Randomized Trial

Intrathecal Dexmedetomidine, Ketamine, and their Combination Added to Bupivacaine for Postoperative Analgesia in Major Abdominal Cancer Surgery

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Background: Intrathecal ketamine has been studied extensively in animals, but rarely in humans. Intrathecal dexmedetomidine prolongs the duration of spinal anesthesia.

Objective: To investigate the efficacy and safety of intrathecal dexmedetomidine, ketamine, or both when added to bupivacaine for postoperative analgesia in major abdominal cancer surgery.

Design: Double-blinded, randomized, controlled trial.

Setting: Academic medical center.

Methods: Ninety patients were randomly allocated to receive either intrathecal 10 mg of hyperbaric bupivacaine 0.5% and 5 µg of dexmedetomidine (group I, n = 30), 10 mg of hyperbaric bupivacaine 0.5% and 0.1 mg/kg ketamine (group II, n = 30), or 10 mg of hyperbaric bupivacaine 0.5% and 5 µg of dexmedetomidine plus 0.1 mg/kg of ketamine (group III, n = 30). Hemodynamics, pain score, time to first request of analgesia, total PCA morphine consumption, sedation score, and adverse effects in the first 24 hours postoperatively were recorded.

Results: Time to first request of analgesia was longer in group II (7.42 ± 1.43 h) and group III (13.00 ± 7.31h) compared to group I (3.50 ± 1.57 h). PCA morphine consumption was less in group III (6.67 ± 2.8 mg) compared to group I (9.16 ± 3.63 mg) and group II (8.66 ± 3.49 mg). Group III showed lower postoperative pain scores, and a higher incidence of postoperative sedation ($P < 0.03$).

Limitations: This study is limited by its relatively small sample size.

Conclusion: In conclusion, the combination of intrathecal dexmedetomidine and ketamine provided superior postoperative analgesia, prolonged the time to first request of rescue analgesia, and reduced the total consumption of PCA morphine, without serious side effects compared to either drug alone.

Key words: Intrathecal, ketamine, dexmedetomidine, lower abdominal cancer surgery

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Opioids are widely used for pain relief, but they often provide sub-optimal analgesia with occasional serious side effects. Furthermore, it was reported that only a single administration of an opioid may also induce a long lasting reduction of threshold of pain sensitivity, leading to delayed hyperalgesia (1).

Ketamine, a phencyclidine derivative, has recently been found to be effective by epidural and intrathecal routes. It possesses some definite advantages over the

conventional local anesthetic agents as it stimulates the cardiovascular system (2,3) and respiratory system (4).

There is evidence from animal studies that ketamine produces sensory (5,6) and motor (6,7) blocks when injected intrathecally. Preservative-free ketamine hydrochloride was introduced as a spinal anesthetic more than 20 years ago and found to have advantages over local anesthetics in that it didn't produce hypotension.

The onset of anesthesia (sensory block) and motor paralysis was found to be earlier than with conventional local anesthetics (3). The intensity of the sensory block is 100% as it is described to be due to the potent analgesic effect of ketamine (8).

Despite extensive discourses, there is still controversy in the literature as to the safety and analgesic efficacy of ketamine through the intrathecal route (9-14). Preservative-free racemic ketamine was shown to be devoid of neurotoxic effects after both single and repeated administration in animals (9-11).

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 (15, 16). α2-agonists are known to reduce anesthetic requirements, and because of their sympatholytic properties, afford hemodynamic stability during the intraoperative period (17).

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 central nervous system (CNS) sites from excessive drug exposure, resulting in robust analgesia without heavy sedation (18). The adverse effects of dexmedetomidine include hypotension, hypertension, nausea, bradycardia, atrial fibrillation, and hypoxia (19,20).

The objective of this study was to investigate the efficacy and safety of intrathecally administered dexmedetomidine, ketamine, or their combination when added to bupivacaine for postoperative analgesia in major abdominal cancer surgery.

Methods

This study was approved by the ethics committee of South Egypt Cancer Institute, Assiut University, Assiut, Egypt. After obtaining a written informed consent, 90 American Society of Anesthesia (ASA) I – II patients aged 30 – 50 years and scheduled for major abdominal cancer surgery were included in the study. Patients with a known allergy to the study drugs; significant cardiac, respiratory, renal, or hepatic diseases; coagulation disorder; infection at the site of intrathecal injection; drug or alcohol abuse; BMI > 30 kg/m2; and psychiatric illness 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 numerical rating scale (NRS), 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 operative theatre, a 16-gauge catheter was introduced intravenously at the dorsum of the hand; lactated ringer's solution 10 mL/kg was infused intravenously over 10 minutes before 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 L2-3 or L3-4 interspaces.

Patients were randomly allocated by selecting sealed envelopes into one of 3 groups of 30 patients each:

- Dexmedetomidine group (group I): in which patients received 10 mg of hyperbaric bupivacaine 0.5% in 2 mL volume and 5 µg of dexmedetomidine in 1 mL volume intrathecally.
- Ketamine group (group II): in which patients received 10 mg of hyperbaric bupivacaine 0.5% in 2 mL volume and 0.1 mg/kg ketamine in 1 mL volume intrathecally.
- Dexmedetomidine + ketamine group (group III): in which patients received 10 mg of hyperbaric bupivacaine 0.5% in 2 mL volume and 5 µg of dexmedetomidine plus 0.1 mg/kg of ketamine in 1 mL volume intrathecally.

Immediately after successful spinal anesthesia, patients were placed in the supine position, general anesthesia was induced with fentanyl 1.5 – 2 µg/kg, propofol 2 – 3 mg/kg, and lidocaine 1.5 mg/kg. Endotracheal intubation was facilitated by cis-atracurium 0.15 mg/kg. Heart rate, systolic, and diastolic blood pressure were recorded at 5, 10, 20, 30, 60, 120, and 180 minutes. Anesthesia and muscle relaxation were maintained by isoflurane 1 – 1.5 MAC in 50% oxygen/air mixture and cis-atracurium 0.03 mg/kg bolus given every 30 minutes.

At the end of surgery, muscle relaxation was reversed by neostigmine 50 µg/kg and atropine 10 µg/kg. Patients were extubated and transferred to the post an-

esthesia care unit (PACU) and monitored for vital signs (heart rate, noninvasive blood pressure, respiratory rate, and O2 saturation) immediately postoperatively and at 2, 4, 6, 12, 18, and 24 hours postoperatively.

NRS scores were assessed at the same time intervals. Rescue analgesia was represented by patient-controlled analgesia (PCA) with intravenous morphine with an initial bolus of 0.1 mg/kg once pain was expressed by the patient, or if NRS was 3 or more (NRS ≥ 3) followed by 1 mg boluses with a lockout period of 5 minutes. The time of first request for analgesia and total analgesic consumption in the first 24 hours postoperatively were recorded.

The patient's level of sedation was assessed at the same time points with sedation score from 0 to 4, where 0 = awake, 1 = easily aroused, 2 = awakens after verbal stimulation, 3 = awakens after tactile stimulation, and 4 = not arousable.

The data collection personnel, the attendant anesthesiologist, and the patient were blinded to the patient's group assignment.

Postoperative adverse effects such as nausea, vomiting, hypotension, bradycardia, cardiac arrhythmias, nystagmus, dissociative effects, strange feelings, dizziness, chest pain, dreams, and sedation were recorded. Hypotension was defined as a 15% decrease in systolic blood pressure from baseline. Bradycardia was defined as a heart rate slower than 50 beats per minute or a decrease in heart rate of 20% or more from baseline; whichever is lowest. Hypoxia was defined as an oxygen saturation of less than 90%. Hypotension was treated with an intravenous bolus 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.

Statistical Analysis

Power of the Study

The primary endpoint was the total dose of intravenous PCA morphine consumption in the first 24 hours postoperatively. Secondary endpoints were the safety profile of the study drugs in terms of predefined adverse events, nausea, vomiting, and level of sedation during the study period. Our aim was to obtain a 20% decrease in intravenous PCA morphine consumption after intrathecal dexmedetomidine + ketamine compared with the other groups. A calculated sample size of 28 would have an 80% power of detecting a difference at a 0.05 level of significance using a confidence interval of 95%.

Data Analysis

Analysis was performed using statistical package for the Social Sciences software, version 20 (SPSS Inc., Chicago IL, USA). Data were presented as mean ± SD, range, numbers, and percentages. ANOVA followed by Post-hoc test were used for comparison of parametric data. Kruskal Wallis test was used to compare non-parametric data while Mann-Whitney was used to compare between 2 groups. Chi-square test was used for comparison between percentages and frequencies. $P < 0.05$ was considered significant.

Results

There were no significant differences between groups in demographic data regarding age, weight, height, BMI, and surgical time ($P > 0.05$) (Table 1).

There was a significant reduction in intra-operative pulse rate in group I compared to groups II and III from 10 and 20 minutes, respectively, until 180 minutes. Also, there was a significant reduction in pulse rate in group III from 10 minutes until 60 minutes compared to group II (Fig. 1). Systolic blood pressure showed a significant reduction in groups I and III from 5 minutes until 120 minutes compared to group II (Fig. 2). The intra-operative diastolic blood pressure significantly decreased in groups I and III from 5 minutes until 180 and 30 minutes, respectively, in comparison to group II (Fig. 3).

There was a significant reduction in postoperative pulse rate in group I immediately postoperative until 12 hours, and 24 hours, respectively, when compared to

Table 1. *Patients' demographics and clinical characteristics.*

Item	Group I (n = 30)	Group II (n = 30)	Group III (n = 30)	*P* value
Age (Years)	44.43 ± 4.05	44.20 ± 4.20	44.63 ± 3.84	0.903
Weight (Kg)	72.70 ± 8.61	72.36 ± 8.58	72.36 ± 8.58	0.985
Height (cm)	164.97 ± 11.81	164.13 ± 12.01	164.70 ± 11.23	0.961
BMI (Kg/m^2)	27.40 ± 7.89	27.73 ± 9.70	27.17 ± 6.21	0.964
Duration of surgery (h)	2.35 ± 0.41	2.33 ± 0.40	2.36 ± 0.43	0.953

Data are expressed as mean ± SD.

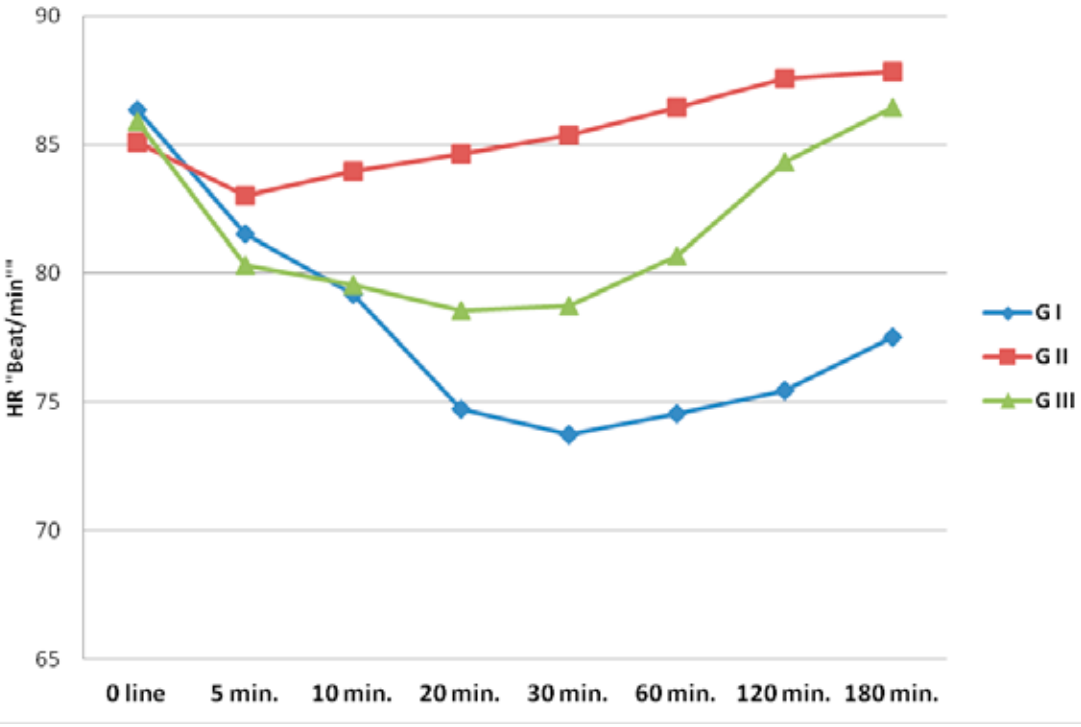

Fig. 1. *Changes in the mean intraoperative heart rate.*

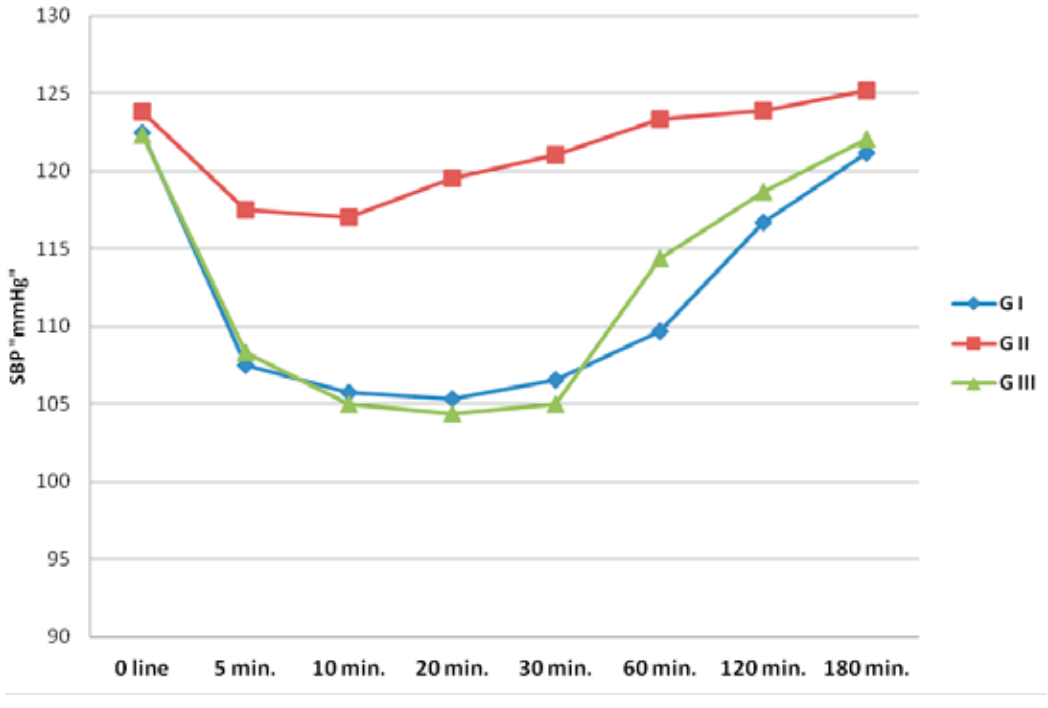

Fig. 2. *Changes in the mean intraoperative systolic blood pressure.*

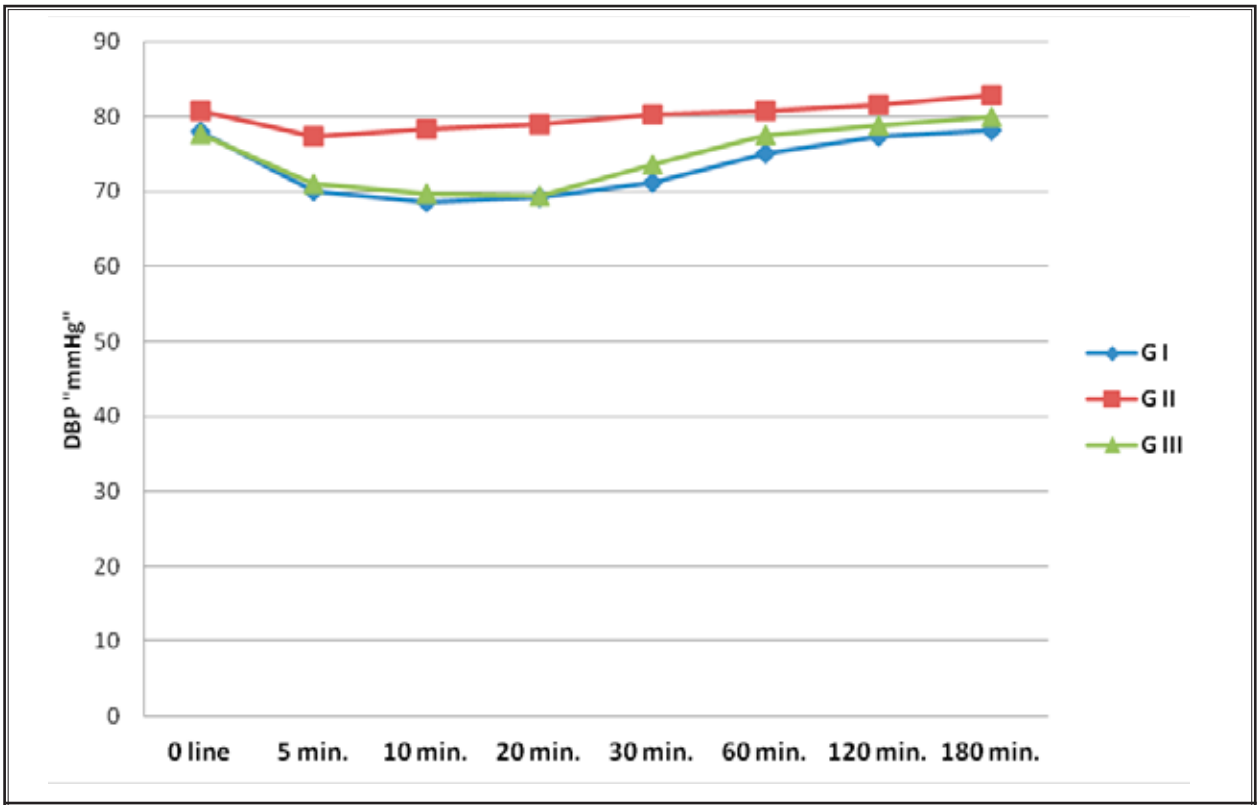

Fig. 3. *Changes in the mean intraoperative diastolic blood pressure.*

groups II and III (Fig. 4). There were no significant differences between groups in postoperative systolic and diastolic blood pressure ($P > 0.05$).

There was a significant reduction in mean NRS score in group III starting immediately postoperative till 12 hours postoperative compared to groups I and II (Fig. 5). The time to the first request of rescue analgesic was significantly prolonged in the groups II and III compared to group I ($P < 0.003$) (Table 2). The mean total consumption of PCA morphine in PACU in the first 24 hours postoperatively was significantly decreased in group III compared to groups I and II ($P < 0.03$) (Table 2). The number of patients who requested rescue analgesia varied remarkably in the 3 groups, where all the patients in group I, 21 patients in group II, and only 3 patients in group III required rescue analgesia in the postoperative period (Table 2).

There was no significant difference among groups regarding postoperative sedation score except immediately postoperative, where there was a significant increase in sedation score in groups II and III compared to group I ($P = 0.02$). There was a significant difference in the incidence of sedation ($P < 0.03$) in groups II and III compared to group I. Groups II and III had a higher incidence of sedation (3 [10.0%] and 5 [16.7%], respectively) compared to group I (0 [0.00%]).

Apart from sedation, there were no significant differences in the incidence of other side effects between the 3 studied groups (Table 3, Fig. 6).

Discussion

The current study demonstrated that the combination of 5 μg dexmedetomidine and 0.1 mg/kg of ketamine co-administered with spinal bupivacaine in addition to general anesthesia in patients undergoing lower abdominal cancer surgery provided superior postoperative analgesia, prolonged the time to first request of rescue analgesics, and reduced the mean total consumption of PCA morphine in the first 24 hours postoperative without serious side effects compared to patients who received either drug alone.

Ketamine is known to produce both motor and sensory block, but the mechanism of action is not clear (21). Ketamine acts at N-methyl-D-aspartate (NMDA),

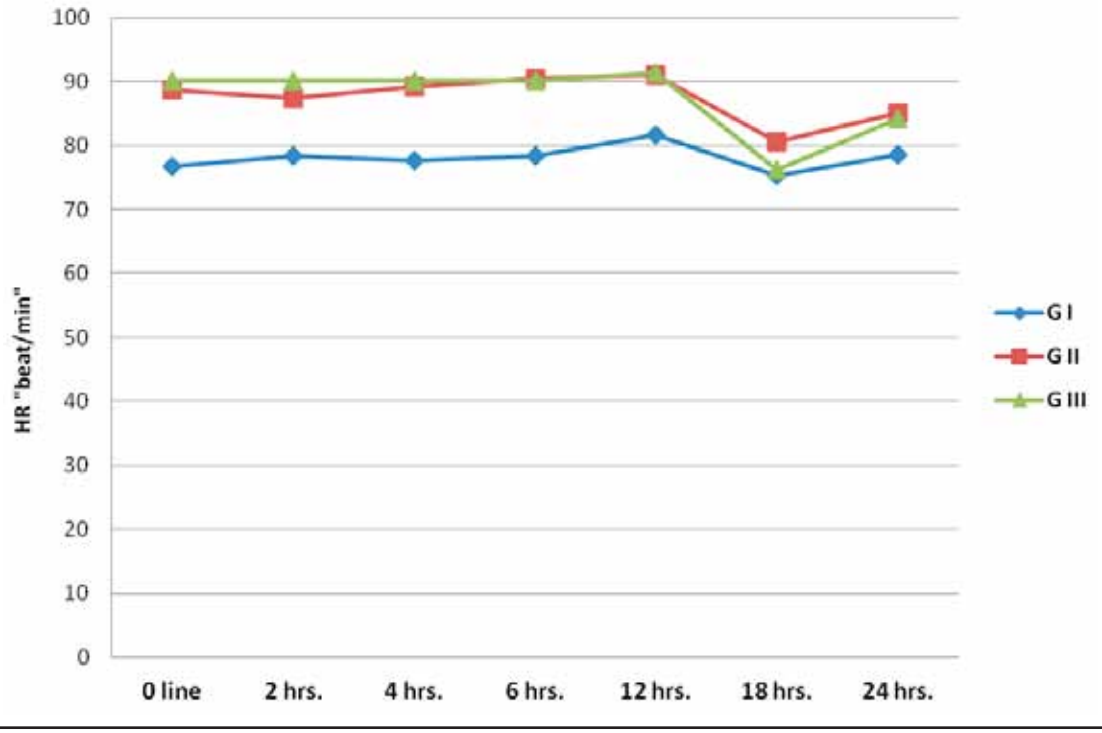

Fig. 4. *Changes in the mean postoperative heart rate.*

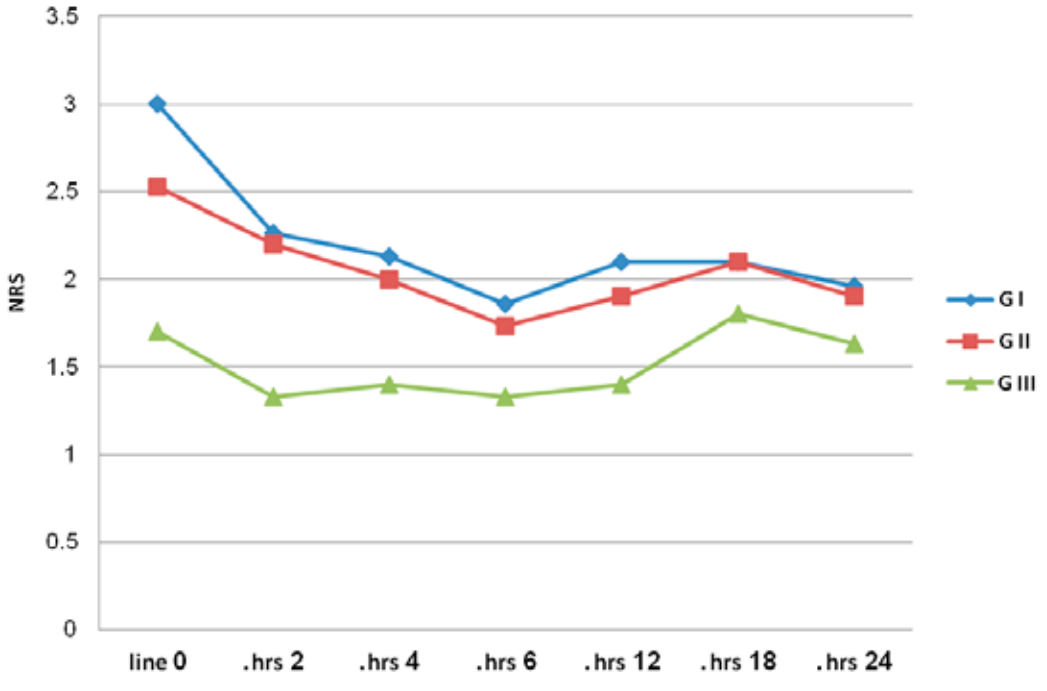

Fig. 5. *Numerical Rating Scale score.*

Table 2. *Time to first request of rescue analgesia and total intravenous PCA morphine consumption (mg) in the first 24 hours postoperatively.*

Item	Group I (n = 30)	Group II (n = 30)	Group III (n = 30)	*P* value
Time of first request (h)	3.50 ± 1.57	7.42 ± 1.43*	13.00 ± 7.31*	< 0.000
Total IV PCA morphine consumption (mg)	9.16 ± 3.63	8.66 ± 3.49	6.67 ± 2.8**	< 0.03
Number of patients requested rescue analgesia No. (%)	30 (100%)	21 (70%)	3 (10%)	--

Data are expressed as mean ± SD.
P: significance between groups.
*= significance to GI.
** = significance to GI and GII.

Table 3. *Postoperative adverse events*.

Item	Group I (n = 30)	Group II (n = 30)	Group III (n = 30)	*P* value
Hypotension	3 (10.0%)	--	1 (3.3%)	0.160
Hypertension	--	--	--	--
Nausea	6 (20.0%)	5 (16.7%)	4 (13.3%)	0.787
Vomiting	4 (13.3%)	4 (13.3%)	4 (13.3%)	1
Arrhythmia	--	--	--	--
Nystagmus	--	1 (3.3%)	1 (3.3%)	0.60
Dissociative effects	--	2 (6.7%)	3 (10.0%)	0.221
Strange feelings	--	2 (6.7%)	3 (10.0%)	0.227
Dizziness	--	2 (6.7%)	--	0.129
Chest pain	--	2 (6.7%)	1 (3.3%)	0.355
Dreams	--	2 (6.7%)	2 (6.7%)	0.351
Sedation	--	3 (10.0%)	5 (16.7%)	<0.03

Data are expressed as number and percentages.
P: significance between groups.

opiate, monoaminergic, and muscarinic receptors (22-24) and voltage-sensitive calcium channel blockers, and it is also thought to have some local anesthetic property (5, 25- 27).

Intrathecal ketamine has been studied extensively in animals, but rarely used in humans. Borgbjerg and Svenssson (11) administered preservative-free ketamine 5 mg intrathecally to rabbits for 14 consecutive days and concluded that it bore no evidence of harmful neurotoxic effects, even after repeated injections. It is suggested that various factors, like preservatives (chlorobutanol and benzethonium chloride), the use of multiple drugs for an extended period of time, and the indwelling intrathecal catheters may be responsible for neurological complications (9-13). By contrast, Yu et al (14) reported that ketamine provided potent protective effects against the ischemic reperfusion in spinal cord injuries.

Hawksworth and Serpell (21) studied intrathecal ketamine (0.75 – 0.9 mg/kg) in patients undergoing transurethral resection of the prostate. Of the 10 patients studied, 6 required general anesthesia because of inadequate surgical analgesia. The study was abandoned because of the high incidence of central effects. Kathirvel et al (28) studied the effect of intrathecal ketamine added to bupivacaine and found that it had a local anesthetic sparing effect, but the high incidence of adverse effects limited its use. Sandler et al (29) suggested that epidural ketamine may have an additive effect on opioids and local anesthetics.

Finck and Ngai (23) reported that ketamine has agonist action at opiate receptors. Bion (30) used ketamine to produce surgical anesthesia, injecting it intrathecally for war injuries, and found no interference with cardiovascular or respiratory functions. Bion (30) used 5 – 50 mg ketamine. The mean onset time of analgesia was

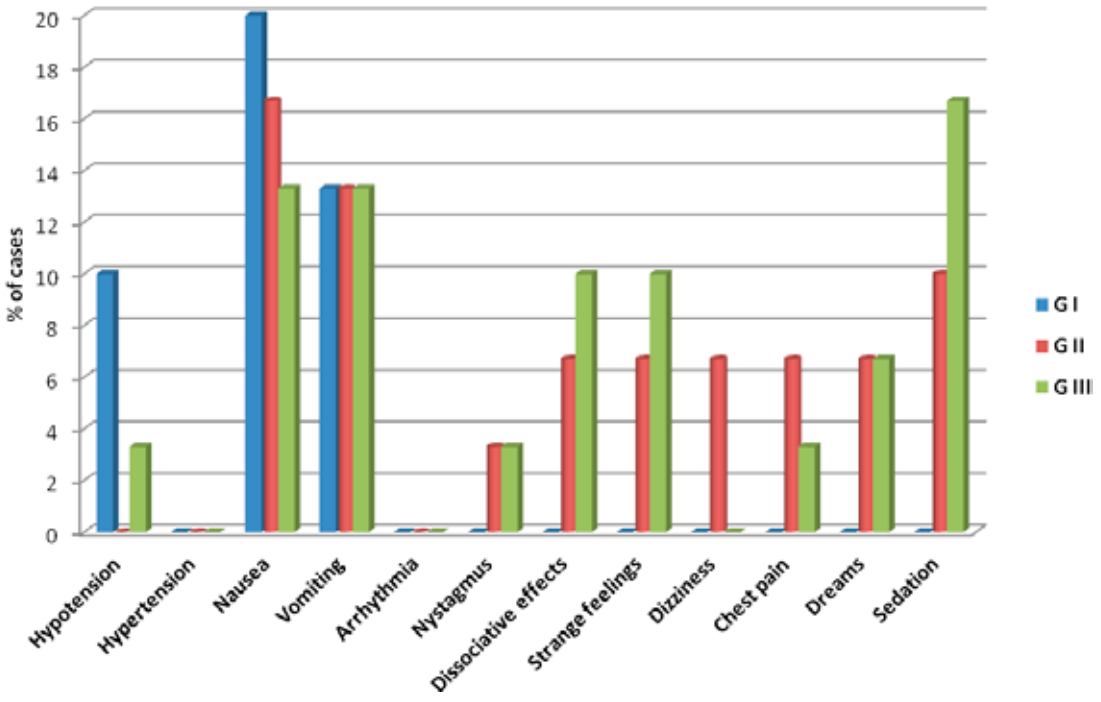

Fig. 6. *Incidence of side effects.*

1.7 minutes and duration was 45 – 90 minutes.

Shrestha et al (31), when comparing intrathecal anesthesia with 2 mL (10 mg) hyperbaric bupivacaine 0.5% plus 25 mg preservative-free ketamine to 2 mL (10 mg) hyperbaric bupivacaine 0.5% plus 25µg fentanyl, concluded that the addition of ketamine produced faster onset of sensory and motor blockade, although it did not prolong the duration of spinal analgesia compared to the addition of fentanyl in parturients undergoing caesarean section with spinal anesthesia.

Khezri and colleagues (32) found that intrathecal ketamine 0.1 mg/kg co-administered with spinal bupivacaine elongated the time to the first analgesic request and reduced the total analgesic consumption in the first 24 postoperative hours in comparison to bupivacaine alone in the control group following elective cesarean delivery.

Togal et al (33) reported that intrathecal S (+) ketamine administered with a low dose of bupivacaine provides shorter motor and sensory block onset time, shorter duration of action, and less motor blockade in elderly men undergoing prostatic surgery.

Dexmedetomidine, an imidazole compound, is the pharmacologically active dextroisomer of medetomidine that displays specific and selective α2-adrenoceptor agonism (34). 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 postsynaptic dorsal horn neurons (35).

Al-Mustafa et al (36) studied the effect of intrathecal 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 (37) compared 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 sulfate.

Mohamed et al (38) concluded that intrathecal 5 µg dexmedetomidine improves the quality and the duration of postoperative analgesia and also provides an analgesic sparing effect in patients undergoing major abdominal cancer surgery.

In our study, there was a statistically significant reduction in pulse rate and systolic and diastolic blood pressure intra-operative in the dexmedetomidine group (group I) and the combined ketamine and dexmedetomidine group (group III) when compared with the ketamine group (group II). In the postoperative period there were no significant differences between groups in postoperative systolic and diastolic blood pressure. This was in agreement with Al-Ghanem et al (39) and Mohamed et al (38) where the use of dexmedetomidine was found to be associated with a decrease in heart rate and blood pressure. Shulka et al (37) and Gupta et al (40) found that the addition of dexmedetomidine to bupivacaine is associated with hemodynamic stability.

The hypotensive effect of dexmedetomidine results from stimulation of α2-inhibitory neurons in the medullary vasomotor center (nucleus reticularis lateralis) of the brainstem, which leads to a reduction in norepinephrine release and sympathetic nerve outflow from the CNS to the peripheral tissues. Bradycardia is caused by an increase in vagal tone resulting from central stimulation of parasympathetic outflow, as well as a reduced sympathetic drive (41).

Our results support the notion that the addition of dexmedetomidine to ketamine improves the analgesic efficacy and reduces possible side effects of both of them. 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 CNS. This is considered a significant mechanism of inhibitory neuronal action of α2-adrenoceptor agonists (42). 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 (42).

Clinically, ketamine has been reported to produce not only general but also local anesthesia (6,30). It also interacts with NMDA receptors (43-45), opioid receptors (46,47), monaminergic receptors (47- 49), and voltage-sensitive Ca+2 channels (50,51).

In this study, the intrathecally administered ketamine as an adjuvant to bupivacaine 0.05% at a dose of 0.1 mg/kg alone or combined with dexmedetomidine 5 µg was not associated with serious central or other side effects. This may be explained by both the low dose of ketamine used, and its combination with dexmedetomidine. To our knowledge, there is no published work in the literature on the combination between intrathecal dexmedetomidine and ketamine for postoperative analgesia following major abdominal cancer surgery.

This study is limited by its small sample size, and the, relatively, short follow-up period. Further studies with a larger sample size and possible extension of the follow-up period for more than 24 hours to see how this can change the efficacy of analgesia and opioid consumption are required.

Conclusion

In conclusion, the combination of intrathecal dexmedetomidine and ketamine provided superior postoperative analgesia, prolonged the time to first request of rescue analgesics, and reduced the total consumption of PCA morphine, without serious side effects compared to either drug alone.

Contribution

Drs. Sahar Abdel-Baky Mohamed, Ahmad Mohammad Abd El-Rahman, Khaled Mohamed Fares had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Drs. Khaled Mohamed Fares and Ahmad Mohammad Abd El-Rahman designed the study protocol. Drs. Sahar Abdel-Baky Mohamed and Khaled Mohamed Fares managed the literature searches and summaries of previous related work and wrote the first draft of the manuscript.

Drs. Sahar Abdel-Baky Mohamed, Ahmad Mohammad Abd El-Rahman, and Khaled Mohamed Fares provided revision for intellectual content and final approval of the manuscript.

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