

Comparison of Norepinephrine and Ephedrine Boluses in the Control of Spinal Anesthesia-Induced Hypotension during Cesarean Section: A Randomized Controlled Trial

H. Errifaïy^{1*}, N. Tajleji¹, N. Ouzlim¹, H. Ribahi¹, A. G. El Adib¹

¹Maternal Anesthesia-Intensive Care Unit, Mother-Child Hospital, Mohammed VI University Hospital, Marrakech, Morocco

DOI: [10.36347/sasjm.2021.v07i11.009](https://doi.org/10.36347/sasjm.2021.v07i11.009)

| Received: 07.10.2021 | Accepted: 13.11.2021 | Published: 27.11.2021

*Corresponding author: H. Errifaïy

Abstract

Original Research Article

Introduction: Phenylephrine and ephedrine are the first-line vasopressors used in obstetric anesthesia to manage maternal hypotension, but phenylephrine is sometimes associated with maternal cardiac depression, limiting its use among mothers with cardiac comorbidities. The use of ephedrine is generally associated with maternal tachycardia along with a decrease in fetal pH. Norepinephrine is another vasopressor that has recently been introduced in obstetrical anesthesia and has attracted increasing attention as a feasible substitute for these two molecules in this context. The objective of our study is to compare two vasopressor agents (norepinephrine vs ephedrine) dedicated to the treatment of post-spinal anesthesia hypotension, and then to define the place of norepinephrine in the pharmacopoeia of the latter. **Materials and Method:** A Randomized controlled study of 80 ASAI parturient randomized to receive either 8µg boluses of norepinephrine (NG) or 6mg boluses of ephedrine (EG). The criteria for judgment included the occurrence of tachycardia, the maintenance of blood pressure, and the number of boluses required, as well as the clinical condition of the neonate. **Results:** The incidence of tachycardia (HR>80bpm) was lower in NG (18%) compared to that in EG (67.6%) p=0.0001, crude Odds Ratio 14.968 95% CI] 4.924, 45.505[. Six in NG (12%) and eight in EG (26.7%) patients experienced nausea, OR 2.667 95% CI] 0.823-8.641[while only three in NG (6%), and four EG (13%) patients experienced vomiting p=0.41 OR:2.41 CI 95%]0.501-11.605[. Blood pressure was stable for both groups but with a superiority of norepinephrine which allowed more marked maintenance: 75% to 112% of the initial systolic value in NG versus 72% to 100% in EG), the difference was highly significant p<0.0001. No significant differences in neonatal outcomes were observed. **Conclusion:** Norepinephrine can maintain blood pressure more effectively than ephedrine with less incidence of tachycardia and with similar neonatal outcomes. This makes it a vasopressor of choice for the treatment of spinal anesthesia-induced hypotension among pregnant women.

Keywords: Phenylephrine, hypotension, spinal anesthesia, cesarean.

Copyright © 2021 The Author(s): This is an open-access article distributed under the terms of the Creative Commons Attribution 4.0 International License (CC BY-NC 4.0) which permits unrestricted use, distribution, and reproduction in any medium for non-commercial use provided the original author and source are credited.

INTRODUCTION

Spinal anesthesia (SA) is the preferred anesthetic technique for the majority of cesarean sections. However, it is accompanied by several adverse events of which arterial hypotension (AH) is the most frequent and most dangerous.

A good quality SA for cesarean section requires a dense sensory block up to T5, which always results in an extensive sympathetic block that requires the introduction of vasopressors [1]. Without vasopressor, more than 60% of women experience post-spinal anesthesia hypotension during cesarean delivery [2, 3].

Until now, phenylephrine and ephedrine are the first-line vasopressors used in obstetric anesthesia to manage maternal arterial hypotension; however, phenylephrine is sometimes associated with maternal cardiac depression, which limits its use on mothers with cardiac co-morbidities [4]. Ephedrine use is generally associated with maternal tachycardia as well as a decrease in fetal pH [5].

Norepinephrine is another vasopressor that has recently been introduced in obstetric anesthesia and has attracted increasing attention as a feasible substitute for phenylephrine in this setting.

The purpose of our study is to compare two vasopressor agents (norepinephrine vs ephedrine) dedicated to the treatment of post-spinal anesthesia hypotension, and then to define the place of norepinephrine in the pharmacopeia of the latter.

MATERIALS AND METHODS

A randomized controlled study was conducted at CHU Mohamed VI over a period of 3 months (from January 15 to April 15, 2018), following the approval of the research ethics committee. Written informed consent was obtained for each patient.

The study included full-term pregnant women aged 18 to 40 years scheduled for cesarean section. Parturients with cardiac comorbidities, pregnancy-related hypertensive disorders, or hemorrhagic complications were excluded.

Upon admission to the operating room, patients were monitored (electrocardiography, pulse oximetry and blood pressure cuff). A crystalloid prefill was started. Spinal anesthesia was performed in the sitting position with 10 mg of hyperbaric bupivacaine in association with 20 µg of fentanyl. Norepinephrine was provided in the form of 8 µg/ml.

We randomly divided our sample into 2 groups: ephedrine group (EG: n=30) and norepinephrine group (NR: n=50). An external physician preparing opaque envelopes containing codes for ephedrine and norepinephrine groups performed the randomization. Each envelope is selected randomly and opened in the operating room by the anesthetist after each parturient is installed and prepared. Once the intrathecal injection was done, the EG parturient received ephedrine boluses of 3 to 6 mg, and the others belonging to the GN received boluses of 8 µg of noradrenaline.

The Compared variables were heart rate, blood pressure (BP), presence of typical symptoms of nausea, vomiting, discomfort, and the clinical condition of newborns (APGAR score).

A baseline blood pressure was measured by averaging three readings. Hypotension is defined as an 80% drop in the initial base value. bradycardia is defined as a heart rate less than 55 beats per minute and tachycardia is defined as a heart rate greater than 80bpm from intrathecal injection to fetal expulsion. Blood pressure measurements were repeated every one to two minutes.

The statistical analysis was carried out using the SPSS version 19.0 software. The descriptive analysis consisted of the calculation of the absolute and relative frequencies for the qualitative variables, and the positioning and dispersion parameters for the quantitative variables (mean standard deviation).

The normal distribution of the variables was studied by the Kolmogorov-Smirnov test. The normal distribution of the variables was studied by the Kolmogorov-Smirnov test. In bivariate analysis, the comparison of qualitative variables used the statistical test of Pearson's Chi2 and Fisher's if necessary. The quantitative variables were compared by the t-test of Students. The significance threshold was selected for $p < 0.05$.

RESULTS

One hundred and fifteen patients were selected for eligibility, 31 refused to participate and 4 were excluded due to failed spinal anesthesia. The study recruited 80 patients and randomized them into two groups: EG (n=30) and NG (n=50) (Figure 1).

There was no significant difference in the characteristics of pregnant women in the two studied groups (Table 1).

The incidence of tachycardia (HR > 80 bpm) was lower in NG (18%) compared to that of EG (67.6%) $p = 0.0001$, Odds Ratio 14.968 95% CI] 4.924, 45.505.

Six NG patients (12%) and eight EG patients (26%) experienced nausea 0.095, OR 2.667 95% CI] 0.823-8.641 while only three NG (6%) and four EG (13%) patients experienced vomiting $p = 0.41$ ORb: 2.41 95% CI] 0.501-11.605 [(Table 2).

PA was maintained in both groups but with superiority with norepinephrine which allowed more marked retention: 75% to 112% of the initial value of systolic in GN versus 72% to 100% in GE), the difference was very significant $p < 0.0001$ (Table 3).

Noradrenaline a helps maintain correct blood pressure with fewer boluses than ephedrine and with a faster time delay (Figure 2).

No significant differences in neonatal outcomes were observed (Table 4).

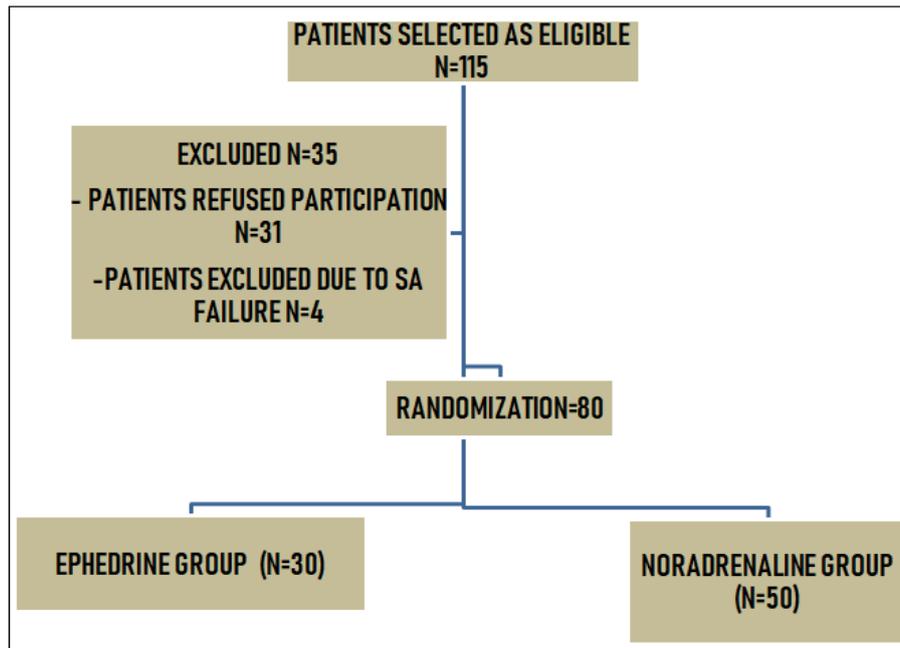


Figure 1: CONSORT diagram showing patient recruitment and flow

Table 1: Characteristics of the two groups

	All (n=80)	NG (n=50)	EG (n= 30)
Average (ET)	31(4.9)	30(5)	31.2(4..2)
Average gestational age (ET)	38(2.5)	38((3.1)	37(1.7)
Average weight (ET)	85(10.2)	84.9(10.9)	86(12.5)
Average IMC (ET)	28.7(5.1)	28.(3.2)	29(3.1)
The Interval between SA and extraction	25(21-27)	25(22-26)	21(21-27.8)
The Interval between incision and extraction	89.5(59-109)	87(60-115)	90(62-119)

Table 2: Comparison of incidents:

	NG (n=50)	EG (n= 30)	OR IC 95%	P value
Tachycardia (n/N)% -(i/I)%	(9/50)18% - (9/32) 28.1%	(23/30)76.7% - (23/32) 71.9%	14.968]4.924-45.505[0.0001
Nausea (n/N)% -(i/I)%	(6/50)12% - (6/14) 42.9%	26.7%(8/30) - (8/14) 57.1%	2.667]0.823-8.641[0.095
Vomiting (n/N)% -(i/I)%	(3/50)6% - 42.9%(3/7)	(4/30)13.3% - (4/7) 57.1%	2.41]0.501-11.605[0.41*

*Fisher exact test

cOR: crude Odds ratio, i: incident number in each group I: incident number in both groups

Table 3: Comparison of the blood pressure variations of the two groups

	NG (n=50)	EG (n= 30)	P value
Average admission BP	120.14(16.597)	120.07(18.571)	0.073
BP after spinal anesthesia	79.74(5.584)	80.10(5.868)	0.78
BP after vasopressor	115.46(9.825)	104.40(12.193)	0.0001

Data are presented as mean ± SD

Table 4: Neonatal Outcome

	NG (n=50)	EG (n= 30)	P value
Birth weight (kg) mean(IQR)	3.08 [2.66–3.41]	3.12 [3.04–3.22]	.75
Apgar score at 1min <7	0	0	-
Apgar score at 5min <7	0	0	-

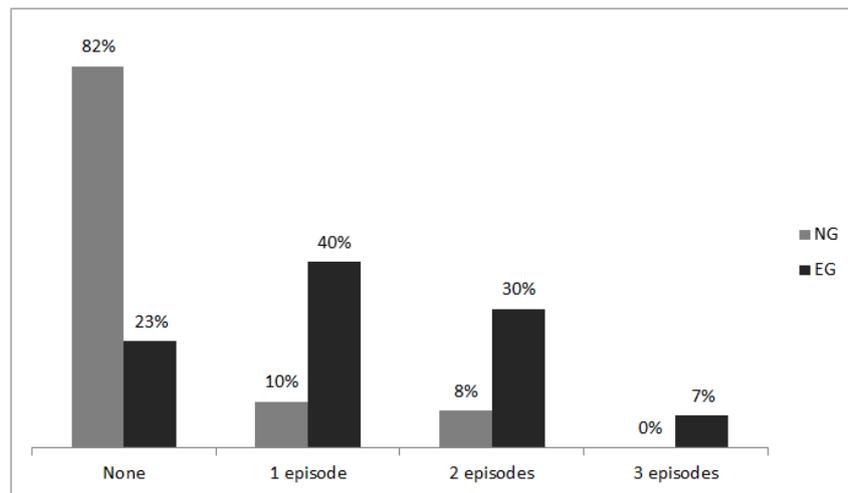


Figure 2: Number of episodes of tachycardia in both groups

DISCUSSION

Vasoplegia following spinal anesthesia induces significant blood pressure drop for pregnant women with compensatory tachycardia to maintain adequate cardiac output [5, 6].

Previous studies have emphasized the importance of maintaining a TA close to the initial baseline for both fetal and maternal well-being [7].

Ephedrine and phenylephrine were the most commonly used vasopressors for the treatment of anesthesia-induced hypotension. However, these are associated with cardiac rhythm disturbances such as tachycardia with ephedrine and a dose-dependent slowing of the heart rate or even a drop in cardiac output with phenylephrine [8, 9].

Some authors then proposed the use of norepinephrine in this context. Ngankee *et al.*, published the results of a randomized controlled trial comparing norepinephrine and phenylephrine in the maintenance of BP in patients undergoing spinal anesthesia [10]. These results indicate equally effective maintenance of BP with less incidence of bradycardia and drop in cardiac output. No difference in fetal prognostic parameters was observed. This is consistent with the results of our study which showed a reduction in tachycardia episodes compared with the ephedrine and average maintenance of 91% of the initial systolic value relative to ephedrine, which allowed maintenance of 80.5% with a significant difference $P=0.0001$.

We used 8 μ g boluses of norepinephrine, which appeared to be effective. In the study of Desire *et al.*, the effectiveness of norepinephrine was also observed, and they estimated a dose of 6 μ g/bolus of norepinephrine [11].

The same dosage (6 μ g) was used in the study of Aidan M *et al.*, with similar results. [12].

In their study, Warwick *et al.*, [13] compared several doses of norepinephrine and suggested a dose of 8 μ g with satisfactory results similar to the results of our study.

Ahmed. M *et al.*, in their study compared the continuous infusion of norepinephrine in three groups and concluded that infusion rates of 0.05/Kg/min and 0.075%/Kg/min effectively reduced post-spinal hypotension with less occurrence of bradycardia [14].

Whereas Daili Chen *et al.*, have demonstrated that an infusion of 5 to 10 μ g/kg/h of norepinephrine reduces the occurrence of hypotension and allows hemodynamic stability during cesarean sections without any adverse effects [15].

The question is the safety of noradrenaline in the peripheral pathways, due to the risk of extravasation and tissue ischemia, which remains a theoretically minimal risk with small boluses. A recent study in which peripheral norepinephrine infusions have been used in hypotensive patients for 3 hours at a maximum rate of 30 μ g/min showed no significant morbidity [16].

Most studies have compared norepinephrine to phenylephrine. However, this study appears to be the first one that compares norepinephrine to ephedrine and has shown very satisfactory results that may guide the design of other comparative studies between norepinephrine and ephedrine.

CONCLUSION

Norepinephrine helps maintain blood pressure more effectively than ephedrine with a reduced occurrence of tachycardia and with similar neonatal outcomes. This makes it a vasopressor of choice for the treatment of spinal anesthesia-induced hypotension among pregnant women.

REFERENCES

1. Kinsella, S. M., Carvalho, B., Dyer, R. A., Fernando, R., McDonnell, N., Mercier, F. J., ... & Ciechanowicz, S. (2018). International consensus statement on the management of hypotension with vasopressors during caesarean section under spinal anaesthesia. *Anaesthesia*, *73*(1), 71-92.
2. Hasanin, A., Aiyad, A., Elsakka, A., Kamel, A., Fouad, R., Osman, M., ... & Hassabelnaby, Y. (2017). Leg elevation decreases the incidence of post-spinal hypotension in cesarean section: a randomized controlled trial. *BMC anesthesiology*, *17*(1), 1-6.
3. Hasanin, A., Soryal, R., Kaddah, T., Raouf, S. A., Abdelwahab, Y., Elshafaei, K., ... & Hassabelnaby, Y. (2018). Hemodynamic effects of lateral tilt before and after spinal anesthesia during cesarean delivery: an observational study. *BMC anesthesiology*, *18*(1), 1-6.
4. Hasanin, A., Mokhtar, A. M., Badawy, A. A., & Fouad, R. (2017). Post-spinal anesthesia hypotension during cesarean delivery, a review article. *Egyptian Journal of Anaesthesia*, *33*(2), 189-193.
5. Dyer, R. A., Reed, A. R., van Dyk, D., Arcache, M. J., Hodges, O., Lombard, C. J., ... & James, M. F. (2009). Hemodynamic effects of ephedrine, phenylephrine, and the coadministration of phenylephrine with oxytocin during spinal anesthesia for elective cesarean delivery. *The Journal of the American Society of Anesthesiologists*, *111*(4), 753-765.
6. Langesæter, E., Rosseland, L. A., & Stubhaug, A. (2008). Continuous Invasive Blood Pressure and Cardiac Output Monitoring during Cesarean Delivery: A Randomized, Double-blind Comparison of Low-dose versus High-dose Spinal Anesthesia with Intravenous Phenylephrine or Placebo Infusion. *The Journal of the American Society of Anesthesiologists*, *109*(5), 856-863.
7. Ngan Kee, W. D., Khaw, K. S., & Ng, F. F. (2004). Comparison of phenylephrine infusion regimens for maintaining maternal blood pressure during spinal anaesthesia for Caesarean section. *British Journal of Anaesthesia*, *92*(4), 469-474.
8. Carvalho, B., & Dyer, R. A. (2015). Norepinephrine for spinal hypotension during cesarean delivery: another paradigm shift?. *Anesthesiology*, *122*(4), 728-730.
9. Ferré, F., Martin, C., & Minville, V. (2017). Contrôle de la pression artérielle en rachianesthésie. *Anesthésie & Réanimation*, *3*(2), 147-155.
10. Ngan Kee, W. D., Lee, S. W., Ng, F. F., Tan, P. E., & Khaw, K. S. (2015). Randomized double-blinded comparison of norepinephrine and phenylephrine for maintenance of blood pressure during spinal anesthesia for cesarean delivery. *Anesthesiology*, *122*(4), 736-745.
11. Onwochei, D. N., Ngan Kee, W. D., Fung, L., Downey, K., Ye, X. Y., & Carvalho, J. C. (2017). Norepinephrine intermittent intravenous boluses to prevent hypotension during spinal anesthesia for cesarean delivery: a sequential allocation dose-finding study. *Anesthesia & Analgesia*, *125*(1), 212-218.
12. Sharkey, A. M., Siddiqui, N., Downey, K., Xiang, Y. Y., Guevara, J., & Carvalho, J. C. (2019). Comparison of intermittent intravenous boluses of phenylephrine and norepinephrine to prevent and treat spinal-induced hypotension in cesarean deliveries: randomized controlled trial. *Anesthesia & Analgesia*, *129*(5), 1312-1318.
13. Ngan Kee, W. D. (2017). A random-allocation graded dose-response study of norepinephrine and phenylephrine for treating hypotension during spinal anesthesia for cesarean delivery. *Anesthesiology*, *127*(6), 934-941.
14. Hasanin, A. M., Amin, S. M., Agiza, N. A., Elsayed, M. K., Refaat, S., Hussein, H. A., ... & Refaie, A. (2019). Norepinephrine Infusion for Preventing Postspinal Anesthesia Hypotension During Cesarean Delivery. *Obstetric Anesthesia Digest*, *39*(4), 219-220.
15. Chen, D., Qi, X., Huang, X., Xu, Y., Qiu, F., Yan, Y., & Li, Y. (2018). Efficacy and safety of different norepinephrine regimens for prevention of spinal hypotension in cesarean section: a randomized trial. *BioMed research international*, 2018.
16. Medlej, K., Kazzi, A. A., Chehade, A. E. H., Eldine, M. S., Chami, A., Bachir, R., ... & Abou Dagher, G. (2018). Complications from administration of vasopressors through peripheral venous catheters: an observational study. *The Journal of emergency medicine*, *54*(1), 47-53.