FWA 00032748 **July 4, 2024**

IORG0011243

Management of Postspinal Anesthesia Hypotension Duing Elective Cesarean Section: Baby Norepinephrine Versus Ephedrine

Study Protocol

Background : Spinal anesthesia emerges as the preferred anesthesia technique for elective cesarean section . It offers a preferable alternative to general anesthesia because it provides better maternal safety and néonatal outcomes. However, spinal anesthesia is not free of inherent risks. Among the feared complications, hypotension remains the most common complication which threates both mother and child . In this perspective, several preventive and curative means have been studied to optimize maternal and fetal homeostasis. The common methods include fluid loading and the use of vasopressors such as ephedrine and phenylephrine. One promising approach is the administration of diluted norepinephrine. Due to its low agonist activity of the ß receptor and its powerful α adrenergic agonist activity, it presents a good alternative to preserve maternal blood pressure while minimizing adverse effects on the mother and fetus. Thus, our study proposes to evaluate the efficacy and safety of diluted norepinephrine boluses compared with ephedrine on the management of post- spinal anesthesia hypotension during scheduled cesarean sections.

Patients and methods : After approval from the Local Ethical Commitee of the Hospital (N° FWA 00032748) , and after obtaining informed written consent this prospective randomized double –blind study will be undertaken from Jun to October 2024 in the Department of Anesthesiology and Intensive care and Gynecology and Obstetrics department of Charles Nicolle Hospital of Tunis.

Inclusion criteria: Singleton full-term consenting pregnant females of ASA grade II, aged 18-38 years, scheduled for elective cesarean section under spinal anesthesia are included in the study.

Non inclusion criteria : Any parturient falling in the category ASA grade III and IV, contrindications to spinal anesthesia, preeclampsia, chronic hypertension, comorbidity with diabetes mellitus, cardiovascular disorders and psychiatric illness are non-included.

Exclusion criteria: They are excluded the case of failure of spinal anesthesia, conversion to general anesthesia, post-partum bleeding, and failure to follow protocol.

Patient groupes:

Sample size: It was calculated by (https://statulator.com/SampleSize/ss2M.html), by adjusting a power of 80%, confidence level of 95%, and margin of error of 5%. The primary outcome variable of our study is to compare the number of vasopressor boluses to maintain mean blood pressure ≥ 80% between the groupes, which was estimated from the study conducted by Elnabtity and Selim. The least number of patients required in each groupe with a standard deviation of 2 is 63.

A total of 126 parturienst are randomly divided into two equal groups by an investigator not directly linked to the study.

Groupe N: patients will received norepinephrine boluses (8 µg) ; prophylactic bolus immediately after spinal anesthesia induction and therapeutic boluses when systolic blood pressure falls to ≤ 20% of baseline. Groupe E : parturients will received ephedrine boluses (6 mg) ; systematic bolus after the induction of spinal anesthesia and therapeutic boluses if hypotention.

The syringes will be labeled as syringe A and syringe B and the anesthesiologist who will give the bolus cannot know if it is ephedrine or norepinephrine.

The preparation of diluted norepinephrine is done by two dilutions: first dilution: 1ml of norepinephrine 2 mg/ml is diluted to 50 ml with 0.9% normal saline to have a concentration of 40 µg/ml. The second dilution: 1ml of norepinephrine 40µg/ml is diluted to 10 ml with 0.9% normal saline in 10 ml syringe prepared as final concentration of 4 µg/ml.

Ephedrine is preparated in 10 ml syringe at a concentration of 3 mg/ml.

Preoperative period: A preanesthesia consultation is performed for patients included in the protocol. The modalities of the young preoperative, the anesthetic technique, the protocol of the study are explained to the parturients. Written and signed informed consent by the patients included in the study is obtained.

Intraoperative setting: On arrival to the operating room after a Check list, The parturient is positioned on the operating table in the supine position with left uterine displacement. Standard monitoring is used including non-invasive blood pressure (NIBP), pulse oxymeter

(SpO2) and electrocardiogram (ECG). We record three values of systolic, diastolic, and mean blood pressure and heart rate before any patient stimulation. An intravenous canula 18 G is inserted and antibiotic prophylaxis is administered 30 minutes before surgical incision using 2 g of cefazoline or 900 mg of clindamycin in case of allergy to penicillins.

Induction of spinal anesthesia: Co fluid loading 10 ml /kg of crystalloids is commenced. In the sitting position, under all aseptic precautions, introduction of spinal needle 25 gauge at L3-L4 or L4-L5 vertebral interespace. After obtaining free flow of cerebrospinal fluid, a standard mixture of anesthetic product : 10 mg of hyperbaric bupivacaine 0.5% (08 mg if parturient's size ≤ 160 cm) with 2.5 µg of sufentanil and morphine 0.1 mg is injected. After intrathecal injection, parturients take quickly their initial position and the first prophylactic bolus of the vasopressor (2 ml) from syringe A or syringe B is administrated. Oxygen is administred by ventimask at rate of 3 l/min till the delivery of the baby. The level of sensory block is evaluated by pin prick test. Successful sensory block is defined as block reaching T4 dermatomal level. If after 20 minutes the sensory block level remains < T10, a conversion to general anesthesia is performed and the patient is excluded from the study.

Heart rate, systolic, diastolic and mean blood pressure are recorded every minute for the first 15 minutes after spinal anesthesia and every five minutes until the end of the intervention.

Management of hypotension: When systolic blood pressure (SBP) decreases to ≤ 20% of baseline, a rescue bolus of vasopressor (2 ml of syringe A or syringe B) is given. Reinjection of the same bolus is repeated after 1 minute if hypotension persists. Administration of boluses is stopped when the value of the SBP finds ≥ 80% of the baseline.

After clamping of the umbilical cord, Oxytocin is given as an initial bolus of 10 UI over 3 minutes followed by slow infusion of 15 UI in 0.9% normal saline. Neonatal APGAR score at 1 minute and five minutes is recorded.

Primary outcome: Number of vasopressor boluses used in each group to treat hypotension (SBP decreases to ≤ 20% of baseline) is recorded.

Secondary outcomes: Complication during the surgery as incidence of hypertension (SBP ≥ 20% of baseline), tachycardia (Heart rate ; HR ≥ 120 beats/min), bradycardia (HR ≤ 60 beats/min), nausea and vomiting are recorded. We'll also recorded neonatal APGAR score of the first and 5th minute.

Statistical study:

Data entry and analysis will be performed by SPSS version 25.0 software

We will use Excel 2019 software to edit the charts. **Descriptive study:** Continuous quantitative variables following a normal distribution will be expressed by their means and standard deviation. Continuous quantitative variables not following a normal law will be expressed by their median and interquartile [25%-75%]. Qualitative variables will be expressed as simple frequencies (n) and relative frequencies as a percentage. **Analytical study:** For the analysis of the association between two qualitative variables, Pearson chi-2 test for the comparison of two frequencies under verified application conditions and the Fischer test otherwise will be used. For the analysis of the association between a qualitative variable and a quantitative variable, T test of Student will be used for the comparison of two means and the non-parametric test of Mann Whitney otherwise. A significance threshold for p 5% will be retained. In the multivariate study, risk was calculated by the Odds Ratio (OR) with a retained confidence interval of 95% (95% CI).

Hôpital Charles Nicolle
Comite D'ETHIQUE LOCAL

Numéro d'approbation :

FWA 00032748

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Tunis, le 16/04/2024

ATTESTATION

Le comité d'Ethique local de l'hôpital Charles Nicolle s'est réuni le 07/02/2024 et a examiné la demande présentée par Docteur Abdelmajid HAFYENE concernant l'étude intitulée :

« Gestion de l'hypotension induite par la rachianesthésie au cours des césariennes programmées : Baby noradrénaline versus éphédrine ».

Ont participé aux délibérations :

- Dr HAMDOUN Moncef
- Dr RAMMEH Soumaya
- Dr BEN ALI Nedia
- Dr MOUELHI Leïla

Le comité a adopté la décision suivante : Avis favorable

Professeur Moncef HAMDOUN

Président du comité d'Ethique local

Hôpital Charles Nicolle

July 4, 2024