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Original Article

A Comparative Study of the Effects of Adding Intrathecal Morphine and Pethidine to Bupivacaine in Spinal Anesthesia During Cesarean Section: A Randomized Clinical Trial

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Abstract

Background: *Intrathecal opioids are routinely used during spinal anesthesia for post cesarean analgesia. In this research, the analgesic effects of adding pethidine or morphine to intrathecal bupivacaine have been compared.*
Methods: In a double-blinded, randomized trial, 110 parturients who were scheduled for elective cesarean section were randomized into two groups of 55 patients each. In one group, 12 mg of bupivacaine (0.5%) plus 200 mcg of intrathecal morphine and in the second group 12 mg of bupivacaine (0.5%) plus 20 mg of pethidine in a total volume of 3 cc was injected as an intrathecal injection. Data variables were recorded at 1st, 4th, and 24th hours postoperatively. The primary outcome was the pain intensity numerical rating scale (0-10). The secondary outcomes were nausea, vomiting, itching, sedation (Ramsey Sedation Scale), shivering, and demand for analgesic medication.
Results: *No statistically significant differences were found between the two groups in terms of shivering, sedation, pain and pain severity, duration of painlessness period, number of demanded analgesics and level of sensory block, at 1st, 4th, and 24th hours post-operatively. At 24 hours after surgery, the rate of nausea and vomiting was significantly lower in the pethidine group (3 vs. 11, p=0.02), but at the same time, itching complaints were higher in the morphine group (10 vs. 0, p=0.001).*
Conclusion: *Adding intrathecal morphine and pethidine to bupivacaine in spinal anesthesia for cesarean section both creates a long-term and acceptable analgesia. However, in controlling itching, nausea and vomiting, pethidine showed to be more effective than morphine. Thus, it is suggested that 12 mg of bupivacaine (0.5%) is applied in combination with 20 mg of pethidine in spinal anesthesia for this surgery.*

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Keywords: : *Intrathecal Injection, Morphine, Pethidine, Bupivacaine, Spinal anesthesia, Cesarean Section.*
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Introduction

Spinal anesthesia is the preferred method for cesarean surgery (1-5). And the most common drug used for this purpose is bupivacaine(3). This method is economical and can be easily performed(4). However, this method is accompanied by several adverse effects such as hypotension(6), shivering, itching, nausea and vomiting, limitation of block time and short-term analgesia after local anesthetic absorption (7, 8). Postoperative pain is one of the most important complaints of mothers after cesarean surgery, which can be moderate to severe pain (8, 9). If this pain is properly managed, the mother can recover faster and take better care of the baby. Also, due to the pain, the mother's activity can be limited and may increase the risk of thromboembolism (10, 11). In spinal anesthesia, to relieve abdominal and somatic pains during surgery and create a long-term period of analgesia after surgery, various adjuvant drugs can be used together with local anesthetics (9, 12, 13). Among these drugs, we can mention fentanyl, sufentanil, morphine, clonidine and pethidine (14, 15). Intrathecal morphine is both cost-effective and convenient due to its long-lasting analgesic effect(16). Intrathecal pethidine has also been considered due to fewer side effects, including respiratory depression(15). In various studies, these sup-

plements have been compared to investigate their effect on postoperative pain and their side effects but they got different results(9, 12, 14, 15). In current study, pethidine or morphine was added to intrathecal bupivacaine for spinal anesthesia during cesarean section. In patients with cesarean section, we didn't find any comparative study about pethidine and morphine as adjunctive in spinal anesthesia with these doses and similar consequences. Its main objective is to compare the adequacy of the analgesic effect of these additives on the intensity of postoperative pain and the secondary objectives were to compare their effect on postoperative nausea, vomiting shivering, and itch, sedation and the time of the first request for an analgesic.

Methods:

Approval was obtained from the Research Ethics Committee of the Hormozgan University, School of Medicine (2017-11-26, HUMS.REC.1396.108). The trial was also registered in the Iranian Clinical Trials registry IRCT20140615018091N10. To calculate the sample size, refer to the study of Sawi et al(9), where the proportion of the patients with mild postoperative pain was 0.86 in the intrathecal morphine compared to 0.63 in the non-morphine group. In this study, α (type I error rate) = 0.05, 1- β (test power) = 0.9 was considered and the calculated minimum sample size was 55 for each group. The study was a double blinded, parallel group randomized clinical trial of 110 pregnant women with a gestational age of over 37 weeks. Inclusion criteria included the American Society of Anesthesiologists physical status I-II, term gestation (37-42 weeks), and desire for a spinal anesthesia.Exclusion criteria included contraindication to spinal anesthesia, cases with the emergency condition, a disease in heart valves, a history of allergy to the target drugs, the addicts or alcoholics, those afflicted with preeclampsia, diabetes and patients who declined consent. Moreover, patients whose spinal anesthesia was changed to general anesthesia for whatever reason were excluded. An extensive explanation of the study protocol was provided to all participating subjects including benefits and possible side effects of adjuvants added to local anesthesia in spinal anesthesia. They were asked to give full consent to take part in the research and they were ensured of the confidentiality of the data they provided and that was collected during the trial. Patients were randomly allocated to one of two study groups: 200 mcg intrathecal morphine or 20 mg intrathecal pethidine. Before study commencement, random allocation software was used to design a permuted block randomization table with a 1:1 allocation. The block sizes of 2, 4, and 6 were used. According to the size of each block concealed opaque sequentially numbered envelopes containing either assigned group A (receiving pethidine + bupivacaine) or B (receiving morphine + bupivacaine) was drawn. Allocation concealment and blinding to the block sizes will be applied to the primary anesthesiologist responsible for applying the study protocol. The patients and nurses were blinded to the group assignments. The research assistant responsible for recording the variable's data during the C/S surgery and postoperative recovery room and ward periods, was also blinded to the protocol groups and drugs applied. The 159 subjects were recruited. 16 were excluded who were not eligible. 17 patients needed drugs to complement of spinal anesthesia. In 10 patients, the anesthesia was changed to general anesthesia. The study was not completed by 6 patients.

The final analysis was applied on 110 patients (55 each group). All parturient went through standard monitoring. Before the study, all received 10 cc/kg of ringer and their initial hemodynamic parameters were recorded. Then, spinal anesthesia was induced in sitting position with a Quincke needle (n.25) [Dr.japan, disposable spinal needle] in the spinal interspaces of L3-L4 or L4-L5. After CSF free flow fluid was detected, The A group received 12 mg of bupivacaine (0.5%) plus 20 mg of preservative free pethidine (Pethidine 50 mg/mL, Exir Pharmaceuticals Co., Iran; www.exir.co.ir) previously prepared in insulin syringe in a total volume of 3 ccs. The B group received 12 mg of bupivacaine (0.5%) (5mg/ml, AstraZeneca, Sweden) plus 200 µg of morphine (Morphine sulfate, Faran Shimi Co. Lim. Iran) previously prepared in insulin syringe in a total volume of 3 ccs as an intrathecal injection. The quantity of morphine and pethidine was the mean recommended doses for intraspinal injection(15, 16).Then, all patients lay on their backs. Intraoperative vital signs and urine output were monitored throughout the surgery. It went on in the 1st, 4th, and 24th hours of the surgery. A systolic blood pressure < 90 mm Hg was defined as hypotension treated with 5 mg of ephedrine. A heart rate of <60 per minute was defined as bradycardia treated with 0.6 mg of atropine. The anesthesia level was checked. Once the block was stabilized at level T4 to T6, the surgery was authorized. All parameters were checked and recorded by the anesthesia assistant after the block.

Patients' severity of post-surgical pain was measured and recorded as patients self-reported NRS (Numeric Rating Scale)(17) in the 1st, 4th, and 24th hours after surgery. The most severe possible pain was scored 10 and total painlessness was scored 0. The other levels of pain ranged from 0 to 10 as self-rated by the patients.

The presence or absence of nausea and vomiting was recorded during surgery and in the 1st, 4th, and 24th hours after surgery. Nausea was treated with ondansetron (4 mg IV).

The presence or absence of itching was measured and recorded during surgery and in the 1st, 4th, and 24th

hour after the surgery. Ramsey Sedation Scale(18) was used during the surgery as well as in the 1st, 4th, and 24th hours as below: the patient is anxious and upset or restless or both (score 1); the patient is relaxed and cooperating (score 2); the patient only abides by the orders (score 3); the patient shows a rapid reaction to loud sound or a slow blow to the area between the eyebrows (score 4); the patient shows a slow reaction to loud sound or a slow blow to the area between the eyebrows (score 5); the patient would show no reaction at all (score 6). The time of the first request for an analgesic agent after the surgery was recorded in the minutes after the surgery. The dose of the analgesic was also recorded as in the number of Diclofenac suppositories (50 mg) applied. In case of repeated complaints of pain, Diclofenac suppositories were prescribed to the patient up to a maximum of 3 suppositories per day. The presence or absence of shivering was evaluated and recorded in all patients.

Statistical methods for the acquired data were applied by SPSS.19 for statistical analysis through descriptive statistics such as mean, standard deviation, percentage, etc. used along with the tests of normality, chi-squared test, Fisher's exact test, independent-sample T-test, and Mann-Whitney U-test. The level of significance was set at $P<0.05$.

Results:

The two research groups were compared in terms of demographic characteristics such as the mean age, weight, and height, and there was no significant difference (Table 1). The block-level was compared between the two groups and in both, it reached 58.2%, i.e., T4, (Table 2).

There was no significant difference between the pethidine and morphine groups regarding the severity of pain at different time points, the onset of pain after operation and the number of suppository analgesics required after the operation (Table 3).

The presence or absence of nausea and vomiting, itching, and shivering was also compared between the two groups at different times (Table 4). In the 24th hour after operation, post-operative nausea and vomiting was significantly higher in the morphine group ($P= 0.022$), additionally itching was also higher at this point in the morphine group ($P= 0.001$) (Table 4). The incidence of shivering was different among the two groups, but it was not statistically significant. The two groups were also compared in terms of the mean RSS (Ramsay Sedation scale), (Table 3) and no significant difference between the two groups was found during the surgery and in post-operative period.

Table 1: Two research groups compared in terms of age, weight and height

Variable	Research group				P-value
	Bupivacaine+pethidine		Bupivacaine+morphine		
	Mean	SD	Mean	SD	
Age (years)	28.23	7.51	30.48	9.66	.226
Weight (kg)	69.18	9.61	69.27	12.00	.844
Height (cm)	156.95	7.51	159.39	9.01	.173

Age and height between groups using independent test and weight between groups with Comparisons were made using the Mann Whitney U test. There was no significant difference ($P>0.05$).

Table 2: Cross-comparison of two research groups in terms of the level of sensory motor block

Sensory block level	Research group			
	bupivacaine plus +pethidine		Bupivacaine +morphine	
	No= total 55	%	No.= total 55	%
T4	32	58.2	32	58.2
T5	1	1.8	6	10.9
T6	22	40.0	17	30.9

Mann Whitney U test was used and there was no significant difference ($P>0.05$)

Table 3: Cross-comparison of two research groups in terms of mean RSS score, severity of pain, time interval between the outset of pain and number of suppositories taken by patients in pain

variable	time	Research group				p-value
		Bupivacaine+pethidine		Bupivacaine+morphine		
		mean	SD	mean	SD	
RSS	During surgery	1.98	0.23	1.95	0.23	0.416
	1st hour	1.98	0.13	1.96	0.19	0.560
	4th hour	2.04	0.19	1.98	0.23	0.182
	24th hour	2.00	0.19	1.98	0.13	0.567
Severity of pain (NRS)	1st hour	0.09	0.48	0.18	0.82	0.637
	4th hour	1.42	1.78	1.78	2.20	0.579
	24th hour	0.78	1.56	0.91	1.71	0.876
Time interval from the outset of pain (min.)		657.27	310.45	743.40	331.40	0.417
No. of suppositories		1.86	0.77	1.00	1.00	0.928

Mann Whitney U test is used. There was no significant difference (P>0.05)

Table 4: Distribution of patients with nausea and vomiting, itching and shivering in the research Groups

variable	time	Response	Research group				p-value
			Bupivacaine+pethidine		Bupivacaine+morphine		
			No.= total 55	%	No.= total 55	%	
Nausea & vomiting	During surgery	Yes	16	29.1	8	14.5	0.065
		no	39	70.9	47	85.5	
	1 hour later	Yes	2	3.6	4	7.3	0.679
		no	53	96.4	51	92.7	
	4 hours later	Yes	4	7.3	7	12.7	0.340
		no	51	92.7	48	87.3	
	24 hours later	Yes	3	5.5	11	20.0	0.022*
		no	52	94.5	44	80.0	
Itching	During surgery	Yes	3	5.5	0	0.0	0.243
		no	52	94.5	55	100.0	
	1 hour later	Yes	11	20.0	11	20.0	-
		no	44	80.0	44	80.0	
	4 hours later	Yes	2	3.6	7	12.7	0.161
		no	53	96.4	48	87.3	
	24 hours later	Yes	0	0.0	10	18.2	0.001*
		no	55	100.0	45	81.8	
shivering	During surgery	Yes	5	9.1	8	14.5	0.376
		no	50	90.9	47	85.5	
	1 hour later	Yes	10	18.2	16	29.1	0.178
		no	45	81.8	39	70.9	

Chi-squared test was used

Discussion:

The main finding of this randomized clinical trial was that the mean severity of pain in the 1st, 4th and 24th hours after surgery was lower in the pethidine group than in the morphine group but the difference was not statistically significant. The painless interval was slightly lower in the pethidine group than in the

morphine group, but this difference was not statistically significant..

Although during the surgery, the rate of nausea and vomiting was 29.1% and 14.5%, in the pethidine and morphine group respectively, this difference was not statistically significant. However, after the surgery, the rate of nausea and vomiting was lower in the former group than in the latter. Within 24 hours after surgery, nausea and vomiting reached 5.5% in the pethidine group while it was 20% in the morphine group. Thus, it can be concluded that nausea and vomiting were better controlled in the pethidine group in the post-operative period.

The rate of shivering during the surgery reached 14.5% in the morphine group and 9.1% in the pethidine group. One hour later, it reached 29.1% in the former and 18.2% in the latter. Therefore, it can be concluded that in one hour the trend of shivering was increased in both groups. Yet this increase was more in the morphine group.

In the present study, during surgery, 5.5% of patients in the pethidine group complained of itching. Yet no patient from the morphine group complained of any itching during surgery. However, in first hour after surgery, 20% of patients in both groups began to complain of itching. In the 4th hour after surgery, itching was reduced in both groups, but this reduction was more in the pethidine group. This decreasing trend continued in the same pethidine group until 24 hours after surgery when there was no complaint anymore. Later on, the rate of itching was slightly increased in the morphine group till it reached a significant level. Thus, it can be concluded that itching was attenuated in the pethidine compared to the morphine group. As far as we have searched this trend of itching issue has not been addressed in the other studies or related literature.

In this research, sedation scores (Ramsey Sedation Scale) did not differ between the two groups and there were no cases of respiratory depression in either group. No similar study was found on this topic.

Saracoglu et al(19). concluded that using morphine would lengthen the painless time after surgery and this painless interval showed to be longer in combination with hyperbaric bupivacaine. In the present study, in both groups 58.2% had a T4 block level. Nevertheless, in the study by Roy et al.(20), the median blocked segment in both groups was T2. The probable reason of such a difference can be due to the use of hyperbaric bupivacaine (0.75%) in the Roy's study instead of hyperbaric bupivacaine (0.5%) in the present research.

In the study conducted by Hong et al. (21), a similar rate of nausea and vomiting was reported in both groups which contrast with the present research. This contrast could possibly be due to different doses of bupivacaine, pethidine and morphine used.

In an investigation by Hong et al(21) the rate of shivering was found to be significantly lower in the pethidine group than the morphine (0.1 and 0.2 mg). They concluded that adding pethidine can better control the shivering in patients with spinal anesthesia for a C/S. In the present research, this difference was not statistically significant. This divergence can be explained by the difference in opioid doses that they used. In another research project by Roy et al. (20) the effect of adding meperidine to bupivacaine was investigated for controlling shivering in spinal anesthesia performed in C/S surgeries. Both groups received hyperbaric bupivacaine (0.75%, 10.5 mg) plus 0.15 mg of morphine. Besides this dose, the intervention group received 0.2 mg meperidine for each kg of body weight while the control group received an equal amount of normal saline. The results showed that the rate of shivering in the meperidine group (9 out of 20 patients, equal to 45%) was lower than the control (17 out of 20, equal to 85%). The rate of shivering in the present research was found to be much lower than that of Roy et al. (20) which can be due to the different doses of drugs (as in the present research 12 mg of bupivacaine (0.5%) was used plus 200 μg of morphine compared to hyperbaric bupivacaine (0.75% and 10.5 mg) plus 150 μg of morphine. Moreover, in the present study, 20 mg of pethidine was used in comparison to the 0.2 mg per kg of body weight). In other research, Nasseri et al. (22) reported the rate of shivering in their morphine group (0.5% hyperbaric bupivacaine plus 200 μg morphine) as 40% though, which was a much higher proportion compared to the present research shivering rate.

Among the limitations of the present study could be that we did not control central temperature and the peripheral body temperatures. Therefore, we suggest adding other options and trying different doses of adjunct opioids in future conducted studies would help to determine the exact effective safe dose of pethidine or morphine for spinal anesthesia in cesarean section surgery.

In Conclusion, we can conclude that adding intrathecal morphine and pethidine to bupivacaine in spinal anesthesia for a cesarean section helps to create a long-term and desirable painlessness. Despite the itching, nausea and vomiting following the addition of either morphine or pethidine to bupivacaine, pethidine showed to perform better considering side effect profile. Thus, it is suggested that a combination of 12 mg of hyperbaric bupivacaine (0.5%) and 20 mg of pethidine may be applied for a spinal anesthesia for the cesarean section surgery.

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Conflict of Interest:
There is no conflict of interest to be declared.

References:

1. Practice Guidelines for Obstetric Anesthesia: An Updated Report by the American Society of Anesthesiologists Task Force on Obstetric Anesthesia and the Society for Obstetric Anesthesia and Perinatology. Anesthesiology. 2016;124(2):270-300.
2. Fettes P, Jansson J-R, Wildsmith J. Failed spinal anaesthesia: mechanisms, management, and prevention. British journal of anaesthesia. 2009;102(6):739-48.
3. Punchuklang W, Nivatpumin P, Jintadawong T. Total failure of spinal anesthesia for cesarean delivery, associated factors, and outcomes: a retrospective case–control study. Medicine. 2022;101(27):e29813.
4. Riley ET, Cohen SE, Macario A, Desai JB, Ratner EF. Spinal versus epidural anesthesia for cesarean section: a comparison of time efficiency, costs, charges, and complications. Anesthesia & Analgesia. 1995;80 (4):709-12.
5. Šklebar I, Bujas T, Habek D. Spinal anaesthesia-induced hypotension in obstetrics: prevention and therapy. Acta Clinica Croatica. 2019;58(Suppl 1):90.
6. Fitzgerald J, Fedoruk K, Jadin S, Carvalho B, Halpern S. Prevention of hypotension after spinal anaesthesia for caesarean section: a systematic review and network meta-analysis of randomised controlled trials. Anaesthesia. 2020;75(1):109-21.
7. Agarwal A, Kishore K. Complications and controversies of regional anaesthesia: a review. Indian journal of anaesthesia. 2009;53(5):543-53.
8. Carvalho B, Butwick AJ. Postcesarean delivery analgesia. Best Practice & Research Clinical Anaesthesiology. 2017;31(1):69-79.
9. Sawi W, Choy Y. A comparative study of post operative analgesia, side effects profile and patient satisfaction using intrathecal fentanyl with and without morphine 0.1 mg in caesarean section. Middle East J Anaesthesiol. 2013;22(1):21-6.
10. Chi X, Li M, Mei W, Liao M. Comparison of patient-controlled intravenous analgesia with sufentanil versus tramadol in post–cesarean section pain management and lactation after general anesthesia–a prospective, randomized, double-blind, controlled study. Journal of pain research. 2017:1521-7.
11. Quinlan JD, Murphy NJ. Cesarean delivery: counseling issues and complication management. American family physician. 2015;91(3):178-84.
12. Marroquin B, Feng C, Balofsky A, Edwards K, Iqbal A, Kanel J, et al. Neuraxial opioids for post-cesarean delivery analgesia: can hydromorphone replace morphine? A retrospective study. International Journal of Obstetric Anesthesia. 2017;30:16-22.
13. Sultan P, Halpern SH, Pushpanathan E, Patel S, Carvalho B. The effect of intrathecal morphine dose on outcomes after elective cesarean delivery: a meta-analysis. Anesthesia & Analgesia. 2016;123(1):154-64.
14. 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. Revista brasileira de anestesiologia. 2012;62:781-7.
15. Farzi F, Mirmansouri A, Forghanparast K, Heydarzadeh A, Abdollahzadeh M, Moghadam FJ. Addition of intrathecal fentanyl or meperidine to lidocaine and epinephrine for spinal anesthesia in elective cesarean delivery. Anesthesiology and pain medicine. 2014;4(1).
16. Patel N, Bryant A, Duncan K, Kukreja P, Powell MF. Cost comparison of intrathecal morphine to intravenous patient-controlled analgesia for the first 24 h post cesarean delivery: a retrospective cohort study. Journal of anesthesia. 2017;31:44-50.
17. Breivik EK, Björnsson GA, Skovlund E. A comparison of pain rating scales by sampling from clinical trial data. The Clinical journal of pain. 2000;16(1):22-8.
18. Oh T. Oh's Intensive Care Manual: Butterworth-Heinemann; 2003.
19. Saracoglu A, Saracoglu KT, Eti Z. Comparative study of fentanyl and morphine in addition to hyperbaric or isobaric bupivacaine in combined spinal anaesthesia for caesarean section. Archives of Medical Science. 2011;7(4):694-9.
20. Roy J-D, Girard M, Drolet P. Intrathecal meperidine decreases shivering during cesarean delivery under spinal anesthesia. Anesthesia & Analgesia. 2004;98(1):230-4.
21. Hong JY, Lee I. Comparison of the effects of intrathecal morphine and pethidine on shivering after Caesarean delivery under combined-spinal epidural anaesthesia. Anaesthesia. 2005;60(12):1168-72.
22. Nasseri K, Ghaderi E, Khezripour E. Comparison of the effects of intrathecal meperidine and morphine on incidence and intensity of shivering after caesarean sections under spinal anesthesia: A randomized controlled trial. Iranian Red Crescent Medical Journal. 2017;19(7).