



The Analgesic Effects of Bupivacaine and Magnesium Sulfate Combination, Bupivacaine, and Adrenaline Combination and Bupivacaine Alone on Post-cesarean Section Pain: A Randomized Clinical Trial

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Abstract

Objectives: The present study was performed to compare the analgesic effects of bupivacaine and magnesium sulfate combination on post-cesarean (C) section pain.

Materials and Methods: The present single-blind randomized clinical trial was conducted on 160 C-section candidates. The participants were randomly divided into four groups. When the fascia healed, the first group received 20 mL of 0.25% bupivacaine and the second group received 20 mL of 0.25% bupivacaine combined with subcutaneous adrenaline. In addition, both groups received 50 mL of intravenous normal saline. Further, the third group received subcutaneous bupivacaine and 50 mg/kg of magnesium sulfate and the fourth group received subcutaneous and intravenous normal saline as a placebo. The pain intensity was assessed 2, 6, 12, 18, and 24 hours after spinal anesthesia using the visual analogue scale (VAS) for pain. The dose of pethidine (as a standard analgesic) and hemodynamic parameters (i.e., heart rate [HR] and blood pressure [BP]) was recorded as well. The obtained data were then analyzed utilizing ANOVA, Tukey's HSD, and repeated measures ANOVA tests.

Results: The intensity of pain and the dose of pethidine decreased significantly in the combination of bupivacaine with magnesium compared to the other groups at all times ($P < 0.001$). However, diastolic BP significantly increased in the bupivacaine + adrenaline group in comparison with the other groups ($P = 0.02$).

Conclusions: Overall, bupivacaine combination with magnesium sulfate is suitable for controlling post-cesarean section pain.

Keywords: Pain, Magnesium sulfate, Adrenaline, Bupivacaine, Cesarean section

Introduction

Cesarean delivery is one of the most common surgeries across the world (1). The cesarean delivery rate has shown a steady rise from 35% in 2000 to 45% in 2005 in Iran (2). According to the latest statistics published by the World Health Organization, Iran ranks first regarding cesarean delivery in the region and has the second place in the world (3). Postoperative pain delays walking, extends hospital stays, increases the incidence of vein thrombosis, and eventually, leads to patient dissatisfaction (4). Pain treatment after the cesarean section is different from general surgery. In particular, a woman needs to recover faster to take care of her baby (5). Therefore, post-cesarean section pain control is a critical issue that leads to a more favorable experience of childbirth for mothers (6).

Several studies are currently being performed on the methods that can help reduce and relieve post-operative pain (5,7,8). These studies have extensively examined the impact of effective pain relief in the first hours after cesarean section (6,7,9). Postoperative pain is often

improperly controlled with opioids even when the patient is resting. There has been growing interest in recent years regarding the use of topical anesthetics for postoperative pain relief due to the analgesic properties of these substances and their lack of adverse effects unlike the case of opioids (10).

The subcutaneous injection of bupivacaine and epinephrine with bupivacaine in place of incisions during surgery reduces pain and the amount of diclofenac in the early hours after cesarean section (11,12). The previous study showed that continuous intravenous infusion of magnesium reduces pain during and after surgery. It also reduces the need for analgesic drugs (13). In another study, an inverse relationship was found between the severity of pain with different painful medical and surgical conditions and the serum magnesium levels (14). However, other studies obtained contradictory results on the use of topical anesthesia after cesarean section (7,9,15-17). In this study, it was hypothesized that the subcutaneous infiltration of bupivacaine with I.V magnesium has the potential to be

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effective in reducing post-cesarean section pain compared with bupivacaine alone or with adrenaline. Therefore, the present study strove to compare the analgesic effects of bupivacaine and magnesium sulfate combination, bupivacaine and adrenaline combination, and bupivacaine alone on post-cesarean section pain.

Cesarean delivery has higher maternal surgical risks for the cesarean and subsequent pregnancies compared with spontaneous vaginal birth. This is balanced against lower rates of perineal injury and short-term pelvic floor disorder. However, cesarean delivery offers lower rates of initial respiratory difficulties for neonates (18). Women with one or more prior cesarean deliveries are at greater risk for subsequent placental disorders including placenta previa, abruption, or morbidity adherent placenta (18).

The reasons for persistently significant cesarean rates are not completely understood, but some explanations can be provided in this regard as follows:

1. Women are having fewer children; thus a greater percentage of births are among nulliparous who are at increased risk for cesarean delivery.
2. The average maternal age is rising and older women, especially nulliparous, are at a higher risk of cesarean delivery.

3. Obesity, which is a cesarean delivery risk, reaches epidemic proportions.
4. Elective cesarean deliveries are increasing because of maternal request (18).

The aim of the study is pain relief sufficient medical indication for its provision.

Materials and Methods

The single-blind randomized clinical trial was conducted under the registration code of IRCT2015090723926N1 in 2015 and was approved by the Regional Committee for Medical Research Ethics at Babol University of Medical Sciences. Written informed consent was obtained from all patients. This study was carried out in accordance with the Code of Ethics of the World Medical Association (Declaration of Helsinki). The study participants consisted of 160 pregnant women who were candidates for elective cesarean section and referred to Ayatollah Rouhani Hospital in Babol, Iran. The flowchart of patient enrolment is shown in Figure 1.

Assuming SD=1(VAS), pain with 80% test power, and 95% confidence level, the required size to identify the difference $d = 1^{scale}$

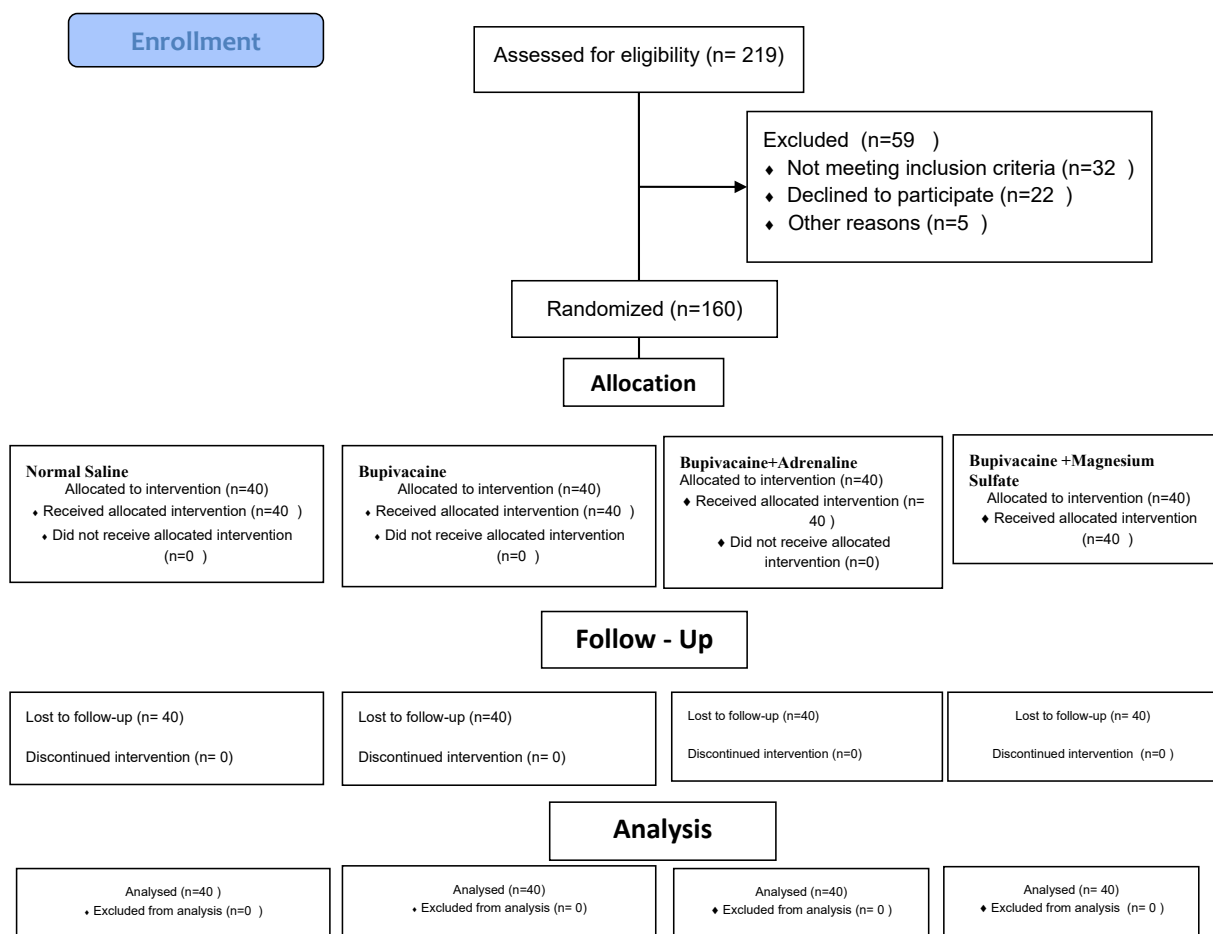


Figure 1. Flowchart of Patient Enrollment, Allocation, Follow-up, and Analysis.

$$N = \frac{2(Z_{1-\frac{\alpha}{2}} + Z\beta)^2 SD^2}{d^2} = \frac{2(1.96 + 0.84)^2 1.5^2}{1^2} = 40$$

Women were included in each group and the total sample size was 160 cases.

The allocated sample size in four groups under study with an equal sample of 40 was able to detect a standardized effect size of 0.6 between the two groups in multiple comparisons with 80% power and 95% confidence level. The inclusion criteria consisted of having a term pregnancy, having a singleton pregnancy, being classified as ASA I or II, being 160-170 cm in height, and weighing 70-100 kg by the end of the pregnancy. In addition, the exclusion criteria were a history of known allergies to topical amide anesthetics (e.g., bupivacaine and lidocaine), magnesium sulfate, and epinephrine, a history of using opioids, coagulation disorders, a history of seizures, and cardiovascular diseases. Further, the other exclusion criteria included psychiatric disorders, asthma and chronic obstructive pulmonary disease, severe intrahepatic cholestasis of pregnancy, renal and liver diseases, atrioventricular block, a history of using calcium channel blockers, postoperative atony, and the duration of surgery longer than 1.5 hours.

After putting the patients on the operating room bed, they underwent heart rate (HR), peripheral oxygen saturation, non-invasive blood pressure (BP), and cardiac monitoring.

Prior to the induction of analgesia, 5-7 mL/kg of Ringer's lactate solution was intravenously infused and all patients underwent spinal anesthesia with the same method (the same type and dose of the drug). All the C-section candidates were first placed in a sitting position and an anesthesiologist injected 12.5 mg of 0.5% bupivacaine (made by AstraZeneca plc) into their lumbar intervertebral space (at L₄₋₅ or L₃₋₄) with a 25-gauge spinal needle (made by B-Braun Medical Inc.) after prepping and draping. The surgery began once the sensory block reached the T₅-T₆ dermatome. In cases of inadequate sensory block, the patient underwent general anesthesia and was excluded from the study.

Furthermore, block randomization was used to allocate an equal sample size for each group. Thus, the participants were randomly divided into groups one to four by the order of their entrance in the operating room.

Group 1: Bupivacaine (N_B=40): At the beginning of the surgery, 50 mL of normal saline was injected intravenously over 15 minutes. After the fascia healed, 10 mL of 0.5% bupivacaine, increased to 20 mL with the addition of 10 mL of normal saline, was injected into the subcutaneous fat on both sides of the incision in 10 separate injections of 2 mL within equal intervals.

Group 2: Bupivacaine and adrenaline combination (N_{BA}=40): At the beginning of the surgery, 50 mL of 0.9% normal saline was injected intravenously over 15

minutes. Following the fascia healed, a combination of 0.1 mL of 1:1000 adrenaline and 10 mL of 0.5% bupivacaine, increased to 20 mL with the addition of normal saline, was injected exactly as in the previous group.

Group 3: Bupivacaine and magnesium sulfate combination (N_{BM}=40): At the beginning of the surgery, 50 mg/kg of 50% magnesium sulfate (3-4 g), increased to 50 mL with the addition of normal saline, was injected intravenously over 15 minutes. After the fascia healed, 10 mL of 0.5% bupivacaine, increased to 20 mL with the addition of normal saline, was injected exactly as in the previous group.

Group 4: Normal saline (N_S=40): At the beginning of the surgery, 50 mL of normal saline was injected intravenously over 15 minutes. After the fascia healed, 20 mL of normal saline was injected into the subcutaneous fat exactly as in the previous groups. All patients were blinded to their group assignment.

Before the surgery, the patients were instructed on the function of the visual analogue scale (VAS) for pain. Thus, the researchers showed them a 10-cm ruler graded from 0 to 10 and explained that selecting 'no pain' and 'the severest pain' are displayed on the ruler by 0 and 10, respectively. The patients specified their intensity of pain on the ruler and their pain was then calculated based on the specified number. The intensity of pain VAS varied from 0 to 10. The 0 showed no pain while 10 represented the highest feeling of pain. Hemodynamic changes in BP and HR were measured 2, 6, 12, 18, and 24 hours after spinal anesthesia. All the patients received 0.5 mg/kg of intramuscular pethidine (max. 0.50 mg/kg) 2 hours after spinal anesthesia since their spinal drug was no longer effective. About 0.25 mg/kg of pethidine (max. 30 mg) was administered and the total analgesic dose administered in a period of 24 hours was recorded if the VAS score was calculated as 4 or above 6, 12, 18, and 24 hours after spinal anesthesia or if the patient expressed pain and asked for an analgesic. The data were analyzed by SPSS software (version 18.0) using the repeated measures ANOVA and Tukey's pair comparison. The *P* values <0.05 were considered statistically significant.

The allowed dosage of bupivacaine and pethidine is 2-3 mg/kg (19) and about 0.5-1 mg/kg, respectively (20).

Results

The demographic details of the participants are provided in Table 1. The mean age (±SD) of the participants was 30.61 ± 4.5 years. In addition, their mean pre-pregnancy body mass index (BMI) was 26.6 ± 3.1 kg/m² and their post-pregnancy BMI was 30.59 ± 3.1 kg/m². There were no differences between the groups in terms of any of the examined variables (*P* > 0.05).

According to the ANOVA (Table 2), the intensity of pain significantly decreased in the group receiving bupivacaine and magnesium sulfate combination compared to all the

Table 1. The Baseline Demographic Characteristics and Anthropometric Measures According to Study Groups

Variable	Normal Saline Mean ± SD	Bupivacaine Mean ± SD	Bupivacaine+Adrenaline Mean ± SD	Bupivacaine +Magnesium Sulfate Mean ± SD	P Value
Age (y)	29.6 ± 4.3	31.9 ± 4.2	29.9 ± 4.6	30.8 ± 4.5	0.093
Pre-pregnancy weight (kg)	72.2 ± 9.2	69.4 ± 7.5	68.1 ± 7.1	70.2 ± 9.3	0.195
Post-pregnancy weight (kg)	82.4 ± 9.6	79.3 ± 7.0	78.4 ± 7.6	81.0 ± 9.9	0.177
Height (cm)	162.0 ± 2.95	161.7 ± 2.7	162.0 ± 3.8	162.2 ± 3.2	0.951
Gravidity	2.4 ± 0.71	2.6 ± 1	2.4 ± 0.9	2.4 ± 1	0.59
Parity	1.2 ± 0.5	1.2 ± 0.5	1.0 ± 0.5	1.1 ± 0.6	0.59
Pre-pregnancy BMI	27.5 ± 3.5	26.5 ± 2.8	25.9 ± 2.7	26.6 ± 3.3	0.166
Post-pregnancy BMI	31.3 ± 3.6	30.3 ± 2.5	29.8 ± 2.4	30.7 ± 3.5	0.149
Education					
Above high school (%)	27.5	38.5	25	43.9	0.215
High school or below (%)	72.5	61.5	75	56.1	0.215

SD: standard deviation; BMI: body mass index.

Table 2. Comparison of Pain Intensity During Different Time points Between and Within Groups

Hours Since Surgery	Normal Saline Mean ± SD	Bupivacaine Mean ± SD	Bupivacaine+Adrenaline Mean ± SD	Bupivacaine +Magnesium Sulfate Mean ± SD	p ^b
2	8.03 ± 0.83	7.31 ± 0.97	6.48 ± 1.08	4.71 ± 1.20	<0.001
6	7.70 ± 0.82	6.74 ± 0.91	5.78 ± 0.92	4.17 ± 1.13	<0.001
12	7.00 ± 1.15	5.85 ± 0.81	4.58 ± 0.74	3.51 ± 0.67	<0.001
18	5.83 ± 1.37	4.36 ± 0.90	3.88 ± 0.75	2.73 ± 0.89	<0.001
24	4.72 ± 1.63	3.56 ± 0.50	3.20 ± 0.60	1.32 ± 0.87	<0.001
p ^a	<0.001	<0.001	<0.001	<0.001	<0.001

^a Repeated measures ANOVA; ^b ANOVA.

other groups at all times ($P < 0.001$). Further, the intensity of pain significantly decreased between the group receiving bupivacaine and adrenaline combination and the groups receiving bupivacaine or normal saline. This intensity also differed between the bupivacaine group and the normal saline group ($P < 0.001$). Based on the results of Tukey's post hoc HSD test, the intensity of pain did not differ significantly between the bupivacaine group and the bupivacaine and adrenaline combination group 18 and 24 hours after spinal anesthesia ($P = 0.38$ and $P = 0.148$, respectively). However, the difference was significant at all the other times.

As shown in Table 3, the dose of pethidine used 6, 12, 18, and 24 hours after spinal anesthesia significantly decreased in the bupivacaine and magnesium sulfate combination group compared to all the other groups ($P < 0.001$). The results of Tukey's post-hoc HSD test indicated that the dose of pethidine used 18 and 24 hours after spinal anesthesia did not differ significantly between the bupivacaine group and the bupivacaine and adrenaline combination group ($P = 0.14$ and $P = 0.38$, respectively). The groups did not differ significantly from each other in terms of their mean systolic BP after spinal anesthesia ($P > 0.05$, Figure 2). Based on the results of the one-way ANOVA, 2 hours after spinal anesthesia, the mean diastolic BP significantly increased in the bupivacaine and adrenaline combination group compared to all the other

groups ($P = 0.02$, Figure 3).

According to Tukey's post-hoc HSD test, 2 hours after spinal anesthesia, the diastolic BP differed significantly between the bupivacaine and adrenaline combination group and the normal saline group ($P = 0.048$).

Discussion

The intensity of pain was measured using the VAS and the dose of postoperative pethidine administration was significantly lower in the bupivacaine and magnesium sulfate combination group compared to all the other groups. In a study by Eldaba et al, subcutaneous infiltration with a combination of bupivacaine and magnesium sulfate 24 hours after surgery resulted in a significant decrease in the intensity of pain and the dose of analgesics administered in the hours following the surgery compared to when the patients were receiving only bupivacaine or only normal saline (21). Tauzin-Fin et al. also found that the infiltration of the incision site with a combination of bupivacaine and magnesium sulfate is effective in reducing the intensity of pain and the dose of analgesics used after the surgery (22), which is consistent with the results of the present study. In another study by Lee et al, the administration of a combination of bupivacaine and magnesium sulfate during surgery reduced the intensity of pain in the first 12 hours after the surgery, which is also in line with the findings of the present study. However,

Table 3. Comparison of Pethidine Dose During Different Time points Between and Within Groups

Hours Since Surgery	Group				<i>p</i> ^b
	Normal Saline (mg) Mean ± SD	Bupivacaine (mg) Mean ± SD	Bupivacaine +Adrenaline (mg) Mean ± SD	Bupivacaine +Magnesium Sulfate (mg) Mean ± SD	
6	25.0 ± 0.0	24.3 ± 4.0	23.7 ± 5.5	7.9 ± 11.8	<0.001
12	16.4 ± 11.9	25.0 ± 0.0	15 ± 12.4	1.8 ± 6.6	<0.001
18	21.9 ± 8.4	9.0 ± 12.2	5.0 ± 10.1	0.6 ± 3.9	<0.001
24	6.2 ± 10.7	0	0	0	<0.001
<i>P</i> ^a	<0.001	<0.001	<0.001	<0.001	

^a Repeated measures ANOVA; ^b ANOVA.

no significant differences were observed between this group and the group receiving normal saline in terms of the intensity of pain 24 hours after the surgery. Moreover, the analgesic doses used 4, 8, 12, and 24 hours after the surgery did not differ significantly between the cases and

the controls. Contrarily, in the present study, a significant difference was observed between the group receiving bupivacaine and magnesium sulfate combination and all the other groups in terms of the dose of administered analgesic (23).

Koinig et al reported that the intravenous injection of magnesium sulfate before and during a knee arthroscopy significantly reduced the intensity of pain and the dose of analgesic administered 4 hours after the surgery compared to the cases receiving normal saline (24). Rezae et al also found that the intravenous injection of magnesium sulfate before elective cesarean section significantly decreased the intensity of pain and the dose of analgesic administered during the first 24 hours after the surgery (25). Additionally, it reduced postoperative pain, as well as the need to use analgesics after the surgery, which is inconsistent with the results of the current study (13).

In the present study, the intensity of pain and the dose of pethidine administered decreased significantly in the group receiving bupivacaine and adrenaline combination in the first 12 hours after spinal anesthesia compared to the group receiving only bupivacaine. Considering that adrenaline causes the vasoconstriction of the surrounding vessels and given the slower systemic absorption of analgesics, a combination of bupivacaine and adrenaline prolongs analgesia more than the administration of bupivacaine alone. In a similar study by Esmailpour et al, the injection of bupivacaine and adrenaline combination between different layers of the abdominal wall during surgery reduced the intensity of pain and the dose of analgesic administered in the first 12 hours after surgery (on hours 1, 2, and 12 of the surgery) compared to the administration of only bupivacaine, which corroborates the findings of the present study (12). In line with the present study, the study by Niklasson et al showed a reduction in the intensity of pain 12 hours after surgery with the subcutaneous injection of bupivacaine and adrenaline combination. However, no significant differences were observed between this group and the controls receiving normal saline 24 hours after the surgery, which may be due to the effect of adrenaline on drug absorption. There were no differences between the two groups in terms of the dose of analgesic administered in the first 24 hours

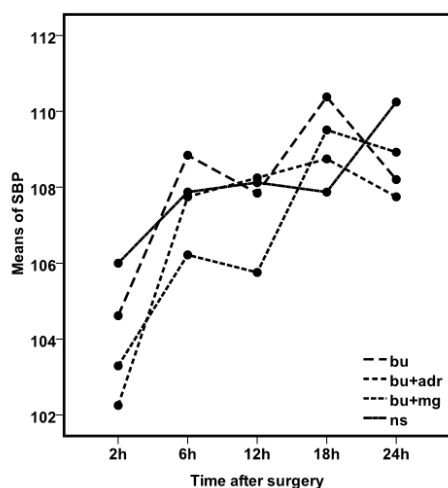


Figure 2. Comparison of Groups in Terms of Systolic Blood Pressure After the Surgery.

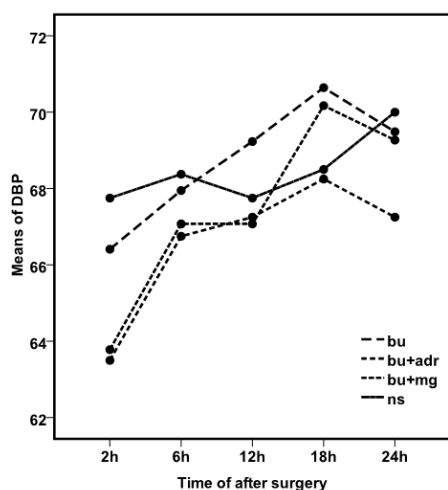


Figure 3. Comparison of Groups in Terms of Diastolic Blood Pressure After the Surgery.

after the surgery. This contradicts the results of the present study since the administration of analgesics was performed at the patient's request in the above-mentioned study while the administration of pethidine was based on the VAS in the current study (26). In the present study, the intensity of pain and the dose of pethidine administered at different times in the group receiving bupivacaine differed significantly from those of the group receiving normal saline, which is in conformity with the results of the study by Tavakoli et al (11).

The study groups were not significantly different in terms of their mean systolic BP in the hours following spinal anesthesia. Rezae et al found a significantly lower mean arterial pressure after the surgery in the group receiving magnesium sulfate, which is not in line with the present findings (25). The disparity of findings may be justified by noting that an increase in BP and HR is a symptom of pain. Moreover, in the study by Rezae et al, the administration of analgesics (Morphine) was performed at the patient's request whereas, in the present study, it was carried out both at the patient's request and based on the VAS. In addition, morphine reduces BP and HR more than does pethidine.

Conclusions

Given that injecting a combination of bupivacaine and magnesium sulfate is an easy technique that requires no special skills or instruments, the researchers propose it as a method of pain relief for women under the cesarean section since it reduces the intensity of pain and the dose of pethidine administered after the surgery.

Conflict of Interests

Authors declare that they have no conflict of interests.

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