann Whitney test. Data were considered significant at p<0,05.

Results

According to (Table 1), the mean value and SD of pH (p=0.374) and PO2 (p=0.198) showed no significant statistical difference between the two groups. Mean and SD of PCO2 (p=0.001) between two groups based on independent t-test showed significant statistical difference. Also, the mean and SD of HCO3 (p=0.004) showed significant difference between the two groups based on the Mann-Whitney test, and yet both groups are at a high level in the ephedrine group.

Table 1. Mean and SD of VBG indices in two study groups

Row	Drug	Mean	Std. Deviation	P-Value
PH	Epinephrine Ephedrine	7.33 7.32	0.07 0.05	0.374
PCO_2	Epinephrine Ephedrine	42.74 48.80	8.15 12.11	0.001
HCO_3	Epinephrine Ephedrine	22.43 24.60	3.69 6.89	0.004
PO_2	Epinephrine Ephedrine	28.65 32.54	10.69 18.25	0.198

According to (Table 2), the frequency distribution of Apgar showed no significant difference between the two groups in the first minute based on the Chi-squared test (p=0.204). Besides, Apgar in the fifth minute was ten on ten in all items in two groups.

Table 2. Mean and SD of Apgar in two study groups

Row		Apgar 1 min			
		7.10	8.10	9.10	Total
Drug	Epinephrine	2	5	56	63
		3.2 %	7.9 %	88.9 %	100.0 %
	Ephedrine	0	9	54	63
		0 %	14.3 %	85.7 %	100.0 %
P-Value		0.204			

According to (Table 3), based on the independent t-test, the mean value of diastolic blood pressure that was the same in early minutes (p>0.05) was increased significantly from the eighth minute in the majority of cases in the ephedrine group compared to the epinephrine group.

Table 3. Mean and SD of diastolic blood pressure in two study groups

Row	Drug	Mean	Std. Deviation	P-Value
Baseline DBP	Epinephrine	74.8095	8.98540	0.665
	Ephedrine	73.7619	9.49315	
DBP 2 min	Epinephrine	63.1270	16.66316	0.754
	Ephedrine	62.5397	13.56564	
DBP 4 min	Epinephrine	53.7937	15.01199	0.185
	Ephedrine	55.8730	13.29988	
DBP 6 min	Epinephrine	52.1429	14.05044	0.262
	Ephedrine	56.4762	13.69937	
DBP 8 min	Epinephrine	52.7937	14.50490	0.001
	Ephedrine	59.1905	13.96408	
DBP 10 min	Epinephrine	52.1111	12.52496	0.004
	Ephedrine	57.1746	15.17908	
DBP 12 min	Epinephrine	49.7937	11.70630	0.0001
	Ephedrine	54.4444	11.81685	
DBP 14 min	Epinephrine	49.6032	12.05838	0.028
	Ephedrine	54.7937	12.45270	
DBP 16 min	Epinephrine	48.3016	11.09001	0.004
	Ephedrine	53.5079	12.03473	
DBP 18 min	Epinephrine	48.8730	13.20373	0.052
	Ephedrine	51.0000	12.43045	
DBP 20 min	Epinephrine	47.9683	10.70117	0.026
	Ephedrine	50.9524	12.18596	
DBP 25 min	Epinephrine	47.4286	11.70706	0.001
	Ephedrine	49.7460	11.34072	
DBP 30 min	Epinephrine	47.3968	12.63577	0.050
	Ephedrine	50.6349	11.02388	
DBP 35 min	Epinephrine	48.4762	14.84203	0.0001
	Ephedrine	51.9683	12.29997	
DBP 40 min	Epinephrine	49.9048	12.29702	0.0001
	Ephedrine	53.2698	12.61234	
DBP 45 min	Epinephrine	52.0159	13.49730	0.0001
	Ephedrine	56.1111	13.58024	

As shown in Table 4, based on the independent t-test, the mean value of systolic blood pressure, which was the same in two groups in early minutes (p>0.05), was significantly increased during minutes 8-16 in the ephedrine group compared to epinephrine group (p<0.05). However, they showed no significant difference in the rest of the time evaluated (p>0.05).

Table 4. Mean and SD of systolic blood pressure in two study groups

Row	Drug	Mean	Std. Deviation	P-Value
Baseline SBP	Epinephrine	121.63	9.28	0.526
	Ephedrine	122.30	7.90	
SBP 2 min	Epinephrine	110.59	14.74	0.829
	Ephedrine	111.41	14.80	
SBP 4 min	Epinephrine	100.05	16.37	0.412
	Ephedrine	104.19	18.43	
SBP 6 min	Epinephrine	101.19	17.47	0.082
	Ephedrine	119.71	129.34	
SBP 8 min	Epinephrine	101.11	15.62	0.013
	Ephedrine	110.06	14.61	
SBP 10 min	Epinephrine	103.86	11.25	0.043
	Ephedrine	110.62	14.70	
SBP 12 min	Epinephrine	103.10	12.63	0.028
	Ephedrine	112.51	14.13	
SBP 14 min	Epinephrine	105.00	14.30	0.019
	Ephedrine	110.29	12.35	
SBP 16 min	Epinephrine	102.78	12.72	0.013
	Ephedrine	109.56	13.10	
SBP 18 min	Epinephrine	103.00	11.41	0.354
	Ephedrine	107.02	11.60	
SBP 20 min	Epinephrine	101.00	11.48	0.147
	Ephedrine	105.51	10.96	
SBP 25 min	Epinephrine	100.24	11.01	0.261
	Ephedrine	106.89	10.47	
SBP 30 min	Epinephrine	102.17	13.47	0.128
	Ephedrine	106.56	11.27	
SBP 35 min	Epinephrine	99.44	11.07	0.153
	Ephedrine	108.17	10.80	
SBP 40 min	Epinephrine	101.75	11.86	0.132
	Ephedrine	109.62	9.85	
SBP 45 min	Epinephrine	102.57	10.67	0.092
	Ephedrine	110.62	14.31	

According to (Table 5), based on the independent t-test, the mean heart rate was the same in two groups in early minutes (p>0.05); although it was increased in the ephedrine group compared to epinephrine (p<0.05) in minutes 10, 25, 35, and 45. However, the two groups showed no significant difference in other times (p>0.05).

Table 5. Mean and SD of heart rate in two study groups (in bpm)				
Row	Drug	Mean	Std. Deviation	P-Value
Baseline HR	Epinephrine	93.49	13.59	0.359
	Ephedrine	95.90	15.73	
HR 2 min	Epinephrine	100.59	16.98	0.524
	Ephedrine	102.52	17.00	
HR 4 min	Epinephrine	99.73	19.16	0.699
	Ephedrine	101.05	19.03	
HR 6 min	Epinephrine	94.30	19.43	0.130
	Ephedrine	99.90	21.76	
HR 8 min	Epinephrine	93.67	19.28	0.051
	Ephedrine	100.14	17.62	
HR 10 min	Epinephrine	94.84	16.66	0.025
	Ephedrine	101.46	16.14	
HR 12 min	Epinephrine	96.30	14.72	0.241
	Ephedrine	99.52	15.96	
HR 14 min	Epinephrine	95.17	14.76	0.545
	Ephedrine	96.75	14.29	
HR 16 min	Epinephrine	95.56	15.21	0.379
	Ephedrine	97.79	13.19	
HR 18 min	Epinephrine	95.46	13.44	0.262
	Ephedrine	97.95	11.31	
HR 20 min	Epinephrine	94.22	13.04	0.056
	Ephedrine	98.51	11.91	
HR 25 min	Epinephrine	94.57	12.95	0.048
	Ephedrine	99.02	12.01	
HR 30 min	Epinephrine	94.13	12.81	0.430
	Ephedrine	95.89	12.13	
HR 35 min	Epinephrine	91.87	11.52	0.018
	Ephedrine	96.68	10.93	
HR 40 min	Epinephrine	91.62	10.66	0.235
	Ephedrine	93.84	10.25	
HR 45 min	Epinephrine	90.37	11.32	0.044
	Ephedrine	94.21	9.83	

Discussion

Previous evidence provided by Chan et al. (1997), indicate that 64 women under CS whom received spinal anesthesia in a protocol of two groups of 20 ml serum per kg, or 0.25mg per kg ephedrine, have shown that 35% of participants in the ephedrine group and 65% in the serum group showed hypotension[19]. Similarly, Vercauteren et al. (2000), demonstrated that when 50 women of CS were exposed to spinal anesthesia in a protocol of two groups of 50 mg ephedrine or normal saline, the frequency of hypotension in the ephedrine group was equal to 8% and 42% in the normal saline group[20]. Furthermore, Desalu et al. (2005), in 60 cesarean section case women received anesthesia in the frame of two groups of ephedrine and normal saline serum, found that 40% of participants in the ephedrine group and 70% in the normal saline group suffered from hypotension[21]. All this finding are consistent with the effectiveness of ephedrine observed in the present study.

Manuchehrian et al. (2011) demonstrated the effect of dosages of 10 and 20 mg intravenous ephedrine to prevent hypotension caused by spinal anesthesia in cesarean section, and the reduction was more evident by the dosage of 20 mg ephedrine[22]. In the present study, desirable effects of ephedrine to maintain the blood pressure was cleared from the eighth minute.

In the study conducted by Jabalameli et al. (2012), 150 cesarean section cases were placed in three groups of serum lactate, ephedrine, and combined group. The results showed that there was no difference between study groups[23]; although the present study showed a significant difference between groups with no combined group.

In the study of Bouchnak et al. (2012), 60 cases of cesarean section were placed in two groups of receiving colloid and crystalloid. It was found that 40% of samples in the colloid group and 66% in the crystalloid group showed hypotension. Also, the number of complications in the newborns and ABG results showed no difference between the two groups[24]. In the present study, no difference was observed between groups in terms of pH and PO2.

In the study of El-Mekawy et al. (2012), 90 cesarean section cases under spinal anesthesia were placed in three groups of ephedrine, Voluven, and lactated ringer. The results showed that the three groups were the same in terms of pH and PCO2 levels[25]. However, in the present study, the pH of the two groups was the same, and PCO2 was significantly different between them.

Farsani et al. (2016) studied the effect of intravenous infusion of phenylephrine and ephedrine in the treatment of hypotension caused by spinal anesthesia in orthopedic surgical operations. The results showed that the prescription of phenylephrine in the treatment of hypotension caused by spinal anesthesia in orthopedic surgery of lower limbs is more suitable than ephedrine[26]. However, the present study showed that ephedrine has better effects than epinephrine.

Conclusion

In general, according to the results obtained from this study, it could be found that ephedrine can increase blood pressure and heart rate more than epinephrine at the time of hypotension and bradycardia. Also, the blood pressure was the same between the two groups up to the eighth minute from the time of spinal anesthesia accomplishment. Hence, it could leave no desirable effect on the fetus, and Apgar and the VBG of the newborn were the same in both groups. Besides, the difference of pressure in both groups 8 minutes after spinal anesthesia was not significant, so that it had no undesirable maternal effects. Also, Tachycardia caused by ephedrine was not highly desirable in the ephedrine group compared to the epinephrine group. According to the findings, in addition to confirmation of using ephedrine in the management of hypotension and bradycardia caused by spinal anesthesia; the suggestion is the clinical use of intravenous epinephrine as an alternative with dosage more than the proposed dosage instead of ephedrine for management of hypotension and bradycardia caused by spinal anesthesia in cesarean sections (CS). Besides, it is recommended to conduct other studies with a larger sample size and higher dosage of epinephrine in form of comparative intervention concerning distorting factors.

References

1. Betrán AP, Ye J, Moller A-B, Zhang J, Gülmezoglu AM, Torloni MR. The increasing trend in caesarean section rates: global, regional and national estimates: 1990-2014. PloS one. 2016;11(2):e0148343.
2. Kee WDN, Khaw KS, Lee BB, Lau TK, Gin T. A dose-response study of prophylactic intravenous ephedrine for the prevention of hypotension during spinal anesthesia for cesarean delivery. Anesthesia & Analgesia. 2000;90(6):1390-5.
3. Miller RD, Eriksson LI, Fleisher LA, Wiener-Kronish JP, Young WL. Anesthesia E-Book: Elsevier Health Sciences; 2009.
4. Ayorinde B, Buczkowski P, Brown J, Shah J, Buggy D. Evaluation of pre-emptive intramuscular phenylephrine and ephedrine for reduction of spinal anaesthesia-induced hypotension during Caesarean section. British Journal of Anaesthesia. 2001;86(3):372-376.
5. Tarkkila PJ, Kaukinen S. Complications during spinal anesthesia: a prospective study. Regional anesthesia. 1991;16(2):101-6.
6. Horlocker TT, McGregor DG, Matsushige DK, Schroeder DR, Besse JA. A retrospective review of 4767 consecutive spinal anesthetics: central nervous system complications. Anesthesia & Analgesia. 1997;84(3):578-84.
7. Shearer VE, Ramin SM, Wallace DH, Dax JS, Gilstrap LC. Fetal effects of prophylactic ephedrine and maternal hypotension duringregional anesthesia for cesarean section. Journal of Maternal-Fetal Medicine. 1996;5(2):79-84.
8. Kee WDN. Phenylephrine infusions for maintaining blood pressure during spinal anesthesia for cesarean delivery: finding the shoe that fits. LWW; 2014.
9. LeeA, Kee WDN, Gin T. A quantitative, systematic review of randomized controlled trials of ephedrine versus phenylephrine for the management of hypotension during spinal anesthesia for cesarean delivery. Anesthesia & Analgesia. 2002;94(4):920-6.
10. CooperDW, Carpenter M, Mowbray P, Desira WR, Ryall DM, Kokri MS. Fetal and maternal effects of phenylephrine and ephedrine during spinal anesthesia for cesarean delivery. Anesthesiology: The Journal of the American Society of Anesthesiologists. 2002;97(6):1582-90.
11. Kee WDN, Lau TK, Khaw KS, Lee BB. Comparison of metaraminol and ephedrine infusions for maintaining arterial pressure during spinal anesthesia for elective cesarean section. Anesthesiology: The Journal of the American Society of Anesthesiologists. 2001;95(2):307-13.
12. Xu C, Liu S, Huang Y, Guo X, Xiao H, Qi D. Phenylephrine vs Ephedrine in Cesarean Delivery Under Spinal Anesthesia: A Systematic Literature Review and Meta-analysis. International Journal of Surgery. 2018.
13. Larsen TR, Kaszala K, Tan AY, Ellenbogen KA, Huizar JF. Paradoxical reflex bradycardia after epinephrine infusion for arrhythmia induction in the electrophysiology laboratory. HeartRhythm case reports. 2018;4(10):455-8.
14. Annane D, Vignon P, Renault A, Bollaert P-E, Charpentier C, Martin C, et al. Norepinephrine plus dobutamine versus epinephrine alone for management of septic shock: a randomised trial. Lancet. 2007;370(9588):676-84.
15. Sharrock NE, Mineo R, Urquhart B. Hemodynamic response to low-dose epinephrine infusionduring hypotensive epidural anesthesia for total hip replacement. Regional anesthesia. 1990;15(6):295-9.
16. Ottesen S, Renck H, Jynge P. II. Haemodynamic Alterations Secondary to Lumbar Epidural Analgesia and their Modification by Plasma Expansion and Adrenaline Administration An Experimental Study in the Sheep. Acta Anaesthesiologica Scandinavica. 1978;22:17-31.
17. Moran DH, Perillo M, LaPorta RF, Bader AM, Datta S. Phenylephrine in the prevention of hypotension following spinal anesthesia for cesarean delivery. Journal of clinical anesthesia. 1991;3(4):301-5.
18. Brooker RF, John IV F, Kitzman DW, Berman JM, Kashtan HI, McKinley AC. Treatment of Hypotension after Hyperbaric Tetracaine Spinal Anesthesia A Randomized, Double-blind, Cross-over Comparison of Phenylephrine and Epinephrine. Anesthesiology: The Journal of the American Society of Anesthesiologists. 1997;86(4):797-805.
19. 19-Chan WS, Irwin MG, Tong WN, Lam YH. Prevention of hypotension during spinal anaesthesia for caesarean section: ephedrine infusion versus fluid preload. Anaesthesia. 1997; 52(9):908-13.
20. 20-Vercauteren MP, Coppejans HC, Hoffmann VH, Mertens E, Adriaensen HA. Prevention of hypotension by a single 5-mg dose of ephedrine during small-dose spinal anesthesia in prehydrated cesarean delivery patients. Anesth Analg. 2000 Feb;90(2):324-7.
21. Desalu I, Kushimo OT. Is ephedrine infusion more effective at preventing hypotension than traditional prehydration during spinal anaesthesia for caesarean section in African parturients? Int J Obstet Anesth. 2005 Oct;14(4):294-9.
22. Manuchehrian N, Nikuseresht M, Kamali A, Seyedena N, Seiferabie A. The effect of 10 and 20 mg intravenous ephedrine on prevention of hypotension due to spinal anesthesia in cesarean section. Arak Medical University Journal. 2011; 14:3.
23. Jabalameli M, Soltani HA, Hashemi J, Behdad S, Soleimani B. Prevention of post-spinal hypotension using crystalloid, colloid and ephedrine with three different combinations: A double blind randomized study. Adv Biomed Res. 2012; 1:36.
24. Bouchnak M, Magouri M, Abassi S, Khemiri K, Tlili F, Troudi H, et al. Preloading with HES 130/0.4 versus normal saline solution to prevent hypotension during spinal anaesthesia for elective caesarean section. Ann Fr Anesth Reanim. 2012 Jun;31(6):523-7.
25. El-Mekawy NM. Comparative study between ephedrine infusion vs. CO/post loading of fluids for prevention of hypotension in emergency cesarean section under spinal anesthesia. Egypt J Anaesthesia. 2012;28: 193-8.
26. MORADI FD, NAGHIBI K, Alikiaei B, Mashayekhi Z. Comparison of the effects of intravenous phenylephrine and ephedrine in treatment of hypotension after spinal anesthesia in orthopedic surgery. 2016.