Norepinephrine versus Ephedrine to maintain arterial blood pressure during spinal anesthesia for cesarean section

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Abstract

Background: Spinal anesthesia is recommended for elective cesarean sections, but maternal hypotension by may occur, resulting in severe maternal complications. To avoid spinal hypotension, many methods were attempted; fluid loading, vasopressors, or combination of both.

Objectives: Our study aimed to compare administration of intermittent i.v. boluses of norepinephrine and ephedrine to guard against hypotensive effect of spinal anesthesia during delivery.

Patients and methods: This study was conducted at Qena University Hospitals, sixty cases undergoing elective cesarean section under spinal anesthesia were enrolled. They were randomly allocated to two equal groups**,** group N received prophylactic i.v. bolus of norepinephrine 5 µg, group E received prophylactic bolus of i.v. ephedrine 10mg immediately after intrathecal block. Incidence of hypotension and the numbers of the boluses of vasopressors used were recorded and considered as primary outcomes, maternal complication during the surgery as secondary outcomes.

Results: According to SBP, DBP, MAP there was significant lower values in groupE compared with group N. The mean number of boluses of vasopressors used during spinal anesthesia was significantly lower in Group N (2.2 vs. 5.8, P = 0.001). the mean number of hypotension episodes was also significantly lower in Group N (2.5 vs. 5.33, P = 0.001). Regarding operative maternal complications, Group N had a significantly lower nausea(16.7% vs. 66.7%, p=.001) vomiting (60% vs. 16.7%, p=0.001). shivering (23.3% vs. 0%, p=0.001).

Conclusion: Norepinephrine can be used as an alternative vasopressor to maintain maternal blood pressure during spinal anesthesia for cesarean delivery, with lower incidence of maternal complication.

Keywords: Norepinephrine; ephedrine; hypotension, maternal complications.

Introduction

Because of the significant complications involved with airway control during breastfeeding, spinal anesthesia is the recommended option for elective cesarean sections **(Macarthur et al.,2007).**

When maternal hypotension caused by spinal anesthesia for cesarean section is extreme and long-lasting, it can result in significant maternal complications, as well as uterine and placental blood flow damage, fetal hypoxia, acidosis, and neurological injury (**Cyna et al.,2006**). Fluid loading, vasopressors, or both have all been studied as ways to avoid spinal hypotension **(Loubert et al.,2012).**

Ephedrine was considered the best treatment for keeping maternal blood pressure in check **(Turkoz et al., 2002).** Its sympathomimetic stimulant action on alpha- and beta-adrenergic receptors has inotropic and chronotropic effects on the heart, as well as maintaining uterine blood flow **(Kee and colleagues, 2015**).

However, ephedrine's vasoconstrictive activity diminishes with prolonged administration (and its sluggish onset of action and comparatively long duration render precise blood pressure titration difficult) (**Kee et al., 2001**). Fetal tachycardia can occur suddenly due to ephedrine's slow onset of action. If tachycardia occurs in conjunction with a pre-existing oxygen deficiency, acidosis may result (**Kee et al.,2015**).

Norepinephrine is a sluggish β-adrenergic and strong α-adrenergic agonist. As a result, it could be a better choice for controlling maternal blood pressure while having less detrimental effects on HR and cardiac activity. (Hoyme and colleagues, 2015) One of the most serious side effects of using -agonists is a reduction of uteroplacental blood supply.

Norepinephrine has little effect on fetal arterial perfusion pressure, and fetoplacental microcirculation was not affected, according to **Minzter et al. (2010).**

Previous studies reported there is little evidence on the use of norepinephrine to relieve hypotension during spinal anesthesia, although there are few records on its use in obstetric patients **(Kee et al., 2015).**

The study based on comparison of the efficacy of intermittent IV boluses of norepinephrine and ephedrine to counterbalance the hypotensive effect of spinal anesthesia during cesarean delivery.

The study compared the efficacy of intermittent IV norepinephrine and ephedrine boluses to counteract the hypotensive effect of spinal anesthesia during cesarean section.

Patient and methods

Our study is a randomized double blind study. it was conducted in Obstetric & Gynecology and anesthesiology departments at Qena Faulty of Medicine Hospitals, South Valley University from date to inclusion criteria were; ASA I &ASA II, age from 18-40 undergoing elective caesarean section operation and singleton pregnancies at term scheduled for elective cesarean section.

We excluded patients with the following criteria: ASA III, IV, Emergency cesarean section, active labor, high-risk pregnancies (intrauterine growth retardation, preeclampsia), maternal cardiovascular or pulmonary diseases, patients allergic to any of the medications used in the study, bleeding disorder and patient's refusal.

Sixty cases undergoing elective cesarean section under spinal anesthesia were

consented after approval from the research ethics committee and enrolled in the study. They were randomly allocated to two equal group using 60 slips labeled.

Group N (n= 30): who received a prophylactic bolus of norepinephrine 5 µg intravenous (i.v.) just immediately after intrathecal block.

Group E (n= 30): who received a prophylactic bolus of i.v. ephedrine 5 mg just immediately after intrathecal block.

Intraoperative setting

Patients were fasted overnight in obstetric department and were given routine antacid prophylaxis. On arrival to the operating room (OR), they were positioned on the operating table in the supine position with left lateral tilt and all patients were connected to the standard ASA monitors including noninvasive blood pressure (NIBP), and pulse oximeter (SPaO2), ECG. An intravenous cannula was inserted, and normal saline solution was infused at 20 ml/kg prior to start of the technique.

Induction of spinal anesthesia via introduction of spinal needle at L3–4 or L4–5 vertebral interspace in the sitting position. After confirmation of free flow of cerebrospinal fluid, a mixture of 12.5 mg of hyperbaric bupivacaine 0.5% and 0.1 mg morphine was injected intrathecally, and the patient was returned to the tilted supine position.

Just after the intra thecal injection, rapid intravenous (i.v.) co hydration of lactated Ringer's solution was commenced through a large-borei.v. cannula. Co hydration was continued to a maximum of 1.5 liter after which the flow was reduced to a slow maintenance rate.

Norepinephrine tartrate, 2mg/ml ephedrine sulfate, 30 mg/ml, was diluted in an identical-coded 10 ml syringes to give norepinephrine 5 µg/ml and ephedrine 5 mg/ml. The study drug was prepared by a physician not involved in any other aspects of the study. This physician held the code for randomization and group allocation.

Group N(norepinephrine group) received a prophylactic bolus of norepinephrine 5 µg i.v. just after intrathecal block, plus rescue boluses of 5 µg norepinephrine, whenever maternal systolic blood pressure (SBP) dropped by 20% or more from the baseline value.

Group E (ephedrine group) received a prophylactic bolus of ephedrine 5 mg i.v. just after intrathecal block, plus rescue boluses of 5 mg ephedrine, whenever SBP dropped by 20% or more from the baseline value.

Incidence of hypotension and the numbers of the boluses of vasopressors used were recorded and considered as the primary outcomes of the study.

Complication during the surgery as incidence of hypertension, incidence of tachycardia, nausea &vomiting and headache were recorded and considered as the secondary outcomes of the study.

HR (beats/min) and SBP (mmHg) were recorded every 2 min after spinal injection until delivery of the baby and then every 5 min till the end of thestudy period.

The incidence of hypotension (defined as a reduction in SBP of >20% from baseline determined just before the administration of spinal anesthesia) was recorded. Reactive hypertension (defined as a rise of SBP >20% of baseline) was also recorded. Tachycardia (defined as a HR >120 beats/min) was also recorded.

Supplemental oxygen was given only when the pulse oximeter reading decreased below 95%.

Data collection

A)-Patient characteristics

Age, weight, height , BMI

B)- Hemodynamics (HR, SBP, DBP, MAP), &SPO2 were noted during various stages of the surgery: -

1. Base line before induction of anesthesia.
2. Each 2 minutes after intrathecal injection till delivery of the baby
3. Each 5minutes from the delivery of the baby till skin closure
4. Each 1 hour after skin closure till 4hours post-operative

C)- Frequency of administration of the drugs of the study.

D)- Complications during the surgery: -

1- Incidence of hypertension

2- Incidence of tachycardia

3-Nausea &vomiting

4- Headache.

Statistical analysis

Sample size was calculated according to the power of the test to 95%, margin of error accepted to 5%, was the minimum sample size required to demonstrate a statistically significant difference between two groups as regards hypotensive episodes and considering the anticipated dropout rate, and 60 patients (30 patients in each group) were included in the study.

Data was analyzed using statistical package for social sciences software program (IBM-SPSS version 23).Continuous variables were presented as mean ±standard deviation (SD).Categorical variables were presented as frequencies and percentages. Bivariate differences across groups with respect to categorical variables were analyzed using Chi-square tests, using Fishers Exact tests when cell counts were small, whereas continuous variables were analyzed using Student's *t*-tests. A two-sided nominal p-value of less than or equal to 0.05 was considered significant.

Results

The patient characteristics were comparable in the two studied groups with no statistically significant differences table 1.

According to SBP,DBP,MAP there was statisticallysignificant lower values in group E compared with group NE(table),while there were statisticallysignificanthigher values of HR in group E than group NE (chart1, 2,3,4)

The mean number of boluses of vasopressors used during spinal anesthesia was significantly lower in Group N compared with Group E (2.2 vs. 5.8, P = 0.001). Further, the mean frequency of tachycardia was significantly lower in Group N compared with Group E (1.27 vs. 3.83, P = 0.001). Furthermore, the mean number of hypotension episodes was also significantly lower in Group N compared with Group E (2.5 vs. 5.33, P = 0.001). However, the mean frequency of bradycardia showed no statistically significant differences between the two studied groups (P = 0.326).Table 2

According to the incidence of maternal complications during the operation, Group N had a significantly lower nausea compared Group E (16.7% vs. 66.7%, p=.001). vomiting was found to be

significantly higher in Group E compared to Group N (60% vs. 16.7%, p=0.001). shivering was found to be significantly higher in Group E compared to Group N (23.3% vs. 0%, p=0.001). while headache and restlessnesswere comparable, and no statisticallysignificant differences were detected between the two studied groups.**Table 3,Fig.1.**

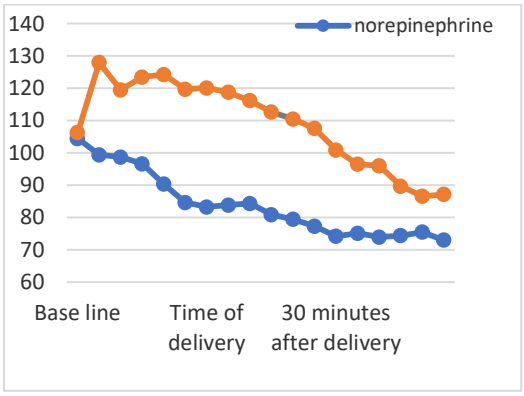

Fig.1. Comparison between norepinephrine &ephedrine groups according to HR. Data presented in (mean±SD) using t-test for comparison.

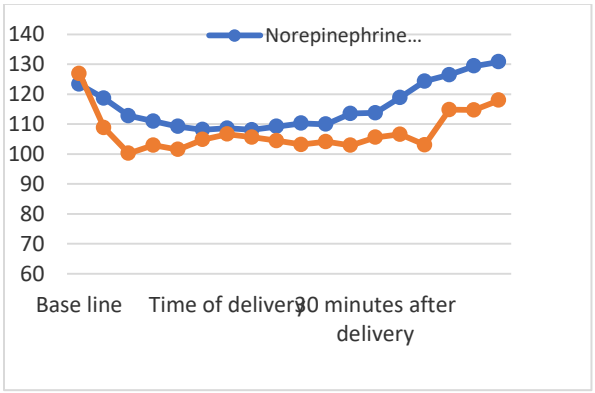

Fig. 2. Comparison between norepinephrine &ephedrine groups according to SBP. Data presented in (mean±SD) using t-test for comparison.

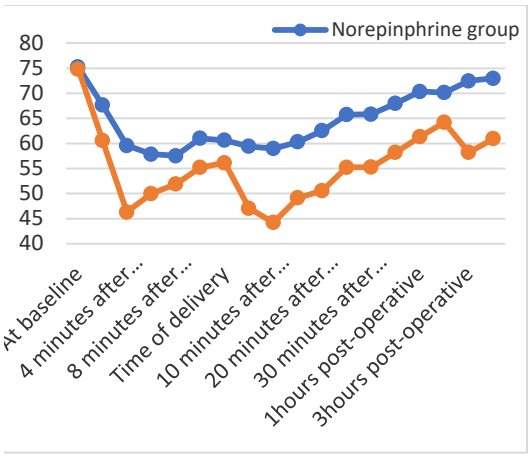

Fig.3. Comparison between norepinephrine &ephedrine groups according to DBP

Data presented in (mean±SD) using t-test for comparison

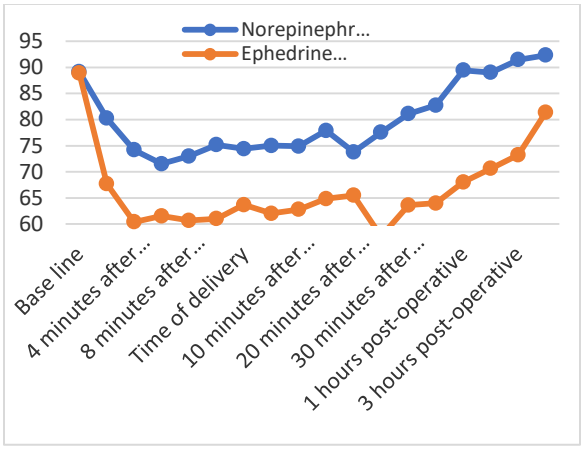

Fig.4. Comparison between norepinephrine &ephedrine groups according to MAP

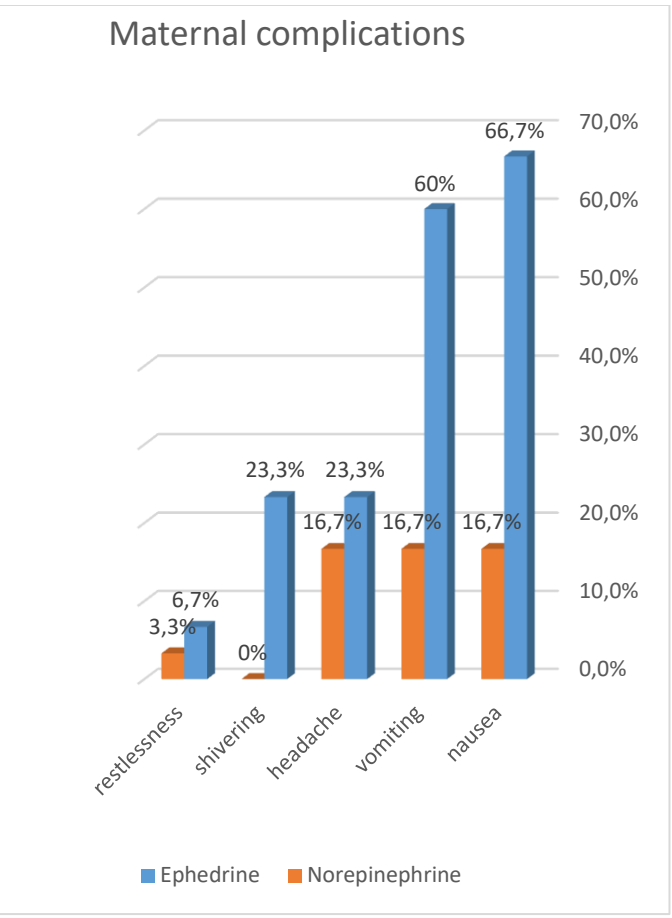

Fig.5. Maternal complications comparison between Norepinephrine and Ephedrine.

Table 1.The patient characteristics

	Norepinephrine group N=31	Ephedrine group N=31	P-value
Age (years)	24.87	25.25	0.716
BMI (kg/m^2)	23.72	24.17	0.607
Weight (kg)	63.213	64.32	0.716
Height (m)	164.31	164.81	0.723

Data presented in (mean) using unpaired t-test for comparison. Data presented in (no. and%) using Chi-square test for comparison. BMI: body mass index

Table 2 Maternal hemodynamics.

Statistically significant difference (p <0.05)

	Norepinephrine (Group N) (N=30)	Ephedrine (Group E) (N=30)	P-value
Number of boluses of vasopressors used	2.2±.664	5.8±1.69	**.001***
Frequency of tachycardia	1.27±.583	3.83±1.68	**.001***
Frequency of bradycardia	.03±.183	0	**.326**
Number of hypotension episodes	2.5±.861	5.33±2.11	**.001***

Statistically significant difference in comparison with baseline data presented in (mean ±SD) using unpaired t-test for comparison. Statistically significant difference (p<0.05*)

Table 3 Maternal complication.

		Norepinephrine (Group N) (N=30)	Ephedrine (Group E) (N=30)	P-value
Maternal complications	Nausea	5 (16.7%)	20 (66.7%)	.001*
	Vomiting	5 (16.7%)	**18 (60%)**	.001*
	Headache	5 (16.7%)	7 (23.3%)	.518
	Shivering	0 (0%)	**7 (23.3%)**	.001*
	restlessness	1 (3.3%)	2 (6.7%)	.55

Statistically significant difference in comparison with baseline data presented in (mean ±SD) using unpaired t-test for comparison

Discussion

This study was conducted in Obstetric & Gynecology and Anesthesiology Departments at Qena University hospital. Sixty (60)cases undergoing elective cesarean section under spinal anesthesia were allocated to two equal groups. **Group N (n= 30)** received a prophylactic bolus of norepinephrine 5 μg intravenous (i.v.) **, Group E (n= 30)** received a prophylactic bolus of i.v. ephedrine 10mg immediately after intrathecal block.

According to SBP,DBP, MAP there were significantly higher in group N compared to group E. According to HR was significantly lower in group N compared to group E.

Our study showed that, the mean number of boluses of vasopressors used during spinal anesthesia was significantly lower in Group N compared with Group E (2.2 vs. 5.8, P = 0.001). Further, the mean frequency of tachycardia was significantly lower in Group N compared with Group E (1.27 vs. 3.83, P = 0.001). Furthermore, the mean number of hypotension episodes was also significantly lower in Group N compared with Group E (2.5 vs. 5.33, P = 0.001). However, the mean frequency of bradycardia showed no statistically significant differences between the two studied groups (P = 0.326).

Elnabtity& Selim(2018) showed that compared with ephedrine, norepinephrine maintained maternal blood pressure and uterine artery blood flow in patients undergoing elective cesarean section under spinal anesthesia. Further, it was associated with lower numbers of hypotension episodes and less frequency of tachycardia during cesarean delivery. Furthermore, the numbers of boluses of vasopressors used during spinal anesthesia were lower in norepinephrine compared with the use of ephedrine **(Elnabtity& Selim, 2018)**. These results are coinciding with the results of our study.

Because uteroplacental blood flow is not autoregulated but directly coupled to maternal blood pressure, maternal hypotension must be treated immediately to avoid the risk of fetal acidosis **(Hoyme et al., 2015).**

Recent studies showed that norepinephrine was also effective for maintaining blood pressure in obstetric patients. It has weak β-adrenergic receptor agonist activity in addition to its α-adrenergic receptor activity and therefore may be a more suitable option for maintaining maternal blood pressure with less negative effects on HR and cardiac output (**Hoyme et al., 2015,Kee et al., 2015**).

El Shafeiet al. compared norepinephrine with ephedrine to prevent spinal anesthesia-induced hypotension in coronary artery disease patients undergoing knee arthroscopy. One hundred patients were randomly allocated to two equal groups to receive either 5 mg of ephedrine or 5 μg of norepinephrine when hypotension occurs. They found thatnorepinephrine is more effective compared with ephedrine in the maintenance of SBP with reduction in HR, which is useful in coronary artery disease patients.

These results are in agreement with the results obtained in our study although we conducted our study on a different category of patients. However, they found no difference between the two groups regarding the incidence of hypotension, hypertension, and bradycardia (**El Shafei et al., 2015**).

The results of our study as we found lower numbers of hypotension episodes and less frequency of tachycardia in the patients treated with norepinephrine.

According to the incidence of maternal complications during the operation, Group N had a significantly lower nausea compared Group E (16.7% vs. 66.7%, p=.001).Vomiting was found to be significantly higher in Group E compared to Group N (60% vs. 16.7%, p=0.001).

Shivering was found to be significantly higher in Group E compared to Group N (23.3% vs. 0%, p=0.001). while headache and restlessness were comparable, and no statistically significant differences were detected between the two studied groups.

A previous study showed that the incidence of maternal complications during the operation (nausea, vomiting, shivering, headache, restlessness, and pruritus) was comparable, and no statistically significant differences were detected between the studied groups (**Elnabtity&Selim, 2018**).

In our study, we administered the vasopressors by intermittent i.v. boluses when SBP drops 20% below the baseline. We found that uterine UtA-PI was lower in women treated with norepinephrine compared with those treated with ephedrine.

This was attributed to the greater cardiac output that improved uterine blood flow in norepinephrine group although there were no significant differences between both groupsregarding the fetal outcome. This was in agreement with the results obtained in the study of **Kee et al (2015).**

Onwochei and his colleagues (2017) studied the effect of different intermittent i.v. boluses of norepinephrine to prevent maternal hypotension during spinal anesthesia for cesarean delivery. The results obtained were feasible and were not associated with significant maternal or fetal adverse effects. These results are coinciding with the results of our study.

Kee et al., (2015) compared the prophylactic continuous i.v. norepinephrine infusion (2.5 μg/min) with a bolus of 1 ml norepinephrine 5 μg/ml (5 μg) given whenever SBP decreased to <80% of the baseline value. The results revealed the superiority of continuous norepinephrine infusion over the intermittent i.v. boluses.

In our study, we compared two different vasopressors and we chose the regimen of intermittent i.v. boluses because of its familiarity to most of the anesthesiologists.

Limitation

It was extended only until the end of surgery; further studies are required for long-term follow-up in the postoperative period till discharge of the patients to home.

Conclusion

In this study we compered intermittent boluses of norepinephrine to ephedrine in patients undergoing elective cesarean section under spinal anesthesia; frequency of hypotension episodes, tachycardia and incidence of maternal complications during the operation was significantly lower in norepinephrine group.

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