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Comparison of analgesic effect and duration of midazolam and fentanyl addition to intrathecal bupivacaine 0.05% in lower limb orthopedic surgeries

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ABSTRACT

Background and Aim: Local anesthesia has gained popularity in recent years; therefore, the present study was aimed to test the effect of adding midazolam and fentanyl to intrathecal bupivacaine in patients with orthopedic surgeries of lower limbs.

Materials and Methods: A double-blind, randomized clinical trial was conducted on 75 patients who underwent orthopedic surgery of their lower limbs in the 5Azar Teaching Hospital in the city of Gorgan, Iran. Patients were randomly allocated to the test groups of bupivacaine plus normal saline (BN), bupivacaine plus midazolam (BM), and bupivacaine plus fentanyl (BF). Duration of analgesia, pain intensity, chills, nausea, vomiting, systolic and diastolic blood pressure as well as pulse rate and SpO_2 were assessed. Descriptive analysis was used to explain the mean and standard deviation. One-way ANOVA, repeated measure ANOVA, and chi-square tests were carried out using SPSS Statistics software version 19.

Results: The mean age of patients was 45.29 ± 14.02, 42.16 ± 15.68, and 40.7 ± 14.72 years respectively in the groups of BF, BM, and BN. Tukey test showed a considerable difference between the BM and BF groups ($p < 0.001$), and BM and BN groups ($p < 0.001$) regarding the duration of analgesia. Moreover, Tukey test showed a significant difference between the BM and BN groups in minutes of 60 ($p = 0.02$) and 90 ($p = 0.001$), the BM and BN groups, and in final, between the BM and BF groups in minutes of 120 ($p < 0.001$).

Conclusion: The combination of either BM or BF may be useful to provide patients with longer duration of analgesia and also enable them to tolerate pain better.

Keywords: Analgesic Effect, Bupivacaine, Fentanyl, Midazolam, Orthopedic Surgery.
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INTRODUCTION

Orthopedic surgery can be performed using regional or topical anesthesia.[1] Spinal and epidural anesthesia techniques are both appropriate. However, local anesthesia is usually preferred by many medical practitioners because patients may benefit from the motor and sensory testing; also, they can find the instant patient feedback during operation.[2,3] Local anesthesia has also gained popularity in recent years for many reasons such as faster recovery compared to conventional techniques of spinal anesthesia, higher success rate (compared to?), and better patients' satisfaction as well as cost-effectiveness compared to general anesthesia.[4-6]

In some major surgeries of the lower limbs, longer analgesia is required.[7] For example, in total knee replacement, minimum postoperative pain is critical to accelerate the recovery time and return of function after orthopedic surgery of lower limbs.[8] Although spinal anesthesia yields better analgesia during the first postoperative compared to general anesthesia, a remarkable relation between topical and anesthesia drugs is not found.[8] It is well-documented that adding intrathecal midazolam to a topical anesthesia have suitable effects on pain control after cesarean section.[9] Several investigations cited that intrathecal midazolam has an effect on type A receptors of GABA (GABA Aminobutyric acid).[10,11] It may also provide an important anesthesia effect by affecting the spinal receptors.[12,13] Numerous clinical studies have reported that midazolam can be added to intrathecal anesthetics to improve analgesia after surgery.[14-16]

Fentanyl is a potent opioid with an effect of 75 to 100 times stronger than morphine.[17] Fentanyl is clinically utilized to provide analgesia during surgery and also to diminish the hypertensive response of intubation.[18] Analgesics mechanisms are different based on their categories.[19] According to studies, a single analgesic cannot effectively control pain.[20] Combination of different types of analgesics may likely have more effective depressant effects with a fewer dose in a single treatment and with less side effect, that could reduce adverse dose-associated complications.[19,21] Under these circumstances, the

current paper was aimed to test the effect of adding midazolam and fentanyl to intrathecal bupivacaine on the extent and duration of the nerve block, the quality of analgesia, spinal block recovery time and postoperative pain intensity in patients undergoing orthopedic surgery of the lower limbs.

MATERIALS AND METHODS

Study design

A double-blind randomized clinical trial was conducted in 5Azar Teaching Hospital, Gorgan City, Iran. The study involved 75 patients aged 18-65 years who underwent orthopedic surgery of the lower limbs (with surgery duration of 150 minutes). This protocol was granted an Iranian Registry of Clinical Trial Code (IRCT2014061810340N9).

Intervention groups of the study

Patients were randomly allocated into the three test groups with 25 patients in each group. The groups are bupivacaine plus normal saline group, bupivacaine plus midazolam group, and bupivacaine plus fentanyl group (hereafter abbreviated as BN, BM, and BF, respectively). Each group in the study used 15 mg of bupivacaine 0.5% (equivalent to 3 cc), with the addition of 0.5 ml of normal saline in the BN group, 0.5 mg of midazolam in the BM group, and 25 µg of fentanyl in the BF group. The regimens were administered via intrathecal route at L3-L4 level with needle gauge 25 Vitacare® in the spinal midline.

Measurements

Patients' heart activity, peripheral partial pressure of oxygen and carbon dioxide, and blood pressure were measured using ECG recordings, pulse oximetry and capnograph, and non-invasive blood pressure monitor on admission to the operating room. Hemodynamic changes were measured and recorded during recovery time. Time of onset was recorded as the time from drug injection to the time when the subject sensed numbness at the tenth thoracic vertebra level (T10), tested using pinprick test. Additionally, the duration of anesthesia after the spinal block was checked by performing the pinprick test every 15 minutes. The end of block time was considered when pain occurred under T10 level or when a retrogression of sensory block up to 2 segments happened. Episodes of nausea and vomiting were recorded in a postoperative setting.

Instruments

To explore the anesthesia effect and hemodynamic changes, the intensity of analgesia was assessed at 30, 60 and 90 minutes after the block using the visual analog scale (VAS). The amount and the intensity of chills in the recovery time was measured using a grading system comprising of 4 levels (level 1 = patient without chills, and level 4 = patient with severe chills).

Randomization technique

At first, in a closed box, 75 labels were written with 25 pieces of each 'BN', 'BM', and 'BF'. Research team randomly selected a label from the box for every subject involved in the study, assign the subject in the test groups accordingly and used the appropriate anesthesia regimen for their surgeries.

Sample size

According to a related study,[17] the mean and standard deviation of 140 ± 22 in the midazolam arm, and the mean and standard deviation of 107 ± 18 in the fentanyl arm, $N = n\sqrt{g-1}$, 90 % power test, and 5 % error, 25 samples were included in the each group (75 patients in total) of the study.

$$n = \frac{\left(s^2_1 + s^2_2\right)^2 \left(z_{1-\frac{\alpha}{2}} + z_{1-\beta}\right)^2}{\left(\overline{x1} - \overline{x2}\right)^2}$$

Participants

Exclusion criteria were as follow; patients with substance abuse, patients with symptoms of neuropathy, and lack of appropriate sensory level after performing the spinal anesthesia. *Inclusion criteria?*

Data analysis

Descriptive analysis was used to explain the mean and standard deviation of some variables. One-way ANOVA, repeated measure ANOVA, and Chi-square tests through SPSS statistic software (version 19) were used to analyze the data.

RESULTS

Seventy-five subjects participated in the study, with 25 subjects in each BN, BM, and BF group. The mean age of patients were 45.29 ± 14.02, 42.16 ± 15.68, and 40. 7 ± 14.72 years old, respectively. In terms of age, one-way ANOVA analysis showed no significant variation.

Gender proportions in the groups were 60% male in BN group, and the same amount of 72% male in BM and BF group. Chi-square test indicated no remarkable difference in gender distribution. Patients who were classified as ASA I category were 18 (65.2%), 19 (76%), and 20 (80%) in the

BF, BM, and BN groups, respectively. Chi-square analysis of the physical status classification also deduced no significant difference between all three groups.

The duration of analgesia in the BF group was 153.28 minutes, in the BM group was 238.6 minutes, and in the BN group was 135.04 minutes with a significant difference between three groups based on one-way ANOVA analysis. With regard to Tukey test, a considerable difference was found between BM and BF groups ($p < 0.001$), BM and BN groups ($p < 0.001$); while the difference between BF and BN groups was not significant ($p = 0.28$). The onset of analgesia in the BF group was 168.92 seconds, in the BM group was 233.72 seconds, and in the BN group was 153.48 seconds. One-way ANOVA analysis stated a significant statistical relationship between three groups. In addition, Tukey test revealed a significant variation between BM and BF groups ($p < 0.001$), and BM and BN groups ($p < 0.001$); however, the onset of analgesia between BF and BN groups was not statistically different ($p = 0.67$).

One-way ANOVA presented a remarkable difference between three groups regarding pain severity. Moreover, Tukey test showed a difference between the BM and BN groups in the pain assessment in 60 minutes ($p = 0.02$) and 90 minutes ($p = 0.001$) after the induction of anesthesia, and between the BM and BF groups in 120 minutes ($p < 0.001$) after the induction of anesthesia.

The incidence of nausea was 11 (44%), 2 (8%), and 7 (28%) in the BF, BM, and BN groups, which is statistically significant with p-value of 0.016 (derived using chi-square test). The incidence of vomiting was 0 (12%) in the BF group 1 (4%) in the BN group, and none of the participants had vomited in the BM group. There was no significant relationship between the three groups. Chi-square test showed a significant relationship between three groups in terms of chills ($p = 0.001$). Additionally, the frequency of chills, nausea, and vomiting presented in the graphs 1, 2 and 3.

Repeated measures with ANOVA analysis showed no significant relationship between the three groups regarding the systolic blood pressure. Bonferroni test also did not state remarkable difference within the groups. In terms of diastolic blood pressure, repeated measures with ANOVA analysis showed no significant association between groups and Bonferroni test showed no significant difference between the groups as well. However, there was a significant difference between minutes of 30, 60 and 90 before and after intervention ($p < 0.001$).

Repeated measures with ANOVA analysis explained no a significant difference between the groups in terms of patients' pulse rate. Also, Bonferroni test showed no significant differences between the groups. According to repeated measures using ANOVA analysis, patients in three groups were not different about pulse. On the other hand, Tukey test showed a remarkable difference between *patients' pulse rate (?)* in BM and BF groups ($p = 0.008$) and Bonferroni test did not show significant differences within groups.

Table 1 **The mean of duration and onset of analgesia in the study groups**

Variables	Groups	Mean	Standard deviation	*p*-value
Duration of analgesia	BF	153.28	35.12	0.001
	BM	238.6	47.38	
	BN	135.04	42.96	
Onset of analgesia	BF	168.92	48.22	0.001
	BM	233.72	60.58	
	BN	153.48	69.58	

Table 2 **The mean of pain intensity in the study groups**

Groups	Time (minute)	Mean	Standard deviation	*p*-value
BF	60	0.64	0.19	0.028
BM		0.12	0.06	
BN		0.8	0.23	
BF	90	0.96	0.28	0.001
BM		0.2	0.08	
BN		1.84	0.43	
BF	120	2.24	0.4	0.001
BM		0.24	0.13	
BN		3.24	0.49	

Table 3 **Comparison of chills, nausea and vomiting in postoperative in the study groups**

		Yes		No		
Variables	Groups	Number	Percent	Number	Percent	*p*-value
Chills	BF	16	64	9	36	0.001
	BM	5	20	20	80	
	BN	17	68	8	32	
Nausea	BF	11	44	14	56	0.016
	BM	2	8	23	92	
	BN	7	28	18	72	
Vomiting	BF	3	12	22	80	0.15
	BM	0	0	25	100	
	BN	1	4	24	96	

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Table 4 Comparison of the systolic and diastolic blood pressure before intervention and in 30, 60 and 90 minutes after intervention in the study groups

Variables	Groups	Before intervention		30 minutes		60 minutes		90 minutes		*p*-value
		Mean	SD	Mean	SD	Mean	SD	Mean	SD	
Systolic blood pressure	BF	132.32	18.07	121.4	11.28	117.92	17.67	119.96	23.46	0.5
	BM	132.92	16.09	119.36	13.79	122.93	14.14	123	15.68	
	BN	148.39	23.3	120.39	19.62	114.21	16.65	118.21	21.63	
Diastolic blood pressure	BF	81.48	10.37	74.72	9.34	71.96	15.71	76.36	14.92	0.61
	BM	80.52	8.86	75.28	9.23	78.12	10.94	75.8	11.12	
	BN	82.43	13.47	70.73	11.63	71.78	12.99	75.26	12.31	

SD = Standard deviation

Table 5 Comparison of the pulse rate and SPO2 before intervention and in 30, 60 and 90 minutes after intervention in the study groups

Variables	Groups	Before intervention		30 minutes		60 minutes		90 minutes		*p*-value
		Mean	SD	Mean	SD	Mean	SD	Mean	SD	
Pulse rate	BF	85.96	16.71	80.8	14.98	83.4	19.65	83.2	18.2	0.18
	BM	89.84	14.23	82.52	14.06	84.04	15.03	83.92	14.24	
	BN	88.8	18.74	83.72	25.23	91.96	19.49	90.52	16.87	
SpO_2	BF	98.68	1.62	98.72	1.51	98.16	1.33	99.12	1.3	0.011
	BM	99.04	1.45	99.64	0.71	99.64	0.9	99.8	0.81	
	BN	99.2	0.96	98.6	1.65	99.28	0.84	99.24	0.83	

SD = Standard deviation

DISCUSSION

Spinal anesthesia has been taken into account by anesthesiologists for its lower mortality compared to general anesthesia. A certain dose of the drug is necessary for suitable anesthesia. In most cases, a sufficient amount of anesthesia occurs, but some pain and side effects might happen as well. To comply with this problem, adding the opiates such as fentanyl or midazolam is recommended.[22] At the present study, spinal anesthesia performance on 25 subjects in the BN group (bupivacaine and normal saline), 25 subjects in the BM group (bupivacaine and midazolam), and 25 patients in the BF group (bupivacaine and fentanyl) were evaluated.

The onset of analgesia was remarkably faster in the BF group than the BM group. A similar result was shown in a study conducted by Imani et al. aimed at exploring the maternal and neonatal effects of adding midazolam to bupivacaine under combined spinal-epidural anesthesia in elective cesarean section, the addition of midazolam was related to the rapid onset of motor and sensory blocks as well as maximum sedation in patients.[23] In a study by Sattari et al., the onset of analgesia was significantly longer in bupivacaine and fentanyl groups than bupivacaine only group.[24] The duration of analgesia was significantly longer in the BM group than two other groups. Other studies cited that midazolam has somatic anesthesia effects in postoperative, but has no effect on visceral pain.[23,25] Other studies also stated longer anesthesia duration in the fentanyl group than bupivacaine group[24,26,27] that was in accordance with our results. Safari et al. in a study investigating anesthesia effect on opium-addicted subjects also found that the duration of spinal anesthesia produced by the combination of fentanyl and bupivacaine is longer than by bupivacaine only.[28] Additionally, in a study by Nasseh and Khezri entitled 'Effects of adding midazolam to intrathecal bupivacaine on pain after cesarean section' described that adding 0.02 mg/kg intrathecal midazolam to bupivacaine increased the duration of anesthesia following cesarean section compared to bupivacaine alone.[29] Furthermore, in another study by Dogan et al., patients in the midazolam and fentanyl group reported higher satisfaction score and lower verbal pain scale scores *compared to?*.[30]

In a study implemented by Hirsh et al. in outpatient colonoscopy, group of 0.05 mg/kg midazolam and fentanyl 2 μg/kg presented a lower pain intensity compared to group of 0.05 mg/kg midazolam and 1 mg/kg tramadol and group of 0.05 mg/kg midazolam and 2 mg/kg tramadol. Also, the patients treated with fentanyl-based analgesia

tolerated colonoscopy better than patients receiving tramado1 only.[31]

In terms of nausea and vomiting, patients in the BM group experienced less nausea than two other groups that are in line with the study by Imani et al..[23] Nevertheless, in the survey conducted by Sattari et al. on opium-addicted patients, there was no significant relationship between fentanyl and bupivacaine groups.[24] Even so, Raji et al. in their study presented that adding fentanyl to lidocaine in spinal anesthesia in patients undergoing cesarean section can likely increase vomiting and nausea.[32] Inquiries by Nasseh and Khezri,[29] and Kim and Lee[14] revealed no remarkable difference of adding of midazolam to bupivacaine which opposed our findings. In contrast, in the study by Karbasfrushan et al., the incidence of nausea and vomiting were higher in the bupivacaine plus midazolam group compared to the incidence in bupivacaine plus normal saline group.[33] These contradictory results may be likely caused by different type of surgeries, dose and subject's characteristic, which necessitate us to do more similar and precise studies in the future. In another investigation, Kashefi et al.[34] showed that adding the 50 μg/kg midazolam to lidocaine shortens the onset of sensory and motor block, and improves quality of anesthesia as well as perioperative analgesia with no side effects, that in conformity with our study.

In the present survey, systolic and diastolic blood pressures were similar in all three groups, in accordance with the study by Nasseh and Khezri with no difference between the midazolam and control groups.[29] The aforementioned effects reported that adding 0.02 mg/kg midazolam using spinal anesthesia to bupivacaine has no detrimental effect on cardiovascular system. Also similar to the previous study, patients' pulse rate and SpO_2 were not significantly different between the groups in the present study.[29] The findings of the study by Peng et al.[2] with two groups of dexmedetomidine-fentanyl (DF) and midazolam-fentanyl (MF) explained that the heart rate, systolic blood pressure, and SpO_2 reduced after the drugs injection in two groups. Heart rate was lower in the DF group at all-time points compared to MF group, hence inconsistent with the current results. This confusion may be caused by the factors such as different drug combinations or doses. Moreover, patients reported higher SpO_2 at three different measurement interval[2] in a study by Peng et al., which contradicts our findings.

CONCLUSION

To conclude, a BM and BF combination may be appropriate alternatives to provide patients with higher duration of analgesia and also enable them to tolerate better pain. In addition, the regimen used in the study might also be applicable, as there was no problem emerged due to such dose.

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CONFLICT OF INTEREST

The authors declared that they have no conflicts of interest.

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