Randomized Trial

Efficacy of Intrathecally Administered Dexmedetomidine Versus Dexmedetomidine With Fentanyl in Patients Undergoing Major Abdominal Cancer Surgery

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Background: Most of the clinical experience gained in the use of intrathecal α2- adrenoceptor agonists has been described with clonidine. Human studies using a combination of intrathecal dexmedetomidine and local anesthetics are lacking.

Objectives: A safety investigation and comparison of the analgesic efficacy of intrathecally administered dexmedetomidine or dexmedetomidine combined with fentanyl in patients undergoing major abdominal cancer surgery.

Study Design: A randomized, double-blind trial.

Setting: Academic medical center.

Methods: Ninety patients were randomly assigned to receive intrathecally either 10 mg bupivacaine 0.5% (control group, n = 30), or 10 mg bupivacaine 0.5% plus 5 μg dexmedetomidine (dexmedetomidine group, n = 30), or 10 mg bupivacaine 0.5% plus 5 μg dexmedetomidine and 25μg fentanyl (dexmedetomidine+ group, n = 30). Assessment parameters included hemodynamics, sedation score, pain severity, time of first analgesics request, total analgesic consumption, and side effects in the first 24 hours.

Results: The mean intraoperative heart rate was significantly reduced in the dexmedetomidine group ($P < 0.05$) and the dexmedetomidine+ group ($P < 0.05$) compared with the control group. Also, there was a significant reduction in mean intraoperative systolic and diastolic blood pressure in the dexmedetomidine group ($P < 0.05$) and the dexmedetomidine+ group ($P < 0.05$) compared with the control group, with no significant differences in postoperative hemodynamics or sedation scores among all the study groups.

The mean visual analog scale scores showed a significant reduction immediately and at 12 hours postoperatively in both the dexmedetomidine and dexmedetomidine+ groups compared to the control group.

The mean time of the first analgesic request was significantly prolonged in the dexmedetomidine group (3.30 ± 0.87 hours, $P < 0.01$) and the dexmedetomidine+ group (5.41 ± 1.23 hours, $P < 0.01$) compared with the control group (0.23 ± 0.11 hours). Moreover, postoperative tramadol consumption was significantly reduced in the dexmedetomidine (142.85 ± 13.04 mg, $P < 0.01$) and the dexmedetomidine+ (131.25 ± 11.96 mg, $P < 0.01$) groups, compared with the control group (310.0 ± 12.08 mg). No significant serious adverse effects were recorded during the study.

Limitations: This study is limited by its sample size.

Conclusion: Dexmedetomidine 5 μg given intrathecally improves the quality and the duration of postoperative analgesia and also provides an analgesic sparing effect in patients undergoing major abdominal cancer surgery. Furthermore, the addition of intrathecal fentanyl 25 μg has no valuable clinical effect.

Key words: dexmedetomidine, fentanyl, intrathecal, postoperative pain

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Dexmedetomidine is a highly selective α2–adrenoreceptor agonist recently introduced to anesthesia. It produces dose-dependent sedation, anxiolysis, and analgesia (involving spinal and supraspinal sites) without respiratory depression (1,2). α2-agonists are known to reduce anesthetic requirements, and because of their sympatholytic properties, afford hemodynamic stability during the intraoperative period (3).

Dexmedetomidine, an imidazole compound, is the pharmacologically active dextroisomer of medetomidine that displays specific and selective α2-adrenoceptor agonism. Activation of the receptors in the brain and spinal cord inhibits neuronal firing causing hypotension, bradycardia, sedation, and analgesia (4). In general, presynaptic activation of the α2-adrenoceptor inhibits the release of norepinephrine terminating the propagation of pain signals. Postsynaptic activation of α2-adrenoceptors in the central nervous system inhibits sympathetic activity and thus can decrease blood pressure and heart rate (5).

The mechanisms of the analgesic action of α2-agonists have not been fully elucidated. The activation of inwardly rectifying G1-protein-gated potassium channels results in membrane hyperpolarization decreasing the firing rate of excitable cells in the central nervous system (CNS). This is considered a significant mechanism of inhibitory neuronal action of α2-adrenoceptor agonists (6).

Another prominent physiologic action ascribed to α2-adrenoceptors is their reduction of calcium conductance into the cell, thus inhibiting neurotransmitter release. These 2 mechanisms represent 2 very different ways of effecting analgesia: in the first, the nerve is prevented from ever firing, and in the second, it cannot propagate its signal to its neighbor (6).

Administration of an α2-agonist via an intrathecal or epidural route provides an analgesic effect in postoperative pain without severe sedation. This effect is due to the sparing of supraspinal CNS sites from excessive drug exposure, resulting in robust analgesia without heavy sedation (7). The adverse effects of dexmedetomidine include hypotension, hypertension, nausea, bradycardia, atrial fibrillation, and hypoxia (8,9).

The objective of this study was to compare the safety and analgesic efficacy of intrathecally administered dexmedetomidine or dexmedetomidine combined with fentanyl in patients undergoing major abdominal cancer surgery.

Methods

This randomized, double-blind study was approved by the local ethics committee of the South Egypt Cancer Institute, Assiut University, Egypt. After written informed consent, 90 American Society of Anesthesiologists physical status 1 and 2 patients (age, 25-55 years; weight, 50-85 kg) who were scheduled for major abdominal cancer surgery were enrolled in the study. Patients with a known allergy to the study drugs, bleeding diathesis, liver or renal impairment, who were drug or alcohol abusers, and those with psychiatric illnesses that would interfere with perception and assessment of pain were excluded from the study. Preoperatively, patients were taught how to evaluate their own pain intensity using the Visual Analog Scale (VAS), scored from 0 - 10 (where 0 = no pain and 10 = the worst pain imaginable).

Oral diazepam (5 mg) was taken the night before surgery. Upon arrival at the operating room, a 16- gauge catheter was inserted intravenously in the dorsum of the hand; lactated Ringer's solution 10mL/kg was infused intravenously over 10 minutes before the initiation of spinal anesthesia. Basic monitoring probes (electrocardiography, noninvasive blood pressure, O2 saturation and temperature) were applied. Patients were placed in the sitting position and a 25-gauge Quincke needle was placed in the L2-L3 or L3- L4 interspaces.

Patients were allocated to one of 3 groups. The control group received 10 mg of hyperbaric bupivacaine 0.5% in 2 mL volume and 1 mL of saline 0.9% intrathecally; the dexmedetomidine group received 10 mg of hyperbaric bupivacaine 0.5% in 2 mL volume and 5 μg of dexmedetomidine in 1 mL volume intrathecally; and the dexmedetomidine+ group received 10 mg of hyperbaric bupivacaine 0.5% in 2 mL volume and 5 μg of dexmedetomidine plus 25 μg of fentanyl in 1 mL volume.

Immediately after their intrathecal injection, the patients were placed in the supine position. After successful spinal anesthesia, general anesthetic technique was induced and standardized in the 3 groups. Heart rate, systolic blood pressure, and diastolic blood pressure were recorded for 120 minutes. Hypotension was defined as a 15% decrease in systolic blood pressure from the baseline. Bradycardia was defined as a heart rate slower than 50 beats per minute or as an inappropriately slow heart rate despite hypotension. Hypoxia was defined as an oxygen saturation value < 90%. Hypotension was treated with intravenous boluses of ephedrine 0.1 mg/kg and normal saline 5 mL/kg; the

same doses were repeated as required. Bradycardia was treated with intravenous atropine 0.01 mg/kg.

At the end of the operation patients were transferred to the Postanesthesia Care Unit and were monitored for vital signs (heart rate, noninvasive blood pressure, respiratory rate, and saturation of peripheral oxygen). The level of sedation was recorded using a modified Observer's Assessment of Alertness/ Sedation Scale where 1 = awake/alert to 5 = sleep/unarousable. The VAS was assessed immediately postoperatively and at hours 2, 4, 6, 8, 12, and 24 of the postoperative period. Intravenous tramadol 100 mg was given when the VAS was ≥ 3 or upon patient request. The time of the first request for analgesia and the total analgesic consumption in the first 24 hours were recorded. Postoperative adverse effects such as nausea, vomiting, hypotension, bradycardia, pruritus, and cardiac arrhythmia were recorded and treated.

Statistical analysis

Analysis was performed using SPSS Software Version 17 (SPSS Inc., Chicago, IL). Data were expressed as mean ± standard deviation, number, and frequencies. Parametric data were analyzed using an analysis of variance test among groups followed by post-hoc test if needed. The Kruskal Wallis test was used to compare nonparametric data among groups. The Mann-Whitney test was used to compare nonparametric data between 2 groups. The chi-squared test was used to analyze frequency and percentage. A P value < 0.05 was considered statistically significant.

Results

There were no significant differences among groups in demographic data, clinical characteristics, and duration of surgery (P > 0.05) (Table 1).

Regarding hemodynamic variables measured during the intraoperative period, there was a significant reduction in pulse rate starting at 20 minutes until 120 minutes in the dexmedetomidine+ group and starting at 20 minutes until 60 minutes in the dexmedetomidine group in comparison to the control group (P < 0.05) (Table 2, Fig. 1). Systolic blood pressure showed a significant reduction starting at 5 minutes until 90 minutes intraoperatively in both the dexmedetomidine and dexmedetomidine+ groups in comparison to the

Table 1. *Demographic data, clinical characteristics and duration of surgery.*

Variable	Dexmedetomidine+ (n=30)	Dexmedetomidine (n=30)	Control (n=30)
Age (year)	44.43±1.57	44.50±1.50	43.83±1.60
Weight (kg)	73±1.65	72.82±1.69	72.60±0.66
Height (Cm)	163.0.63±1.41	164.07±1.47	163.70±1.34
Male/Female	8/22	12/18	10/20
ASA I/II	25/5	27/3	26/4
Duration of surgery (hour)	3.17±1.04	3.13±0.88	2.88±1.03

Data are expressed as mean ± SD and number.

Table 2. *Intra-operative heart rate changes.*

Variable	Control (n=30)	Dexmedetomidine (n=30)	Dexmedetomidine+ (n=30)
T0	90.67±1.37	83.33±1.68	89.83±1.53
5 minutes	83.50±2.24	81.03±1.55	80.17±2.06
10 minutes	84.17±2.99	82.33±1.38	78.17±1.82
15 minutes	85.67±2.71	82.07±1.19	81.67±1.50
20 minutes	86.33±1.79	82.13±1.26*	84.33±1.35*
25 minutes	88.16±2.40	82.27±1.34*	85.33±1.19*
30 minutes	87.17±1.31	86.00±1.00*	82.70±1.34*
60 minutes	92.10±1.25	86.63±1.06*	82.33±1.26 *
90 minutes	91.17±1.26	87.83±1.11	81.63±1.30*
120 minutes	90.67±1.09	87.67±1.01	82,40±1.25 *

Data are expressed as mean ± SD. T0= just after GA induction. *= significant compared to control group.

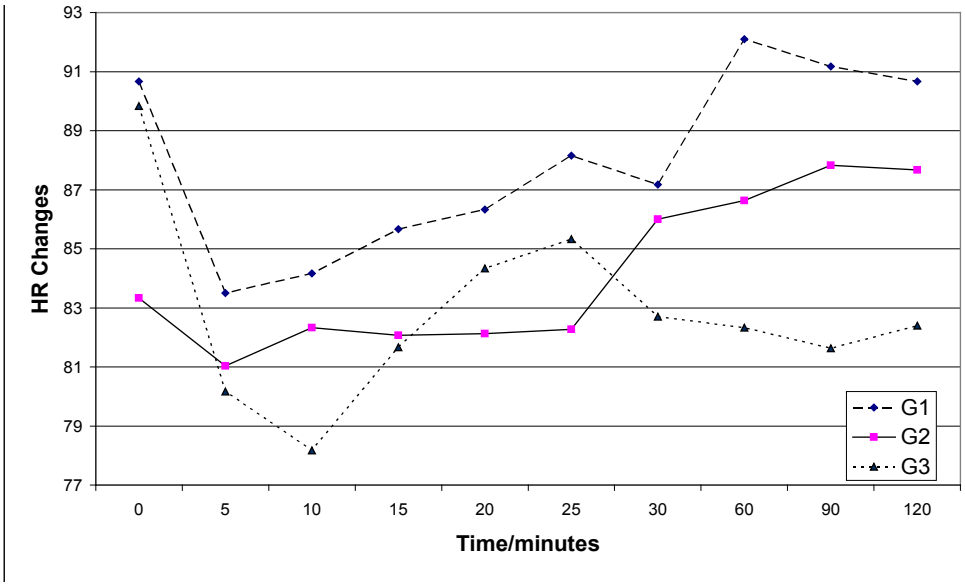

Fig.1. *Intra-operative HR changes in studied groups (HR= Heart Rate).*
G1= Control. G2= Dexmedetomidine. G3= Dexmedetomidine +

Table 3. *Blood pressure changes intra-operative.*

Variable	Systolic Blood Pressure			Diastolic Blood Pressure		
	Control (n=30)	DEX (n=30)	DEX+ (n=30)	Control (n=30)	DEX (n=30)	DEX+ (n=30)
T0	127.67±2.52	127.50±2.31	128.33±2.40	76.33±1.95	78.00±1.67	79.33±1.86
5 min	120.33±2.60	99.67±2.81*	106.17±2.22*	72.67±1.91	63.50±1.29*	69.50±1.95*
10 min	120.00±2.35	91.17±3.00*	98.33±3.16*	77.67±1.24	59.67±1.93*	63.33±1.94*
15 min	127.17±2.14	89.83±3.39*	101.67±3.52*	78.00±1.39	62.33±1.74*	65.00±1.78*
20 min	126.83±1.98	99.50±2.79*	113.50±3.17*	76.67±1.54	68.83±1.55*	69.17±1.73*
25 min	128.33±1.98	109.50±2.75*	117.33±2.14*	77.00±1.45	74.83±1.62	73.33±1.46
30 min	128.33±2.30	115.00±2.87*	122.00±1.88*	76.67±1.54	74.67±1.71	76.33±1.39
60 min	128.83±2.24	121.33±2.57*	123.57±2.25*	77.33±1.43	77.33±1.85	77.00±1.09
90 min	128.50±2.02	121.33±1.84*	125.67±2.38*	78.33±1.52	77.00±1.16	77.3±1.26
120 min	128.33±1.98	128.67±1.90	128.67±1.84	80.33±1.39	78.00±1.01	78.67±1.24

Data are expressed as mean±SD.
T 0= just after GA induction, min= minutes, DEX= Dexmedetomidine group and DEX+ = Dexmedetomidine+ group.
*= significant compared to Control group.

control group ($P < 0.05$). There was a significant reduction in intraoperative diastolic blood pressure starting at 5 minutes untl 20 minutes intraoperatively in both the dexmedetomidine and dexmedetomidine+ groups in comparison to the control group ($P < 0.05$) (Table 3, Figs. 2 and 3).

There were no significant differences between groups in hemodynamic variables measured during the postoperative period ($P > 0.05$).

Also, there were no significant differences in sedation scores among all groups ($P < 0.05$).

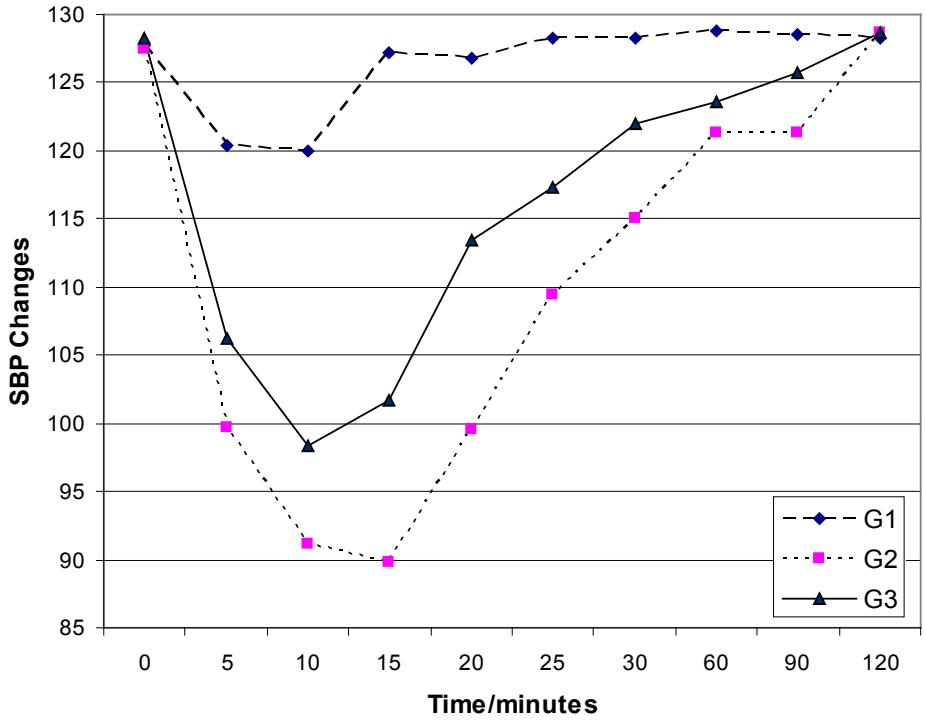

Fig. 2. *Intra-operative SBP changes in studied groups (SBP= Systolic Blood Pressure).*
G1= Control. G2= Dexmedetomidine. G3= Dexmedetomidine +

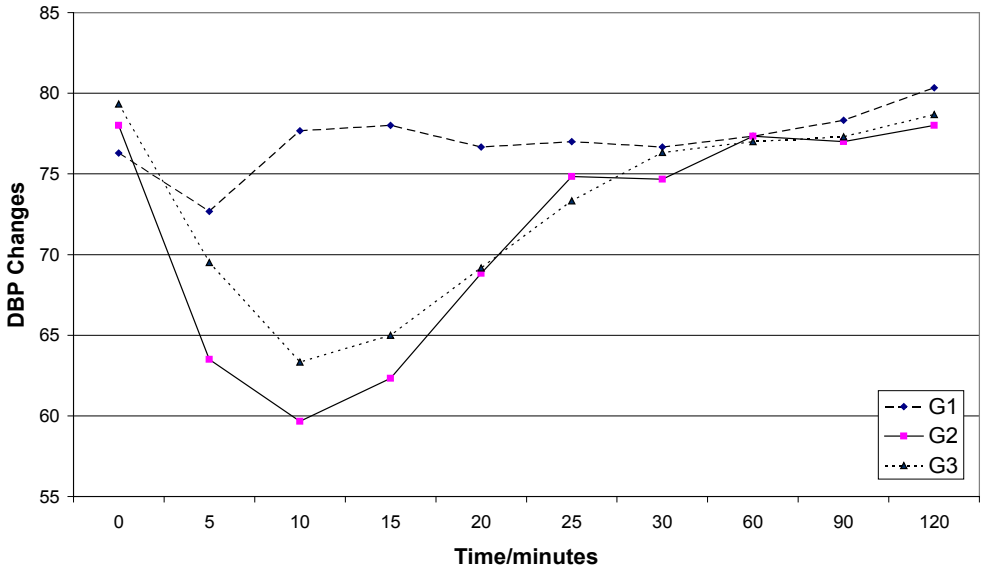

Fig.3. *Intra-operative DBP changes in studied groups (DBP= Diastolic Blood Pressure).*
G1= Control. G2= Dexmedetomidine. G3= Dexmedetomidine +

Table 4. *VAS score postoperative.*

Variable	Dexmedetomidine+ (n=30)	Dexmedetomidine (n=30)	Control (n=30)	*P* value
T0	2.67±0.28*	3.07±0.33*	5.50±0.28	0.001
2 hours	2.37±0.21	2.53±0.22	2.63±0.30	0.744
4 hours	2.27±0.19	2.40±0.20	2.73±0.20	0.224
6 hours	2.27±0.19	2.40±0.81	2.70±0.17	0.179
8 hours	2.57±0.24	2.40±0.18	2.80±0.20	0.456
12 hours	2.37±0.21*	2.03±0.03*	2.63±0.17	0.027
24 hours	2.20±0.14	2.23±0.14	2.43±0.15	0.463

Data are expressed as mean±SD. T0= immediate postoperative. *= significant compared to Control group.

Table 5. *Time to first analgesic request and tramadol consumption in first 24 hours postoperative.*

Variable	Dexmedetomidine+ (n=30)	Dexmedetomidine (n=30)	Control (n=30)	*P* value
Time to first analgesic (hours)	5.41±1.23*	3.30±0.87 *	0.233±0.11	0.001
Tramadol consumption(mg)	131.25±11.96*	142.85±13.04 *	310.00±12.08	0.001

Data are expressed as mean±SD.
*= significant compared to Control group.

Table 6. *Adverse effects.*

Variable	Control (n=30)	Dexmedetomidine (n=30)	Dexmedetomidine+ (n=30)	*P* value
Nausea	8(26.6%)	4(13.3%)	5(16.6%)	0.056
Cardiac arrhythmia	0(0.0%)	0(0.0%)	0(0.0%)	0.643
Vomiting	6(20.0%)	4(13.3 %)*	3(10.0%)*	0.034
Itching	0(0.0%)	0(0.0%)	2(6.6%)*†	0.021

Data are expressed as number (%).
*= significant compared to Control group.
†= significant compared to Dexmedetomidine group.

The mean VAS scores showed a significant reduction immediately postoperatively and at 12 hours postoperatively in both the dexmedetomidine group and the dexmedetomidine+ group in comparison to the control group ($P < 0.05$) with no significant difference between the dexmedetomidine and dexmedetomidine+ groups (Table 4). The time of the first rescue analgesic requirement was significantly prolonged in the dexmedetomidine group and the dexmedetomidine+ group in comparison to the control group, with no significant difference between the dexmedetomidine and dexmedetomidine+ groups.

The mean total consumption of intravenous tramadol rescue analgesia in the Postanesthesia Care Unit in the first 24 hours postoperatively was significantly decreased in the dexmedetomidine (142.85 ± 13.04) and dexmedetomidine+ (131.25± 11.96) groups compared to control group (310.00 ± 12.08) mg but with no significant difference between the dexmedetomidine and dexmedetomidine+ groups (Table 5). There were significant differences in the incidence of vomiting ($P < 0.05$) but not in nausea among groups. There were significant differences regarding pruritus among groups ($P < 0.05$). Cardiac arrhythmia was absent in all the study groups (Table 6).

Discussion

Animal studies conducted in rats, rabbits, dogs and sheep have used intrathecal dexmedetomidine at

a dose range of 2.5-100 μg without any neurological deficits (10-17). Fukushima et al (18) administered 2μg/kg dexmedetomidine epidurally for postoperative analgesia in humans without any reports of neurological deficits. Maroof et al (19) used dexmedetomidine epidurally at approximately 1.5μg/kg to decrease the incidence of postoperative shivering without any reports of neurological deficit.

In a study by Kanazi et al (20), the 2-week follow-up questionnaire showed that intrathecal, preservative-free dexmedetomidine at a dose of 3μg was not associated with any new onset of back, buttock, or leg pain or weakness. Most of the clinical experience gained in the use of intrathecal α2- adrenoceptor agonists has been described with clonidine. The use of intrathecal clonidine has a well established synergetic effect with local anesthetics (21-24). Studies using a combination of intrathecal dexmedetomidine and local anesthetics are lacking. Kalso et al (25) reported that dexmedetomidine affinity to α2-adrenoceptor agonists is 10 times that of clonidine. A small intrathecal dose of dexmedetomidine (3μg), used in combination with bupivacaine in human beings for spinal anesthesia, has been shown to produce a shorter onset of motor block and a prolongation in the duration of motor and sensory block with hemodynamic stability and lack of sedation. (20). Our study showed that the addition of 5 μg dexmedetomidine to 10 mg bupivacaine or 5 μg dexmedetomidine to 10 mg bupivacaine and 25 μg fentanyl intrathecally before induction of general anesthesia in major abdominal cancer surgery induced a significant reduction in the intraoperative pulse rate and blood pressure. This was in agreement with Al-Ghanem et al (26), where the use of dexmedetomidine was found to be associated with a decrease in heart rate and blood pressure. Shukla et al (27) and Gupta et al (28) found that the addition of dexmedetomidine to bupivacaine is associated with hemodynamic stability, in comparison to the present work, where the difference in the hemodynamic variables may be attributed to the combination of spinal and general anesthesia.

The mean VAS score was low in all groups as our Intensive Care Unit protocols recommend keeping the VAS score at ≤ 3 for postoperative patients. They were significantly reduced immediately and at 12 hours postoperatively in the dexmedetomidine group and the dexmedetomidine+ group. The time of the first rescue analgesic requirement was significantly prolonged in the dexmedetomidine group (3.30 hours) and the dexmedetomidine+ group (5.41 hours) compared to the control group (0.233 ± 0.11 hours). The mean total consumption of intravenous tramadol in the first 24 hours postoperatively was significantly decreased in the dexmedetomidine (142.85 ± 13.04) and dexmedetomidine+ (131.25 ± 11.96) groups, compared to the control group (310.00 ± 12.08) but there was no significant difference between the dexmedetomidine and dexmedetomidine+ groups. The mechanism may be due to an additive or synergistic effect secondary to the different mechanisms of action of local anesthetic and α2-adrenoceptor agonists.

Local anesthetic acts by blocking sodium channels, whereas an α2-adrenoceptor agonist acts by binding to presynaptic C-fibers and postsynaptic dorsal horn neurons; they produce analgesia by depressing the release of C-fiber transmitters and hyperpolarization of postsynaptic dorsal horn neurons (29-33). On the other hand, Gupta et al (28) compared the role of intrathecal dexmedetomidine and fentanyl as adjuvants to bupivacaine. They concluded that intrathecal dexmedetomidine is associated with prolonged motor and sensory block, hemodynamic stability, and reduced demand for rescue analgesics in 24 hours as compared to fentanyl. In another study, Gupta et al (34) found that the addition of 5μg of dexmedetomidine to 3 mL 0.75% isobaric ropivacaine intrathecally produced a prolongation in the duration of the motor and sensory block in lower limb surgeries.

In our study, there were no significant differences in sedation scores among groups. Intrathecally administered $\alpha\alpha$2-agonists have a dose-dependent sedative effect. (35-36). Memis (37) noted that the addition of 0.5μg/kg dexmedetomidine to lidocaine for intravenous regional anesthesia improves the quality of anesthesia and perioperative analgesia without causing side effects. Al-Mustafa et al (38) studied the effect of dexmedetomidine 5 μg and 10μg with bupivacaine in urological procedures and found that dexmedetomidine prolongs the duration of spinal anesthesia in a dose–dependent manner. Shukla et al (27) compared intrathecal dexmedetomidine with magnesium sulfate used as an adjuvant to bupivacaine for both lower abdominal and lower limb procedures and concluded that the onset of anesthesia was rapid and of prolonged duration in the dexmedetomidine group compared to magnesium sulphate.

Conclusion

We conclude that intrathecal 5 μg dexmedetomidine improves the quality and the duration of postop-

erative analgesia and also provides an analgesic sparing effect in patients undergoing major abdominal cancer surgery. Furthermore, the intrathecal addition of 25 μg fentanyl has no valuable clinical effect. Further clinical studies are required to prove the efficacy and safety of different dosages of intrathecal dexmedetomidine combined with general anesthesia in major abdominal surgeries.

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