Subarachnoid versus intravenous dexmedetomidine and fentanyl for minimizing stress response in laparoscopic cholecystectomy

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Background The magnitude of stress response depends on several factors such as duration and intensity of surgical trauma, patient's age, surgical method, anesthetic technique, blood loss, and postoperative pain.

Aim of the work The aim of this work was to study the effect of intravenous versus intrathecal dexmedetomidine and fentanyl on stress response during laparoscopic cholecystectomy.

Patients and methods Sixty patients fulfilling the inclusion criteria who were undergoing laparoscopic cholecystectomies were randomly assigned to receive either intravenous fentanyl and dexmedetomidine (group I) or intrathecal fentanyl and dexmedetomidine (group II). Mean arterial blood pressure and heart rate were recorded before induction of anesthesia (T0), 5 min after intubation (T1), 30 min after start of surgery (T2), at skin closure (T3), 6 h postoperatively (T4), and 24 h postoperatively (T5). The number of patients who required intraoperative intravenous fentanyl and total intraoperative fentanyl consumption (μg), and the number of patients who required intravenous morphine at the end of surgery were recorded. Visual analogue scale and total postoperative morphine consumption (mg) at the end of surgery (M0), and at 6, 12, 18, and 24 h (M1, M2, M3, and M4, respectively) were recorded. Blood interleukin-6, cortisol, and glucose were measured before anesthesia (F0) and after recovery (F1). Postoperative complications were recorded.

Results Heart rate and mean arterial blood pressure were statistically lower in group II at T2 and T3. The number of patients requiring intraoperative intravenous fentanyl and total intraoperative fentanyl consumption (μg), and the number of patients requiring intravenous morphine at the end of surgery were statistically lower in group II. Visual analogue scale and postoperative morphine consumption (mg) were statistically lower in group II at M0 and M1. Blood cortisol and blood glucose level were statistically lower in group II at F1. There were no statistical differences as regards complications.

Conclusion Apart from lowering heart rate and BP, intrathecal dexmedetomidine and fentanyl was superior to intravenous dexmedetomidine and fentanyl, wherein it lowered pain score and analgesic consumption with attenuation of stress response.

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Introduction

The stress response to surgery is initiated by neuronal activation of the hypothalamic pituitary–adrenal axis, resulting in sympathetic nervous system stimulation, with an increased secretion of catecholamines and presynaptic norepinephrine release, which causes tachycardia and hypertension with modification of the function of some organs, including the liver, kidney, and pancreas [1].

The magnitude of stress response depends on several factors such as duration and intensity of surgical trauma, patient's age, surgical method, anesthetic technique, intraoperative blood loss, and postoperative pain [2].

Surprisingly, despite reduction of surgical trauma with laparoscopy, the endocrine response to open and laparoscopic cholecystectomy, and anesthetic requirements, do not differ significantly after both procedures [3].

Dexmedetomidine, an imidazole derivative, is an adrenoceptor agonist with high selectivity for α2 to α1 selectivity ratio 1620 : 1 compared with 220 : 1 for clonidine [4].

Dexmedetomidine produces dose-related analgesia sedation, and anxiolysis, (at supraspinal and spinal sites) without respiratory depression. Postoperative intrathecal or epidural α2-agonist administration produces an analgesia without severe sedation [5].

Dexmedetomidine, when given with opioids, may produce an additive or a synergistic effect [6].

Although opioids are highly effective in pain control, opioid use can lead to extended hospital stay due to undesirable adverse effects such as respiratory depression, nausea, vomiting, pruritus, and urinary retention [7].

Fentanyl administration intrathecally is simple and reliable. It improves the quality of intraoperative and early postoperative subarachnoid block when added to hyperbaric bupivacaine [1].

Patients and methods

This study was carried out at Al-Azhar University Hospitals, after approval from the local ethical committee, and the Departments of Anesthesia and Intensive Care, and after written informed consent was obtained from each patient during the period spanning from December 2016 to August 2017.

Sixty patients of both sexes aged between 20 and 60 years old, having American Society of Anesthesiologist Physical Status I and II and scheduled for elective laparoscopic cholecystectomy were included in the study.

Exclusion criteria included American Society of Anesthesiologist Physical Status (III–IV), contraindications to regional anesthesia, patients who used opioids or corticosteroids on a regular basis, chronic steroid therapy, hypertension, diabetes mellitus, hypersensitivity to medication used, pregnant or lactating women, operation time more than 90 min and BMI more than or equal to 25 kg/m^2.

All patients were evaluated preoperatively by full medical history. Clinical examination included the following: vital signs, cardiovascular, respiratory, and neurological examination with evaluation of the airway. Laboratory investigations included ECG, full blood picture, bleeding and coagulation times, fasting blood glucose, liver (SGOT, SGPT) and renal functions (urea, creatinine), and hepatitis marker.

Before the operation, patients received instructions about the visual analogue scale (VAS) for pain.

After arrival to the operating room, a peripheral venous cannula was inserted, and routine monitors were applied for recording heart rate, mean arterial blood pressure, oxygen saturation values, and end-tidal carbon dioxide, and ECG leads II and V5 were displayed continuously.

The following baseline values were recorded at T0: heart rate, systolic and diastolic arterial blood pressures and mean arterial blood pressure. Simultaneously, a blood sample was taken to determine the plasma concentrations of interleukin-6, cortisol, and glucose.

Before induction of anesthesia, the 60 patients were allocated randomly by sealed envelopes into two equal groups (30 patients each):

Group I: patients received intravenous fentanyl (1 μg/kg) and dexmedetomidine (0.5 μg /kg) slowly over 5 min (intravenous group).
Group II: patients received intrathecal injection of fentanyl (25 μg) and dexmedetomidine (5 μg) both diluted in normal saline with a total volume of 3 ml (intrathecal group). With the patient in the sitting position, a 25-G Quincke spinal needle was inserted under complete aseptic condition in the L3–L4 interspace, and the prepared solution for the intrathecal group was slowly injected. Thereafter, the patient lay in the supine position for 5 min before induction of anesthesia.

Induction of general anesthesia was performed after preoxygenation for 3–5 min using intravenous propofol 2 mg/kg and atracurium 0.5 mg/kg to facilitate orotracheal intubation. Anesthesia was maintained with isoflurane (1.2%) in oxygen and intravenous atracurium (0.15 mg/kg), as required. Mechanical ventilation was adjusted to maintain end-tidal carbon dioxide between 35 and 40 mmHg.

All patients received intravenous infusion of lactated Ringer's solution (15 ml/kg/h).

If analgesia is considered clinically insufficient during surgery, as indicated by increased heart rate (≥15 bpm) and systolic blood pressure (≥30 mmHg), compared with baseline, lacrimation, or sweating, intravenous 25 μg fentanyl was injected every 5 min until all these signs disappeared. The number of patients requiring intraoperative intravenous fentanyl and total intraoperative fentanyl consumption (μg) was recorded.

Isoflurane was discontinued at the end of the procedure, and the patients were extubated after receiving intravenous neostigmine (40 μg/kg) with atropine (10 μg/kg), and after meeting the standard criteria of extubation. Durations of surgery and anesthesia were recorded.

All patients were transferred to the recovery unit for close monitoring over the next 30 min (heart rate,

blood pressure, oxygen saturation, respiratory rate, and level of consciousness). When sufficiently awake, patients were asked to score their pain on The VAS (this evaluation defined T0). Patients with a score more than 3, received initial titration with 2 mg intravenous morphine every 10 min, until the VAS became equal or less than 3, provided the respiratory rate was more than 10/min.

Mean arterial pressure and heart rate were recorded before induction of anesthesia (T0), 5 min after intubation (T1), 30 min after start of surgery (T2), at skin closure (T3), 6 h postoperatively (T4), and 24 h postoperatively (T5).

The VAS and total postoperative morphine consumption were recorded at the end of surgery (M0) and thereafter every 6 h until 24 h postoperatively (M1, M2, M3, and M4, respectively). The number of patients who required intravenous morphine at the end of surgery was recorded.

Visual analogue scale

It has the advantages of easy scoring, multiple response options and no difficulties related to age. The words 'o pain' and 'worst possible pain' represent the 0 and 10 ends of the scale, respectively [8].

Plasma levels of interleukin-6, cortisol, and blood glucose were measured before induction of anesthesia (F0) and after complete recovery (F1).

Serum cortisol was measured, by electrochemiluminescent technique on automated chemical cobas 6000, using the kit supplied by Ro Diagnostic, Roche Molecular Systems, Inc, USA (DSNOV20-Cortisol_Saliva-18042013-ab_lot_3141). Interleukin-6 was measured by enzyme-linked immunosorbent assay, using the kit supplied by Biosience (Interleukin-6 ELISA kit product ABIN365163).

The following complications were recorded: nausea and vomiting (treated with ondanosetron 0.1 mg/kg), pruritis (treated with intravenous naloxone 0.4 mg), urinary retention (requiring bladder catheterization), severe hypotension (treated by ephedrine titration), and shoulder tip pain.

Statistical analysis

Data were expressed as mean±SD, number or percentage and compared using statistical package for the social sciences, IBM SPSS Statistics for Windows, Version 24.0. Armonk, NY: IBM Corp., version V17. The *t* test was utilized for parametric data. χ^2 test was used for the percentages and incidence. *P* value less than 0.05 was considered statistically significant.

Aim

The aim of this work was to study the effect of intravenous versus intrathecal dexmedetomidine and fentanyl on stress response during laparoscopic cholecystectomy.

Results

There were no statistically significant differences between the two groups as regards the patients' demographic data (Table 1).

There was no statistical difference between the two groups as regards heart rate, except at T2 and T3, wherein it was statistically lower in group II than in group I.

With respect to mean arterial pressure, there were no statistical differences between the two groups, except at T2 and T3, wherein it was statistically lower in group II than in group I.

As regards the number of patients requiring intraoperative intravenous fentanyl and total intraoperative fentanyl consumption, they were statistically lower in group II than in group I (Table 2).

As regards the number of patients requiring initial titration of intravenous morphine at the end of surgery, it was statistically lower in group II than in group I. There were no statistical differences with respect to postoperative morphine consumption (mg), except at M0 and M1, wherein they were statistically lower in group II than in group I (Table 3).

Table 1 Demographic data of the patients

	Group I (mean±SD)	Group II (mean±SD)	
Age (years)	37.3±7.7	35.2±8.2	0.314
Sex [*n* (%)]			0.748
Male	7 (23.3)	5 (16.7)	
Female	23 (76.7)	25 (83.3)	
Weight (kg)	78.37±8.08	75.27±10.65	0.209
Physical status [*n* (%)]			1.00
ASA I	30 (100)	29 (96.7)	
ASA II	0 (0)	1 (3.3)	
Duration of surgery (min)	50.13±8.14	52.2±7.3.	0.304
Duration of anesthesia (min)	62.57 ±10.09	63.5±12.15	0.748

ASA, American Society of Anesthesiologist.

Table 2 Number of patients requiring intraoperative Intravenous fentanyl and total intraoperative fentanyl consumption (μg)

	Group I	Group II	*P* value
Number of patients requiring intraoperative intravenous fentanyl [*n* (%)]	13 (43.3)	4 (13.3)	0.022*
Total intraoperative fentanyl consumption (mean±SD) (μg).	23.1±19.5	7.7±12.7	<0.001*

P, χ^2 test values for comparison between the two groups. *Significant at *P* value less than or equal to 0.05, moderately significant at *P* value less than or equal to 0.01, highly significant at *P* value less than or equal to 0.001.

Table 3 The number of patients who required Intravenous morphine at the end of surgery and total postoperative morphine consumption were recorded

	Group I [*n* (%)]/ (mean±SD)	Group II [*n* (%)]/ (mean±SD)	*P* value
Number of patients who required Intravenous morphine at the end of surgery	12 (33.3)	4 (10)	0.041*
Total postoperative morphine consumption (mg)			
Morphine consumption at the end of surgery (M0)	0.78±1.4	0.2±0.55	0.039*
Morphine consumption 6 h postoperatively (M1)	1.2±1.5	0.08±0.33	0.001*
Morphine consumption 12 h postoperatively (M2)	0.7±1.1	0.7±0.9	1.00
Morphine consumption 18 h postoperatively (M3)	0.4±0.7	0.35±0.8	0.798
Morphine consumption 24 h postoperatively (M4)	0.5±1.3	0.4±0.97	0.737

P, Student's independent sample *t* test values for comparison between the two groups. *Significant at *P* value less than or equal to 0.05, moderately significant at *P* value less than or equal to 0.01, highly significant at *P* value less than or equal to 0.001.

There were no statistical differences regarding VAS except at M0 and M1, where they were statistically lower in group II than in group I (Table 4).

As regards blood interleukin-6 levels (ng/ml) at F0 and F1, there were no statistical differences between the two groups, and it was statistically higher at F1 than at F0 in the same group. With respect to blood cortisol (μg/dl) and blood glucose levels, there were no statistical differences between the two groups at F0, but they were statistically higher in group I than in group II at F1, and they were statistically higher at F1 than at F0 in the same group (Table 5).

As regards complications, there were no statistical differences between the two groups (Table 6).

Discussion

There were no statistical differences between the two groups as regards heart rate and mean arterial pressure, except at 5 min after intubation and 30 min after start of surgery, wherein they were statistically lower in the intrathecal group than in the intravenous group.

Unfortunately, there was no comparative study between the hemodynamic effects of intrathecal and intravenous dexmedetomidine during laparoscopic cholecystectomy under general anesthesia; but Sharma and Shankaranarayana [9] observed that intrathecal fentanyl (25 μg) showed significant reduction in heart rate and mean arterial pressure at pneumoperitoneum until extubation than intravenous fentanyl (2 μg/kg) in laparoscopic hysterectomies under general anesthesia.

El Kalla *et al.* [10] examined the effect of preanesthetic fentanyl and dexmedetomidine on minimizing stress response in pre-eclamptic patients during cesarean delivery and found that mean arterial blood pressure was statistically lower ($P<0.05$) in the dexmedetomidine group throughout the study, except at baseline, and two patients showed bradycardia in the dexmedetomidine group, and were treated with intravenous atropine 0.5 mg, and one patient in each group showed hypotension and were treated by increasing intravenous infusion of crystalloid without the need for ephedrine.

Contrary to these results, Hamed and Talaat [11] noticed that intravenous dexmedetomidine (0.5 μg/kg) produced significant heart rate reduction than intrathecal dexmedetomidine (3 μg) in lower limb orthopedic surgery under spinal anesthesia. This may be due to different types of operations, different doses of intrathecal dexmedetomidine, or the hemodynamic differences between general and spinal anesthesia.

Dexmedetomidine causes stimulation of postsynaptic α2 receptors in the central nervous system, which causes sympathetic inhibition, and so can decrease heart rate and blood pressure [5].

As regards the number of patients requiring intraoperative intravenous fentanyl, they were statistically lower in the intrathecal group (six patients) than in the intravenous group (16 patients).Moreover, in this study, intraoperative fentanyl consumption was statistically lower in the intrathecal group (7.7±12.7) than in the intravenous group (23.1±19.5).

In the present study, there were no statistical differences with regard to the numeric rating scale and total postoperative morphine consumption (mg), except at the end of surgery and at 6 h postoperatively, wherein they were statistically lower in the intrathecal group than in the intravenous group. As regards the number of patients requiring initial titration of intravenous morphine at the end of surgery, it was statistically lower in the intrathecal group than in the intravenous group.

This is concomitant with Hamed and Talaat [11], who compared spinal block with bupivacaine in combination with intravenous dexmedetomidine (0.5 μg/kg) or intrathecal dexmedetomidine (3 μg), and observed that intrathecal dexmedetomidine produced significant analgesia prolongation with decreased tramadol requirement in the first postoperative 24 h, compared with intravenous dexmedetomidine.

Our results matched with those of Park *et al.* [12], who noted that intravenous dexmedetomidine administration (1 μg/kg 10 min before induction and then 0.5 μg/kg/h by intravenous infusion until the gall bladder removal), in laparoscopic cholecystectomy, caused postoperative pain score reduction only during the first hour postoperatively, with significant analgesia reduction in the first postoperative 24 h.

Furthermore, Bhatia *et al.* [13] observed that intrathecal dexmedetomidine (5 μg) caused significant prolongation of spinal anesthesia, thereby extending analgesia, as indicated by delayed analgesic requirement postoperatively.

Pain arises from the incision and trocar sites (50–70%), and from the rapid distension of peritoneum (20–30%), with traction on vessels and nerves, irritation of the phrenic nerve, and intra-abdominal trauma (10–20%), with release of inflammatory mediators. Shoulder pain is usually mild and persists for 24 h [14].

In the current study, interleukin-6 showed no significant difference between two groups before and after surgery; this was in agreement with that stated by Kang *et al.* [15], who examined the effects of intravenous dexmedetomidine on inflammatory responses during laparoscopic cholecystectomy, and demonstrated that it resulted in intraoperative and postoperative reduction of secretion of cytokines including interleukin-6, but the reduction was not significant in comparison with the saline group.

In the present study, blood cortisol and blood glucose levels (mg/dl) showed no significant difference between two groups at baseline, but, after complete recovery, it was increased in both groups, and it was statistically lower in the intrathecal group than in the intravenous group. These results were in concordance with that of Yacout *et al.* [16], who examined the effect of

Table 4 Visual analogue scale

	Group I (mean±SD)	Group II (mean±SD)	*P* value
VAS at the end of surgery (M0)	3.1±1.3	0.9±1.2	<0.001*
VAS 6 h postoperatively (M1)	3.2±1.8	1.5±1.4	<0.001*
VAS 12 h postoperatively (M2)	2.9±1.7	2.6±1.5	0.472
VAS 18 h postoperatively (M3)	1.8±1.3	1.7±1.1	0.749
VAS 24 h postoperatively (M4)	2.3±1.2	2.2±1.3	0.758

VAS, visual analogue scale. *P*, Student's independent sample *t* test values for comparison between the two groups. *Significant at *P* value less than or equal to 0.05, moderately significant at *P* value less than or equal to 0.01, highly significant at *P* value less than or equal to 0.001.

Table 5 Laboratory investigations

	Group I (mean±SD)	Group II (mean±SD)	*P* value
Blood IL-6			
IL-6 at baseline (F0)	0.042±0.039	0.045±0.041	0.773
IL-6 after complete recovery (F1)	0.065±0.043	0.069±0.051	0.774
P_1	0.034*	0.049*	
Blood cortisol level (μg/dl)			
Cortisol at baseline (F0)	14.55±2.9	14.49±3.2	0.940
Cortisol after complete recovery (F1)	26.4±7.8	20.5±7.2	0.004*
P_1	<0.001*	<0.001*	
Blood glucose level (mg/dl)			
Blood glucose level at baseline (F0)	85.6±14.82	87.2±11.5	0.642
Blood glucose level after complete recovery (F1)	139.8±25.1	122.1±17.4	0.002*
P_1	<0.001*	<0.001*	

IL-6, interleukin-6. *P*, Student's independent sample *t* test values for comparison between the two groups. P_1, paired- sample *t* test values for comparison between T0 with T1. *Significant at *P* value less than or equal to 0.05, moderately significant at *P* value less than or equal to 0.01, highly significant at *P* value less than or equal to 0.001.

Table 6 Complications

	Group I [*n* (%)]	Group II [*n* (%)]	*P* value
Nausea and vomiting	2 (6.7)	0 (0)	0.0492
Urinary retention	2 (6.7)	3 (10)	1.000
Shoulder tip pain	3 (10)	1 (3.3)	0.612
Hypotension	3 (10%)	3 (10)	1.00
Pruritis	0 (0)	1 (3.3)	1.00

P, χ^2 test values for comparison between the two groups.
*Significant at *P* value less than or equal to 0.05, moderately significant at *P* value less than or equal to 0.01, highly significant at *P* value less than or equal to 0.001.

intravenous dexmedetomidine infusion on stress hormones in major abdominal surgery, and found that it increased the concentration of blood interleukin-6, cortisol, and glucose, after complete recovery, in both the dexmedetomidine and saline groups, but with significantly lower value in the dexmedetomidine group compared with the saline group.

These results were quite similar to that of Gupta *et al.* [17] who examined the effect of intravenous dexmedetomidine (1 μg/kg) versus intravenous fentanyl (2 μg/kg) on blood glucose during laparoscopic cholecystectomy, and found that it increased blood glucose concentration during surgery, which remained increased postoperatively in both groups, but was significantly more pronounced in the fentanyl group.

As regards stress hormones and cytokines, the endocrine response was stimulated by afferent impulses from the site of injury. After major surgery, the main cytokines released are interleukin-1, tumor necrosis factor-α, and interleukin-6, which stimulate ACTH, which increases cortisol secretion, which in turn inhibits cytokine production by negative feedback effect [18].In the present study, there were no statistical differences in the incidence of complications (nausea, vomiting, shoulder tip pain, hypotension, and pruritis) between the two groups.

Mohamed *et al.* [19], who evaluated the effect of intrathecal dexmedetomidine and fentanyl combination in major abdominal surgery, found that they caused a decrease in the incidence of nausea and vomiting, but increased the incidence of pruritis.

Contrary to these results, Magdy *et al.* [20], who compared the effect of intrathecal (5 μg) versus intravenous (0.5 μg/kg/h) dexmedetomidine, as an adjuvant to spinal bupivacaine anesthesia for cesarean section, found that the incidence of nausea and vomiting was lower in the intravenous group than in the intrathecal group (may be due to different types of operations and anesthesia or the use of intravenous infusion of dexmedetomidine).

Bhatia *et al.* [13] showed that the intrathecal bupivacaine–dexmedetomidine combination (three patients of 30) caused significant reduction of the incidence of shoulder tip pain compared with those who received intrathecal bupivacaine (27 patients of 30) alone for laparoscopy.

Niu *et al.* [21] examined the effect of intravenous and intrathecal dexmedetomidine in spinal anesthesia and noticed that dexmedetomidine did not increase the incidence of hypotension.

Unfortunately, there was no comparative study between intravenous and intrathecal dexmedetomidine and their effects on hemodynamics and stress hormones during laparoscopic cholecystectomy under general anesthesia.

Conclusion

Apart from lowering heart rate and blood pressure, intrathecal dexmedetomidine and fentanyl combination was superior, to intravenous dexmedetomidine and fentanyl, wherein it lowered pain score and analgesic consumption with decreasing stress response.

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Conflicts of interest

There are no conflicts of interest.

References

1 Al-Ghanem SM, Massad IM, Al-Mustafa MM, Al-Zaben KR, Qudaisat IY, Qatawneh AM, Abu-Ali HM. Effect of adding dexmedetomidine versus fentanyl to intrathecal bupivacaine on spinal block characteristics in gynecological procedures: a double blind controlled study. *Am J Appl Sci* 2009; **6**:288.

2 Marana E, Scambia G, Maussier ML, Parpaglioni R, Ferrandina G, Meo F, *et al.* Neuroendocrine stress response in patients undergoing benign ovarian cyst surgery by laparoscopy, minilaparotomy, and laparotomy. *J Am Assoc Gynecol Laparosc* 2003; **10**:159–165.

3 Joris JL. Anesthesia for laparoscopic surgery. In: Miller RD, Eriksson LI, Fleisher LA, Wiener-Kronish JP, Young WL (eds.). *Miller's anesthesia*. 7th ed. Philadelphia: Churchill Livingstone; 2010. 2185–2202

4 Bansal S, Bansal S, Saini S, Kaur D, Kaul A, Jaggy XX. To evaluate the efficacy and safety of dexmedetomidine on hemodynamic stability in patients undergoing laproscopic cholecystectomy. *Indian J Clin Anaesth* 2015; **2**:146–150.

5 Fahmy AA, Aboulghate MK, Amin SM, Abd elhakim AR. A randomized control study to compare intrathecal dexmedetomidine used as adjuvant to intrathecal bupivacaine with intrathecal bupivacaine alone in orthopedic surgeries. *Med J Cairo Uni* 2015; **83**:85–89.

6 Kim JE, Kim NY, Lee HS, Ki HK. Effects of intrathecal dexmedetomidine on low-dose bupivacaine spinal anesthesia in elderly patients undergoing transurethral prostatectomy. *Biol Pharm Bull* 2013; **36**:959–965.

7 Nagelhout JJ. Opioid agonists and antagonists. In: Nagelhout JJ, Plaus K, (eds.). *Nurse anesthesia*. 5th ed. St Louis, MO: Elsevier Saunders 2013; 145–157.

8 Kendrick DB, Strout TD. The minimum clinically significant difference in patient-assigned numeric scores for pain. *Am J Emerg Med* 2005; **23**:828–832.

9 Sharma AN, Shankaranarayana P. Hemodynamic stability with intrathecal fentanyl alone in laparoscopic hysterectomies under general anesthesia – a pilot study. *Karnataka Anaesth* 2015; **1**:46–49.

10 El Kalla RS, Abdullah MA, Abu Elyazed MM. Intubation stress responses: pre-anesthetic dexmedetomidine versus fentanyl in pre-eclamptic patients undergoing caesarean delivery: a prospective double blind randomized study. *Egypt J Anesth* 2017; **33**:175–181.

11 Hamed A, Talaat S. Effect of intravenous versus intrathecal low-dose dexmedetomidine on spinal block in lower limb orthopedic surgery. *Ain-Shams J Anesthesiol* 2014; **7**:205–210.

12 Park JK, Cheong SH, Lee KM, Lim SH, Lee JH, Cho K, *et al.* Does dexmedetomidine reduce postoperative pain after laparoscopic cholecystectomy with multimodal analgesia?. *Korean J Anesthesiol* 2012; **63**:436–440.

13 Bhatia T, Bhatia J, Attri JP, Singh S, Khetarpal R. Intrathecal dextmedetomidine to reduce shoulder tip pain in laparoscopic cholecystectomies under spinal anesthesia. *Anesth Essays Res* 2015; **9**:320–325.

14 Sarakatsianou C, Georgopoulou S, Tzovaras G. Acute pain management in laparoscopic cholecystectomy: is there a role for pregabalin? A review. *Greek E J Perioper Med* 2016; **14**(a):15–24.

15 Kang SH, Kim YS, Hong TH, Chae MS, Cho ML, Her YM, Lee J. Effects of dexmedetomidine on inflammatory responses in patients undergoing laparoscopic cholecystectomy. *Acta Anaesthesiol Scand* 2013; **57**:480–487.

16 Yacout AG, Osman HA, Abdel-Daem MH, Hammouda SA, Elsawy MM. Effect of intravenous dexmedetomidine infusion on some proinflammatory cytokines, stress hormones and recovery profile in major abdominal surgery. *Alex J Med* 2012; **48**:3–8.

17 Gupta K, Maggo A, Jain M, Gupta PK, Rastogi B, Singhal AB. Blood glucose estimation as an indirect assessment of modulation of neuroendocrine stress response by dexmedetomidine versus fentanyl premedication during laparoscopic cholecystectomy: a clinical study. *Anesth Essays Res* 2013; **7**:34–38.

18 Paola A, Carlo L, Cinzia DR, Valter P, Pieruigi N, Liliana S. Stress response to surgery, anesthetics role and impact on cognition. *J Anesth Clin Res* 2015; **6**:539.

19 Mohamed A, Fares K, Mohamed S. Efficacy of intrathecally administered dexmedetomidine versus dexmedetomidine with fentanyl in patients undergoing major abdominal cancer surgery. *Pain Physician* 2012; **15**:339–348.

20 Magdy H, Mohsen M, Saleh M. The effect of intrathecal compared with intravenous dexmedetomidine as an adjuvant to spinal bupivacaine anesthesia for cesarean section. *Ain-Shams J Anesthesiol* 2015; **8**:93–99.

21 Niu XY, Ding XB, Guo T, Chen MH, Fu SK, Li Q. Effects of intravenous and intrathecal dexmedetomidine in spinal anesthesia: a meta-analysis. *CNS Neurosci and Ther* 2013; **19**:897–904.