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The Effect of Intrathecal Administration of Different Doses of Morphine on Headache after Dural Puncture in Cesarean Sections Under Spinal Anesthesia: A Randomized Double-Blind Controlled Study

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Introduction: Intrathecal morphine is used to prevent post-dural puncture headache (PDPH). We aimed to investigate the effect of administering different doses of morphine intrathecally on PDPH in whom a cesarean section (CS) was performed under spinal anesthesia.

Materials and Methods: 80 ASA I-II pregnant women were included in the study. They were randomly divided into four groups: *F25*: 2ml of hyperbaric bupivacaine+25µg of fentanyl intrathecally, *M100*: 2ml of hyperbaric bupivacaine +100µg of morphine intrathecally, *M150*: 2ml of hyperbaric bupivacaine+150µg of morphine intrathecally and *M200*: 2ml of hyperbaric bupivacaine+200µg of morphine intrathecally. The patients were monitored for postoperative headache, development of PDPH, the requirement for epidural blood patch (EBP), the EBP number, the duration of hospitalization, and side effects that might occur within the first 24 hours (drug allergy, nausea, vomiting, itching, apnea, desaturation). All patients were assessed using the visual analog scale (VAS) for seven days postoperatively.

Results: The lowest rate of PDPH was determined in the M200. The highest VAS score of M200 was significantly lower than the other groups ($p<0.05$). The nausea-vomiting and itching rates were significantly lower in M100, M150, and M200.

Conclusion: PDPH rate was significantly low in the group that 200 µg of morphine was administered. In the groups in which morphine was administered, the incidence of side effects was significantly higher than the group which administered fentanyl dose-independently.

Keywords: Spinal anesthesia, cesarean section, post-dural puncture headache, intrathecal morphine

Introduction

The Spinal anesthesia (SA) is commonly used in cesarean sections (CS), and one of its most frequent side effects is post-dural puncture headache (PDPH) (1). PDPH is significantly more common in patients who had CS than other patients operated under SA, and its

incidence is varied between 0.1-36%, according to the published studies. Nausea, vomiting, photophobia, vertigo, and other quality of life-impairing symptoms accompany PDPH (2). Recently, intrathecal morphine has been used to prevent unwanted PDPH, and contradictory

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results have been reported regarding the effects of morphine in PDPH prevention and treatment, which might have been related to the intrathecal dose of morphine (3). Opioids may be used as adjuvants to increase sensory block levels, reduce the incidence of hypotension, and provide postoperative analgesia in CS (4).

The study aimed to investigate the effects of different doses of morphine used for this purpose on PDPH development in pregnant women scheduled for CS.

Materials and Methods

American Society of Anesthesiologists (ASA) I-II patients, aged between 18-40 years, undergoing CS under SA in the University Medical Faculty, who accepted to participate were included in the study after the Ethics Committee's approval and obtaining the patients' verbal and written consent. Patients with a history of PDPH or migraine, those with more than 1000 ml of intraoperative blood loss, obese cases with Body Mass Index (BMI), and patients in whom regional anesthesia was contraindicated (sepsis, local infection, coagulopathy, cardiac disorder, hypovolemia) were excluded from the study. A total of 80 patients were included in this randomized, double-blind controlled study and divided into four groups of 20 patients as Group F25: 10mg of hyperbaric bupivacaine+25µg of fentanyl intrathecally, Group M100: 10mg of hyperbaric bupivacaine+100µg of morphine intrathecally, Group M150: 10mg of hyperbaric bupivacaine +150µg of morphine intrathecally, Group M200: 10mg of hyperbaric bupivacaine + 200µg of morphine intrathecally. All the patients were routinely monitored for Electrocardiography (ECG), Peripheral oxygen saturation (SpO₂), heart rate (HR), and blood pressure after

placing them on the operating table. Their systolic arterial pressure (SAP), diastolic arterial pressure (DAP), mean arterial pressure (MAP), HR, and SpO₂ values were recorded. The patients' demographic data (age, gravida, parity, gestational age, BMI), operation times, the amounts of intraoperative blood loss, and intraoperative transfusions were recorded. SA was performed in a sitting position in all patients, using a 25 Gauge (G) sharp-tip spinal needle. A bilateral headache, with symptoms changing with the position, developing within the seven days following the dural puncture, and disappearing within 14 days was defined as PDPH. The occurrence of postoperative headaches, PDPH development, Epidural blood patch (EBP) requirement and its number, duration of hospitalization, and the maximal headache severity according to the visual analog scale (VAS) between 1-10 were recorded. The patients were monitored for side effects (nausea, vomiting, itching, desaturation), including drug allergies, within the first 24 hours.

The Treatment Protocol Used for Patients Developing Post-Dural Puncture Headache

The patients were assessed for dehydration. In dehydrated patients, oral fluid intake of 1500 to 3000 ml was provided daily. In the patients developing PDPH, an infusion of theophylline 200 mg (200 mg of theophylline in 100 mL of 5% dextrose) was made intravenously within 30 minutes. Four hours following the infusion, the patients were questioned in standing position about their VAS scores, and then the scores were compared. The second infusion of theophylline was administered under the same circumstances in the patients expressing a <50% reduction in VAS scores at 4 hours after theophylline infusion. For analgesic treatment, paracetamol 250 mg/propyphenazone 150 mg

/caffeine 50 mg were administered orally every six hours when required (5).

Statistical Analysis

The mean, median, minimum, maximum and standard deviation values were used for frequency and ratio regarding descriptive statistics of the data. The variables' distributions were evaluated using the Kolmogorov Smirnov test. The Kruskal-Wallis and Mann-Whitney U tests were used for the analysis of independent quantitative variables. The Chi-square test was used for the analysis of independent qualitative data. SPSS 22.0 was used for statistical analysis.

Results

A total of 96 patients participated in the study. Since four patients participating in the study changed their minds on the operating table and underwent general anesthesia, they could not be included in the study. Since spinal anesthesia failed in seven patients, general anesthesia was performed, and they had to be excluded.

Because spinal anesthesia could not be achieved at the first puncture in three patients (was successful in the second or third attempt), those patients were also excluded. Finally, two patients were excluded from the study due to

more than 1000 ml of intraoperative blood loss. The study was completed with 80 patients in total. The patients' demographic data were presented in Table-1. The 5th-day VAS score was significantly higher in Groups F25 and M150 than Groups M100 and M200 ($p<0.05$). The PDPH treatment ratio in Group F25 was significantly higher than the ratio in Group M200 ($p<0.05$). All groups were similar regarding the ratio of pain other than PDPH ($p>0.05$) (Table 2). The highest VAS score in Group M200 was significantly lower than those of the F25 and Group M100 and M150 ($p<0.05$). The F25 and Group M150 and M150 did not differ significantly ($p>0.05$) regarding the highest VAS score (Figure 1).

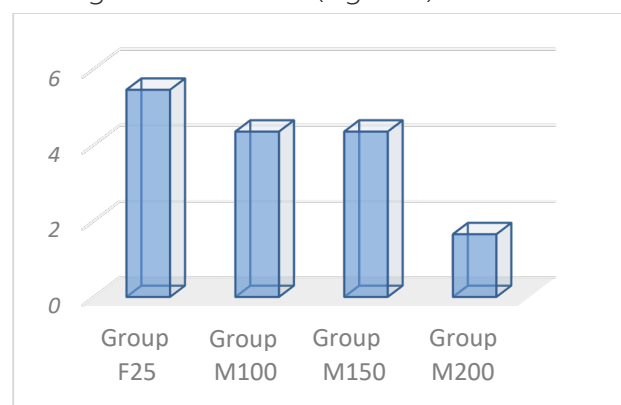


Figure 1. Comparison of the highest VAS scores

Table 1. Comparison of age, height, weight, BMI, ASA risk classification, gravida, parity, gestational age (weeks/days), and 1st-5th minute APGAR scores of the patients according to the groups

Variables	F25		M100		M150		M200		p
	Mean/%	Median	Mean/%	Median	Mean/%	Median	Mean/%	Median	
Age	29.5±6.4	29	31.1±4.9	31	28.9±5.7	29	33.2±4.7	32	0.103
Height (cm)	162.6±6.5	162.5	162.1±6.7	163	160.5±3.9	161.5	163.4±4.1	162.5	0.349
Weight (kg)	73.4±8.6	74	72±8.6	74	71.9±4.3	72	75.8±6.2	75.5	0.249
BMI	27.6±1.8	28	27.5±1.8	28.2	27.9±1.4	28.3	28.3±1.4	28.9	0.367
ASA-II	20 (100%)		20 (100%)		20 (100%)		20 (100%)		1
Gravida	3±1.7	3	3.8±2.3	3.5	3.3±1.2	3	4.4±2.9	4	0.482
Parity	1.9±1.5	2	2.4±1.9	2	2.1±1.2	2	3.1±2.8	2.5	0.529
GA	36.7±2.1	37	35.6±3.1	36.5	37.5±1.6	38	37.5±2.4	38	0.052
Day	2.9±2.3	3	3±1.8	3.5	1.8±1.9	1.5	1.8±1.9	1.5	0.11
Apgar 1 st min	7.6±0.6	8	7.3±0.8	7	7.4±1.2	8	7.4±0.8	8	0.733
Apgar 5 th min	8.6±0.6	9	8.4±0.7	8	8.6±1.1	9	8.4±0.8	9	0.472

Kruskal-Wallis / Chi-square test - BMI: Body mass index, GA: Gestational Age

On the fifth postoperative day, the PDPH VAS scores of Groups F25 and M150 were significantly higher than those of Groups M100 and M200 ($p < 0.05$) (Figure-2). The comparison of the patients treated according to their groups was shown in Figure-3. There were no significant differences among the patient groups regarding their intraoperative and postoperative diastolic blood pressures, SpO_2 value, and pulse rate ($p > 0.05$). The 20-minute systolic blood pressure and blood pressure were significantly higher in Group F25 and M150 than M200 (Supplemental Table 1-5).

Operative times, amounts of blood loss, hospitalization duration, and requirement rates for EBP of all groups were presented in Table-3. The nausea-vomiting rate was lower in the F25 than M100, M150, and M200 (Table-3).

The itching rate was lower in the F25 than M100, M150, and M200. Groups M100, M150, and M200 did not differ regarding the itching rate.

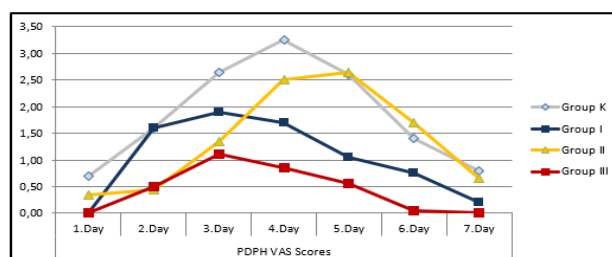


Figure 2. VAS scores of the groups according to days

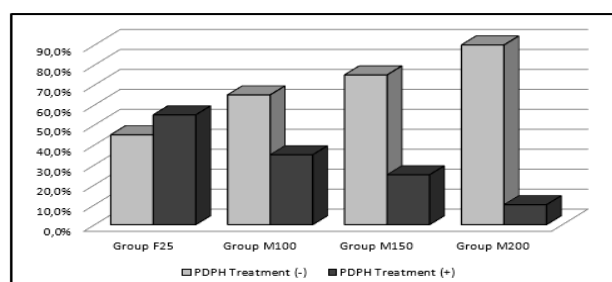


Figure 3. Distribution of treatment status of PDPH

Table 2. Comparison of the VAS scores by days, treatment status of PDPH, and presence of non-PDPH pain

PDPH VAS Score	F25		M100		M150		M200		p
	Mean/%	Median	Mean/%	Median	Mean/%	Median	Mean/%	Median	
1 st day	0.7±2.3	0	0	0	0.4±1.6	0	0	0	0.103
2 nd day	1.6±2.7	0	1.6±2.5	0	0.5±1.4	0	0.5±1.6	0	0.117
3 rd day	2.7±3.5	0	1.9±2.6	0	1.4±2	0	1.1±2.3	0	0.426
4 th day	3.3±3.5	2	1.7±2.8	0	2.5±3.2	1	0.9±2.1	0	0.06
5 th day	2.6±3.6	0	1.1±2.7	0	2.7±3.6	1	0.6±1.4	0	0.037
6 th day	1.4±2.9	0	0.8±2.3	0	1.7±2.7	0	0.1±0.2	0	0.064
7 th day	0.8±2	0	0.2±0.9	0	0.7±1.5	0	0±0	0	0.145
PDPH treatment	(-)	9(45%)	13(65%)		15(75%)		18(90%)		0.019
	(+)	11(55%)	7(35%)		5(25%)		2(10%)		
Non-PDPH Pain	0.1±0.3	0	0.1±0.2	0	0.1±0.2	0	0.1±0.3	0	0.87

Kruskal-Wallis (Mann-Whitney *u* test) / Chi-square test

Table 3. Comparison of the groups according to the parameters of the operation time, blood loss, duration of hospitalization, the requirement for EBP, and side effect profile (nausea-vomiting, itching, desaturation, apnea)

Variables	F25		M100		M150		M200		p
	Mean/%	Median	Mean/%	Median	Mean/%	Median	Mean/%	Median	
Operation time (min)	46.8±12.1	40	51.8±14.4	47.5	43.8±9.3	45	44.5±3.7	37.5	0.187
Blood Loss (cc)	328±146	300	388±148	400	282±106	275	365±143	375	0.069
Hospitalization(days)	2±0.6	2	2.2±0.7	2	2.1±0.9	2	2±0.5	2	0.825
Epidural Blood Patch	0(0%)		0(0%)		0(0%)		0(0%)		1
Nausea-vomiting	1(5%)		12(60%)		11(55%)		15(75%)		0.0001
Itching	0(0%)		9(45%)		12(60%)		15(75%)		0.0001
Desaturation	0(0%)		0(0%)		0(0%)		0(0%)		1
Apnea	0(0%)		0(0%)		0(0%)		0(0%)		1

Kruskal-Wallis / Chi-square test

Supplemental Table 1. Comparison of the groups according to pulse rate and time

Pulse Rate	F25		M100		M150		M200		p
	Mean	Median	Mean	Median	Mean	Median	Mean	Median	
-5 th minute	86.7±12.3	87	92.1±16.2	90	88.3±10.4	86	93.2±16.1	91	0.638
0 minute	86.7±13.2	83.5	94.3±16.5	97.5	90.2±15	89.5	92.3±14.4	88	0.459
2 nd minute	95.7±16.4	98.5	90.9±13.9	91	96±16.9	91.5	97.1±20.3	92	0.754
4 th minute	90.5±15.8	88	90.7±16.9	88.5	98.6±15	96.5	98±22.4	95	0.258
6 th minute	91±18.4	90	90.4±18.8	84.5	93.9±15.5	91.5	91.8±19.5	92	0.878
8 th minute	91.4±18.7	88	91.4±15.6	91.5	94.6±15.3	92.5	86.9±15	82.5	0.447
10 th minute	91.8±20.7	84.5	90.6±17.6	91	91.5±19	90	89.9±13.9	86.5	0.997
15 th minute	90.2±16	90	87.5±15.7	85.5	96.3±19.8	96.5	91.5±14.6	92	0.461
20 th minute	91.7±15.3	91.5	91.9±16.6	87.5	93.2±16.6	98.5	93.2±15.7	91	0.908
25 th minute	90.8±14.7	97.5	93.2±12.8	95	97.4±14	97	89.4±13.5	90.5	0.411
30 th minute	90.4±13.2	94.5	96.2±14	97	92±14.4	92.5	90.5±14.1	89.5	0.565
Postop 5 th minute	87±13.2	90	89.2±10.9	87.5	87.3±14	90	87.3±11.6	89	0.988

*Kruskal-Wallis***Supplemental Table 2.** Comparison of the groups according to systolic arterial pressure values and time

Systolic Pressure	F25		M100		M150		M200		p
	Mean	Median	Mean	Median	Mean	Median	Mean	Median	
-5 th minute	134±15.1	135.5	131±19.7	128.5	133.5±13.9	131	125.3±15	122.5	0.149
0 minute	130.3±15	132	124.8±17.2	125.5	131.9±13.4	134	129.5±16.5	124.5	0.687
2 nd minute	121.2±17.7	118.5	116.4±17.2	113.5	117.6±17.8	116	121.3±12.4	119.5	0.625
4 th minute	113.1±18.7	107.5	110.2±15.8	110.5	113±19.1	111	111.5±17.5	116	0.972
6 th minute	110.9±17.6	109	107±18.8	101.5	107.1±14.5	108	107.7±14.6	108.5	0.788
8 th minute	110±16.8	109.5	108±17.3	104.5	109±17.6	105	108.6±11.5	106	0.909
10 th minute	110.8±14.3	106.5	108.8±20.3	105.5	110.5±14.8	106	106.6±11.6	106.5	0.704
15 th minute	114.7±14.3	113.5	109.7±18.4	106.5	113.7±12	113	108.8±13.8	107	0.371
20 th minute	115.2±12.1	115.5	109.7±16.4	104.5	116.6±15.3	112.5	103.2±11.6	103	0.004
25 th minute	109.7±12.5	105.5	116.1±19.2	116.5	108.9±13.3	106	106.9±13.5	104.5	0.356
30 th minute	108.2±13.8	105.5	115.4±16.3	116	109.2±12.2	104.5	108.2±10.2	109	0.349
Postop 5 th minute	117.3±13.6	119	116.3±15.6	114.5	115±15.3	113.5	112.6±12.7	112	0.692

*Kruskal-Wallis***Supplemental Table 3.** Comparison of the groups according to diastolic arterial pressure values and time

Diastolic Pressure	F25		M100		M150		M200		p
	Mean	Median	Mean	Median	Mean	Median	Mean	Median	
-5 th minute	77.5±11.7	79	77.2±14	73.5	82.3±7.5	82	77.3±9.3	75.5	0.269
0 minute	76±9.6	77	76.2±14.1	76.5	78.6±11.5	78.5	75.1±8.9	75	0.755
2 nd minute	67.9±11.4	64.5	67.3±14.2	66	69.5±12	72	69.3±9.7	68.5	0.742
4 th minute	63.7±12.3	59.5	64.6±13.3	61.5	65.3±13.3	67.5	61.3±13.3	60.5	0.771
6 th minute	61.2±12.2	59.5	59.7±10.9	58.5	61.8±10.1	59.5	61.2±11.5	60	0.912
8 th minute	63±11.1	61	61.2±12.1	60	60.9±12.2	57.5	63.4±7.7	62.5	0.607
10 th minute	63.2±10.1	64.5	59.9±11.4	60	60.2±11.9	60.5	58.8±10.8	58	0.503
15 th minute	61.9±7.8	61	63.1±11.9	63	60.8±7.9	60.5	59.3±12.2	61	0.823
20 th minute	62.2±10.7	61.5	59.9±10	61	63±13.4	61	55.9±10	55	0.162
25 th minute	58±11.7	56.5	62.2±9.9	61	55.7±11.2	56.5	56.8±9.6	56.5	0.226
30 th minute	56±9.2	55	63.5±10	60.5	56.7±10.7	56.5	57.1±8.1	57	0.098
Postop 5 th minute	64.5±8.8	61	65.7±9.1	66.5	63.7±10.5	65.5	61.1±8.4	58	0.482

Kruskal-Wallis

Supplemental Table 4. Comparison of the groups according to mean arterial pressure values and time

Mean Arterial Pressure	F25		M100		M150		M200		p
	Mean	Median	Mean	Median	Mean	Median	Mean	Median	
-5 th minute	99.2±11.6	100.5	96.6±13.5	95	100.7±9.6	100	95.1±9.1	94	0.317
0 minute	97.0±10.7	96.5	94.6±14.6	95.5	99.2±11.1	98.5	95.9±10	97	0.674
2 nd minute	88.5±13.6	86.5	86.7±12.7	88	87.4±14	88.5	89.1±9.6	91.5	0.873
4 th minute	83.9±13.8	80	82.1±13.4	80	83.3±15	81	80.4±14.4	83.5	0.961
6 th minute	80.7±12.9	79.5	78±12.8	73	78.9±9.9	80.5	79.4±11.4	81	0.910
8 th minute	82.2±11.6	79.5	78.9±13.1	75.5	78±13.4	74.5	79.8±8.4	80	0.430
10 th minute	80.9±11.2	80.5	79.3±13.3	76	81.1±11.9	79.5	77.9±10.3	79	0.770
15 th minute	82±10	81	81.8±14.4	79	81.6±8.1	81	78.7±12.4	76	0.765
20 th minute	82.8±9.1	81	77.9±12	77.5	84.2±13.4	82.5	73.8±10.9	72.5	0.009
25 th minute	78.3±11.9	76	82.8±12.9	82	75.7±12.4	73	75.9±10.1	74.5	0.190
30 th minute	76±9.5	74.5	83.4±12	85.5	76.6±9.9	76	76.5±8.9	76	0.113
Postop 5 th minute	84.1±9.3	82.5	84.3±10.3	84	82.7±12.2	82.5	81.5±8.5	80	0.759

Kruskal-Wallis (Mann-Whitney U test)

Supplemental Table 5. Comparison of the groups according to SpO₂ values and time

SpO ₂	F25		M100		M150		M200		p
	Mean	Median	Mean	Median	Mean	Median	Mean	Median	
-5 th minute	96.5±1.3	96	96.4±1.6	97	96.2±1.3	96	95.9±1.3	95	0.307
0 minute	96.2±1.5	96	96.7±1.5	97	96.3±1.2	96	96±1.3	96	0.404
2 nd minute	96.6±1.8	97	97.2±1.5	97	96.7±1.3	97	96.8±1.2	97	0.721
4 th minute	97±1.5	97	97.4±1.2	97.5	97.3±1.3	97	96.9±1.3	96.5	0.583
6 th minute	97.2±1.8	97	97.9±1.5	98	97.9±1.7	98	97.8±1.6	98	0.533
8 th minute	97.6±1.9	98	98±1.6	99	98±1.4	98	98±1.6	98	0.905
10 th minute	97.9±1.6	98	98.1±1.7	99	97.8±1.8	98	98.2±1.5	98	0.910
15 th minute	97.6±1.8	97.5	98.3±1.6	98.5	98.1±1.3	98	98.4±1.4	98.5	0.463
20 th minute	97.7±1.3	97.5	98.4±1.5	99	98±1.5	98	98.1±1.7	98.5	0.422
25 th minute	97.5±1.5	97	98.2±2	99	98.1±1.2	98	98.1±1.6	98	0.240
30 th minute	97.2±1.6	97	98.1±1.6	99	98.1±1.6	98	98±1.7	98.5	0.215
Postop 5 th minute	97.3±1.8	97.5	97.9±1.3	98	97.5±1.7	97.5	97.2±1.6	97	0.478

Discussion

PDPH is the most common complications of SA widely used in CS (1). It is significantly more common in patients who had CS than in other patients operated under SA, and its incidence varies between 0.1 and 36% (2). Controversial study results have been reported regarding preventing unwanted PDPH by morphine administered intrathecally (3). Whitacre and Sprotte-type spinal needles have a lower risk of PDPH (6). Most frequently, it has been reported in patients in whom a 20-22G

standard Quincke needle was used for diagnostic lumbar puncture (7). The incidence of PDPH was reported as 8.7 in patients in whom a 25G Quincke needle was used. This study investigated the effects of intrathecal administration of different doses of morphine and fentanyl on post-dural puncture headache development after CS under spinal anesthesia, and PDPH occurred in 31% of pregnant women. However, many reasons affect the development of PDPH regardless of the needle type.

Methods such as rehydration, analgesia, resting, and EBP have been used for treating PDPH (8). In the present study, oral fluids were administered in dehydrated patients to treat PDPH. Additionally, infusion of 200 mg of theophylline intravenously and a combination of paracetamol 250 mg/propyphenazone 150 mg/cafeine 50 mg was orally administered when required. PDPH regressed with treatment, and none of the patients required an EBP.

PDPH was most common in the fentanyl group, whereas its last occurrence was in M200. The other groups did not differ significantly regarding the incidence of PDPH. The highest VAS score of Group M200 was significantly lower than those of Groups F25, M100, and M150 ($p < 0.05$). Groups F25, M100, and M150 did not differ regarding the highest VAS score ($p > 0.05$). No significant differences were determined between the postoperative first four days and the postoperative sixth and seventh days regarding the VAS scores. Abboud et al. (9) investigated the effect of morphine on PDPH in their study involving 82 cesarean cases in ASA I and II risk groups. They divided the cases into two groups, and in addition to the local anesthetic, they administered 0.2 mg of morphine intrathecally in 40 patients in the first group and 0.2 ml of saline in 42 patients in the second group. They monitored their patients for three days regarding PDPH. Similar to our study results, they did not determine significant difference for PDPH between the groups within the first postoperative three days. When we analyzed nausea-vomiting, desaturation, itching, apnea, and as the cases' side effect profiles, no difference was present for desaturation and apnea rates.

Sawi et al. (10), in their study involving 60 ASA I-II cesarean cases, compared intrathecal administration of morphine + bupivacaine + fentanyl with intrathecal bupivacaine + fentanyl. They determined that postoperative nausea-vomiting and itching incidences were higher in the group that received intrathecal morphine than the group that received intrathecal fentanyl only. Pinar et al. reported a higher incidences of postoperative nausea-vomiting and itching in the morphine (11). Similarly, we determined in our study that Group F25 had significantly lower nausea-vomiting and itching rates than Groups M100, M150, and M200. No significant differences were present among Groups M100, M150, and M200 regarding the nausea-vomiting and itching rates. Pinar et al., in their study involving 60 cesarean cases in ASA I and II risk groups, compared intrathecal levobupivacaine + fentanyl with intrathecal levo bupivacaine + morphine (11). They could not find any significant difference among the intraoperative hemodynamic parameters in the morphine group. Similar to the literature, we could not determine any significant difference among the groups regarding the evaluated hemodynamic data (pulse, SAP, DAP, MAP, and SpO_2). However, the 20th minute SAP value was significantly higher in groups F25 and M150 than Group M200. Besides, the 20th minute MAP values of Groups F25, M100, and M150 were significantly higher than Group M200. However, there are plenty of factors affecting parameters, such as the fetus's emergence time, the amount of bleeding, and vasodilator effect of oxytocin when applied differently from each other. Postpartum eclampsia and subdural hematoma, angiopathy, meningitis, cerebral vein thrombosis and sinuses, stroke, pituitary tumor, and choriocarcinoma may be mentioned

in the etiology of secondary headache in the postpartum period (12). In our study, no significant differences were present among the groups regarding headaches other than PDPH. The limitation of this study is its small sample size.

Conclusion

The incidence of PDPH was lower in the group that 200 µg of morphine was administered intrathecally. In the morphine receiving groups, the incidence of side effects (nausea-vomiting, itching) was dose-independently higher than the fentanyl administered group. Because of its small sample size, our studies should be supported by more extensive studies to reach definitive conclusions.

Ethical Statement

Van Yüzüncü Yıl University Faculty of Medicine ethics committee approval was obtained for the study and the informed consent was obtained from all the patient.

Conflicts of Interest

The authors declared no conflict of interest for the present article.

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