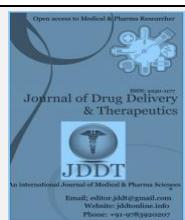
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Case Series

Bupivacaine-Fentanyl vs Ropivacaine-Fentanyl: Evaluation of two Spinal Anesthesia Protocols for Emergency Cesarean Section

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Abstract

Objective: Evaluation of the hemodynamic, respiratory and fetal side effects of two protocols for spinal anesthesia (P1: bupivacaine-fentanyl; P2: ropivacaine-fentanyl).

Material and Method: Prospective pseudo-randomized study comparing two spinal anesthesia protocols for emergency cesarean section conducted in the operating room of the regional hospital center of Saint Louis in Senegal. Study duration was 4 months. We studied, age, indication for Caesarean section, medical and surgical history, P1 and P2 protocols, hypotension, bradycardia, Apgar scores at birth and at 5min. Univariate and bivariate analysis was performed on the R software.

Result: A total of 115 patients were collected, with a mean age of 27.1 years (E: 15 - 45) and a standard deviation of 7.6. Indications for Caesarean section were maternal and fetal dystocia for 67 patients (58%), fetal distress for 39 parturients (34%), and pre-eclampsia for 5 patients (4%). The P1-Bupi spinal protocol was used in 42 patients (36.5%) and the P2-Ropi spinal protocol was used in 73 patients (63.5%). Anesthetic complications such as low blood pressure, bradycardia and desaturation were found in a total of 30 patients, i.e. in 26% of cases. The mean Apgar score at birth for newborns from the P1-Bupi protocol was 8 (Extremes: 7, 9); the mean Apgar score at birth for newborns from the P2-Ropi protocol was 7.5 (Extremes: 2, 10). There was a significantly negative correlation between the P1-bupi protocol and the appearance of hypotension with p-value: 0.04 and a significantly positive correlation between the P2-ropi protocol and the appearance of hypotension with p-value: 0.04.

Discussion/ Conclusion: Ropivacaine certainly has a better cardiovascular and neurological tolerance and a better efficacy in terms of analgesia. However, during caesarean sections, it is important to consider the risk of hypotension and possible fetal complications related to its use.

Keywords: Ropivacaine - Bupivacaine - Spinal anesthesia - Caesarean section

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Introduction:

Hemodynamic and/or respiratory complications related to spinal anesthesia (SA) during emergency cesarean sections are feared by anesthetists. They can be life threatening in the absence of appropriate prevention and management. They have a multifactorial origin and must be considered from the pre-anesthetic visit to the postoperative monitoring room. Bupivacaine hyperbaric-fentanyl on the one hand and ropivacaine-fentanyl on the other hand are protocols used for spinal anesthesia during emergency caesarean sections. The objective of this work is to compare the hemodynamic, respiratory and fetal side effects of these two protocols during emergency cesarean sections.

Material and method:

We conducted a prospective study comparing two spinal anesthesia protocols for emergency cesarean section. The study was conducted in the operating room of the regional hospital center of Saint Louis in Senegal. It took place over 4 months from 01/02/2019 to 31/05/2019 and involved all patients admitted for emergency Caesarean sections. We excluded patients with preoperative hemodynamic instability, known heart disease, anemia with a hemoglobin level < 9 g/dl and those whose cesarean section was performed under general anesthesia. All our patients benefited from the previously established emergency spinal anesthesia (SA) protocol. Indeed, from the moment they are

admitted to the maternity department, all patients benefit from a minimal biology (blood count and coagulation studies, blood group - rhesus if not done in prenatal care). Admission to the operative room as soon as the obstetricians indicate a caesarean section, setting up of a peripheral venous line with pre-filling of 500ml of crystalloid, bladder catheterization, standard monitoring (ECG, NIBP, SpO₂, CO₂-Expired if necessary). The choice of the anesthetic technique was made according to the degree of emergency, the patient's condition and the condition of the fetus. Spinal anesthesia is the best technique, considering contraindications and the clinical condition of the patient. We used on the basis of a pseudo-randomized draw either the P1-Bupi protocol (7.5 mg to 10 mg hyperbaric bupivacaine 0.5% - 25 microgram fentanyl and 100 microgram morphine) or the P2-Ropi protocol (12 to 15 mg isobaric Ropivacaine 0.75% - 25 microgram fentanyl and 100 microgram morphine). The puncture was performed with fine needles of 25, 26 or 27 G at the L3-L4 or L4-L5 spaces. A pre-filling of 300 to 500ml of crystalloid was carried out associated with second generation cephalosporin-based antibiotic prophylaxis. After intrathecal administration of the product, a dorsal decubitus installation was performed with a discreet lifting of the right buttock by a cushion and continuous monitoring of BP, SpO₂, HR, RR, diuresis. A block height at T8 - T9 was sufficient to indicate the incision. Oxytocin was administered as soon as the umbilical cord was clamped (5 IU bolus then bolus of 01 IU to 02 IU as needed). The parameters studied were age, indication for Caesarean section, medical and surgical history, products used for SA (bupivacaine hyperbaric-fentanyl-morphine vs ropivacaine-fentanyl-morphine), intraoperative hypotension (SBT < or equal to 80 mm hg) ephedrine-responsive or not, bradycardia (HR < 45 b/min), low blood oxygen level (SpO₂ < 95%) and/or total spinal anesthesia, Apgar score at birth and APGAR score at 5min. The data were collected on an Excel database and then analyzed using R software. A univariate descriptive analysis and then a bivariate analysis were carried out to determine the risk or favorable factors when the p-value is < 0.05.

Results:

A total of 115 patients were collected during the study period, with a mean age of 27.1 years (E: 15 - 45) and a standard deviation of 7.6. The indications for Caesarean section were maternal-fetal dystocia in 67 patients, i.e. in 58% of cases, fetal distress in 39 parturients, i.e. in 34% of cases, pre-eclampsia in 5 patients, i.e. in 4% of cases, and fetal malformation in 2 patients, i.e. in 2% of cases (Table 1). The P1-Bupi protocol of spinal anesthesia was used in 42 patients, i.e. in 36.5% of cases, and the P2-Ropi protocol of spinal anesthesia was used in 73 patients, i.e. in 63.5% of cases. Anesthetic complications such as hypotension, bradycardia and low blood oxygen level were found in a total of 30 patients, i.e. in 26% of cases. Systolic arterial hypotension (SBP < 80 mm hg) was found in 26 patients, i.e. in 87% of cases, bradycardia (HR < 45 b/min) in 3 patients, i.e. in 10%, and low oxygen blood level (SpO₂ < 95%) in 1 patient, i.e. in 3% of cases (Table 2). At fetal extraction, an Apgar-birth score > 7 was noted for 96 newborns (84%) and an Apgar-birth score ≤ 7 was noted for 19 newborns (16%). The mean Apgar score at birth for newborns from the P1-Bupi protocol was 8 (Extremes: 7, 9); the mean Apgar score at birth for newborns from the P2-Ropi protocol was 7.5 (Extremes: 2, 10); however, the mean Apgar scores at 5 minutes for the P1-Bupi and P2-Ropi protocols were 9.5 (E P1-Bupi: 7, 10 and E P2-Ropi: 3, 10). Figures 1 and 2 show the distribution of Apgar scores at birth and at 5 min for P1-Bupi and P2-Ropi. In our series, there was a significantly negative correlation between the P1-bupi protocol and the appearance of hypotension with p-value: 0.04 and a significantly positive correlation between the P2-ropi protocol and the appearance of hypotension with p-value: 0.04. In addition, the relation between the P1-Bupi and/or P2-Ropi protocols and the appearance of desaturation, bradycardia and/or changes in Apgar scores were not significant. (Figures 3 and 4).

Table 1: Distribution of indications for Caesarean section according to the use of bupivacaine and ropivacaine

Caesarean section Indication	Bupivacaine	Ropivacaine	Total (%)
Fetopelvic dystocia	25	42	67 (58)
Fetal distress	13	26	39 (34)
Preeclampsia	02	03	05 (04)
Hemorrhage	02	00	02 (02)
Fetal malformation	01	01	02 (02)
Total	42	73	115 (100)

Table 2: Distribution of complications according to P1-Bupi and P2-Ropi protocols

Complications	Bupivacaine	Ropivacaine	Total (%)
Arterial hypotension	05	21	26 (87)
Bradycardia	01	02	03 (10)
Low blood oxygen level	01	00	01 (03)
Total	07	23	30 (100)

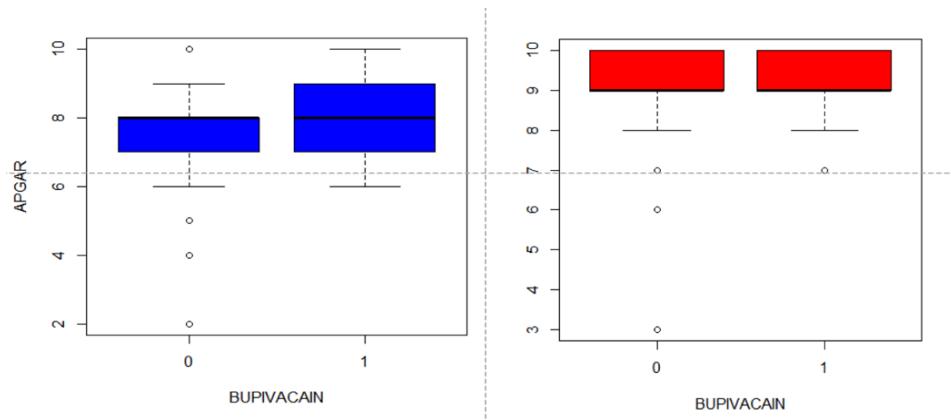


Figure 1: Distribution of Apgar scores at birth and at 5 minutes according to the P1-Bupi protocol

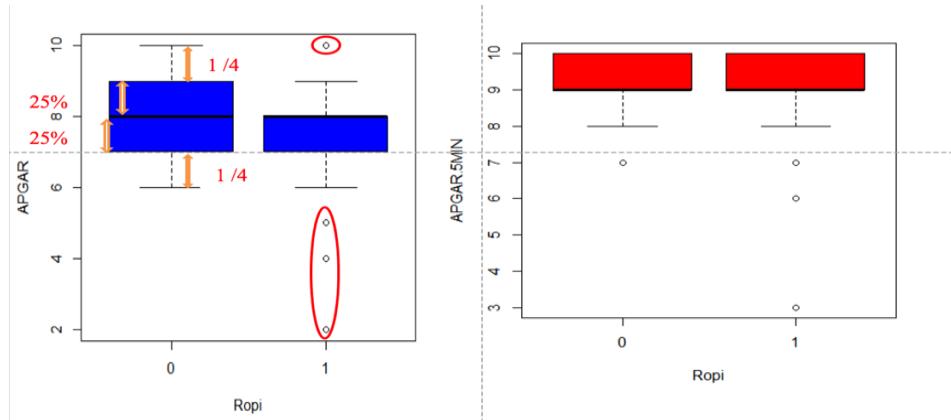


Figure 2: Distribution of Apgar scores at birth and at 5 minutes according to the P2-Ropi protocol

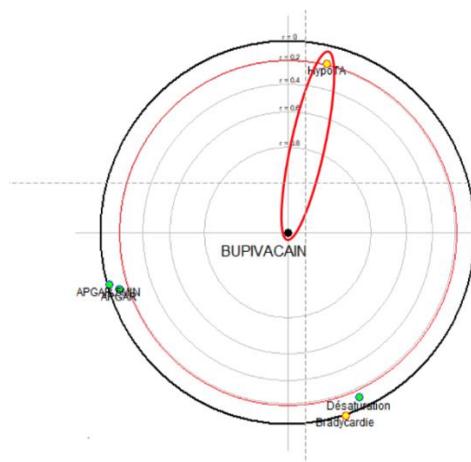


Figure 3: Relation between P1-Bupi and complications

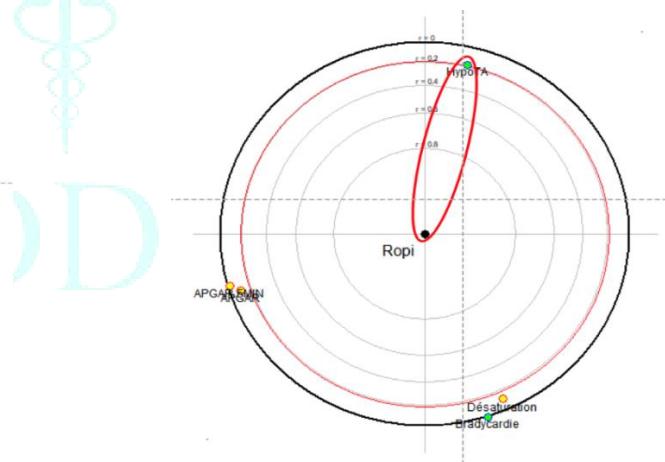


Figure 4: Relation between P2-Ropi and complications

Discussion:

Spinal anesthesia is a commonly used anesthetic technique for Caesarean section. Adapted equipment with "pencil-point" needles limits the risk of post-puncture headaches and numerous studies have made it possible to better adapt the control of induced arterial hypotension (hypo BP) ¹. It is the first choice technique unless the patient refuses, a platelet count < 50 000/l, uncontrolled infection, bleeding or anticoagulants, neurological disease in flare-up, some heart diseases, tight stenosing valvulopathy, code red. The use of a local anesthetic combined with a short-acting morphine and low-dose morphine makes it possible in most cases to perform an SA Caesarean section safely and to anticipate

postoperative pain ¹. However, the choice of local anesthetists does not follow such a strict codification. It depends mainly on pharmacokinetic and pharmacodynamics knowledge, side effects, duration of the sensory-motor block. The effects of bupivacaine and ropivacaine on the sensory-motor blocks are well described in the literature. There is a preference for ropivacaine for ambulatory procedures due to the rapid wear off of the motor block and a possible lower risk of urine retention ². However, the obsession in the choice of local anesthetics lies in their cardiac and respiratory side effects.

Indeed, ropivacaine causes a reversible inhibition of the influx of sodium ions and thus blocks the impulse conduction of nerve fibers ³. This action is potentiated by the dose-

dependent inhibition of the potassium channels that it induces⁴. Ropivacaine is less lipophilic than bupivacaine and is less likely to penetrate the large myelinated motor fibers; therefore, it has a selective action on the pain-transmitting nerves A_β and C rather than on the A_β fibers, which are involved in motor function.⁵ Ropivacaine is less lipophilic than bupivacaine and this, together with its stereoselectivity properties,⁵ contributes to ropivacaine having a significantly higher threshold for cardiac toxicity and central nervous system (CNS) toxicity than bupivacaine in animals⁶ and healthy volunteers⁷. The lower lipophilicity of ropivacaine compared to bupivacaine was correlated with the lower cardiac depressant effects of both ropivacaine isomers compared to bupivacaine isomers in animal studies.⁵

The incidence of cardiac toxicity and CNS toxicity resulting from inadvertent intravascular injection of ropivacaine appears to be low.⁶ Based on pooled analysis of data from 3000 patients in 60 clinical studies, the incidence of probable accidental IV injection of ropivacaine was \approx 0.2% (six patients) and only one patient experienced seizure; no patients showed symptoms of cardiac toxicity⁶. The seizure local anesthetic doses of bupivacaine and ropivacaine have been studied in different animal models; bupivacaine has a seizure threshold 1.5 to 2.5 times lower than ropivacaine. In addition, when injected directly into the coronary artery of sheep at doses that minimize CNS effects, ropivacaine produced less myocardial depression and conduction changes than bupivacaine⁷. Santos et al⁸ and Nancarrow et al⁹ in the sheep model and Feldman et al¹⁰ in the dog model found that death was higher in those given ropivacaine than bupivacaine. Santos et al⁸ also demonstrated that, contrary to reports,¹¹ local anesthetic toxicity is not increased during pregnancy. The study by Feldman et al¹⁰ may be of particular clinical relevance because the animals in this study received a rapid IV bolus to induce cardiac arrhythmia and death, whereas in other studies the animals received continuous IV infusion at low flow rates. This is particularly important because most cases of clinical toxicity practice are from inadvertent rapid IV bolus inadvertently rather than increased serum levels that may result from absorption. Based on animal and volunteer studies, it can be concluded that ropivacaine appears to be less neurotoxic and cardiotoxic than bupivacaine.¹² Bernhard M. et al. also confirmed the cardiotoxicity of bupivacaine superior to ropivacaine during direct intravenous infusions through the atrioventricular block induced by bupivacaine¹³.

In our study, no neurological side effects such as seizure were found. Moreover, the side effects that could be secondary to cardiotoxicity (hypotension, bradycardia) were the majority in parturients who received ropivacaine and this is probably related to the non-homogeneous sampling, even if a significant relationship is noted between the use of ropivacaine and the onset of hypotension. The plasma concentration of ropivacaine is dependent on the total dose administered and the route of administration, as well as on the hemodynamic and circulatory status of the patient and the vascularity of the administration site¹⁴. When ropivacaine was administered intravenously to subjects, its pharmacokinetics were linear and dose-proportional up to 80 mg¹⁴. Absorption of 150 mg ropivacaine from the epidural space is complete and biphasic. The mean half-life of the initial phase is approximately 14 minutes, followed by a slower phase with a mean half-life absorption of approximately 4.2 hours.

Ropivacaine is 94% bound to plasma proteins, mainly to the glycoprotein α 1-acid. The increase in total plasma concentration during continuous epidural infusion of ropivacaine^{14,15} is caused by an increase in the degree of

protein binding and a subsequent decrease in the clearance of ropivacaine¹⁵.

Ropivacaine rapidly crosses the placenta during epidural administration for Caesarean section, resulting in an almost complete equilibrium of the free fraction of ropivacaine in the maternal and fetal circulation.^{5,16} However, the total plasma concentration of ropivacaine was lower in the fetal circulation than in the maternal circulation, reflecting the binding of ropivacaine to the acid glycoprotein α 1, which is more concentrated in maternal plasma than in fetal plasma⁵. On the other hand, the cardiovascular effects of SA are proportional to the extent of spinal-induced sympathetic block¹⁷.

In SA, with the most commonly used local anesthetic drugs, the dose required to achieve satisfactory anesthesia (ED95) is accompanied by a high incidence of hypotension (40-80%), which prophylactic measures most often fail to completely suppress¹⁸. This finding was also noted in our series with a high prevalence of post spinal hypotension which is 87% despite pre-filling and other prophylactic measures.

In 2009, the Cochrane DataBase provided an update on this subject by reviewing all the randomized trials comparing techniques for preventing hypotension during Caesarean section SA; 75 studies including more than 4,600 patients were included in this meta-analysis¹⁹. Vascular filling was effective. The vasoconstrictors ephedrine and phenylephrine (Neosynephrine®) significantly reduced the incidence and severity of hypotension; however, the superiority of phenylephrine over ephedrine could not be established in this meta-analysis, but the use of high doses of ephedrine (>20 mg) was responsible for maternal hypertension and tachycardia, as well as neonatal acidosis. Lower limb compression also helped prevent the hemodynamic impact of SA. However, none of these measures completely prevented hypotension in SA. The addition of lipophilic morphine to the local anesthetic drug improves the quality of anesthesia²⁰. The use of hyperbaric solution can significantly reduce the incidence of hypotension compared to isobaric or hypobaric bupivacaine²¹. The combined use of phenylephrine (Neosynephrine®) and ephedrine reduces the frequency and intensity of hypotension and nausea compared to ephedrine alone²². Finally, rapid associated crystalloid filling is more effective than pre-filling²³. Nevertheless, the major parameter responsible for the hemodynamic repercussions remains the dose of bupivacaine used, as it determines the level and kinetics of sympathetic block installation. The insertion of an epidural catheter offers the possibility of decreasing the initial dose of intrathecal local anesthetic drug and then being able to adjust the upper level of the sympathetic block if necessary. The expected effect is a "damping" of the hypotension over time and therefore a better control of its occurrence.¹⁸. In our series, the low prevalence of hypotension in parturients having received bupivacaine could be secondary to the hyperbaric nature of the solution used.

It is obvious that the practice of obstetrical anesthesia, whether for a caesarean section or a vaginal delivery, can have adverse effects on the newborn. The doses injected intrathecally are extremely low and do not cause significant placental passage [24s]. The major effects of spinal anesthesia on the fetus are related to the maternal hypotension it may induce and the drugs used to control it. Sympathetic spinal blockade is responsible for a decrease in venous return, systemic vascular resistance, cardiac output and consequently uteroplacental perfusion output. Maternal hypotension and its resultant neonatal acidosis are the most

frequently encountered adverse effects. Maternal hypotension, although severe, although very common, does not significantly impact neonatal well-being. Moreover, acidosis observed after spinal anesthesia is not correlated with Apgar score or outcome²⁵. A pH below 7 and a base deficit above 12, which are criteria related to the risk of moderate to severe neonatal encephalopathy, are never found outside emergency situations and are not due to the anesthetic technique itself^{26,27}. To limit hypotension, vasoconstrictors, ephedrine and neosynephrine, are used for treatment or prevention. A 2012 review confirms the superiority of neosynephrine in terms of neonatal pH and base deficit despite identical control of maternal blood pressure and a neosynephrine-related decrease in cardiac output²⁸. Ephedrine has a greater placental passage and is responsible for true metabolic acidosis via an increase in fetal metabolic activity. This is confirmed by a higher incidence of fetal acidosis defined by a pH below 7.2 with this product²⁹. However, neonatal outcome does not appear to be impacted by the use of a particular vasoconstrictor^{19,28,29}.

In our series, the lower mean Apgar scores at birth in newborns born under the P2-ropi protocol were probably related to the higher prevalence of hypotension in P2-ropi subjects. However, it should be noted that in our series, Apgar scores at 5 min for all protocols combined (P1-bupi and P2-ropi) were favorable with a mean of 9.5 for both protocols.

Conclusion:

The obsession with the use of local anesthetists (ropivacaine or bupivacaine) during spinal anesthesia for Caesarean sections is based on their cardiac and/or neurological toxic side effects. Ropivacaine certainly has a better cardiovascular and neurological tolerance and a better efficiency in terms of analgesia. However, during Caesarean sections, it is important to consider the risk of low blood pressure and possible fetal complications related to its use.

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