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Comparison of the Dexmedetomidine and Sufentanil Added to Spinal Anesthesia with Bupivacaine for Hemodynamic Stability and Postoperative Analgesia in Elective Cesarean Section Surgery: A Single-Blinded Randomized Clinical Trial

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Abstract

Background: Hemodynamic instability, including hypotension and bradycardia, can occur due to spinal anesthesia by bupivacaine. However, it is possible to reduce the chance of hemodynamic changes by the reduction of the dose of bupivacaine and/or the addition of adjunctive agents.

Objectives: This study aimed to compare the effects of the addition of intrathecal dexmedetomidine and sufentanil to spinal anesthesia with bupivacaine in elective cesarean section (CS).

Methods: This prospective single-blinded randomized clinical trial with parallel groups was performed on 60 pregnant women who were candidates for elective CS in Imam Reza Hospital in Kermanshah, Iran. In addition to receiving 10 mg of hyperbaric bupivacaine 0.5%, they were randomly divided into two groups to receive intrathecal sufentanil 5 µg (30 cases) or dexmedetomidine 5 µg (30 cases). Changes in blood pressure, heart rate, and occurrence of side effects (e.g., nausea, vomiting, headache, and shivering) were recorded within 1 h after the injections. Moreover, the postoperative analgesia rate and duration (using a visual analog scale [VAS]) were recorded within the first 24 h after the completion of the CS. Headache severity (using a VAS) was also measured during the first week after CS.

Results: Patients declared their satisfaction with analgesia after surgery. No significant difference was found between the two groups in terms of heart rate and systolic and diastolic blood pressure changes during the first 60 min. Similarly, no significant difference was observed between the two groups in terms of the severity of incision pain in the first 24 h after CS surgery. On days 3, 4, and 5, none of the patients in the sufentanil and bupivacaine group had headaches (VAS=0), but patients in the dexmedetomidine and bupivacaine group had some degree of headache (P=0.040).

Conclusion: Based on the results, intrathecal administration of bupivacaine with either sufentanil or dexmedetomidine in CS did not have significantly different effects, except for slightly more severe headaches in the dexmedetomidine group. Therefore, no superiority of one drug over the other was observed for intrathecal administration with bupivacaine in CS.

Keywords: Bupivacaine, Cesarean section, Dexmedetomidine, Hemodynamic, Sufentanil

1. Background

The preferred method of anesthesia for cesarean section (CS) delivery is spinal anesthesia (1). Spinal anesthesia with agents, such as bupivacaine, can have adverse effects, like hemodynamic instability (hypotension and bradycardia) (2). These effects are due to the sympathetic nervous blockade from sacral to visceral fibers (3). The prevalence of hypotension during CS following spinal anesthesia is very high (50-90%) and if not prevented, can lead to complications for the mother or the fetus or both (2).

In addition, other complications, including nausea, vomiting, and headache which are more pronounced in the first 6 h after spinal anesthesia are common in this blocked condition (4). Nausea and vomiting after pain are the most common complications after surgery, which is reported in more than 66% of patients who undergo a spinal cesarean section. Nausea and vomiting after surgery are influenced by various factors, including the characteristics of the patient, the type of surgery, and the used anesthesia method (4).

To address the abovementioned side effects, efforts have been made to add adjunctive agents to local anesthetics. Opioid agents, such as fentanyl or sufentanil, and alpha-2 agonists, namely clonidine and dexmedetomidine, have been studied for this purpose. It has been suggested that the addition of these adjuvants to local anesthetics can avoid postoperative complications, prolong the duration of analgesia, stabilize hemodynamics with sufentanil (5), alleviate shivering by dexmedetomidine (6), improve anesthetic quality, and reduce the administered local anesthetics (7, 8).

Sufentanil performs selectively as the µ-receptor agonist to produce potential analgesic outcomes. The potent opioid can prompt many adverse effects, comprising respiratory depression, vomiting, nausea, and other adverse effects after surgery (9, 10). Its intrathecal use in CS patients has been demonstrated to reduce the required dose of bupivacaine by 28%

(11). However, hypotension and itching are some side effects of sufentanil (12). Nevertheless, some studies have shown that added fentanyl (20 µg) or sufentanil (2.5 µg) were not associated with maternal or fetal adverse effects in CS (13). Moreover, although a reduction in the dose of bupivacaine (e.g., lower than 8-10 mg) is associated with fewer hypotension events, it has adverse effects on regional anesthesia (1).

Dexmedetomidine is a selective α2 agonist used for premedication as an adjuvant for general anesthesia and for sedation in the intensive care unit and has anesthetic properties. Dexmedetomidine has been used as an intrathecal adjuvant in CS patients (0.5 mcg/kg) without causing significant nausea, vomiting, or pruritus (14). It is also associated with longer postoperative analgesia in lower limb surgeries (15) and CS (16) patients.

2. Objectives

Since limited studies have been performed on the comparison of sufentanil and dexmedetomidine as adjunctive to bupivacaine in CS patients, we intended to conduct this study to address this gap in knowledge and provide evidence-based recommendations for healthcare providers. By comparing these two adjunctives, we aim to determine which one provides better hemodynamic stability, postoperative pain duration, and fewer side effects, and hence, could potentially improve the quality of care for CS patients. This study is important not only for the scientific community but also for patients, healthcare providers, and policymakers in making informed decisions about anesthesia management in CS procedures.

3. Methods

3.1. Study design and population

This prospective single-blinded randomized clinical trial with parallel groups was performed in Imam Reza Hospital in Kermanshah, Iran. The participants were 60 pregnant women aged 18-45 years old with singleton pregnancy and no underlying diseases who were candidates for elective CS surgery. This research plan was registered in the Iranian Registry of Clinical Trials (IRCT) (IRCT2017101814333N82) and the Ethics Committee of Kermanshah University of Medical Sciences approved the study (KUMS.REC.1395.257). Written informed consent was obtained from all patients. All investigators, including nurses and anesthetists, received standardized training. The effects of adding intrathecal dexmedetomidine and sufentanil to spinal anesthesia with bupivacaine in elective CS were compared.

3.2. Sample size and sampling method

According to the results of a previous study (17), the mean and standard deviation values of painless labor duration in the dexmedetomidine group were reported at 221±35 min. Therefore, since no study was exactly similar to the present study regarding the comparison of the two groups, and according to other studies on non-Caesarean patients, it was expected that in the dexmedetomidine group, at least 20% of the duration of painless labor is longer than the group receiving sufentanil.

As a result, with a 95% confidence level and 90% test power, the minimum sample size was calculated using the PASS‖ software and based on the following formula: $\sqrt[n]{10} * 10$. Based on the results, 16 patients were determined in each group. To increase the power of the study, it was decided to randomly allocate 30 patients to each of the groups using the random permutation block method. The statistical population in this study consisted of pregnant women aged 18-45 years old who had a singleton pregnancy without any underlying diseases with American Society of Anesthesiologists (ASA) class 1 who had a CS less than four times and had referred to Imam Reza Hospital of Kermanshah, Iran for elective CS.

3.3. Inclusion and exclusion criteria

Regarding the inclusion criteria, pregnant women at term with singleton pregnancy (age range: 18-45 years old) with a body mass index (BMI) of 18-30, and ASA class I, who were candidates for elective CS surgery were selected. Exclusion criteria were having an underlying medical condition, including cardiovascular diseases (ischemic heart disease, cardiomyopathy), preeclampsia, high blood pressure, neurologic diseases, such as migraine headaches, psychiatric diseases, and any record of allergic responses to local anesthetics, emergency CS, fourth CS or higher, and requirement for general anesthesia during the surgery (17).

3.4. Randomization

Patients were randomly allocated to two groups (using permuted block randomization method with block size 2). One group received intrathecal sufentanil 5 µg and 10 mg of hyperbaric bupivacaine 0.5% (SB) while the other group received dexmedetomidine 5 µg and 10 mg of hyperbaric bupivacaine 0.5% (DB) (Figure 1). The random sequence was generated by an individual outside the study team. All patients remained blinded to the allocation sequence. According to other studies in non-CS patients, the dexmedetomidine group received at least 20% longer duration of analgesia, compared to the sufentanil group (17).

3.5. Data collection

Demographic data (age and BMI) were documented. Hemodynamic variables (heart rate [HR], diastolic blood pressure [DBP], systolic blood

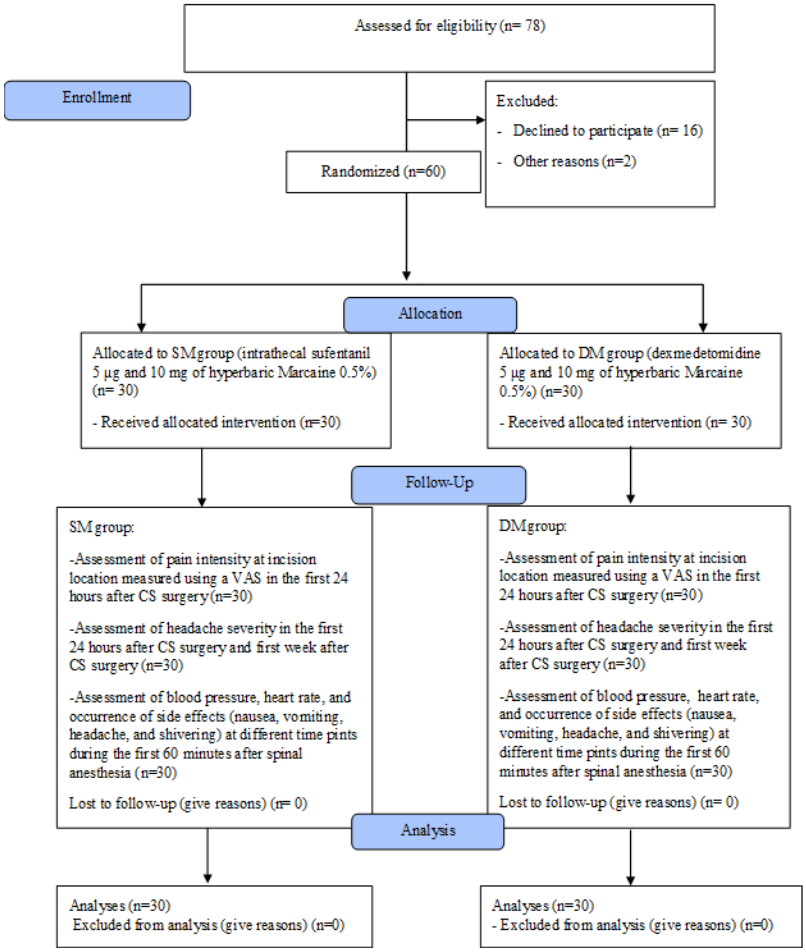

Figure 1. Flow diagram of the study

pressure [SBP], and possible side effects, including nausea, vomiting, shivering, pruritus, and headache were logged with 5 min intervals for the first 30 min after spinal anesthesia as well as after 60 min.

In addition, pain at the incision site in the first 24 h after completion of the surgery and headache during the first week were evaluated. To measure the severity of pain, a visual analog scale (VAS) was used (0=no pain and 10=severe pain) (17). Moreover, the weight, height, and BMI of the participants were recorded. Afterward, hemodynamic variables, including SBP, DBP, and HR, and complications, such as shivering, nausea, pruritus, vomiting, and headache were captured and registered at 1, 5, 10, 15, 20, 25, 30, and 60 min after spinal size.

Afterward, the complications and pain at the site of surgery in the first 24 h, and headache during the first week after surgery were followed up and recorded in the relevant forms and the results were analyzed (to assess the severity of headache and pain at CS, a VAS was used to quantify pain severity from 0 for painless conditions to 10 for the most severe pain possible according to the patient).

3.6. Intervention

After selecting patients based on the exclusion and inclusion criteria, the participants were allocated to one of the two groups: SB (sufentanil and bupivacaine recipients) and DB (dexmedetomidine and bupivacaine recipients). The duration of surgery was 1 h and the type of surgical incision was Pfannenstiel. The position of patients was sitting and their lumbar regions were sterilized by an anesthesia assistant and anesthetized using a spinal needle Quinke G25 at the L3-L4 site under aseptic conditions by injecting adjuvants that were injected into the subarachnoid space.

After injection and anesthesia, the participants took a supine position and oxygen was transferred at a rate of 4 liters per min through a mask. Changes in heart rate, blood pressure, vomiting, headache, nausea, and shivering were obtained at 5, 1, 15, 20, 25, 30, 10, and 60 min after injection. In case of hypotension up to 30% below baseline or below 90 mm Hg, it was treated with intravenous ephedrine and fluid therapy, and in case of bradycardia, it was treated with atropine. The participants were

monitored by pulse oximetry, electrocardiogram, and Non-invasive blood pressure (17).

3.7. Statistical analyses

The data were summarized in SPSS software (version 21) and the results of quantitative variables were reported through the mean score and standard deviation (SD), while qualitative variables results were reported using percentage and frequency. The Kolmogorov-Smirnov test was employed to check the normality of the data. Independent t-test, Fisher's exact test, and Mann-Whitney U test were used to make a comparison of the intended variables. Moreover, to analyze the repetitive measurements, repeated measures test was used. A *P* value of less than 0.05 was considered statistically significant.

4. Results

The mean ages of the SB and DB groups were 27.6±5.15 and 29.86±5.69 years, respectively. Moreover, the mean BMI of the SB and DB groups were 28.43±1.91 and 26.9±2.16 kg/m^2, respectively. The characteristics (age, weight, height, and BMI) of the patients were not significantly different in the two groups (*P*>0.05, Table 1). It should be mentioned that the patients declared their satisfaction with postoperative analgesia.

4.1. Hemodynamic changes of patients

4.1.1. Systolic blood pressure

The mean systolic blood pressures of the SB and DB groups were higher in the first minute after spinal anesthesia (120 mmHg), compared to other minutes. The lowest mean systolic blood pressure at min 30 in group DB was about 110.4±8.59 mmHg. There was a significant difference between the mean blood pressure of the two groups at min 60 (*P*=0.002). According to the results of the repeated measurements design, while controlling for age (*P*=0.709) and BMI (P=0.944), no significant difference was observed between the two study groups regarding the changes in systolic blood pressure (*P*=0.220, Table 2).

Table 1. Comparison of the characteristics of sufentanil and bupivacaine (SB) with those of dexmedetomidine and bupivacaine (DB) groups

Variables	SB Group	DB Group	*P* value
Age	27.6±5.15	29.86±5.69	0.542$
Weight	75.93±7.26	73±7.67	0.291&
Height	163.3±4.01	164.63±6.02	0.347&
BMI	28.43±1.91	26.9±2.16	0.221&

Values are presented as mean±standard deviation, $: Mann–Whitney U test, &: independent sample t-test, BMI: body mass index

Table 2. Systolic and diastolic blood pressure values and heartrate in sufentanil and bupivacaine (SB) group vs. dexmedetomidine and bupivacaine (DB) group

	Systolic BP			Diastolic BP			Heart rate		
Times	**SB group**	**DB Group**	***P* value***	**SB group**	**DB Group**	***P* value***	**SB**	**DB**	***P* value***
Minute 1	120.70±13.49	120.16±11.37	0.970	73.26±2.94	74.03±10.09	0.657	89.23±15.51	95.8±16.87	0.071
Minute 5	112.66±18.83	111.73±14.22	0.834	66.56±14.41	64.66±12.23	0.584	90.9±14.85	101.03±17.47	0.054
Minute 10	117.86±12.95	114.46±3.64	0.252	71.46±11.24	67.4±12.12	0.183	87.0±18.05	95.46±17.04	0.108
Minute 15	117.4±12.4	113.96±8.2	0.212	68.86±13.03	64.86±8.33	0.169	91.53±17.16	93.26±17.32	0.587
Minute 20	114.26±11.77	111.9±9.63	0.398	65.1±13.08	63.33±8.63	0.601	91.9±19.88	95.03±15.16	0.461
Minute 25	116.03±8.89	113±9.58	0.257	64.86±11.3	62.73±12.08	0.515	90.73±16.38	93.63±16.87	0.429
Minute 30	114.4±8.66	110.4±8.59	0.078	65.9±10.92	61.06±11	0.093	89.0±14.37	90.6±15.6	0.803
Minute 60	118.83±8.79	112.4±6.75	0.002	70.5±7.64	67.23±10.05	0.162	84.93±13.027	86.30±12.97	0.455
***P* value within groups**			0.220**			0.088**			0.175**

Values are presented as mean±standard deviation,*: independent sample t-test, **: repeated measures analysis of variance test

4.2. Diastolic blood pressure

The DBP was higher in group SB and DB in the first minute and the lowest mean value was observed at min 30 in group DB (61.06±11). There was no significant difference between the two groups in terms of mean blood pressure in all minutes. Based on the results of the repeated measures design, while controlling for age (*P*=0.208) and BMI (*P*=0.357), no significant difference was observed between the two studied groups in terms of the changes in DBP (*P*=088, Table 2).

4.3. Heart rate

The mean heart rates of the SB and DB groups in the first minute were 89.23±15.53 and 95.8±16.87, respectively. Therefore, the number of heartbeats in the first minute in the DB group was higher. The highest mean value of heartbeats at min 5 belonged to the DB group (101.03±17.4). Furthermore, the lowest mean number of heartbeats at min 60 belonged to the SB group. Based on the results of the repeated measurements design, while controlling for age (*P*=0.717) and BMI (*P*=0.449), there was no significant difference between the two study groups in terms of the changes in the number of heartbeats (*P*=0.175, Table2).

4.4. Side effects during surgery

Table 3 summarizes the frequency of nausea, vomiting, shivering, pruritus, and headache at 1, 5, 10,

Table 3. Comparison of side effects during cesarean section surgery between sufentanil and bupivacaine (SB) group vs. dexmedetomidine and bupivacaine (DB) group

Variables	groups	Min 1	Min 5	Min 10	Min 15	Min 20	Min 25	Min 30	Min 60
	SB	1 (3.3%)	5 (16.7%)	2 (6.7%)	0	1 (3.3%)	0	0	0
Nausea	DB	1 (3.3%)	4 (13.3%)	1 (3.3%)	0	4 (13.3%)	0	1 (3.3%)	0
	P value*	0.990	0.990	0.990	-	0.353	0.990	0.492	-
	SB	0	2 (6.7%)	0	0	0	0	0	0
Vomiting	DB	0	2 (6.7%)	0	0	1 (3.3%)	0	0	0
	P value*	-	0.990	-	-	0.990	-	-	-
	SB	0	1 (3.3%)	0	0	0	1 (3.3%)	1 (3.3%)	1 (3.3%)
Shivering	DB	0	1 (3.3%)	0	0	0	0	1 (3.3%)	0
	P value*	-	0.990	-	-	-	0.990	0.990	0.990
	SB	1 (3.3%)	1 (3.3%)	1 (3.3%)	1 (3.3%)	2 (6.7%)	3 (10%)	3 (10%)	3 (10%)
Pruritus	DB	0	0	0	0	0	0	0	0
	P value*	0.990	0.990	0.990	0.990	0.492	0.237	0.237	0.237
	SB	0	2 (6.7%)	1 (3.3%)	3 (10%)	2 (6.7%)	2 (6.7%)	1 (3.3%)	1 (3.3%)
Headache	DB	0	0	1 (3.3%)	1 (3.3%)	1 (3.3%)	2 (6.7%)	2 (6.7%)	2 (6.7%)
	P value*	-	0.492	0.990	0.612	0.990	0.990	0.990	0.990

Values are numbers (percentage), *: Fisher's exact test

15, 20, 25, 30, and 60 min after the start of spinal anesthesia. As observed, there was no significant difference between the groups regarding the frequency of the side effects at any time point during the first 60 min (Table 3).

4.5. Side effects after completion of cesarean section

None of the patients in either group experienced nausea or vomiting in the first 24 h after the end of CS. In the DB group, no report of itching was recorded. In the SB group, five (16.7%), three (10%), one (3.3%), and one (3.3) patients experienced itching at 1, 2, 4, and 6 h after the end of CS, respectively. Nevertheless, the observed differences between the two groups were insignificant. Shivering was only reported at 1 h after CS among four patients in the SB group (13.3%), and one patient in the DB group (3.3%, *P*=0.353).

4.6. Incision pain

Table 4 summarizes pain intensity values at the incision location which were measured using a VAS. As observed, in the first 24 h after CS surgery, the severity of pain in the SB group was higher than in the DB group, but these differences were not statistically significant (Table 4).

4.7. Headache

Table 5 summarizes headache severity and its comparison between the two groups in the first week after CS surgery. Only on days 3, 4, and 5, a significant difference was found between the groups (*P*=0.040); accordingly, on these days none of the patients in the SB group had a headache (VAS=0), but the patients in the DB group had some degree of headache. Most of the measurements of headache severity were not significantly different between the groups; however, they were higher on the third, fourth, and fifth days in group DB, which received dexmedetomidine and bupivacaine, compared to group SB (Table 5).

Table 4. Comparison of incision pain between the sufentanil and bupivacaine (SB) group and dexmedetomidine and bupivacaine (DB) group using a visual analog scale

Times	SB group	DB Group	*P* value*
Hour 1	1.93±1.17	1.5±0.73	0.206
Hour 2	2.6±1.77	1.73±0.73	0.065
Hour 4	3.23±1.81	2.66±1.15	0.286
Hour 6	3.6±2.02	3.3±1.29	0.994
Hour 8	4.2±2.07	3.73±1.41	0.469
Hour 10	4.2±1.9	4.06±1.87	0.663
Hour 12	4.2±2.22	3.8±1.95	0.398
Hour 16	3.66±1.93	3.33±1.72	0.486
Hour 20	3.16 (±1.78)	2.9±1.58	0.593
Hour 24	2.6±1.45	2.56±1.38	0.927

Values are presented as mean±standard deviation; VAS=0-10, *: Mann-Whitney U test

Table 5. Comparison of headache severity between sufentanil and bupivacaine (SB) and dexmedetomidine and bupivacaine (DB) groups using a visual analog scale (VAS)

Times	SB group	DB Group	*P* value*
Hour 1	0.1±0.4	0.13±0.73	0.584
Hour 2	0.06±0.25	0.16±0.91	0.584
Hour 4	0.1±0.4	0.16±0.91	0.584
Hour 6	0.1±0.4	0.16±0.91	0.584
Hour 8	0.1±0.4	0.13±0.73	0.584
Hour 10	0.03±0.18	0.13±0.73	0.981
Hour 12	0.03±0.18	0.1±0.54	0.981
Hour 16	0.03±0.18	0.1±0.54	0.981
Hour 20	0.03±0.18	0.1±0.54	0.981
Hour 24	0.03±0.18	0.1±0.54	0.981
Day 2	0	0.2±0.76	0.154
Day 3	0	0.48±1.2	0.040
Day 4	0	0.44±1.1	0.040
Day 5	0	0.37±0.97	0.040
Day 6	0.1±0.54	0.4±0.93	0.097
Day 7	0.1±0.54	0.3±0.7	0.102

Values are presented as mean ±standard deviation; VAS = 0-10, *: Mann–Whitney U test

5. Discussion

In this study, the effects of dexmedetomidine and sufentanil added to spinal anesthesia with bupivacaine on hemodynamic stability and postoperative analgesia in elective CS surgery were compared. Based on the results, no significant difference was observed between SB and DB groups regarding hemodynamic stability and side effects during/following CS. Hemodynamic changes and possible side effects, especially headaches after spinal anesthesia, are important clinical parameters in women who undergo CS (1).

Investigation of different agents added to local anesthetics has become important as they provide evidence of their several beneficial effects. hemodynamic changes and possible side effects should be considered for the selection of the adjunctive agent (1). It should be noted that in the present study, 10 mg of bupivacaine was used. Some studies have suggested even lower doses of bupivacaine to decrease the risk of local anesthetics-related side effects.

The use of adjunctive sufentanil has been shown to reduce the required dose of bupivacaine (12). In the present study, adding sufentanil (5 mcg) and decreasing the bupivacaine dose from 12.5 mg to 10 mg did not change the anesthesia quality. Similar to our findings, those of a previous study (16) showed no significant difference among the effects of bupivacaine, bupivacaine, and fentanyl, and bupivacaine and dexmedetomidine in terms of bradycardia and hypotension. Perhaps the reason for this similarity is the similarity of the purpose of both studies. Still, shivering and nausea/vomiting were slightly more common in the bupivacaine and fentanyl groups. This difference may be due to the larger number of participants in the aforementioned study, compared to the present study, or the difference between fentanyl and sufentanil.

In another study (5), comparing the effects of fentanyl and sufentanil on CS patients, no difference was observed regarding hemodynamic changes; however, pruritus was more common in the fentanyl group. This difference can also be due to the difference between fentanyl and sufentanil. Considering these findings of the previous studies (5, 16), it can be concluded that sufentanil is superior to fentanyl, at least in terms of pruritus occurrence after its use as an intrathecal injection in CS patients.

No exact similar study to the present study was found regarding the comparison of the effects of dexmedetomidine and sufentanil in CS patients. Given that not enough studies have been performed on CS patients regarding the comparison of these two drugs to assess hemodynamic changes and their complications, the present study was conducted with this purpose. In a study on patients undergoing urologic procedures, adding dexmedetomidine (5 and 10 mcg) to bupivacaine (12.5 mg) did not change the occurrence of hypotension or nausea/vomiting (18). Dexmedetomidine has the benefit of decreasing the occurrence of pruritus (19).

Based on the results of the present study, the shivering frequency was not different between the two groups that received dexmedetomidine or sufentanil. On days 2 to 5, none of the patients had headaches in the SB group. However, the severity of headaches was higher in the DB group. In a former study performed on orthopedic surgery patients, headache frequency was comparable between two groups who received dexmedetomidine or clonidine in addition to bupivacaine (20). Similar to the present research, in another study performed on CS patients to compare the effects of fentanyl and sufentanil, none of the patients had headaches in the sufentanil or fentanyl group (21). Based on the results of this study, no superiority of one drug over the other can be recommended for intrathecal administration with bupivacaine in CS.

5.1. Limitations

This study had some limitations which need to be

expressed. First, no bupivacaine-only group was included to compare the hemodynamic alterations between the three groups. In addition, neonatal conditions and Apgar scores were not assessed to investigate the effect of added agents (sufentanil and dexmedetomidine) on neonatal status and respiratory changes. Finally, the need for personal consent to enter and continue the study was the main limitation of the research.

5.2. Strengths of the study

Despite the limitations of this study, its results are still valuable and can serve as a foundation for future research in this field. The strength of this study lies in the fact that no statistically significant difference was observed between the two drugs, sufentanil, and dexmedetomidine, in terms of the variables under study. Furthermore, in future studies, by collecting more data while respecting legal and ethical conditions, better results can be obtained. One limitation of this study was the issue of obtaining patient consent, which can be addressed in future research.

6. Conclusion

Intrathecal sufentanil (5 µg) was similar to intrathecal dexmedetomidine (5 µg) added to spinal anesthesia with bupivacaine in CS patients. Except for headache, which was slightly more severe in the dexmedetomidine group, no other studied variable was different. Due to the fact that in this study, no statistically significant difference was found between the groups, it is better to increase the number of participants in future studies to achieve more accurate results or change the dose, for example, increase dexmedetomidine to 10 µg to reassess variables.

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Footnotes

Conflicts of Interest: None to declare.

Authors' Contributions: J. A. S. and M. A. were responsible for the conception and design of the study. M. J. N., and S. R., collected and analyzed the data. M. A. and S. R. prepared the first draft of the manuscript. All authors read and approved the final manuscript.

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Ethical Considerations: Ethical approval for this study (No.IR. KUMS.REC.1395.257) was provided by the Ethics Committee of Kermanshah University of Medical Sciences, Kermanshah, Iran on July 13, 2016. This study is registered at the Iranian Registry of Clinical Trials on October 25, 2017 (code: IRCT2017101814333N82). This study was conducted in compliance with the guidelines of Consolidated Standards of Reporting Trials and written informed consent was obtained from the participants.

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