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SCIENTIFIC ARTICLE

Sufentanil in combination with low-dose hyperbaric bupivacaine in spinal anesthesia for cesarean section: a randomized clinical trial

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KEYWORDS
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Abstract A double blind randomized clinical trial of sufentanil as an adjunct in spinal anesthesia for cesarean section and, thereby, be able to reduce the dose of bupivacaine, a local anesthetic, with the same result of an anesthetic block with higher doses but with fewer perioperative side effects, such as hypotension.

PALAVRAS-CHAVE
Sufentanil;
Raquianestesia;
Bupivacaína;
Hiperbárica;
Cesariana

Associação de sufentanil a dose reduzida de bupivacaína hiperbárica em raquianestesia para cesariana: ensaio clínico randomizado

Resumo Ensaio clínico randomizado duplamente encoberto sobre o uso do sufentanil como adjuvante em raquianestesia para cesariana e, possibilitando a redução da dose do anestésico local, a bupivacaína, com o mesmo resultado de bloqueio anestésico com doses mais elevadas, mas com menos efeitos colaterais no perioperatório, como hipotensão.

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Introduction

Compared to general anesthesia, neuraxial anesthesia for cesarean section (C-section) presents advantages, such as reduced risk of intubation failure and aspiration of gastric contents, reduced use of depressants (hypnotics and opioids), and the mother's consciousness that allows mothers undergo the birth experience.[1,2] Spinal anesthesia is currently the most widely used technique for C-section, as it provides intense sensory block and rapid installation. However, this technique can be accompanied by significant hypotension, its most important side effect, with reported incidence of 20–100%.[3–5]

Several strategies have been described to prevent the occurrence of hypotension in C-section, such as left uterine displacement, crystalloid or colloid administration, lower limb wrapping, prophylactic use of ephedrine or phenylephrine, but none of them eliminated hypotension.[6,7]

The relationship between the local anesthetic (LA) dose used and the occurrence of maternal hypotension is well established, with higher doses related to a higher incidence of hypotension.[8] However, the reduction of LA dose leads to increased incidence of intraoperative pain.[3,9]

It has been shown that the combination of lipophilic opioids with local anesthetics in spinal anesthesia allows LA dose reduction and promotes effective anesthesia with less side effects on maternal hemodynamics.[10–14]

Sufentanil, highly soluble, enhances analgesia and comfort during surgery, with a short latency period (5–10 min) and duration of action of up to 7 h.[10,15–17] The use of morphine, soluble opioid, is recommended to ensure longer postoperative analgesia.[10,18]

The aim of this study was to compare the efficacy of anesthesia and the incidence of side effects between two hyperbaric bupivacaine doses in spinal anesthesia for C-section with combined sufentanil at the lowest dose.

Material and methods

After approval by the Ethics Committee, the randomized double-blind trial was started with 94 women, aged 18–45 years, undergoing C-section under spinal anesthesia. After obtaining written informed consent and consulting the randomization table, patients were allocated to one of two study groups: Group A (bupivacaine 12.5 mg + morphine 80 μg) and Group S (bupivacaine 10 mg + morphine 80 μg + sufentanil 5 μg). Syringes preparation and spinal anesthesia administration were performed by an anesthesiologist blinded to data collection. All the investigators involved in the study were blinded to the assignment of each group. Pregnant women unable to decide on their participation in the study or unable to provide the necessary information, ASA IV or V, requiring emergency obstetric care, with a history of hypersensitivity or allergy to any of the study drugs, and those with any contraindication to the technique proposed were excluded.

With the patient in a sitting position, subarachnoid puncture was performed in the L2–L3, L3–L4 or L4–L5 interspace, with 25G or 27G Quincke needles, and the drugs were administered according to the group for which it was randomized. Local anesthetics and opioids were delivered in separate syringes for a total time of 15 s. The patients were immediately placed in the supine position, manually shifting the uterus to the left at an angle of 15°.

Blood pressure and heart rate measurements were recorded before spinal anesthesia and at every 3 min in the first 15 min, and at 30 and 45 min after the blockade. Hypotension was defined as a decrease in systolic blood pressure (SBP) up to 20% from baseline and controlled with intravenous ephedrine (5 mg). Bradycardia, defined as a heart rate below 80% of baseline or below 50 bpm of baseline value, was treated with intravenous atropine (0.5 mg). The level of sensory block at T6 dermatome was tested at 5, 10, and 15 min after the blockade by pinprick with a 22G needle.

Symptoms or adverse events, such as nausea, vomiting, drowsiness, pain above three on the Visual Analog Scale (VAS > 3) or abdominal discomfort, in addition to the neonate Apgar score in the first and fifth minute, need to use vasopressor for hypotension treatment, fetal extraction time, and duration of surgery were recorded. Abdominal pain or discomfort during surgery was treated with fentanyl bolus doses of 50 μg, repeated at the assistant physician discretion.

Postoperative nausea, vomiting, itching, and pain at rest (VAS > 3) at two, six, and 12 h after anesthesia were recorded.

Statistical analysis was performed using the Epi Info® 7.1.3.0 software. Quantitative variables were analyzed using mean and standard deviation (SD) and submitted to the Student *t*-test and the frequency of qualitative variables were submitted to the chi-square and Fisher exact tests (the latter when the occurrence of variables was less than five and this test could be performed).

Results

In total, 94 patients were selected and submitted to randomization, 46 patients in Group A and 48 in Group S. There were two losses in Group A due to inadequate completion of the questionnaire and one loss in Group S due to spinal anesthesia total failure and need for a second puncture.

There was no statistically significant difference between the two groups regarding age and body mass index (BMI) of patients and gestational age (Table 1). The most commonly used puncture site was L3–L4, and 27G needle was the most used in both groups (Table 2).

The mean time for fetal extraction was 14.16 ± 4.8 min for Group A and 14.51 ± 4.7 min for Group S, and the mean duration of surgery was 56.06 ± 11.75 min for Group A and 57.21 ± 10.88 min for Group S (Table 3).

The use of ephedrine to treat hypotension was similar in both groups (30 patients in Group A and 36 patients in Group S, 68.18% and 76.6%, respectively) (Table 4).

The latency to reach T6 dermatome was similar in both groups, although the number of patients who reached this level in 5 min was higher in Group S than in Group A (85.11% vs. 70.45%), but not statistically significant. Over 90% of patients achieved this level up to 10 min in both groups (Table 5).

Table 1 Characteristics of patients.

	Group A ($n = 44$)		Group S ($n = 47$)		
	Mean	SD	Mean	SD	p[a]
Age (years)	26.0227	6.36	27.34	5.99	0.3114
BMI (kg m^{-2})	30.64	6.36	32.13	5.43	0.2322
Gestational age (weeks)	37.9373	2.32	38.31	1.95	0.3976

SD, standard deviation.
[a] Student's t-test.

Table 2 Spinal puncture data.

	Group A		Group S		
	$n = 44$	%	$n = 47$	%	p[a]
Puncture level					0.5436
L2–L3	4	9.09%	2	4.26%	
L3–L4	37	84.09%	43	91.49%	
L4–L5	3	6.82%	2	4.26%	
Needle					0.6615
25G	14	31.82%	17	36.17%	
27G	30	68.18%	30	63.83%	

[a] Chi-square test.

Table 3 Surgical times.

	Group A ($n = 44$)		Group S ($n = 47$)		
	Mean	SD	Mean	SD	p[a]
Duration of birth (min)	14.16	4.8	14.51	4.7	0.7252
Duration of surgery (min)	56.06	11.75	57.21	10.88	0.6307

[a] Student's t-test.

Intraoperative incidence of pruritus and drowsiness was higher in Group S (36.17% and 23.4%) than in Group A (4.55% and 0%, respectively).

There was a greater tendency of bradycardia in Group S (59.57%) than in Group A (43.18%), but this difference was not statistically significant.

There was no significant difference between groups in the incidence of hypotension, nausea, vomiting, decreased oxygen saturation by hemoglobin (SpO_2), abdominal discomfort, and intraoperative pain (Table 6).

Table 4 Intraoperative need of ephedrine.[a]

	Group A ($n = 44$)		Group S ($n = 47$)	
	n	%	n	%
Yes	30	68.18	36	76.6
No	14	31.82	11	23.4

[a] $p = 0.8074$; chi-square.

There was no significant difference between Apgar scores at one and 5 min, 95.45% of newborns in Group A and 95.75% of newborns in Group S had scores between 7 and 10 at 1 min and all infants had score between 7 and 10 at 5 min (Table 7).

Postoperative evaluation (Table 8) showed a higher incidence of pruritus 2 h after intrathecal injection in Group S compared to Group A (61.7% vs. 30.23%, respectively), a statistically significant difference. There was no significant difference in the incidence of pruritus during revaluation

Table 5 Latency time of sensory block to reach T6.[a]

	Group A ($n = 44$)		Group S ($n = 47$)	
	n	%	n	%
Up to 5 min	31	70.45	40	85.11
6–10 min	9	20.45	3	6.38
11–15 min	1	2.27	3	6.38
>15 min or not reached	3	6.82	1	2.13

[a] $p = 0.1093$, chi-square.

Table 6 Intraoperative complications.

	Group A ($n = 44$)		Group S ($n = 47$)		
	n	%	*n*	%	*p*
Hypotension	36	81.82	37	78.72	0.7111[a]
Bradycardia	19	43.18	28	59.57	0.1178[a]
Nausea	17	38.64	16	34.04	0.6487[a]
Vomiting	9	20.45	6	12.77	0.3232[a]
Pruritus	2	4.55	17	36.17	[c]0.0001[b]
$SpO_2 < 95\%$	3	6.82	1	2.13	0.3504[b]
Drowsiness	0	0	11	23.4	[c]0.0005[b]
Abdominal discomfort	5	11.36	1	2.13	0.1032[b]
Pain	1	2.27	1	2.13	1.0[b]

[a] Chi-square.
[b] Fisher's exact.
[c] $p < 0.05$.

Table 7 Apgar scores.

Valor	Apgar, 1 min[a]				Apgar, 5 min[b]			
	Group A ($n = 44$)		Group S ($n = 47$)		Group A ($n = 44$)		Group S ($n = 47$)	
	n	%	*n*	%	*n*	%	*n*	%
<7	2	4.55	2	4.26	–	–	–	–
7–10	48	95.45	45	95.74	44	100	47	100

[a] $p = 0.6663$; Fisher's exact.
[b] $p = 1$; Chi-square

times at six and 12 h, as well as the incidence of nausea and vomiting in all times (2, 6, and 12 h). Of the five patients who experienced episodes of vomiting in the reevaluation after 2 h, only one persisted with vomiting in the 2nd revaluation (6 h). The other four occurrences in the revaluation at 6 h corresponded to new cases.

Regarding the occurrence of pain at rest (VAS > 3), there was a higher incidence in Group A compared to Group S in the revaluation at 6 h after the procedure (18.18% vs. 6.38%, respectively), but statistically not significant. The incidence of pain (VAS > 3) 12 h after spinal anesthesia tended to be similar between groups (Table 9).

Table 8 Postoperative side effects.

	Group A ($n = 44$)		Group S ($n = 47$)		*p*
	n	%	*n*	%	
Pruritus					
After 2 h[c]	13	30.23	29	61.7	0.0027[a,c]
After 6 h	13	30.23	18	38.3	0.4212[a]
After 12 h	6	13.95	8	17.02	0.6883[a]
Nausea					
After 2 h	5	11.63	5	12.77	0.8692[a]
After 6 h	3	6.98	4	8.51	0.5502[b]
After 12 h	4	9.3	1	2.13	0.1538[b]
Vomiting					
After 2 h	1	2.33	4	8.51	0.2094[b]
After 6 h	1	2.33	4	8.51	0.2094[b]
After 12 h	0	0	0	0	–

[a] Chi-square.
[b] Fisher's exact.
[c] $p < 0.05$.

Table 9 Postoperative pain at rest (VAS > 3).

	Group A ($n = 44$)		Group S ($n = 47$)		p
	n	%	n	%	
After 2 h	3	6.82	4	8.51	0.5372[b]
After 6 h	8	18.18	3	6.38	0.0795[b]
After 12 h	13	29.55	13	27.66	0.0396[a,c]

[a] Chi-square.
[b] Fisher's exact.
[c] $p < 0.05$.

Discussion

To obtain adequate anesthesia for C-section, an intense blockade covering from the sacral (S2–S4) to the visceral fibers (T4–T12) is needed. A blockade with such extension results in hypotension by blocking the sympathetic fibers.[10] The local anesthetic commonly used is 0.5% hyperbaric bupivacaine at doses ranging from 7.5 to 15 mg. The use of 10 mg alone or 8 mg combined with opioids is reported as ''low dose'' by some authors,[10] while others consider ''low dose'' only when the bupivacaine mass does not exceed 8 mg.[3]

Although the literature show a trend toward bupivacaine dose reduction up to doses as low as 8 mg, either with or without the addition of lipophilic opioids, reducing this dose to levels below 10 mg without epidural catheter insertion may be unsafe due to the potential risk of failure in obtaining an adequate level of blockade or inadequate blockade duration for surgical time, which increases the need for intravenous analgesic agents (fentanyl) or conversion to general anesthesia.[3,8,9]

Higher incidence of intraoperative hypertension has been was reported in patients receiving intrathecal sufentanil at a dose of 5 μg.[17] Other studies of sufentanil at doses ranging from 2.5 to 10 μg failed to establish a significant relationship between the use of intrathecal sufentanil and hypotension,[3,4,15,19] a result similar to that observed in our study. However, it is possible that the addition of sufentanil is responsible for the non-occurrence of the expected decrease in the incidence of hypotension with the hyperbaric bupivacaine dose reduced from 12.5 to 10 mg.

Although there was a higher incidence of bradycardia in patients who received sufentanil, this difference was not statistically significant. This relationship was not observed previously in a study that evaluated the incidence of bradycardia in patients receiving sufentanil (10 μg) or morphine (200 μg) by the same route of administration.[15]

Several studies have shown that intrathecal sufentanil is related to sedation[15,17,19] and that sufentanil is more sedating than spinal morphine (30% vs. 5%, respectively).[15] These results coincide with those observed by us, as drowsiness occurred in 23.4% of patients receiving sufentanil and was absent in the group that received only morphine as an adjuvant.

A study comparing different doses of bupivacaine alone for C-section under spinal anesthesia reported 35% incidence of intraoperative pain with a dose of 8 mg, 20% with a dose of 10 mg, and absent with a dose of 12 mg.[9] We found no differences in the occurrence of this effect when comparing hyperbaric bupivacaine (12.5 mg) combined with only morphine with hyperbaric bupivacaine (10 mg) combined with morphine and sufentanil. It is probable that the addition of sufentanil is responsible for maintaining the quality of analgesia with a dose reduction, which is in line with the results observed in other studies shown that the addition of lipophilic opioid drastically reduces the occurrence of intraoperative pain when bupivacaine is used at doses between 8 and 10 mg.[3,9,20]

When the incidence of pruritus was compared between patients who received intrathecal bupivacaine alone and patients who received sufentanil (10 μg) or morphine (200 μg) combined with bupivacaine, it was observed that the incidence was significantly higher in patients receiving sufentanil compared to those receiving morphine (30% vs. 10%, respectively).[15] It was also shown that pruritus resulting from the use of intrathecal sufentanil is dose-dependent, ranging from 34.3% with a dose of 2.5 μg to 68.6% with a dose of 5 μg.[17] Pruritus induced by intrathecal morphine is also dose-dependent, especially in doses above 0.1 mg.[21] In our study, a significantly higher difference in pruritus was seen in patients receiving sufentanil, in the intraoperative period and at the first assessment 2 h after anesthesia, sufentanil action period.

Thus, in the present study, the dose reduction of 0.5% hyperbaric bupivacaine from 12.5 10 mg, combined with sufentanil (5 μg) at the lowest dose, maintained the same quality of anesthesia, but did not reduce the incidence of hypotension and increased the incidence of pruritus and sedation.

Conflicts of interest

The authors declare no conflicts of interest.

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