Post-spinal hypotension management for cesarean section in low resource settings: efficiency and safety of two very low-dose boluses of norepinephrine, a randomized double-blinded controlled trial

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Abstract

Spinal anesthesia is the gold standard anesthetic technique for cesarean section. However, its major complication is hypotension. Norepinephrine has recently been described as an efficient and safe alternative to Phenylephrine. The aim of this study was to determine the effective target bolus of Norepinephrine to prevent and treat post-spinal anesthesia hypotension. We conducted a prospective controlled randomized study including 126 parturients scheduled for cesarean delivery under spinal anesthesia. We compared two groups that received a prophylactic bolus of either 1 µg/kg or 0.5 µg/kg of Norepinephrine without fluid loading. The rescue intravenous bolus of Norepinephrine was half the dose of the prophylactic bolus. The main outcomes were the percentage of decrease in systolic and mean blood pressure. The secondary outcomes included the timing of the first hypotension, duration of hypotension, number of rescue boluses, total Norepinephrine consumption, incidence of hypotension and maternal adverse effects and fetal outcomes. Our primary outcome has shown similarities between groups; delta systolic blood pressure before delivery was 19.4% in group 1 µg/kg versus 20.5% in group 0.5 µg/kg. Both groups were similar for all secondary outcomes, except that the higher dose of Norepinephrine resulted in more hypertension. Fetal outcomes were similar in both groups. Bolus of 0.5 µg/kg followed by rescue doses of 0.25 µg/kg of Norepinephrine was efficient in preventing and treating spinal anesthesia-induced hypotension. These doses may be recommended for routine use in healthy parturients.

Introduction

Caesarean section is a frequent surgery that is most often performed under spinal anesthesia which is considered the anesthetic technique of choice. The major problem with this technique remains arterial hypotension resulting from the extensive sympathetic block with a decrease in cardiac output and uteroplacental output with a consequent decrease in fetal oxygenation with acidosis and bradycardia if hypotension is prolonged beyond 4 minutes.[1-3] Ephedrine has long been considered the favorite vasopressor for the management of hypotension in obstetrics. In fact, it preserves uteroplacental flow due to its lack of vasoconstrictive effect in this territory. However, because of its placental passage, ephedrine, at high doses, is responsible for neonatal acidosis and maternal tachycardia limiting its prophylactic use.[4] Currently, phenylephrine is the vasopressor of choice for the prevention and treatment of spinal-induced arterial hypotension in parturients.[5] As phenylephrine is a potent alpha-adrenergic receptor agonist, its use is often associated with a dose-dependent slowing of heart rate and a fall in maternal cardiac output. A low dose of norepinephrine or noradrenaline (NAD) has been proposed as an effective alternative to phenylephrine with less bradycardia and less drop in cardiac output.[6,7] Norepinephrine appears to be a promising vasopressor in obstetric anesthesia. It is also an interesting molecule in limited resource settings because of its availability and low cost. Most studies have investigated the use of noradrenaline as a continuous infusion; however, bolus administration has not been sufficiently studied. Therefore, bolus administration of norepinephrine for the prevention and treatment of arterial hypotension after spinal anesthesia during caesarean section is based on a low level of evidence, and there is currently no recommendation for its use in this setting. The aim of our study was to compare the efficiency of two bolus doses of norepinephrine in preventing and treating hypotension induced by spinal anesthesia.

Materials and Methods

This is a prospective randomized controlled study, in a double-blind, which took place in the Department of Anesthesia and Intensive Care of the Maternity and Neonatology Center of Tunis in 2018 and lasted over a period of 4 months. We included pregnant women aged between 18 and 45 years, classified as ASA 2 (pregnant women with no notable pathological history or major dysgravidia), with a full-term progressive mono-fetal pregnancy with a gestational age over 36 SA, proposed for a pro-

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Key words: norepinephrine; cesarean section; hypotension; spinal anesthesia; vasopressor.

Contributions: FB, article writing; IE, case collection and application of the study protocol; SB, the concept of work and supervision; HM, team leader. All the authors approved the final version to be published.

Conflict of interest: the authors declare no potential conflict of interest.

Ethical approval and consent to participate: our work was previously approved and registered in clinicaltrials.gov with this NCT public number: 03706755. In cases where we could not obtain written consent, we clearly explained the study protocol to the patient, and oral consent was requested from participants before including them in the study.

Informed consent: all patients participating in this study signed a written informed consent form for participating in this study.

Patient consent for publication: written informed consent was obtained from a legally authorized representative(s) for anonymized patient information to be published in this article.

Availability of data and material: data and materials are available by the authors.

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grammed or semi-urgent caesarean section with an extraction time over 15 minutes (this implies that there is not life-threatening acute fetal distress exposing the fetus to acidosis), under spinal anesthesia.

We did not include parturients with ASA class >2, body mass index <18.5 kg/m2 or >35 kg/m^2, major dysgravidia, women taking serotonin reuptake inhibitors, with a history of multiple pregnancies, abnormal placental insertion, fetal pathologies (hydrops fetalis, intrauterine growth retardation), chorioamnionitis or with contraindications to spinal anesthesia. Patients who refused to participate in the study were not included.

Exclusion criteria for the study were the failure of spinal anesthesia, the extension of anesthetic block requiring tracheal intubation and mechanical ventilation, the occurrence of an allergic reaction to any of the anesthetics used, the occurrence of an intraoperative complication requiring additional surgery and conversion to general anesthesia for any reason. The preparation and labeling of the product were carried out by an operator who was aware of the outcome of the randomization and who was different from the second operator who conducted the anesthesia, carried out the protocol, and collected data. The parturient was also unaware of which product she had received. Randomization was carried out immediately on arrival of the parturients in the operating room by drawing lots in order to produce a balanced series of 10 patients.

The parturients were randomized into two groups: Group A, in which patients received a preventive bolus of slow intravenous diluted NAD over 15 seconds immediately after spinal anesthesia at a dose of 1 µg /Kg; Group B in which women received a preventive bolus of 0.5µg/Kg over 15 seconds immediately after spinal anesthesia.

These preventive doses were administered in order to prevent the occurrence of a sympathetic block after spinal anesthesia to maintain systolic blood pressure between 80 and 100% of its baseline value, and in all cases >100 mm Hg, given that both groups did not receive fluid loading either before or during spinal anesthesia. The sham of administration was exactly the same for both groups, they only differ in doses.

Then, to achieve this objective throughout the caesarean section, curative boluses at half the dose of the preventive boluses of NAD (0.5µg /Kg for group A; and 0.25µg /Kg for group B) were administered systematically and as much as necessary whenever the systolic blood pressure (SBP) drops by 20% of its initial reference value or was simply below100 mm Hg; and this with a

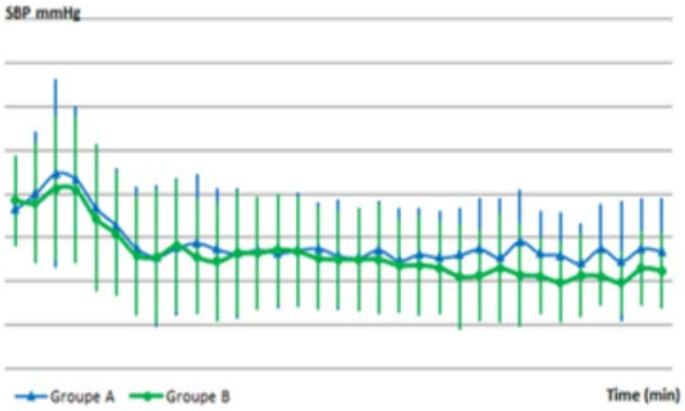

Figure 1. The variation in systolic blood pressure throughout the caesarean section was comparable between groups except at few points of time: (25-27, 30-32, 34, 35, and at 38 min) knowing that the average duration of the caesarean section was 36 min. The systolic blood pressure time curves were nearly superimposable.

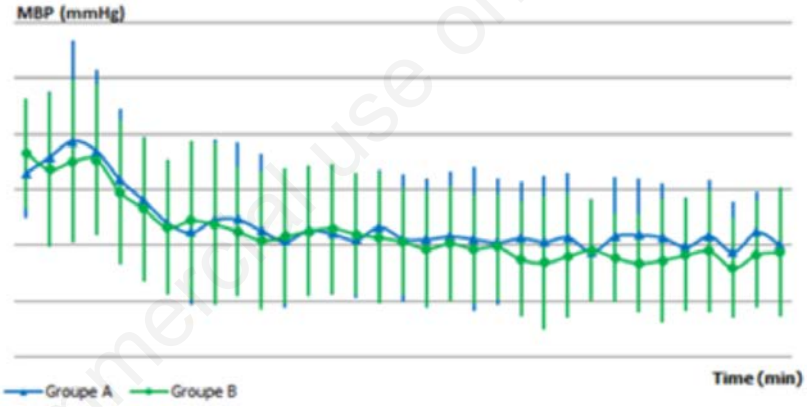

Figure 2. The variation in mean blood pressure throughout the caesarean section was comparable between groups except at few points of time: (32 and 35 min) knowing that the average duration of the caesarean section was 36 min. The mean blood pressure time curves were nearly superimposable.

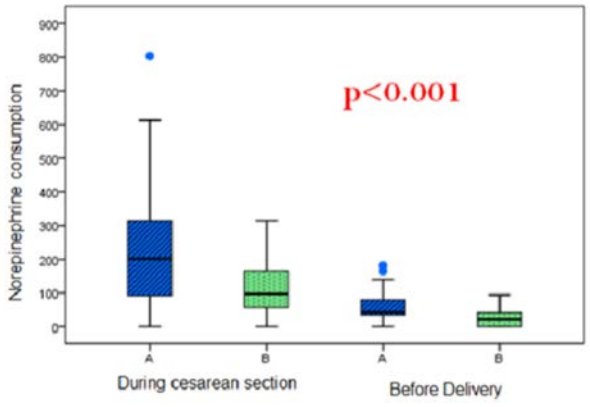

Figure 3. Mean total norepinephrine consumption was significantly greater in group A than in group B during the whole caesarean section (225±183 µg and 126±100 µg respectively; P<10-3) and before fetal extraction (57±46 µg in group A versus 30±30 µg in group B; P<10-3).

minimum delay of 02 minutes between rescue boluses. Blood pressure (BP) was measured every minute.

No other vasopressors were used during the study. In the case of hypertension (BP>120% of baseline), the course of action was to withhold treatment. For bradycardia under 40 bpm without hypotension, atropine (1 mg) was administered.

Our primary outcome was the depth of hypotension which was estimated by: i) percentage decrease in SBP (Δ SBP/reference SBP) before delivery (Δ SBPd) and throughout the caesarean section (Δ SBP: defined as the difference between reference SBP and min SBP (the minimum value of SBP measured during the caesarean section); ii) percentage drop in mean blood pressure (MBP) (Δ MBP/baseline MBP) before delivery (Δ MBPd) and throughout the caesarean section.

Secondary endpoints were time to first hypotensive episode, duration of the first hypotensive episode and the number of rescue boluses, total NAD consumption during caesarean section and before delivery (including preventive bolus), the incidence of hypotension during caesarean section and before delivery, Incidence of severe hypotension (drop in SBP below 60% of baseline), the total dose of atropine, maternal outcome (Incidence of bradycardia (HR<50), incidence of heart rhythm disturbance, incidence of reactive hypertension and Intraoperative nausea/vomiting) and finally the neonatal impact [Apgar score (at 1st and 5th min) and fetal pH (fetal acidosis defined as fetal pH from umbilical cord blood below 7.2)].

The data were processed by SPSS® software in its 22nd edition. The number of parturients required in each group was calculated using the online software Biosta TGV. The risk of error of the first kind α was fixed at 0.05 and a power 1-β at 80% in a two-sided test, to detect a difference of 5% between the two groups, the number of necessary subjects calculated was fixed at 126 patients or 63 in each group. Categorical variables were expressed as percentages and medians and compared by Pearson's and Fisher's chi-square tests. Quantitative variables were expressed as means±standard deviation with extremes if necessary. Comparisons of means were made by Student's t-test. A P-value less than 0.05 was considered statistically significant. The anonymity and security of patients' personal data were respected.

In cases where we could not obtain written consent, we clearly explained the study protocol to the patient, and oral consent was requested from participants before including them in the study. Participation was voluntary and patients did not receive any financial reward in return.

We did previously obtain the written agreement of the ethics committee and our work was previously approved and registered in clinicaltrials.gov with this NCT public number: 03706755.

Results

Demographic, anthropometric, and obstetric data were comparable between the groups. In our study, we collected 126 parturients, 63 in each group. Two parturients were excluded, the first one from group A because of a placenta accreta with bleeding, and the second one from group B because of an aorto-caval syndrome requiring the use of fluid and ephedrine before spinal anesthesia. Finally, 124 patients were included.

Until fetal extraction ,the results were comparable between groups .In fact, the SBP decreased by 19.4±11.5% in group A versus 20.5±10.6%; (P=0.57) and the MBP decreased by 24.5±15.5% in group A versus 27.5±12.5% in group B; (P=0.22). Regarding the variation in SBP and MBP throughout the caesarean section, the SBP has fallen by 24.7±9.1% in group A versus 27.6±9.4% in group B (P=0.08) throughout the caesarean section, the MBP has fallen by 36.7±9.5% in group A versus 39.3±10.5% in group B (P=0.15) (Table 1). These results were comparable between groups except at a few points of time: (25-27, 30-32, 34, and 35 and at 38 min for SBP, 32 and 35 min for MBP) knowing that the average duration of the caesarean section was 36 min. The SBP and MBP time curves were nearly superimposable (Figures 1, 2).

The first hypotension episode occurred at 6.3±3.3 min in group A versus 7.9±6 min in group B; (P=0.07), these results were comparable between groups.

Both groups were similar regarding post-spinal hypotension incidence during cesarean section (P=0.54) and before delivery (80.6% in group A and 67.8% in group B; P=0.07), duration of hypotension (1.6±1 min in group A versus 2±1.2 min in group B; P=0.08) and cumulative rescue boluses (with a median of 5 during the whole caesarean section, 1 before delivery for both groups). However, mean total norepinephrine consumption was significantly greater in group A than in group B during the whole caesarean section (225±183 µg and 126±100 µg respectively; $P<10^{-3}$) and before fetal extraction (57±46 µg in group A versus 30±30 µg in group B; $P<10^{-3}$) (Figure 3). No significant difference was found in the incidence of bradycardia, arrhythmia, nausea, and vomiting with the mother. However, the higher dose of norepinephrine resulted in more hypertension (40%) than the lower dose (18%); P<0.001.

Fetal outcomes (Apgar score and fetal pH) were similar in both groups. In fact, at one minute of life, 35% of newborns had an apgar score of 7-8 in group A versus 29% in group B; the apgar score was 9 in 65% of cases in group A versus 71% in group B; p=0.76. At 5 minutes, 26.7% of newborns had an Apgar score of 8-9 in group A versus 27.4% in group B; the Apgar score was 9 in 73.3% of cases in group A versus 72.6% in group B; p=0.99. Fetal ph was 7.33±0.08 in group A versus 7.33±0.09 in group B; p=0.8 (The incidence of fetal acidosis was negligible: 2 newborns presented a pH<7.2 in group A versus 4 in group B; p=0.28).

Discussion

The aim of our study was to determine the effective target bolus of Norepinephrine

Table 1. Percentage drop and lowest systolic blood pressure and mean blood pressure values.

	Group A	Group B	P
Delta SBP*	24.7±9.1	27.6±9.4	0.08
Delta SBPd*	19.4±11.5	20.5±10.6	0.57
Delta MBP*	36.7±9.5	39.3±10.5	0.15
Delta MBPd*	24.5± 15.5	27.5±12.5	0.22
Lowest SBP**	87.4±11.3	85.2±11	0.27
Lowest SBPd**	93.8±14.9	93.8±12.8	0.99
Lowest MBP**	52.2±7.6	52.1±8.3	0.96
Lowest MBPd**	62.3±12.7	62.2±10.1	0.98

*Percentage drop (%); **Mean±Standard deviation (mm Hg); SBP, systolic blood pressure; MBP, mean blood pressure; SBPd, percentage decrease in SBP (Δ SBP/reference SBP),[Δ SBP: defined as the difference between reference SBP and min SBP (the minimum value of SBP measured during the caesarean section)]; MBPd, percentage decrease in mean blood pressure (Δ MBP/baseline MBP).

to prevent and treat post-spinal anesthesia hypotension during caesarean delivery.

Our primary outcome has shown similarities between groups regarding the percentage decrease in SBP before delivery and throughout the caesarean section, as well as for the percentage drop in MBP. The secondary outcomes found that both doses were similar regarding post-spinal hypotension incidence, timing to the onset of the first hypotension episode, duration of hypotension, and cumulative rescue boluses. The incidence of maternal hypotension after spinal anesthesia for caesarean section is still high.[8,9]

The literature review shows that several preventive measures have been deployed and have proven insufficient, namely the use of mechanical means such as left lateral decubitus,[10] compression of the lower limbs (by bandages or compression stockings),[11] and leg raising as well as vascular fluid loading to increase venous return.

Indeed, it has recently been shown that post-spinal anesthesia hypotension is essentially the result of a drop in systemic vascular resistance due mainly to arteriolar vasodilation and to a lesser degree to venous vasodilation.[12,13] This explains why vasopressors currently play a major role in maintaining blood pressure after spinal anesthesia. These vasoconstrictor agents, by restoring vascular tone, have become the mainstay of treatment for spinal anesthesia-induced hypotension.[14]

For a long time, ephedrine was the vasopressor of choice for hypotension in the parturient after spinal anesthesia, as it preserves uteroplacental perfusion and is easy to use. However, its prophylactic use is limited by a slow onset and duration of action which can lead to tachycardia, reactive hypertension, and fetal acidosis when large doses are used.[15]

Currently, phenylephrine has become the gold standard in obstetric anesthesia.[16] It is a direct-acting α-adrenergic agonist that produces less fetal acidosis and nausea and vomiting compared to ephedrine.[17] Nevertheless, phenylephrine, especially at high doses, induces reflex bradycardia with a drop in cardiac output that can be harmful to the mother and her fetus.[18] This has led to research into other alternatives such as NAD.[19]

Indeed, NAD is a sympathomimetic amine with a very powerful direct action on α-adrenergic receptors and a more moderate action on β-adrenergic receptors. This mild beta-adrenergic agonist activity makes NAD more suitable for the physiology of hypotension induced by spinal anesthesia in the parturient.

This positive inotropic effect is in addition to the potent vasoconstrictor effect, resulting in a smaller decrease in heart rate and output compared to phenylephrine.[19] In addition, for fetal safety, NAD does not cross the placenta.[20]

The *in vitro* maternal-fetal transfer in the perfused human placenta was 11.6±0.6%;[21] the fetoplacental microcirculation was not compromised after NAD administration as reported in the study by Minzter *et al*.[22]

Although continuous infusion of the vasopressor offers better hemodynamic stability with fewer fluctuations in blood pressure and fewer interventions by the anesthetist,[23] this mode of infusion may not be common practice in limited-resource countries given the high cost of continuous infusion (due to the use of pumps).

The studies concerning NAD bolus are recent, some have chosen a fixed preventive bolus just before starting the NAD infusion,[24] while others have compared boluses of NAD alone,[25] with ephedrine or phenylephrine.[20,26] The efficacy and safety of bolus NAD as an alternative to phenylephrine for blood pressure maintenance after spinal anesthesia for caesarean section has been proven in many international studies,[21] but also by our team in previous work.[27]

Low-dose intermittent bolus NAD has proven to be effective and even superior to phenylephrine in a recent study published in 2019.[28]

Other studies have compared NAD to ephedrine for prophylaxis either as a bolus or continuous infusion where NAD has proven to be effective with less effect on maternal heart rate and fetal well-being.[26]

The efficacy of NAD has often been studied by comparing it with equivalent doses of phenylephrine or ephedrine.[26,29]

This stage of the literature has established the concept of prevention with NAD. However, the ideal dose of NAD must be sought by comparing different doses of this molecule with the purpose of determining the more effective and safer bolus dose for the management of hypotension after spinal anesthesia for caesarean section, and at the same time for both mother and fetus.

This was done in the study by Onwochei published in 2017 in which a preventive and/or curative efficacy was demonstrated without major adverse effects on either the mother or the fetus.[25]

These results were comparable to those found in our study in which we compared two boluses of norepinephrine to determine the optimal dose per weight to prevent and treat hypotension induced by spinal anesthesia for caesarean section without any vascular filling.

However, we found in our study that the incidence and depth of arterial hypotension after spinal anesthesia were comparable between groups as well as a similarity in hemodynamic status throughout the procedure between the two groups, and we can therefore infer that the 0.5μg/kg dose of NAD combined with half-dose rescue boluses is sufficient to maintain intraoperative hemodynamic stability comparably to that of the 1μg/kg.

The fact that a comparable number of rescue boluses were found between the two groups meant that the need to maintain the hemodynamic state would lie not in the injected dose but in the time interval between injections, which is in perfect agreement with the short half-life of NAD.

In fact, the usefulness of the preventive bolus is to anticipate arterial hypotension before it occurs, and the short half-life of NAD makes it necessary to use rescue injections to maintain blood pressure.

In summary, a preventive bolus of 0.5μg/kg followed by rescue boluses of 0.25μg/kg at a regular time interval of at least 2 min is sufficient to maintain a stable hemodynamic state intraoperatively.

This same result can be achieved with the preventive dose of 1μg/kg and rescue boluses of 0.5μg/kg at minimum 2 min time intervals although it is associated with a higher incidence of hypertension.

According to our study, NAD at the dose of 0.5μg/kg as a preventive bolus and rescue doses of 0.25μg/kg can be used safely for the prevention and treatment of arterial hypotension induced by spinal anesthesia during caesarean section, especially as this strategy can be adopted in limited-resource settings thanks to the low cost of NAD.

On the other hand, Apgar scores at 1 and 5 minutes of life and cord blood pH were comparable between the groups, with a negligible incidence of fetal acidosis, suggesting that even in case of fetal distress, the administration of norepinephrine to the mother will probably not cause or worsen potential fetal acidosis.

In addition, reestablishing blood pressure will certainly improve perfusion and oxygen supply to the mother and fetus which usually results in a better pH value.

Conclusions

Bolus of 0.5μg/kg with rescue doses of 0.25 μg/kg of Norepinephrine was respectively efficient in preventing and treating spinal anesthesia-induced hypotension. These doses may be recommended for routine use in healthy parturients.

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