Intrathecal versus intravenous infusion of dexmedetomidine during subarachnoid block in lower abdominal surgeries

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Background Adjunct analgesic strategy is an alternative to prolong the analgesic duration and decrease the potential risk of side effects. The objective of this study was to evaluate the efficacy of dexmedetomidine as an adjuvant to subarachnoid anesthesia during lower abdominal surgeries compared with dexmedetomidine intravenous infusion.

Patients and methods Forty patients, classified as American Society of Anesthesiologists I and II patients, aged 20–50 years, undergoing elective lower abdominal surgeries, were randomly allocated into two equal groups. Group I (*n*=20) consisted of patients who received intrathecal 0.5% hyperbaric bupivacaine 15 mg (3 ml)+dexmedetomidine (10 μg) for subarachnoid block. Group II (*n*=20) consisted of patients who received intravenous infusion of dexmedetomidine 0.5 μg/kg/h (without loading) after subarachnoid block. The onset and duration of sensory and motor block, the hemodynamic effects, the duration of analgesia and the incidence of side effects were recorded. Interleukin-6 level was estimated.

Results Hemodynamic data were comparable between both groups. The mean time taken for the sensory block to reach T10 dermatome and motor block to reach B3 was significantly fast in group I as compared with group II. The time for two segment regressions and regression of sensory block to S2 dermatome and B0 motor block were significantly prolonged in group I compared with group II. The time to first rescue analgesic was prolonged, and the amount of analgesic/24 h was decreased significantly by the addition of dexmedetomidine to bupivacaine. Ramsay sedation scores were highly significant, being higher in group II. The level of interleukin-6 and the incidence of side effects were significantly lower in group I compared with group II.

Conclusion In lower abdominal surgery, the use of intrathecal dexmedetomidine as an adjuvant to local anesthesia provides good motor and sensory blockade and is associated with mild sedation, decreased incidence of side effects, and inflammatory response compared with intravenous infusion.

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Introduction

Neuraxial anesthesia and analgesia provide a solid analgesic effect by inhibiting nociceptive transmission from peripheral to the central neuronal system [1,2].

However, their analgesic advantages might be limited by the short life of current local anesthetics (LAs). Therefore, adjunct analgesic strategy is an alternative to prolonging the analgesic duration and decreases the potential risk of side effects by reducing the dose of LA [3].

Dexmedetomidine is a highly selective alpha 2 (α_2)-adrenergic agonist that has several actions during the perioperative period. Intrathecal α_2 receptor agonists are found to have an antinociceptive action for both somatic and visceral pain [4]. Intrathecal dexmedetomidine prolongs both sensory and motor block and has a nociceptive action for both visceral and somatic pain [5]. They act by binding to presynaptic C-fibers and postsynaptic dorsal horn neurons. The prolongation of effect may result from synergism between LA and α_2-adrenoceptor agonist [6]. Dexmedetomidine produces sedation and anxiolytic effect by binding to α_2 adrenoceptors in the locus ceruleus, which diminishes and inhibits sympathetic activity. The cause of sedation after intrathecal dexmedetomidine may be related to its systemic absorption and vascular redistribution to higher centers or cephalad migration in the cerebrospinal fluid [7]. Cytokines are immune mediators that direct the inflammatory response to sites of injury and infection that is essential for wound healing. An exaggerated production of proinflammatory cytokines from the primary site of injury can manifest systemically as hemodynamic instability or metabolic derangements [8]. Circulating interleukin-6 (IL-6) level appears to be proportional to the extent of tissue injury during surgery. IL-6 stimulates the

acute-phase reaction, which enhances the innate immune system and protects against tissue damage [9]. We purpose to study the effect of intrathecal dexmedetomidine compared with intravenous dexmedetomidine infusion among patients subjected to lower abdominal surgeries under spinal anesthesia.

Patients and methods

This study is a cross-sectional comparative study carried out after approval of the Hospital Ethical Committee in Al-Zahraa University Hospital, and informed consent was obtained from all patients. This study was carried out during the period spanning from December 2015 to May 2016; 40 patients selected consecutively who were classified as American Society of Anesthesiologists I or II, of both sexes, and aged 20–50 years who were scheduled for elective lower abdominal surgery were included in the study. Patients with infection at the puncture site, coagulopathy, having true hypersensitivity to the drugs used, diabetes and hypertension, and psychiatric and neurological diseases were excluded from the study. Morbid obesity and any contraindications to spinal anesthesia were excluded from the study. The night before surgery, a thorough evaluation of the patient was carried out. When the patients arrived to the operating room, the study protocol was explained to each patient. An eighteen-gauge intravenous cannula was inserted in both groups, preload (8 ml/kg Ringer's solution) was started and another cannula was inserted in group II for drug infusion. Continuous monitoring for SPO_2, ECG, and noninvasive blood pressure was carried out.

The patients were randomly allocated into two equal groups by computer-generated random sequence. The assignment to study groups was placed in serially numbered opaque envelopes; group I (n=20), in which subarachnoid block was performed at level L3–4 or L4–5 interspace, a midline approach was used, using 25 G pencil-point spinal needles. After confirmation of free flow and clear cerebrospinal fluid, 10 μg dexmedetomidine (Precedex, Hospira Inc., Lake Forest, Illinois, USA) diluted with normal saline to 1 ml was added to 0.5% hyperbaric bupivacaine 15 mg (Marcaine Spinal Heavy; Astra Zeneca, Södertälje, Sweden) in the same syringe to reach 4 ml volume; it was injected and the patients turned to the supine position with head elevation.

Group II (n=20), subarachnoid block was performed, 0.5% hyperbaric bupivacaine 15 mg (3ml) +1 ml normal saline was added in the same syringe to reach 4ml volume. The intravenous infusion solution, which was prepared by 200 μg dexmedetomidine diluted in 50 ml normal saline, which was infused at a rate of 0.5 μg/kg/h through an infusion syringe pump, started after completion of the block, and the patient was turned to the supine position, to the end of the operation.

CONSOLT chart

Outcome

The onset and duration of sensory and motor blockade is the primary outcome. The effect on hemodynamics and postoperative analgesic requirement is the secondary outcome.

Parameters observed were the hemodynamic parameters: mean arterial blood pressure was monitored every 5 min for the first 15 min, then every 15 min for 1 h, and every 30 min for the next 2 h. Sensory block was assessed by pinprick using 25 G needle for the time taken for the sensory block to reach T10 dermatome and the time to regress to dermatome S2. Motor blockade was assessed using Bromage scale. The time to reach B3 (maximum motor block) and the time to regress to B0 (no motor block) were assessed.

Assessment of the level of sedation was carried out throughout the operation using Ramsay sedation score (RSS) preoperatively, intraoperatively and 1, 2, 6, and 12 h postoperatively.

Assessment of the postoperative pain was carried out using the visual analog pain scale ranging from 0, no pain to 10, maximum intensity of pain at the immediate, 4th, 6th, 12^{th}, and 24th postoperative hours. If visual analog scale more than 4, intravenous pethidine 50 mg was given.

The first request for analgesia and the total amount of analgesic requirement/24 h were recorded IL-6 preoperatively, and 6 h and 24 h postoperatively, were also recorded. The incidence of side effects was also noted.

Statistical analysis

The sample size was calculated using Epi Info program, version 7 (Centers for Disease Control and Prevention, Atlanta, Georgia, USA); adjusting the confidence interval to 95%, the margin of error accepted was set to 5% and power of the test to 80%. Thus, it was found to require at least 18 patients per group to detect sensory and motor block time. Data were collected, revised, coded, and entered into the statistical package for the social science (IBM

SPSS, IBM Corporation, Armonk,NY), version 20. The qualitative data were presented as number and percentages while quantitative data were presented as mean, SDs, and ranges when their distribution was found to be parametric and were presented as median with interquartile ranges when their distribution was found to be nonparametric. Qualitative data were compared using the χ^2 test. The comparison between two independent groups with quantitative data and parametric distribution was carried out by using the independent *t* test while data with nonparametric distribution were compared between the two groups using the Mann–Whitney test. The confidence interval was set to 95%, and the margin of error accepted was set to 5%. Hence, the *P* value was considered significant as follows: *P* value less than 0.05: significant, *P* value less than 0.01: highly significant.

Results

Demographic data

The studied groups were comparable (P=0.05) as regards age, sex, weight, height, duration of surgery, and American Society of Anesthesiologists physical status (Table 1).

Hemodynamic parameters

There was no statistically significant difference between both groups as regards mean arterial blood pressure (P<0.05) at all measured time points (Table 2).

Sensory blockade time

As presented in Figs 1 and 2, the patients in group I showed significantly lower time to reach maximum sensory block (5.48±0.66 min) when compared with group II (7.47±0.67 min). Furthermore, the time of two segment regression from highest sensory level (170.33±9.00 min in group I and 130.00±20.84 min in group II) and the time of regression to S2 dermatome were significantly longer in group I (288.67±35.98 min) compared with group II (220.00 ±24.07 min) (P<0.001).

Data are presented as mean±SD value using the independent *t* test. *P* value less than 0.05 was considered significant.

Motor blockade time

With regard to the time to B3, it was significantly shorter in group I compared with group II (5.87±0.59 vs. 64±0.70 min, P<0.01), and the time to B0 was significantly longer in group I compared with group II (289.33±34.41 min in group I vs. 155.00±20.84 min in group II, P<0.01) (Fig. 3).

Data are presented as mean±SD value using the independent *t* test. *P* value less than 0.05 was considered significant, and *P* value less than 0.01 was considered highly significant.

Ramsay sedation score

Intraoperatively and 1 h postoperatively, RSS was significantly higher in group II (2–5) compared with group I (1–3) (P<0.01), with no significant difference between both groups (P>0.05) on the other occasions (Table 3).

Postoperative pain (visual analog scale)

Pain scores were significantly lower in group I at 4 and 6 h (P<0.01), and it was significantly lower (P<0.05) at 12 h postoperatively, compared with group II (Table 4).

Postoperative analgesia

As shown in Fig. 3, the time for the first request of analgesia postoperatively was significantly longer in group I (340.33±13.98 min) compared with group II (225.50±16.28 min, P<0.01). The total dose of analgesic requirements (pethidine) was significantly

Table 1 Demographic data in both groups

	Group I (N=20)	Group II (N=20)	*P* value
Age (years)	37.93±11.25	42.10±6.87	0.165
Sex (male/female)	10/10	9/11	0.752
Weight (kg)	75.40±8.42	77.70±8.16	0.385
Height (cm)	164.20±4.69	162.60±5.23	0.315
Duration of surgery (min)	100.67±9.63	103.50±13.27	0.445
ASA I/II	9/11	10/10	0.752

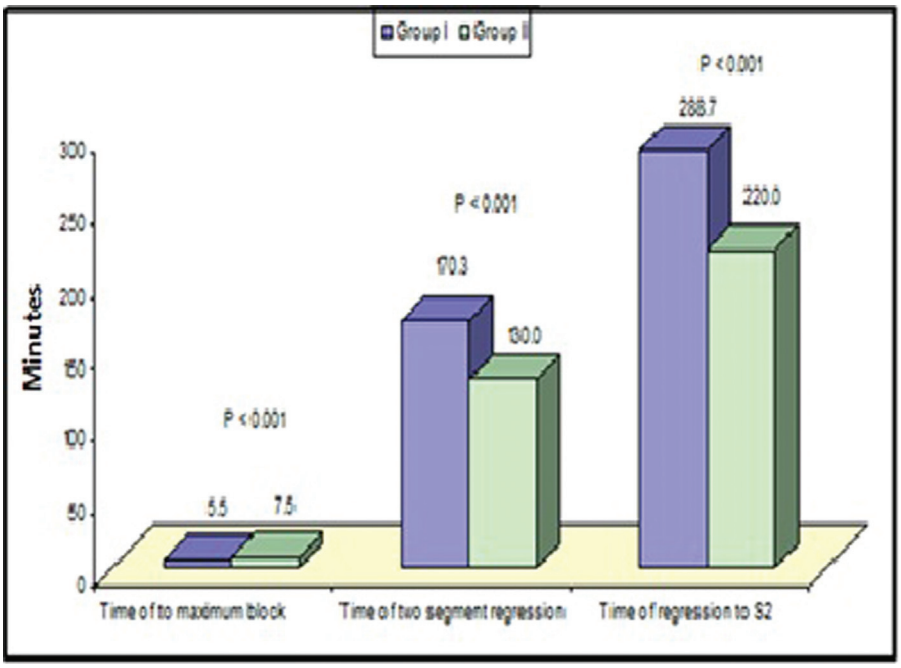
Values are presented as mean±SD or *n*. ASA, American Society of Anesthesiologists. *P* value less than 0.05, significant; *P* value less than 0.01, highly significant.

Table 2 Mean arterial blood pressure changes in both groups (mmHg)

	Group I	Group II	*P* value
Baseline	93.93±8.76	94.40±9.69	0.873
5 min	81.93±11.13	75.80±15.46	0.158
10 min	81.87±9.99	80.70±11.82	0.737
15 min	80.20±6.67	79.80±10.48	0.886
30 min	80.33±7.12	83.00±8.99	0.304
45 min	80.35±7.21	83.10±8.95	0.305
60 min	80.47±8.29	82.20±4.61	0.419
90 min	81.47±7.22	83.90±5.54	0.239
120 min	81.47±7.22	83.90±5.54	0.239

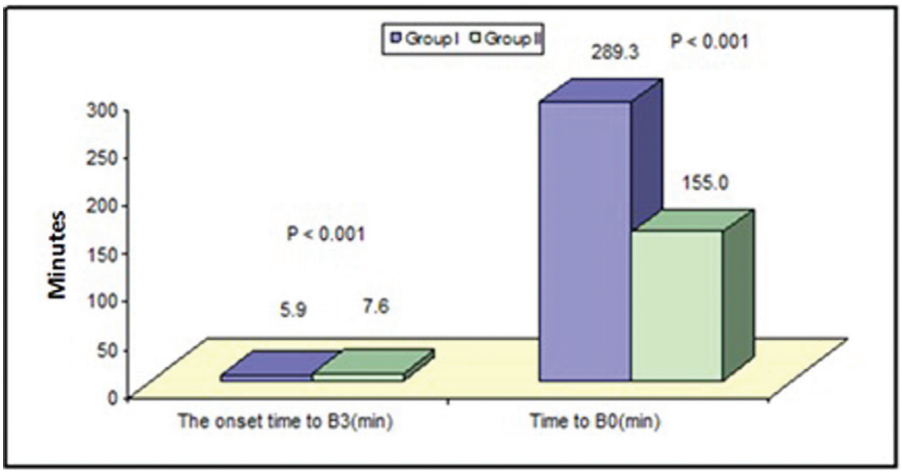
Values are presented as mean±SD. *P* value less than 0.05, significant; *P* value less than 0.01, highly significant.

Figure 1



Comparison between both groups in sensory blockade time (min).

Figure 2



Comparison between both groups in motor blockade time (min).

lower in group I (70.67±9.00 mg) compared with group II (98.00±6.10 mg, $P<0.01$).

Data are presented as mean±SD value using the independent t test. P value less than 0.05 was considered significant and P value less than 0.01 was considered highly significant.

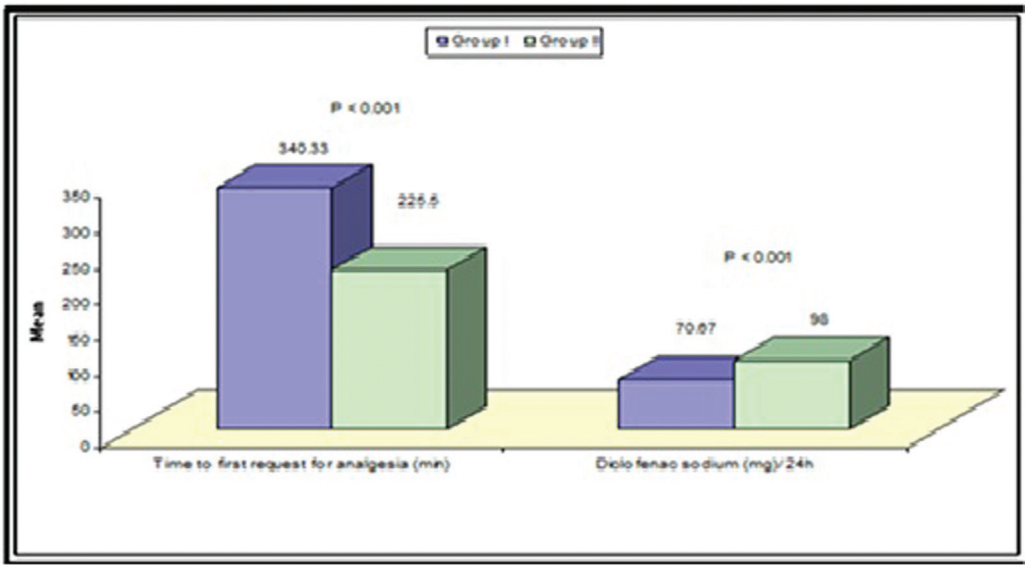
Interleukin-6

The level of IL-6 was significantly lower in group I when compared with group II ($P<0.01$). At 6 h postoperatively, the IL-6 level was 85.5 pg/ml in group I and 213.23 pg/ml in group II, while at 24 h postoperatively it was 65.1 pg/ml in group I and 120.15 pg/ml in group II (Table 5).

Side effects

The incidence of bradycardia (50 beats/min), hypotension (systolic blood pressure <90 mmHg) and shivering was significantly lower in group I compared with that in group II ($P<0.05$) (Table 6). The incidence of nausea was lower in group I compared with that in group II [2 (10.0%) vs. 4 (20.0%)].

Figure 3



Comparison between both groups as regards the time to first request for analgesia postoperatively.

Table 3 Comparison between both groups with regard to Ramsey sedation score

Ramsey sedation score	Group I	Group II	*P* value
Preoperative	1 (1–3)	1 (1–3)	0.619
Intraoperative (after 30 min)	2 (1–3)	3 (2–5)	<0.001
Intraoperative (after 60 min)	2 (1–3)	3 (2–5)	<0.001
Post 1 h	2 (1–3)	3 (2–5)	<0.001
Post 2 h	2 (1–3)	2 (1–3)	0.738
Post 6 h	2 (1–3)	2 (1–3)	0.781
Post 12 h	2 (1–3)	2 (1–3)	0.849

Ramsey sedation score is presented as median (interquartile range). *P* value less than 0.05, significant; *P* value less than 0.01, highly significant.

Table 4 Comparison between both groups as regards visual analog scale

VAS	Group I (*N*=20)	Group II (*N*=20)	*P* value
Immediately postoperatively	0.6 (0.3–0.8)	0.7 (0.4–1)	0.677
4 h	2 (1–3)	3 (2–5)	<0.001
6 h	4 (3–7)	6 (4–9)	<0.001
12 h	5 (3–7)	6 (4–9)	0.004
24 h	4 (3–7)	5 (3–7)	0.214

Ramsey sedation score is presented as median (interquartile range). VAS, visual analog scale. *P* value less than 0.05, significant; *P* value less than 0.01, highly significant.

Discussion

In this study, we found that intrathecal dexmedetomidine as an adjuvant to LA significantly quickened the time to reach T10 and B3, prolonged the duration of motor (to reach B0) and sensory blockade (two segment and S2 regressions) and increased the analgesic effect of subarachnoid block, as evidenced by the significantly decreased amount of postoperative analgesic requirement compared with the intravenous group. Moreover, we found a mild effect on hemodynamics and an association with mild degree of sedation with decreased incidence of side effects in comparison with dexmedetomidine intravenous infusion. Intrathecal dexmedetomidine also decreased the level of proinflammatory mediator IL-6.

In different studies by Gupta *et al.* [4] and Al-Ghanim *et al.* [10], they reported no significant effect on blood pressure or heart rate on using dexmedetomidine as an adjuvant to intrathecal LA. Kubre *et al.* [11] studied the effect of single-dose intravenous dexmedetomidine with spinal anesthesia and found minimal hemodynamic changes during lower abdominal surgery.

In disagreement with our study, Abdalhamid and El-lakany [12] designated 62 patients to be randomly divided into one of two groups: group D received 3.5 ml volume of 0.5% hyperbaric bupivacaine and 5 μg dexmedetomidine in 0.5 ml of preservative-free normal saline intrathecally. Group P received 0.5 ml normal saline added to the same dose of heavy 0.5% bupivacaine and served as the placebo group, and Hong *et al.* [13] studied 51 elderly patients undergoing transurethral resection of the prostate who were randomized into two groups receiving either 1.0 μg/kg DMT (DMT group, *n*=26) or normal saline (control group *n*=25) intravenously before spinal anesthesia with 1.2 ml of bupivacaine, 5 mg/ml.

Table 5 Interleukin-6 level in both groups (pg/ml)

	Group I	Group II	*t* test	*P* value
Preoperative	46.2±5.3	110.8±10.3	24.940	<0.001
6 h postoperative	85.5±10.3	213.23±12.6	35.100	<0.001
24 h postoperative	65.1±8.3	120.15±9.7	19.284	<0.001

Values are presented as mean±SD. *P* value less than 0.05, significant; *P* value less than 0.01, highly significant.

Table 6 Side effects between both groups

	Group I	Group II	*P* value
Bradycardia	2 (10.0)	7 (33.3.0)	0.029
Hypotension	2 (10.0)	6 (26.68.0)	0.037
Nausea	2 (10.0)	4 (20.0)	0.035
Vomiting	0 (0.0)	2 (10.0)	0.146
Pruritis	0 (0.0)	0 (0.0)	1.000
Shivering	1 (10.0)	4 (35.0)	0.0449

Value are presented as *n* (%).

Both found a significant decrease of intraoperative heart rate and mean arterial blood pressure. Moreover, in a study by Harsoor *et al.* [14], they used intravenous dexmedetomidine infusion at the same dose we used during spinal anesthesia compared with the placebo group; while in our study we compared intrathecal versus intravenous administration, they found a significant decrease in heart rate and blood pressure.

In agreement with the result of the present study, Gupta *et al.* [15] used 10 μg dexmedetomidine with bupivacaine intrathecally. Rajesh *et al.* [16] investigated 5 μg dexmedetomidine intrathecally as an adjuvant to 3.5 ml bupivacaine. Shaikh and Dattatri [17] examined different doses (5, 10, 20 μg) of dexmedetomidine as an adjuvant to intrathecal bupivacaine. However, Gupta *et al.* [4], through their study, found more prolongation in sensory and motor blockade than our results.

Dar *et al.* [18] and Rani and Upendranath [19] observed that dexmedetomidine infusion enhances the onset, prolongs the duration of sensory and motor block, increases the regression time to S2 dermatome and for B0. Moreover, they found that it increases the time for the first request of analgesia and decreases the dose of analgesic/24 h and decreases the postoperative pain scores.

The mechanism of intravenous dexmedetomidine on spinal anesthesia remains unclear; however, supraspinal, direct analgesia, and/or vasoconstriction activities are involved. The administration of intravenous dexmedetomidine in spinal anesthesia may actually have a dual effect by both enhancing the LA action and providing sedation [20].

In concomitance with our result, Rajesh *et al.* [16] reported a decreased need for intraoperative sedation by the use of 5 μg dexmedetomidine intrathecally with bupivacaine RSS less than 4. Moreover, Hamed and Talaat [21] reported minimal sedation with low dose intrathecal and single intravenous dose dexmedetomidine during spinal analgesia.

On using infusion dexmedetomidine during spinal anesthesia, Dar *et al.* [18] and Rani and Upendranath [19] observed that RSS ranged from 2 to 5), which was satisfactory and easily arousable.

As regarding pain score and analgesic requirement, Anjan *et al.* [2] studied different doses of intrathecal dexmedetomidine (5, 10 μg), Rajesh *et al.* [16], and Hamed and Talaat [21] in their study, and Abdalhamid and El-lakany [12], the dose was 5 μg dexmedetomidine intrathecal with bupivacaine, they all found that pain scores and amount requirement/24 h for analgesia were decreased and the first time to request analgesia was prolonged with the use of intrathecal dexmedetomidine.As regards side effects, Hamed and Talaat [21] concluded that the use of dexmedetomidine intrathecally and by single low, intravenous dose during spinal anesthesia was associated with low incidence of side effects.

Rajesh *et al.* [16] and Dar *et al.* [18] found that the incidence of side effects was less with the use of intrathecal dexmedetomidine, whereas Anjan *et al.* [2] observed a significant bradycardia on using 10 μg intrathecal dexmedetomidine but no other side effects.

Rani and Upendranath [19] and Stevie *et al.* [22] in their studies about intravenous dexmedetomidine infusion during spinal anesthesia reported that they found an increased incidence of side effects.

IL-6 is an immune mediator that can be detected 60 min after injury; it peaks after 4–6 h, and can be continuously detected up to 10 days [23]. In this study, the level of IL-6 was significantly lower in group I when compared with group II ($P<0.01$) at 6 and 24 h postoperatively.

Results observed by Bekker *et al.* [24] indicated that dexmedetomidine infusion during multilevel spinal fusions moderately improved the quality of recovery and possibly reduced fatigue in the early postoperative period. Moreover, it reduced plasma levels of cortisol and IL-10 in comparison with the control group. The perioperative use of dexmedetomidine significantly

decreased postoperative IL-6, IL-8, and TNF-α. In a Yacout *et al.* [8] study that investigated the effects of dexmedetomidine on proinflammatory cytokine, IL-6 levels increased two-fold in the dexmedetomidine group compared with baseline at 24 h postoperatively.

Conclusion

This study supported the use of dexmedetomidine as an adjuvant to LA in spinal anesthesia for lower abdominal surgery, as it fastens the onset and prolongs the duration of sensory and motor blockade of the subarachnoid block and decreases the postoperative analgesic requirement.

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Conflicts of interest

There are no conflicts of interest.

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