

NOREPINEPHRINE AND ETILEFRIN AS PREVENTION OF MATERNAL HYPOTENSION IN CESAREAN SECTION UNDER SPINAL ANESTHESIA

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ABSTRACT

Introduction: In Bolivia there is the difficulty on availability of the drug such as phenylephrine, there is the immediate need to evaluate another drug with pharmacological characteristics that are useful for this purpose

Objetivo: To compare the use of norepinephrine versus etilefrine as prevention of maternal hypotension after spinal anesthesia in elective cesarean section.

Methods: Was conducted a randomized double-blind clinical trial in 126 patients undergoing Cesarean section under spinal anesthesia divided into three groups of 42 patients. Group E received Etilefrine bolus 2 mg, group NB norepinephrine bolus 5 µg and group NI norepinephrine infusion 0,01 µg /kg/ min to control hypotension control of mean arterial pressure, heart rate, were performed an analysis of drug cost and scores of APGAR. Was performed the statistical analysis in SPSS 22 and Microsoft Excel 2010.

Results: Mean arterial blood pressure was similar until before birth, later it is better controlled with norepinephrine infusion (p 0,000). The most stable heart rate in the NB group (p 0,000). There were maternal adverse effects and in the newborn. There is a higher cost to use bolus ethylephrine 42.5 ± 8.36 (bolivianos) than to use norepinephrine in infusion 0.50 ± 0.15 (bolivianos) and bolus norepinephrine 0.45 ± 0.14 (bolivianos) there is a statistically significant difference (p 0,000).

Conclusions: The use of norepinephrine in infusion compared to etilefrine is effective because the hemodynamic variables were better controlled at a very low cost for the management of maternal hypotension after spinal anesthesia.

INTRODUCTION

Regional anesthesia is preferred for caesarean section because it avoids maternal risks of general anesthesia such as aspiration of gastric contents and difficulty in the management of the airway¹. The Standard Gold for cesarean section continues being spinal anesthesia and hypotension is a very common complication caused by sympathetic vasomotor blockage accompanied by maternal symptoms such as nausea, vomiting and adverse effects in the fetus including low Apgar scores and umbilical acidosis. This has been correlated with the duration and severity of hypotension².

The incidence of maternal hypotension after spinal anesthesia during cesarean section without prophylactic therapy is reported from 60% to 95% in normal women^{3,4}.

The management and prevention of hypotension after spinal anesthesia is continuously investigated, can be managed by fluid loading (preload or cocharge), vasopressors and maternal position protocols (Relieving aortocaval compression and increased venous return)^{5,6}.

Phenylephrine is the first ideal vasopressor for the prevention and treatment of maternal hypotension during spinal anesthesia for caesarean section⁷.

Norepinephrine is similar to phenylephrine in being a potent α -adrenergic agonist, but also has weak β -adrenergic agonist activity. Plasma clearance by the lungs (45%), kidneys (8%), hepato-mesenteric system (25%) is dependent on cardiac output. It is metabolized by monoamine oxidase and catechol-O-methyltransferase to vanillylmandelic acid. It has a half-life of 1 to 2 minutes. It increases arterial blood pressure due to vasoconstriction and an increase or maintenance of heart rate, blood volume and cardiac output⁸.

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In Bolivia there is the difficulty of availability of the drug such as phenylephrine, there is an immediate need to evaluate another drug with pharmacological characteristics that are useful for this purpose. In the daily clinical practice of the country Ethylephrine is the vasopressor mostly used for the treatment of hypotension after spinal anesthesia in this context. There is the availability of two drugs in our environment ethylephrine and norepinephrine which will be compared in this work, but access to Ethylephrine in the hospital is limited.

The aim of the study is to compare norepinephrine versus etilefrine as prevention for the management of maternal hypotension in cesarean section under spinal anesthesia in the Obstetrics Department of Hospital Obrero N° 2.

MATERIALS AND METHODS

The present study is an analytical, randomized, double-blind clinical trial and was approved by the Department of Obstetrics and Gynecology in the Hospital Obrero N° 2 "CAJA NACIONAL DE SALUD" (National health center) in the city of Cochabamba - Bolivia.

The study population was all patients undergoing elective cesarean section and 126 patients were obtained, based on the following inclusion criteria: Patients with a gestational age of 37 to 42 weeks, classification of physical status ASA I and II, age over 18 years of age, without contraindications for regional anesthesia and who accepted informed consent. Exclusion criteria: hypertensive disorders associated with pregnancy, cardiovascular or cerebrovascular disease, non-reassuring fetal status, emergency patients and those who refused to participate in the study.

Groups

All participants were randomized into three groups, with a sample of 42 patients per group. The groups were formed: group E (etilefrine in bolus), group NB (norepinephrine in bolus) and group NI (norepinephrine in infusion).

Procedures:

Spinal anesthesia

The patient was prepared with peripheral venous catheter of caliber # 18, the sites of choice were the antecubital, cephalic or basilic, avoiding skin folds, ensuring permeability and functioning before and during the administration of the vasopressors used.

In the patients in the operating room, the basic monitoring of vital signs was carried out.

In the patients in the sitting position, asepsis and antisepsis were performed, lumbar puncture by median approach with spinal needle pencil point Whitacre No. 27 at the space level L3 - L4, L4 - L5; confirming the correct placement of the needle by the free flow of cerebrospinal fluid, anesthetic solution containing: 10mg of 0,5% hyperbaric Bupivacaine, Fentanyl 20µg and morphine 100µg was administered. Patient in su-

pine position with the pelvic wedge to move the uterus to the left. The basic monitoring of non-invasive blood pressure, continuous electrocardiogram, heart rate and pulse oximetry was carried out; control of these parameters was performed in the pre-anesthetic consult (2 weeks prior), upon admission to the operating room, 5 minutes after admission to the operating room, during the administration of local anesthetic, after the administration of local anesthetic, before birth, after administration of oxytocics and after surgery.

Crystalloid solutions were administered at a rate of 15ml / kg, and the duration of the surgical procedure and the APGAR score at minute and 5 minutes were recorded.

Vasopressor administration protocol

a.- Etilefrine at a 2 mg dose per bolus. One ampule of 10mg diluted with 9 ml of distilled water (concentration 1mg / ml); of the same preparation, once the anesthesia finished. The medication was applied as many times as necessary to treat episodes of maternal hypotension.

b.- Norepinephrine bolus dose response of 5µg/kg per bolus; Once the surgery was started, the medication was applied as many times as necessary to treat episodes of maternal hypotension. Prepared at a concentration of 10µg / ml, take 5ml in a 10ml syringe, diluting it with 5ml distilled water, obtaining a concentration of 5µg / ml.

c.- Norepinephrine once the surgical act is started on the BRAUN® SPACE 8713050 infusion pump at a rate of 0.01µg / kg/min, the infusion was maintained throughout the surgery and was discontinued at the end or when any adverse effect occurred in the patient. Solution of 500ml of 5% dextrose was discarded 100ml; leaving 400ml of it, and then a 4mg norepinephrine ampoule (concentration 10µg / ml) was diluted. Atropine 0.5mg was used in case of presenting a heart rate less than 50 beats per minute (HR <50).

Statistic analysis

A database constructed in Microsoft Excel version 2013 was used and analyzed by means of the statistical program SPSS version 22. For the description of numerical and categorical variables the mean and the mode respectively were used. The contrast of hypothesis and the comparison between groups was carried out using the chi-square and the t-student, as appropriate.

P values less than 0.05 were considered statistically significant.

TABLE N° 1: DEMOGRAPHICAL DATA

	ETHYLEPHRINE BOLUS	NOREPINEPHRINE BOLUS	NOREPINEPHRINE INFUSION	GROUP Ey 2	GROUP Ey 3	GROUP NB y 3
	Mean-DE*	Mean- DE	Mean-DE	VALUE P	VALUE P	VALUE P
AGE (years)	28,64 ± 5,39	32,48 ± 5,23	32,19 ± 4,28	0,103	0,10	0,785
BMI*	30,08 ± 4,01	31,04 ± 4,50	32,42 ± 5,49	0,305	0,028	0,209
GESTATIONAL AGE (weeks)	38,41 ± 0,72	38,51 ± 0,70	38,86 ± 0,75	0,499	0,006	0,032
SURGICAL TIME (minutes)	71,07 ± 6,40	70,12 ± 8,80	65,71 ± 16,25	0,572	0,05	0,126

*BMI: Body Mass Index. *DS: Deviation Standard

FIGURE N°1. MEAN BLOOD PRESSURE

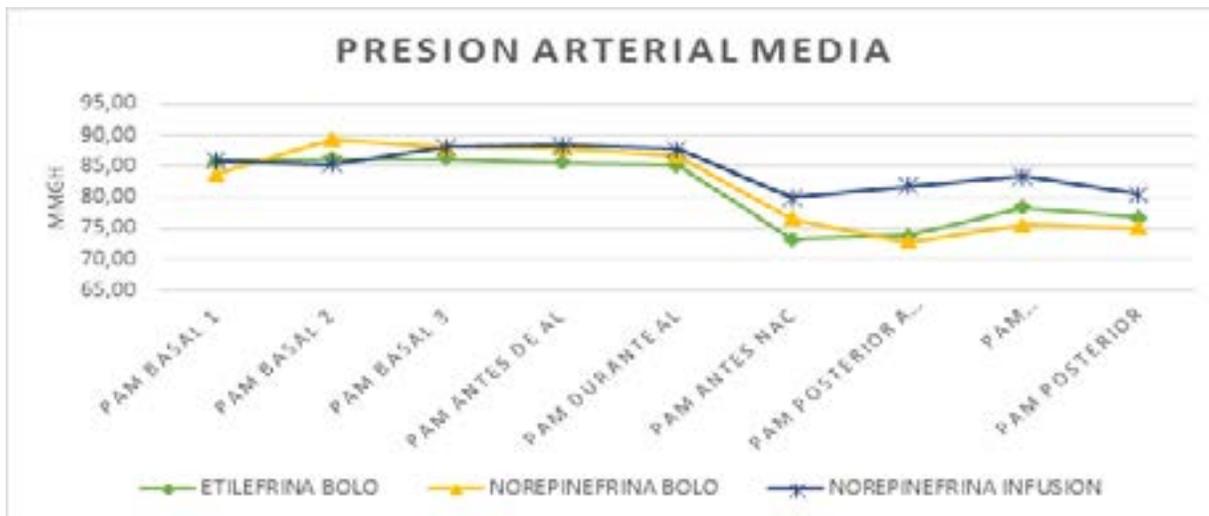
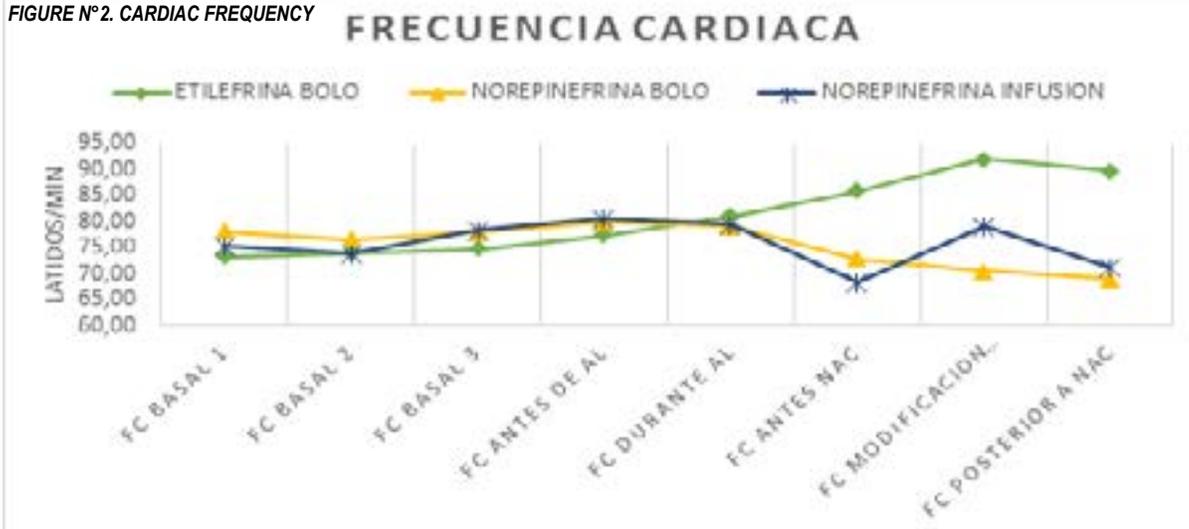


FIGURE N°2. CARDIAC FREQUENCY



RESULTS

During January 2017 to January 2018, 126 patients scheduled for cesarean section who met the inclusion criteria for the present study were studied.

They were divided randomly into three groups of 42 patients each, to whom they were administered, for group E (ethylephrine), group NB (norepinephrine in bolus) and group NI (norepinephrine in infusion).

The average age of the E group (Ethylephrine) is $29 \pm 5,39$ years, the NB group (norepinephrine in Bolus) is $32 \pm 5,23$ years and the NI group (norepinephrine in infusion) is $32 \pm 4,28$ years. There is no significant difference between the groups (p value $\Rightarrow > 0,05$).

There is no significant difference in the Body Mass Index (BMI), gestational age and surgical time among the three study groups (p value $\Rightarrow > 0,05$). (See Table N° 1)

The classification of the physical state of the American Society of Anesthesiology was found ASA I: group E = 15 pa-

tients, group NB = 13 patients and group NI = 11 patients and ASA II: group E = 27 patients, group NB = 29 patients and group NI = 31 patients. Value $p = 0,640$.

In the APGAR assessment there is no significant statistical difference. The APGAR at the minute was 8 points and at 5 minutes of 9 points. Value $p = 0,046$.

There were no maternal complications or secondary findings due to the use of vasopressors by peripheral route.

The baseline values of mean arterial pressure (MAP) taken before the administration of local anesthetic are similar values Group E MAP = $86,17 \pm 5,9$ mmHg. Group NB MAP = $88,08 \pm 6,97$ mmHg. NI PAM group = $88,10 \pm 9,15$ mmHg. P value between group E and group NB is 0,175; P value between group E and group NI is 0,252; P value between NB group and NI group is 0,993. The mean blood pressure before birth, after birth, modified with oxytocics and at the exit of the operating room is statistically significant in groups E

and Group NI (P value: 0,000, 0,000, 0,001 and 0,004 respectively) and in group NB and Group NI (P value: 0,013, 0,000, 0,000 and 0,000 respectively). Regarding group E and Group NB, there is no significance between the two groups (P value: 0,005, 0,288, 0,053 and 0,207 respectively). Figure N ° 1 The best controlled heart rate occurred in the NB norepinephrine group in bolus, in the group of Ethylephrine in Bolus after the administration tachycardia was evident and in the norepinephrine group in infusion there were oscillations of the same. Statistical significance was observed in 2 groups taking the heart rate before the birth of the product, after the use of oxytocics and after the birth of the product. Group E and Group NB (P value: 0,000, 0,000 and 0,000 respectively). Group E and Group NI (P value: 0,000, 0,000 and 0,000 respectively). In Group NB and Group NI it is not significant before birth and after birth of the product, but it is significant after the use of oxytocics (P value: 0,005, 0,000 and 0,184 respectively). Figure No. 2

To the average of the cost analysis it is evidenced, a higher cost to use Ethylephrine in bolus $42,5 \pm 8,36$ (Bolivians) than to use norepinephrine in infusion $0,50 \pm 0,15$ (Bolivians) and norepinephrine in bolus $0,45 \pm 0,14$ (Bolivians) there is a statistically significant difference. Group E and group NB (value P = 0,000), Group E and Group NI (value P = 0,000) and Group NB and Group NI (value P = 0,077). The total volume of vasopressors used during the surgical act is not statistically significant. See table 2.

DISCUSSION

The present study evaluates and compares the effectiveness of norepinephrine and ethylephrine, two vasopressor drugs widely used in clinical practice.

The study demonstrates that it is statistically significant when using norepinephrine in infusion compared to group E-NI and NB-NI since the hemodynamic changes are more stable, according to Hasanin's report the administration protocols for vasopressors in prevention and management of hypotension it is not clear both for infusion and for bolus management of vasopressors⁵. Ngan reported that norepinephrine has similar efficacy to phenylephrine but in maintenance of cardiac output and maternal heart rate is better⁹.

In the study conducted it was found that the use of norepinephrine despite having a biological half-life and duration of less than Ethylephrine, its use in controlled infusion showed greater efficacy in terms of the prevention of maternal hypotension, similar reported in his work. Ngan et al. indicate that manual infusion of $5 \mu\text{g} / \text{ml}$ norepinephrine was effective in decreasing the incidence of hypotension during spinal anesthesia for caesarean section¹⁰. Also in another study by Ngan et al. that the accuracy of blood pressure control was better with norepinephrine compared with phenylephrine used by the computer-controlled

TABLE N° 2 MEDICAMENTS COST ANALYSIS

	ETYLEPHRINE BOLUS	NOREPINEPHRINE BOLUS	NOREPINEPHRINE INFUSION	VALUE P GROUP Ey 2	VALUE P GROUP Ey 3	VALUE P GROUP NB y 3
	Mean DE	Mean DE	Mean DE			
COST (Bs.)	$42,5 \pm 8,36$	$0,45 \pm 0,14$	$0,50 \pm 0,15$,000	,000	,077
TOTAL VOLUME (ml/a)	$4,1 \pm 0,76$	$4,45 \pm 1,4$	$5,04 \pm 1,54$,110	,000	,077

*Bs: Bolivians. ° ml: milliliters.

infusion system¹¹, on the contrary, in the case of the bolus etilefrin group, a good response was obtained from the first bolus but with an increase in the level of the heart rate, probably due to its β adrenergic effect.

Bolus norepinephrine administration of $5 \mu\text{g}$ was easier to dose since the effective dose 90 is $5,49 \mu\text{g}$ determined by Onwochei et al¹². Conversely Ngan in his study indicates that the equivalent dose of $7,6 \mu\text{g}$ (95% CI) , 6 to $10 \mu\text{g}$ is equal to $100 \mu\text{g}$ of phenylephrine¹³.

Regarding heart rate, the group that showed the best control was the NB group of $5 \mu\text{g} / \text{ml}$, while in the NI group, it showed decreases of approximately 8 beats from one shot to the next, but no bradycardia was reported. Similar recommendation according to Ngan that norepinephrine can be an alternative to phenylephrine with the advantage of lower decrease in heart rate and cardiac output¹⁴. Contrary to the study by Dong et al. They administered $10 \mu\text{g}$ boluses ($10 \mu\text{g} / \text{ml}$) where they reported an incidence of bradycardia of 2% (defined bradycardia <60 beats per minute)¹⁵.

The total volume of the NI group was $4,6 \text{ ml} / \text{h}$ equivalent to $0,38 \mu\text{g} / \text{min}$. Ngan et al. use $2,14 \mu\text{g} / \text{min}$ for elective caesarean section and $1,81 \mu\text{g} / \text{min}$ in non-elective caesarean section, this difference is probably due to the type of Latin American population versus the American population¹⁶. (Weight and height)

There were no significant differences between study groups with respect to APGAR scores and side effects in the newborn.

There were no adverse effects at the peripheral level due to administration of Ethylephrine and norepinephrine in any of the study groups, the use of norepinephrine was diluted because it is usually very concentrated and its use is limited, only in areas of intensive therapy and cardiac anesthesia, without However, the use of norepinephrine in the obstetric field will be a challenge and requires large-scale intravenous access and diluted norepinephrine solutions according to Carvalho et al¹⁷.

When comparing the cost - benefit of both drugs (Norepinephrine - Ethylephrine), according to the protocol of preparation of vasopressors and its use in both infusion and bolus, the presence or absence of adverse effects, norepinephrine has a greater advantage in terms of cost and benefit when using it in the form of infusion.

In conclusion, it was observed that the use of norepinephrine in infusion maintains better the maternal hemodynamic parameters without repercussion in the APGAR scores obtained in the study, in addition it was evidenced that the cost is too accessible and that if we have this medication in the Hospital.

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