ISSN: 1607-8322, e-ISSN: 2220-5799 Anaesthesia, Pain & Intensive Care
Vol 27(4); August 2023 DOI: 10.35975/apic.v27i4.2191

ORIGINAL RESEARCH REGIONAL ANESTHESIA

Dexmedetomidine vs. fentanyl as adjuvants to hyperbaric bupivacaine for unilateral spinal anesthesia in lower limb orthopedic surgeries: a randomized trial

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ABSTRACT

Background & Objective: Opioids and α2 adrenergic receptor agonists are commonly used as adjuvants to intrathecal local anesthetics to improve the quality and duration of spinal anesthesia (SA). Fentanyl and dexmedetomidine (DEX) are the most commonly used opioid and α2 agonist respectively. We compared the efficacy of these two when used as adjuvants to hyperbaric bupivacaine for SA for lower limb surgeries.

Methods: A total of 54 patients were randomly assigned to receive unilateral spinal anesthesia with bupivacaine 2.5 ml. Group F (n = 27) received 25 µg fentanyl, and Group D received 10 µg DEX added to the spinal bupivacaine. Time to first analgesic request was the primary outcome, while sensory and motor block characteristics, nalbuphine consumption as rescue analgesic, pain scores, side effects and sedation levels were the secondary outcomes.

Results: Patients receiving dexmedetomidine as an adjuvant to hyperbaric bupivacaine for spinal anesthesia for lower limb surgeries had a significantly longer time to rescue analgesia than those receiving fentanyl. The mean time to rescue analgesia in Group D was 409.63 ± 74.60 min vs. 295.93 ± 36.72 min (P = 0.000) in the Group F. Also, patients in Group D had significantly longer sensory and motor blocks.

Conclusion: Intrathecal dexmedetomidine 10 µg seems to be a good alternative to fentanyl 25 µg when used as an adjuvant in unilateral spinal anesthesia for lower limb orthopedic surgeries with better quality postoperative analgesia and with minimal side effects.

Abbreviations: DEX - Dexmedetomidine; NYHA - New York Heart Association; BMI - Body mass index; MBP - Mean blood pressure; SBP- Systolic blood pressure; DBP- Diastolic blood pressure; VAS - Visual Analog Scale

Key words: Dexmedetomidine; Fentanyl; Bupivacaine; Anesthesia, Spinal

Citation: Ghaly SI, Shafik AM, AlTaher WAMM, Motawashleh MG, Alansary AM. Dexmedetomidine vs. fentanyl as adjuvants to hyperbaric bupivacaine for unilateral spinal anesthesia in lower limb orthopedic surgeries: a randomized trial. Anaesth. pain intensive care 2023;27(4):456−463. **DOI:** 10.35975/apic.v27i4.2191

Received: March 30, 2023; **Reviewed:** April 22, 2023; **Accepted:** April 22, 2023

1. INTRODUCTION

Unilateral spinal anesthesia (SA) with a low dose and volume of anesthetics is suitable for lower limb surgeries because it achieves stable hemodynamics (particularly in the elderly), rapid recovery, and prevents unnecessary paralysis in the contralateral limb. On the other hand, the onset of sensory and motor loss is slower and the duration of the block is shorter when compared to bilateral spinal anesthesia.[1]

Many drugs can be used as adjuvants to intrathecal local anesthetics (LA) to improve the quality of spinal anesthesia, including opioids, e.g., morphine, fentanyl, and sufentanil; α2 adrenergic agonists, e.g., dexmedetomidine (DEX) and clonidine; magnesium sulfate, neostigmine, ketamine and midazolam.[2]

The synthetic opioid fentanyl is a powerful lipophilic drug with a short half-life, rapid onset, and little tendency to cause respiratory depression. For regional anesthesia, it is the adjuvant drug that is most frequently used. Opioids can be administered intravenously to reduce pain without affecting dorsal root axons or somatosensory evoked potentials or the nociceptive afferent input from Aδ and C fibers.[3]

In both the peripheral and central nervous systems, DEX functions as an agonist for α2 receptors. While the analgesic action of intrathecal α2-adrenoceptor agonist is by depressing the release of C-fiber transmitters and by hyperpolarization of postsynaptic dorsal horn neurons; stimulation of the receptors in the brain and spinal cord inhibits neuronal firing, causing hypotension, bradycardia, sedation, and analgesia.[4]

We compared the efficacy of addition of DEX versus fentanyl, to bupivacaine in unilateral spinal anesthesia in lower limb orthopedic surgery regarding the duration of postoperative analgesia, total postoperative nalbuphine consumption, hemodynamic changes, and potential postoperative adverse effects.

2. METHODOLOGY

This prospective, randomized comparative trial was authorized by the research ethics committee of the Faculty of Medicine, Ain-Shams University (No. FMASU MD232/2021), and the protocol was registered at Pan-African Clinical Trials Registry with No. IDPACTR202209726231234. Patient enrollment started in May 2022 and the study ended in January 2023. The principles of the Declaration of Helsinki were followed. The study was conducted at the Department of Orthopedic Surgery, Ain Shams University Hospital.

The primary outcome was the time to rescue analgesia. The secondary outcomes were time from spinal injection to the highest sensory level, the time to two-segment regression from the highest sensory level, time for sensory regression to S1 from the highest sensory level, time from injection to Bromage III (in blocked limb), time to regression to Bromage 0 (in blocked limb), total nalbuphine consumption in the first 24 h, side effects like nausea, vomiting, shivering or respiratory depression for 4 h after performing spinal anesthesia and sedation level using modified Ramsay scale.

We enrolled 54 adult patients in the study, 21–65 y old, of both sexes, ASA-I and II, who were scheduled for elective orthopedic surgeries of the lower limb. All patients provided fully informed consent.

Patients were excluded from the study if they refused to participate, or they had a body mass index (BMI) >35 kg/m2, uncorrected coagulopathy, heart failure (NYHA class III, IV), neuropathy, uncontrolled hypertension, drug abuse or allergy to the study drugs or had any contraindication to spinal anesthesia, e.g., patients who couldn't be placed in a lateral position (e.g., due to pelvis fracture) and infection at the injection site.

Patients were randomly assigned to one of the two groups using computer-generated random numbers; Group F (n = 27) to undergo unilateral spinal anesthesia with 2.5 ml of hyperbaric bupivacaine plus 25 µg fentanyl (0.5 ml), while patients in Group D (n = 27) to receive 2.5 ml of hyperbaric bupivacaine plus 10 µg DEX (0.5 ml). After enrolling the patients, a sealed envelope containing the group allocation number was cracked open. A consultant anesthesiologist with more than five years of experience in regional anesthesia, blind to the medication to be used, performed the spinal blocks.

2.1. Anesthetic technique

A wide-bore IV cannula was inserted, then 10 ml/kg of lactated Ringer's solution was administered. Standard monitoring including heart rate (HR), blood pressure (BP), and oxygen saturation (SpO2) was used. Patients were placed in a lateral position with the effected limb dependent on the operating table, with both hip and knee joints flexed.

Spinal anesthesia was performed with a 25-gauge Quincke needle with a midline approach and bevel facing downward. All patients received intrathecal hyperbaric bupivacaine plus the adjuvant as per group allocation. After 15 min, patients in both groups were gently turned to the position required for the surgery. HR and SpO2 were monitored continuously and readings were recorded every minute in the first 10 min and then every 10 min for one hour. BP was monitored every 5 min for one hour. Sensory block was assessed by pinprick method with 27G hypodermic needle, and motor block by Bromage scale, before the spinal

injection, then every 2 min after injection until reaching the highest sensory level and to Bromage III.

Hypotension (MBP < 20% from the baseline value) was treated with 250 ml ringer lactate and 3−6 mg ephedrine intravenously, and 0.01 mg/kg IV atropine was administered to treat bradycardia (HR < 50 beats/min).

After surgery, an assessment was performed every 10 min until the time to regression of 2 sensory levels, then every 20 min until the regression time to the dermatome S1 and motor scale to Bromage 0.

After surgery, each patient was transferred to the post-anesthesia care unit (PACU) to be observed by an anesthetist blinded to the study's protocol. In the PACU and in the ward, pain was assessed with visual analog scale (VAS). If VAS > 3, 0.1 mg/kg nalbuphine was given for analgesia and the total amount of given nalbuphine was recorded.

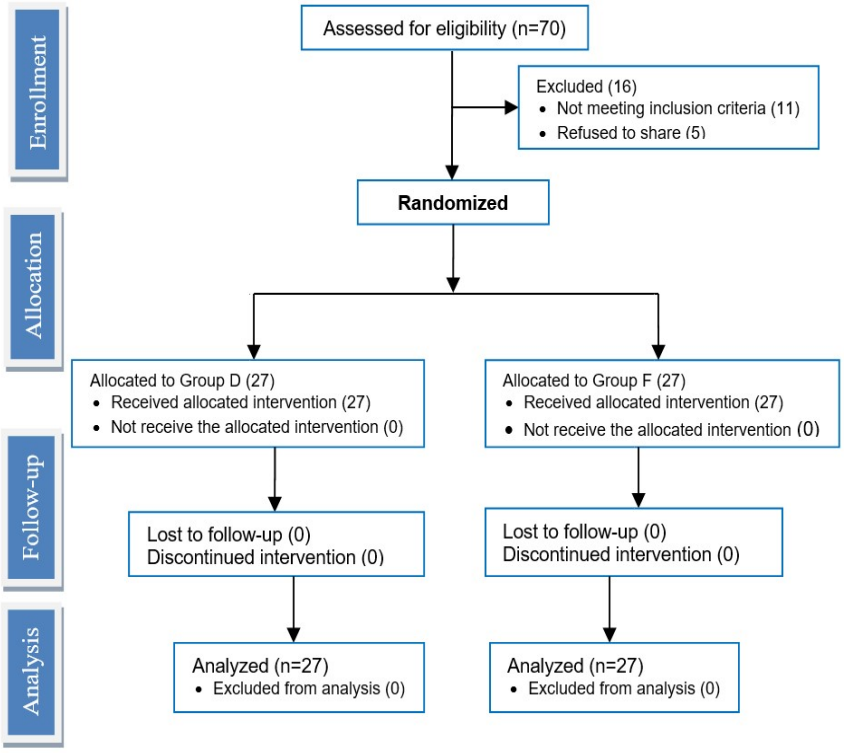

Figure 1: The CONSORT flowchart of the study

2.2. Sample size calculation

Sun et al. conducted a meta-analysis of 9 studies comparing the two adjuvants and showed that dexmedetomidine resulted in a statistically significant longer duration of stable sensory block, sensory block, motor block, and pain-free period.[2] In the four parameters, the effect size was large. Accordingly, a sample size of 27 cases per group (total number of cases is at least 54) will detect an effect size of 0.80 using a two-independent samples t-test with a level of significance of 0.05 and power of at least 0.80.

2.3. Statistical analysis

The Statistical Package for Social Science (IBM SPSS) version 23 was used to collect, edit, code, and input the data. When the quantitative data were parametric, they are shown as mean ± standard deviations or ranges; when they were non-parametric, they are shown as medians with interquartile ranges (IQR). Qualitative variables are also shown as percentages and numbers. When the expected count in any cell is < 5, the Chi-square test and/or Fisher exact test are used to compare the groups' qualitative data. The Independent t-test is used to compare two independent groups with quantitative data and a parametric distribution, and the Mann-Whitney test is used for non-parametric data. The accepted margin of error is set at 5%, and the confidence interval at 95%.

P > 0.05 indicates non-significant (NS), P = 0.05 indicates significant (S), and P < 0.01 indicates highly significant (HS).

3. RESULTS

A total of 70 patients were assessed for eligibility in the study, 11 patients were excluded because they did not meet the inclusion criteria, and 5 patients refused to share in the study. Finally, 54 patients, who fulfilled all the inclusion criteria, were randomized into two equal groups, Group D and Group F, each consisting of 27 patients. All the patients completed the study (Figure 1).

Demographic data, including age, sex, ASA classification, and BMI, were comparable in the two groups. Similarly, the duration of surgery did not differ significantly in the two groups (Table 1).

here were statistically no differences in MBP or HR in two groups before performing spinal anesthesia (basal), intraoperatively or after spinal anesthesia (Figure 2A & 2B).

There was no significant difference between the two groups regarding the highest sensory level, time to reach

Table 1: Demographic data

Variable		Group D No. = 27	Group F No. = 27	Test value	P-value
Gender	Female	8 (29.6)	8 (29.6)	0.000*	1.000
	Male	19 (70.4)	19 (70.4)		
Age (y)		36.33 ± 10.20	37.15 ± 6.64	-0.348•	0.729
BMI (kg/m^2)		28.18 ± 2.54	28.61 ± 2.35	0.651	0.518
ASA	ASA I	23 (85.2)	24 (88.9)	0.164*	0.685
	ASA II	4 (14.8)	3 (11.1)		
Type of surgery	Pott`s fracture	6 (22.2)	7 (25.9)	1.996*	0.850
	Fracture neck femur	5 (18.5)	2 (7.4)		
	Fracture shaft femur	3 (11.1)	4 (14.8)		
	Lateral malleolus fracture	3 (11.1)	3 (11.1)		
	Knee arthroscopy	6 (22.2)	5 (18.5)		
	Total knee replacement	4 (14.8)	6 (22.2)		
Duration of surgery (h)		2.03 ± 0.55	2.24 ± 0.47	-1.537•	0.130

*Data presented as mean ± SD or n (%); P < 0.05 considered as significant (S); * Chi-square test; • Independent t-test*

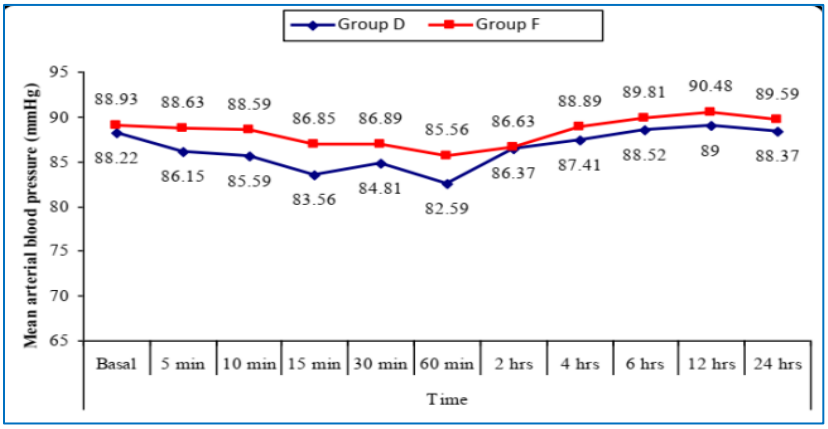

Figure 2A: Comparative mean blood pressure changes in two groups

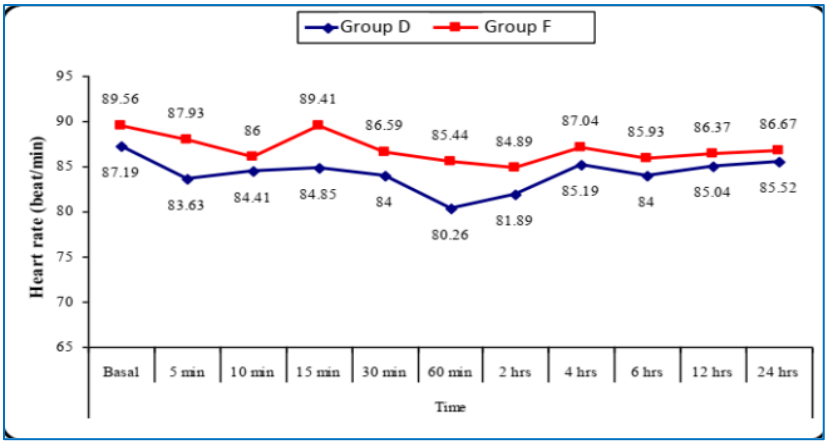

Figure 2B: Comparative heart rate changes in two groups

the highest sensory level, and time to reach Bromage III, as shown in Table 2. Time to two-segment regression and the time for sensory regression to S1 were longer in Group D compared to Group F, and the difference was highly significant (Table 2).

The time to regression to Bromage 0 longer in Group D compared to Group F, and the difference was highly significant (Table 2).

There was a highly significant difference between the two groups regarding time to rescue analgesia, being longer in Group D than in Group F. The total dose of nalbuphine used in Group D was less than that used in Group F, also the frequency of analgesic requirement was lower in Group D than Group F, the difference in values being highly significant (Table 3).

There was no significant difference in the VAS scores at 30 min and 1 h postoperatively. But the difference was highly significant postoperatively, and were less in Group D than in Group F (Figure 3). The sedation scores of patients in Group D ranged from 1-3, being more than those in Group F (1-2) but the difference was not significant. No

Table 2: Comparative block characteristics

Block characteristics		Group D (n = 27)	Group F (n = 27)	Test value	P-value
Highest sensory level	T4	2 (7.4)	3 (11.1)	3.224•	0.521
	T5	3 (11.1)	7 (25.9)		
	T6	10 (37.0)	6 (22.2)		
	T7	5 (18.5)	6 (22.2)		
	T8	7 (25.9)	5 (18.5)		
Time to reach the highest sensory level (min)		6.71 ± 1.33	7.30 ± 1.10	-1.722•	0.091
Time to two-segment regression (min)		153.15 ± 42.90	91.67 ± 7.84	7.325•	0.000**
Time for sensory regression to S1(min)		472.96 ± 43.04	186.48 ± 21.65	30.897•	0.000**
Time to reach Bromage III (blocked side) (min)		11.44 ± 3.34	11.1 ± 2.85	0.177	0.860
Time to regression to Bromage 0 (blocked side) (min)		384.44 ± 54.94	184.44 ± 25.47	17.162	0.000**

*Data presented as mean ± SD or n (%); *P < 0.05: Significant (S); **P < 0.01: highly significant (HS)*
**: Chi-square test; •: Independent t-test*

Table 3: Comparative analgesic requirements

Analgesic requirement	Group D (n = 27)	Group F (n = 27)	Test value•	P-value
Time to rescue analgesia (min)	409.63 ± 74.60	295.93 ± 36.72	7.106	0.000***
Total nalbuphine (mg) used per 24 h	9.63 ± 1.36	14.74 ± 2.63	-8.979	0.000***
Frequency of rescue analgesia (per 24 h)	1.74 ± 0.45	2.74 ± 0.45	-8.228	0.000***

****P < 0.01: highly significant; •: Independent t-test*

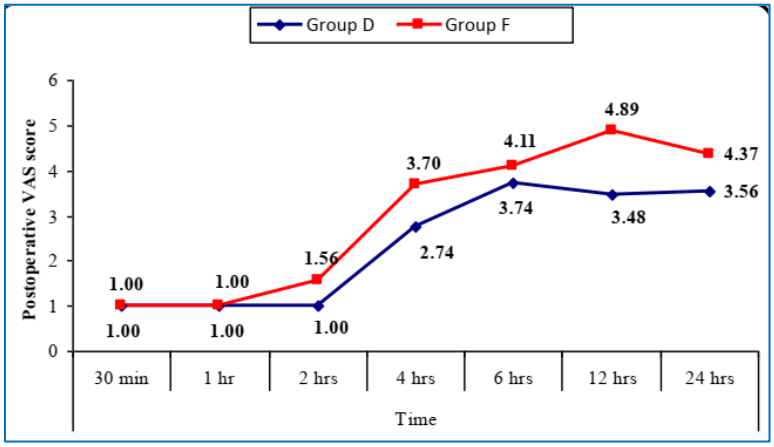

Figure 3: Postoperative VAS score

patient developed respiratory depression in both groups, one patient in Group D and 2 in Group F suffered from nausea and vomiting. The incidence of shivering was less in Group D (one patient) than in Group F (3 patients), but it was statistically insignificant. Pruritus was not observed Group D, but in Group F 2 patients developed pruritus, the difference between the two groups being not significant.

4. DISCUSSION

This prospective, randomized study showed that the time to rescue analgesia was longer in the group, which received DEX than the group that received fentanyl, also the total dose of nalbuphine required for postoperative pain was significantly less in the DEX group than fentanyl group and the frequency of its requirement was less in Group D than Group F. Also, VAS scores estimated during the first 24 h postoperatively were significantly less in Group D than in Group F postoperatively. These results are consistent with the results of the studies done by Gupta et al. and Rahimzadeh et al. which compared intrathecal DEX 5 µg and fentanyl 25 µg as adjuvants to bupivacaine in patients scheduled for lower abdominal and lower limb surgeries respectively.[5,6]

Mostafa et al., who compared intrathecal DEX 5 µg and magnesium sulfate 50 mg for postoperative analgesia

and stress response after cesarean delivery, found that VAS scores were significantly lower in the group who received DEX than the group who received magnesium sulfate. Also, the time to the first request of postoperative analgesia was significantly longer in Group D and more patients in DEX group needed a second dose of analgesia than those who received magnesium sulphate.[7]

Mazy et al., compared DEX plus fentanyl versus DEX as adjuvants to bupivacaine in patients undergoing orthopedic procedures expected to extend more than 4 h, found that the time to the first request for analgesia and the total morphine consumption was not different between the two groups, VAS scores also showed no significant differences in their study.[8]

Yektaş and Belli, who compared the effects of 2 μg and 4 μg of DEX in combination with intrathecal hyperbaric bupivacaine on spinal anesthesia in patients undergoing elective inguinal hernia repair, found that the mean time to onset of pain was longer in the group who received 4 μg than the other group.[9] Also according to Rai and Bhutia, adding 5 μg DEX as an additive to spinal anesthesia in orthopedic patients undergoing lower limb surgeries was superior to 3 μg in prolonging time to rescue analgesia.[10]

According to the study by Taher-Baneh et al., done on patients undergoing elective calf surgery under unilateral spinal anesthesia, found that the amount of meperidine used as a rescue drug for pain relief in 24 h was comparable in both groups and there was no significant difference.[11]

In our study hemodynamic readings of MBP and HR were lower in Group D than Group F in the first hour after spinal anesthesia, yet there was no statistical significance between both groups at any time.

These results are consistent with the results of the study done by Gupta et al., as they found that hypotension was more in the DEX group than in the fentanyl group, but it was not statistically significant.[5] Also, Ravipati et al., who compared intrathecal isobaric ropivacaine 0.75% plus DEX 5 μg and isobaric ropivacaine 0.75% plus fentanyl 20 μg for lower limb surgeries, found that the fall in SBP, DBP, and MBP was comparable between both groups and the magnitude of fall was similar in both groups, and it was clinically or statistically insignificant.[12]

Unlike these results, Rahimzadeh and his colleagues found that reduction in SBP and DBP were significantly higher in patients who received fentanyl than those who received DEX, and they assumed these different results were due to the response of each individual to the drug, demographic profile, the volume of intrathecal injected anesthetic mixture and volume of diluent used.[6]

Also, Kalbande et al. found that falls in HR, SBP, and DBP were higher and steeper in the group who received fentanyl 25 μg than those who received DEX 5 μg and were statistically significant.[13]

According to block characteristics, our results showed that there was no statistical significance between both groups as regards the highest sensory level, the time taken to reach Bromage III in the side blocked and the time taken to reach the highest sensory level. But time to two-segment regression, time for sensory regression to S1 and time to regression to Bromage 0 in the side blocked, were longer in Group D than Group F, and these differences were highly significant.

The results agreed with the meta-analysis done by Shen et al., which revealed that intrathecal DEX in patients undergoing cesarean section significantly reduced the onset time of sensory block and motor block and prolonged the block duration.[14] Mostafa et al. in their study revealed that DEX shortened the onset of sensory block and prolonged the duration of regression to S1.[7]

The results of our study are consistent with the study done by Elshahawy et al., which compared intrathecal DEX and dexamethasone in emergency orthopedic lower limb operations, as it revealed DEX shortened the onset of the sensory and motor block with no difference in the highest sensory level, also the longer duration of sensory and motor block.[15]

Also, according to the meta-analysis done by Liu et al., intrathecal DEX 5μg prolonged the durations of sensory and motor block and hastened the onsets of both sensory and motor block, also delayed the time to the first analgesic request, but the onsets of sensory and motor block lacked clinical significance.[16]

In contrast to this study's results, Taher-Baneh et al. found that intrathecal fentanyl 5μg increased the duration and the quality of motor and sensory block in the dependent limb more than DEX 5μg.[11]

The mechanism by which α2-adrenoceptor agonists augment the motor and sensory block when added to intrathecal local anesthetics is not well known. They bind to presynaptic C-fibers and postsynaptic dorsal horn neurons and lead to depression of the release of C-fiber transmitters and hyperpolarization of postsynaptic dorsal horn neurons. The augmentation of the block may result from the synergistic effect between them and the local anesthetics, which act by blocking sodium channels.[6]

The hypnotic effect of DEX is like normal sleep, it is mediated by the triggering of neurotransmitters that decrease histamine due to inhibition of the descending noradrenergic inhibitory pathway.[8] Sedation score in our study were comparable in both groups with no significant difference between the two groups.

Mazy et al. found that 48% of patients who received intrathecal DEX and 75% of those who received DEX and fentanyl had sedation scores > 2 and that was statistically insignificant.[8]

Regarding the side effects, no patient had had respiratory depression, 1 patient in Group D and 2 in Group F had vomiting, 1 (3.7%) patient in Group D compared to 3 (11.1%) in Group F had shivering, but the difference was statistically insignificant; no patient in Group D had pruritus compared to 2 in Group F, the difference being statistically significant. These results are supported by the results of Gupta et al.[5]

5. LIMITATIONS

We didn't assess the other lower limb which wasn't blocked whether it was unblocked or not, and the duration of partial sensory and motor block.

6. CONCLUSION

In this comparative study, intrathecal dexmedetomidine (10 µg) seems to be a good alternative to fentanyl (25 µg), when used as an adjuvant in unilateral spinal anesthesia in lower limb surgeries, with better quality of postoperative analgesia and with minimal side effects.

7. Availability of data

The datasets that support the findings of the current study are available with the corresponding author on a reasonable request.

8. Competing interests

The authors declare that they have no competing interests.

9. Funding

The authors have no external or industry sources of funding to declare for this study.

10. Authors' contributions

SIG: Data collection

AMS: Data analysis; Revising paper

WAM: Study design and supervision; Data collection; Project administration; Revising manuscript

MGM: Study design and supervision; Project administration,

AMA: Study design and supervision; Data analysis

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