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Spinal Anesthesia for Cesarean Section. Use of Hyperbaric Bupivacaine (10 mg) Combined with Different Adjuvants

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Summary: Braga AA, Frias JAF, Braga FS, Potério GB, Hirata ES, Torres NA – Spinal Anesthesia for Cesarean Section. Use of Hyperbaric Bupivacaine (10 mg) Combined with Different Adjuvants.

Background and objectives: Combination of local anesthetics (LA) with adjuvants for spinal anesthesia improves block quality and prolongs the duration of analgesia. It was evaluated the maternal effects and neonatal repercussions of sufentanil, morphine, and clonidine combined with hyperbaric bupivacaine for elective cesarean section.

Method: Prospective, randomized, blinded study of 96 patients allocated into four groups: Group I (no adjuvant), Group II (sufentanil 5.0 μg), Group III (morphine 100 μg), and Group IV (clonidine 75 μg). It was evaluated the onset and level of sensory block, perioperative analgesia, degree and recovery time of motor block, duration of analgesia, sedation, and maternal-fetal repercussions.

Results: The onset of blockade was significantly faster in groups with adjuvants compared with Group I. Patients in Groups I and III reported pain during the perioperative period. Duration of analgesia was significantly higher in Group II and time to motor block recovery was significantly higher in Group IV. Pruritus occurred in Groups II and III. Sedation was significant in Group IV and there was prolonged arterial hypotension in Group IV.

Conclusion: Addition of sufentanil and clonidine to hyperbaric bupivacaine provided adequate anesthesia for cesarean section and good postoperative analgesia. Clonidine caused more perioperative sedation and longer time to motor block recovery. Pruritus was evident when opioids were used.

Keywords: Anesthesia, Spinal; Bupivacaine; Cesarean Section; Clonidine; Morphine; Sufentanil.

INTRODUCTION

Spinal anesthesia performed with fine gauge disposable needles and administration of hyperbaric bupivacaine 0.5% combined with adjuvant drugs have become the method of choice for elective cesarean section and urgent and emergency situations. This drug combination has been proposed in order to improve the quality of blockade and extend the duration of analgesia. Furthermore, addition of adjuvants allows reducing the dose of bupivacaine and minimizes the hemodynamic effects [1].

The adjuvants most commonly used in combination with bupivacaine are opioids and clonidine. Morphine has been used to control postoperative pain, as it is ionized and highly hydrophilic. Thus, as a result of its pharmacokinetic effects when applied into the subarachnoid space, morphine has a slow onset of action but long duration of analgesia. On the other hand, the addition of sufentanil, a lipophilic opioid, reduces the onset time to blockade, improves perioperative analgesia, and extends postoperative analgesia up to 7 hours [2-4].

Clonidine, imidazoline compound and partial α2-adrenergic agonist with anxiolytic and hypnotic properties, used as an adjunct to spinal anesthesia provides a dose-dependent increase in the duration of sensory and motor block, in addition to having antinociceptive properties [4,5].

In the cesarean section, the recommended dose of morphine to provide intra- and post-operative satisfactory analgesia is 100-200 μg, while the recommended dose of sufentanil and clonidine ranges from 5 to 7.5 μg and 15 to150 mg, respectively [2,3,6-8].

The aim of this study was to evaluate comparatively, in women undergoing cesarean section under spinal anesthesia, the effectiveness of hyperbaric bupivacaine combined with different adjuvants on quality of blockade and maternal and neonatal repercussions.

METHOD

This study was conducted after the Medical Research Ethics Committee approval and signed informed consent. Term pregnant women, ASA physical status I-II, undergoing elec-

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tive cesarean section under spinal anesthesia were consecutively included in this randomized, double-blind clinical trial. Exclusion criteria were preeclampsia, ASA III-IV, prematurity, multiple gestation, and contraindications to spinal block.

The sample size was calculated on assumptions of clinically relevant differences between groups regarding the following variables: 1) need for intraoperative supplementation with local anesthetic in epidural space and/or intravenous drugs and 2) motor block recovery time. We determined a 25% difference in the need for intraoperative supplementation and consider it reasonable to establish a difference of 30% for blockade recovery time as clinically relevant. To construct a confidence interval of 95% (alpha error = 5%) and a power of 80% (beta error = 20%) based on these values, a sample size of 20 and 24 cases in each group would be needed for variables 1 and 2, respectively. Ninety-six subjects were randomly allocated into four groups (24 in each group) using SAS 9.1 software. Both the anesthesiologist who performed the blockade and who evaluated the studied parameters were unaware of the anesthetic solution used.

In all four groups, the local anesthetics (LA) used was hyperbaric bupivacaine 0.5% at a fixed dose of 10 mg (2 mL) combined with adjuvants (sufentanil or clonidine or morphine). Four groups were formed: Group I, bupivacaine + saline 0.9% (2 mL); Group II, bupivacaine + sufentanil (1 mL; 5 μg) + saline solution 0.9% (1 mL); Group III, bupivacaine + morphine (1 mL; 100 μg) + saline solution 0.9% (1 mL), and Group IV, bupivacaine + clonidine (0.5 mL; 75 μg) + saline 0.9 % (1.5 mL). Saline 0.9% was added to all groups to obtain a total volume of 4 mL. The drugs used were commercial products from a single manufacturer, without batch determination. Solution densities were analyzed by the drugs manufacturing laboratory using an Anton Paar DMA 4500 digital densimeter, previously calibrated with milli-Q water at 37°C. The resulting solutions' characteristics are shown in Table I.

Spinal block is a routine technique used in this institution for cesarean section. In addition to spinal block, epidural puncture and catheter insertion were performed in all patients of four groups for possible need of LA supplementation, in cases of pain complaints during surgery, and maintenance of adequate analgesia for performing the surgery. Pain measurement was done with the aid of verbal numeric scale (VNS) and pain reported by the patient was considered as a criterion for LA supplementation via catheter (VNS $\geq$ 3). In such cases, the use of lidocaine 2.0% with vasoconstrictor (5.0 mL; 100 mg) was recommended.

Patients were fasted and received no premedication. In the operating room, all patients were continuously monitored with cardioscope in DII lead, noninvasive blood pressure, and pulse oximetry. After venous access with an 18-gauge cannula and before anesthesia induction, Ringer's lactate (500-750 mL) was infused. With patient in the sitting position, epidural puncture with 16-gauge Tuohy needle at L2-L3 interspace was done initially and epidural catheter introduced in cephalic direction. Spinal block was performed with Withacre 27G or 25G Quincke needle at L3-L4 interspace, and anesthetic solution injected at a rate of 1 mL.15s^{-1} without barbotage. After blockade, patients were placed in the supine position and a Crawford wedge was used to displace the uterus to the left until birth. Oxygen supplementation (2-5 L.min^{-1}) was provided with the aid of a nasal catheter. Hydration was maintained with Ringer's lactate (10 mL.kg^{-1}.hour^{-1}).

The following parameters were studied: 1) sensory block latency – time elapsed between the end of anesthetic solution injection into the subarachnoid space (assessed every minute) and loss of pain sensitivity to pinprick at T10; 2) maximum level of sensitive block – evaluated 20 minutes after anesthetic solution injection; 3) maximum degree of motor block – evaluated 20 minutes after anesthetic solution injection, according to the modified Bromage scale (0 = free movement of lower limbs [null], 1 = ability to bend knees and move feet, 2 = ability to flex feet only, 3 = complete immobility of lower limbs); 4) time to motor block complete recovery – time elapsed between the end of solution injection into the subarachnoid space and free movement of lower limbs (0; null); 5) total duration of analgesia – time elapsed between the end

Table I – Characteristics of Anesthetic Solutions

	Volume	Density at 37 ºC	Bupivaicane	Glucose	Adjuvant
	(mL)	(g.mL^{-1})	(total dose; mg)	(mg.mL^{-1})	
Group I	4	1.0117	10	40	No adjuvant
Group II	4	1.0117	10	40	sufentanil (5 μg)
Group III	4	1.0116	10	40	clonidine (75 μg)
Group IV	4	1.0118	10	40	morphine (100 μg)

n = 24 for all groups.

of solution injection into the subarachnoid space and spontaneous complaint of pain (NVS ≥ 3) reported by the patient in the post anesthesia recovery. We standardized the use of tenoxicam (40 mg) and dipyrone (30 mg.kg^{-1}) only after the first pain complaint (NVS ≥ 3) and during PACU stay; 6) intraoperative discomfort – pain complaint (NVS ≥ 3) requiring supplementation via epidural catheter; 7) maternal respiratory and cardiovascular parameters: systolic blood pressure (SBP – mm Hg), heart rate (HR; bpm), respiratory rate (rpm), and oxygen saturation (SpO_2;%) were evaluated at the following times: before blockade (M0), immediately after blockade (M1), every five minutes during procedure (M2), at the end of procedure (M3); 8) level of consciousness in perioperative period according to the scale proposed by Filos et al. [9] and modified by Braz et al. [10] (1 = awake [anxious, agitated], 2 = awake [calm], 3 = drowsy, 4 = sleeping [awaken to verbal stimuli]); 9) intraoperative maternal side effects: nausea, vomiting, pruritus, respiratory depression ($SpO_2 \leq 90\%$ and respiratory rate less than 10 bpm); 10) neonatal repercussions: Apgar score in the first and fifth minutes.

Arterial hypotension was defined as a decrease in systolic blood pressure greater than 20% of baseline value or below 100 mm Hg and, if present, treated with rapid crystalloid infusion and, if persistent, treated with intravenous bolus of ephedrine (5 mg). Bradycardia was defined as a heart rate decrease to values below 50 bpm and treated with atropine (10 to 20 μg.kg^{-1}). In anxious and agitated patients, intravenous midazolam (1.0 to 5.0 mg) was used.

Duration of surgery (min) was defined as the time elapsed between skin incision and end of surgery and time for fetal extraction (minutes) as the time between the beginning of surgery and delivery.

For statistical analysis of patients' characteristics, ANOVA test was used. To study sensory block latency, duration of analgesia, and time to motor block recovery, ANOVA was used with Tukey's test. Fisher's exact test was used for analysis of the degree of motor block, sensory block level, need for ephedrine, maternal side effects, and level of consciousness. Chi-square test was used to assess the need for intraoperative LA supplementation and incidence of hypotension. In statistical analysis of cardiocirculatory and respiratory parameters, M2 time was considered the mean of the mean values obtained at 5-minute intervals during surgery and the ANOVA test was used. We considered a significance level of 5%.

RESULTS

There was no significant difference between groups regarding patients' physical characteristics (Table II). Mean times and standard deviation of the surgical and fetal extraction times (min) were: 79.5 ± 17.24 and 16.5 ± 6.76 in Group I (bupivacaine); 77.2 ± 19.31 and 16.21 ± 6.09 in Group II (bupivacaine + sufentanil); 80.9 ± 17.10 and 16.7 ± 6.39 in Group III (bupivacaine + morphine); and 71.75 ± 10, 02 and 15.6 ± 5.28 in Group IV (bupivacaine + clonidine).

Sensory block latency time in Group I was significantly higher compared to other groups. Time to motor block recovery was different between groups. It was significantly higher ($p < 0.001$) in Group IV (bupivacaine + clonidine) compared to other groups. In Group III, the time motor block recovery was similar to Groups II ($p = 0.33$) and I ($p = 0.21$) and in Group II, it was significantly higher ($p < 0.001$) than in Group I. In all groups, all patients had grade 3 motor block. The maximum level of sensory block ranged from T2 to T8, predominantly in T4, with no significant difference between the groups. Total duration of analgesia was significantly higher ($p < 0.01$) in Group II compared to other groups (Table III). In 18 patients of Group I (bupivacaine) and in seven of Group III (bupivacaine + morphine), tLA supplementation via epidural catheter was needed during surgery at mean times of 60.39 and 65.29 minutes, respectively. In Group I, the number of patients requiring supplementation was significantly higher ($p < 0.001$) than in Group III.

All patients maintained respiratory rates greater than 10 breaths per minute and peripheral O_2 saturation between 95 and 100%. Intraoperative hypotension was seen in 13 (54.2%), nine (37.5%), 12 (50%), and 15 (62.5%) patients in Groups I, II, III, and IV, respectively, with no significant difference between groups ($p = 0.372$). Ephedrine was needed to treat hypotension in 7, 3, 7, and 15 patients in groups I, II, III, and IV, respectively. Data analysis showed that the number of

Table II – Characteristics of Patients

	Group I	Group II	Group III	Group IV	p
Age (years)*	27.66 ± 5.17	28.37 ± 5.85	29.87 ± 6.52	28.70 ± 5.99	0.62
Weight (kg)*	73.44 ± 10.97	75.80 ± 13.99	81.27 ± 11.49	79.46 ± 12.34	0.12
Height (m)*	1.56 ± 0.05	1.57 ± 0.08	1.58 ± 0.05	1.61 ± 0.05	0.08
BMI (kg.m^{-2})*	29.87 ± 4.13	30.41 ± 4.68	32.25 ± 3.81	30.70 ± 4.89	0.28

Values expressed as mean ± SD; ANOVA. n = 24 for all groups.

Table III – Characteristics of Blockade

	Group I	Group II	Group III	Group IV	p
Latency (min)*	6.00 ± 1.66 #	4.54 ± 1.95	4.16 ± 1.37	4.29 ± 1.23	< 0.01
Maximum Degree of Motor Block**					0.45
3	24	24	24	24	
Maximum Level of Sensory Block**					0.3
T2	02 (8.3%)	05 (20.8%)	02 (8.3%)	05 (20.83%)	
T4	18 (75.0%)	18 (75.0%)	17 (70.83%)	14 (58.34%)	
T6	03 (12.5%)	01 (4.16%)	04 (16.7%)	05 (20.83%)	
T8	01 (4.16%)	00 (0%)	01 (4.16%)	00 (0%)	
Time to Motor Block Recovery (min)*	149.45 ± 26.86	201.87 ± 42.60 ¶¶	177.66 ± 45.95	255.12 ± 73.32 ¶	< 0.001
Total Duration of Analgesia (min)*	148.37 ± 23.55	269.12 ± 58.67	138.69 ± 39.33	167.82 ± 40.52	< 0.01

Values expressed as Mean ± SD; number of patients; %: percentage of patients; *: ANOVA with Tukey's test; **: Fisher's exact test; #: significant difference compared to Groups I, III, IV; ¶: p < 0.001 for Group IV vs. Group I, II, III; ¶ ¶: p < 0.001 for Group II vs. Group I. n = 24 for all groups.

patients requiring ephedrine was significantly higher (p < 0.01) in Group IV than in groups I, II, and III. The mean dose of ephedrine used ranged from 13 to 16 mg.

In all groups, Apgar scores ranged from 8-10 and 9-10 in the first and fifth minutes, respectively. The incidence of pruritus was significantly higher (p < 0.01) in both groups receiving opioids. Nausea and vomiting occurred similarly in all four groups (p = 0.34).

In Group IV, nine patients were observed sleeping (score 4) with significant difference compared to other groups (p < 0.001) and 15 were drowsy (score 3). In Group II, 11 patients were drowsy (score 3), 12 awake/calm (score 2), and one patient requiring midazolam (score 1). In Groups I and III, 12 and 8 patients, respectively, had anxiety (score 1) and required perioperative midazolam. Statistical analysis showed a significant difference (p = 0.01) regarding Groups II and IV.

DISCUSSION

Most cesarean sections are performed with spinal anesthesia, which involves various combinations of anesthetics and analgesics injected into the subarachnoid space. Although this technique is widely used, once this study was conducted at a university hospital in which surgical procedures are often performed by physicians in training and duration of surgery is higher, we also opted for installing a catheter into the epidural space, foreseeing a possible need of LA supplementation when there were spontaneous complaints of pain (VNS > 3) by the patient in the perioperative period.

The isolated use of hyperbaric bupivacaine in the subarachnoid space requires higher doses (12-15 mg) to prevent visceral pain, nausea, and vomiting resulting from peritoneal traction occurring in this type of procedure [2,11-13]. However, the major factor triggering the incidence of hypotension associated with spinal anesthesia (50% to 85%) in cesarean section is the local anesthetic dosage, along with other factors such as oxytocin infusion and those involved in cephalad spread of local anesthetics in cerebrospinal fluid [14-17].

As previously described, the use of low dose bupivacaine (7.5 to 10 mg) has been proved insufficient to promote adequate perioperative analgesia, with pain incidence about 71%, a problem that can be minimized by adding adjuvants to local anesthetics [1].

Combination of clonidine and opioids (morphine, fentanyl, sufentanil) with local anesthetics has been a very common practice because it improves the quality of intraoperative analgesia and prolongs postoperative analgesia in addition to allowing the use of smaller doses of local anesthetics, with reduced risk of maternal hypotension and harm to the fetus [1-5,7,8,18]. Morphine contributes little to the quality of surgical analgesia due to its pharmacodynamic characteristics, such as slow onset of action and prolonged duration. Nonetheless, it is effective in controlling postoperative pain, although its use may trigger delayed adverse effects [2,19,20]. In this study, we used morphine (100 μg), a dose often recommended for subarachnoid space application in cesarean section, combined with hyperbaric bupivacaine with or without other adjuvants. At this dosage, the incidence of late adverse effects is lower and does not affect the quality of postoperative analgesia [6,19-25].

Due to morphine side effects and slow onset of action, liposoluble opioids (fentanyl and sufentanil) are used intrathecally in combination with local anesthetics for cesarean section. The high lipid solubility coupled with great affinity for μ-receptors are pharmacokinetic characteristics able to explain the decrease in latency of local anesthetics and rapid installation of sensory block. Previous studies demonstrated that the combination of sufentanil (5 μg) with intrathecal hyperbaric bupivacaine in cesarean section provided effective and safe anesthesia and prolonged postoperative analgesia with low incidence of maternal side effects [2,3,18]. The use of higher doses results in higher incidence of adverse effects, such as nausea and vomiting, respiratory depression and pruritus, but without increasing the duration of analgesia [3,21].

Clonidine, an imidazoline compound and partial α2-adrenergic receptor agonist, interacts with local anesthetics, blocks the stimulus conduction in the AΔ- and C-fibers, and increases potassium conductance in isolated neurons. This action enhances the effects of local anesthetics, indirectly reduces its absorption by the postsynaptic vasoconstrictive effect of α_2-receptors, and improves the quality of anesthetic block, both regarding the duration of surgical anesthesia and motor block [4,5]. When used in neuraxis, the analgesic effect of clonidine is evident due to the action on spinal and supraspinal α_2-adrenergic receptors in central nervous system (CNS), which includes the activation of α_2- postsynaptic receptors of noradrenergic descending pathways of cholinergic neurons and nitric oxide release and enkephalin-like substances [5,7]. In addition to the analgesic properties, it has also antihyperalgesic properties, which reinforces the noradrenergic inhibitory effect on dorsal horn of spinal cord [8]. In the subarachnoid space, it is used in different doses, either alone or in combination with local anesthetics and opioids [4,7,8,23,26-28].

In this study, the addition of sufentanil and clonidine to hyperbaric bupivacaine was effective in controlling pain during surgery, which was different from groups I and III, in which 75% and 29% of respective patients reported perioperative pain (NVS > 3) and required lidocaine via epidural catheter for pain control. This finding in Group I may be explained by the isolated use of bupivacaine (10 mg), as well as by the prolonged time of surgery, and in Group III, in addition to prolonged time of surgery, the pain complaint may be attributed mainly to the slow onset of action of morphine.

These results differ from those observed by other authors who reported effective analgesia with low incidence of pain without painkillers or sedatives during surgery. However, the mean surgical time in these studies was shorter (57-67 minutes) than that observed in our study, which was conducted at a university hospital and therefore extended beyond 70 minutes (71-80 minutes) [2,6,8,19,26].

Total duration of analgesia was significantly higher in the sufentanil group, a result similar to that previously described by Braga et al. [3] who assessed the effectiveness of hyperbaric bupivacaine combined with different doses of sufentanil in patients undergoing Cesarean section. The authors [3] observed the first complaint of pain 7 hours after the subarachnoid injection of hyperbaric bupivacaine (12.5 mg) combined with sufentanil (5 μg). However, in addition to the opioid, the use of higher doses of local anesthetics may justify the longer duration of analgesia.

Regarding time to complete motor block recovery, clonidine confirmed its peripheral neurologic effects. Therefore, motor block recovery in Group IV occurred over 2 hours after surgery, which was significantly different from other groups. Motor block in this group was longer than analgesia, which confirm literature data [4,26,27].

Clonidine, due to the activation of α_2-adrenergic receptors in the CNS, promotes decreased release and action of noradrenaline from locus coeruleus, which results in increased activity of inhibitory interneurons (GABA) and provides sedation, anxiolysis, and hypnosis. This effect of clonidine is dose-dependent, independently of the route of administration, with onset of action between 20 and 30 minutes [5].

Opioids alter the level of consciousness by acting on receptors κ (kappa) in the CNS, which occurs only after the systemic administration of high doses, an effect that is more evident with morphine [2]. However, soluble opioids, mainly spinal sufentanil, promote earlier sedation because of its pharmacodynamic action.

In the present study, all patients receiving clonidine remained drowsy or asleep after birth, but responded to simple verbal stimuli. In sufentanil group, patients were calm and sleepy. These results corroborate the findings of previous studies, which demonstrated the anxiolytic activity of clonidine and sufentanil [3,23,27,28]. However, in Groups I and III, patients were awake and anxious due to perioperative pain, especially in the group without adjuvant, and required midazolam. These results differ from those found by other authors who used higher doses of hyperbaric bupivacaine and morphine [2,19].

The incidence of adverse side effects was similar between groups, except for pruritus seen in both groups who used opioids. Unlike opioids, often responsible for the incidence of nausea, vomiting, pruritus, and respiratory depression – both intra- and post-operatively –, the use of subarachnoid clonidine is not associated with the occurrence of such effects. Although respiratory depression is the most troubling side effect of opioids, the incidence is low and dose-dependent. In a prospective study of 856 patients undergoing cesarean section and receiving spinal morphine (200 μg), this complication was seen in only 0.9% of cases [29]. In other studies, with a smaller number of subjects, there were no cases of respiratory depression, comparable to the results of this study [2,3,19].

Hypotension was seen in all groups. However, since there is no significant difference between groups, one may infer that there was little influence of the drug in its occurrence. Although the statistical analysis did not show a significant difference between groups, in clonidine group hypotension was maintained for longer time and the need for ephedrine was significantly higher than in other groups.

Due to its sympatholytic action in the CNS and peripheral nerve endings, systemic or spinal clonidine has hypotensive and bradycardic effects, which is characterized by dose-dependency, slow installation, and easily corrected with admin-

istration of α- and β-adrenergic agonists, such as ephedrine that, even in the presence of clonidine, increases systolic and diastolic blood pressures and cardiac rate and output [8,10,23,30].

Incidence of hypotension in all four groups was lower than that reported in literature and controlled by displacing the uterus to the left, volume expansion, and intravenous ephedrine – strategies used for preventing hypotension associated with spinal anesthesia [14-16]. Thus, in all four groups, newborns showed no signs of fetal distress, evidenced by Apgar scores between 8 and 10 at 5 and 10 minutes, respectively, which confirmed the safety of the product in the conceptual combination of drugs studied, results similar to those described in literature [2,3,23,27].

The results support the conclusion that in patients undergoing spinal anesthesia for elective caesarean section, the addition of sufentanil (5.0 μg) and clonidine (75 μg) to hyperbaric bupivacaine provided adequate anesthesia and postoperative analgesia. Clonidine caused more perioperative sedation and extended time to motor block recovery. Pruritus was evident with the use of opioids.

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