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ORIGINAL RESEARCH

Dexmedetomidine versus fentanyl on stress response and pain control in adult patients undergoing laparoscopic surgery

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Abstract

Laparoscopic procedures are widely indicated; however, the ideal approach for pain control remains debatable. This trial compared between the effects of dexmedetomidine and fentanyl infusion on stress response and pain control in patients undergoing elective laparoscopic surgeries. A prospective randomized double-blinded comparative study included 82 adult participants randomly allocated into two equal-sized groups. Group D received 1 μg/kg of intravenous (IV) dexmedetomidine over 10 min as a loading dose just before induction of anesthesia, then 0.2–0.7 μg/kg/h till 10 min before the surgery ends. Group F received 1 μg/kg of IV fentanyl as a loading dose, then 0.2–0.7 μg/kg/h. Primary objective was postoperative analgesic consumption in 24 h. Collected data were heart rate (HR), mean arterial blood pressure (MAP), blood glucose and serum cortisol levels, visual analogue score (VAS), and the perioperative analgesic consumption. Group D consumed significantly less postoperative morphine doses in 24 h (p = 0.003), and 41.5% of Group D patients did not need any postoperative morphine. Group D had better-controlled hemodynamic changes 5 min post-extubation (HR and MAP p = 0.021 and p = 0.022 respectively), showed significantly less postoperative stress response as manifested in the blood glucose and serum cortisol levels 4 h postoperatively (p = 0.006 and p = 0.001 respectively), and less VAS pain scores at early and late postoperative periods. Intraoperative IV dexmedetomidine administration as a sole analgesic agent for patients undergoing elective laparoscopic surgeries serves as a convenient anesthetic approach, since it provided a good postoperative pain control, and reduced the surgical stress response and the perioperative analgesic consumption.

Keywords

Dexmedetomidine; Laparoscopic surgery; Postoperative pain; Stress response; VAS score; Opioid-free anesthesia

1. Introduction

Laparoscopic surgery has substituted various conventional open surgeries due to many advantages, such as minimal invasiveness, less postoperative pain, and an earlier discharge [1]. It has plenty of indications such as cholecystectomy, appendectomy, hernia repair, splenectomy, colorectal surgeries, gastroesophageal reflux repair, bariatric, gynecologic, and urologic procedures [2–4]. Surgical stress response is a cascade of events that starts with laryngoscopy and endotracheal intubation stimulating a marked sympathetic response [5]. Laparoscopy involves abdominal cavity insufflation with carbon dioxide (CO_2) to an intraabdominal pressure (IAP) of 12–15 mmHg [6]. Pneumoperitoneum and CO_2 absorption have different systemic physiological effects and stimulate sympathetic response [1]. Various factors determine the extent of this response such as surgical trauma severity and duration, anesthetic method, and postoperative pain [7]. Hypothalamic stimulation during stress initiates a sudden increase in cortisol level [8]. The perioperative period also witnesses a decrease in insulin concentration and a significant increase in insulin resistance leading to increased glucose levels [9]. Current anesthetic research aims to find a "stress-free anesthetic method" to attenuate the neuroendocrine, inflammatory, and humoral responses [7].

Pain has been regarded as the fifth vital sign. Inadequately managed acute pain may have a deleterious effect on the recovery process [10]. Opioid-based anesthesia offers hemodynamic stability and decreases intraoperative stress episodes. However, opioids like fentanyl cause adverse reactions such as nausea, vomiting, drowsiness, and respiratory depression [11]. Dexmedetomidine is an α_2-agonist with α_2:α_1 specificity of 1620:1. Activation of adrenoceptors in the locus coeruleus induces sedation, which mimics the natural stage 2 nonrapid eye movement sleep [12]. Evidence has demonstrated an analgesic impact of dexmedetomidine on postoperative pain, ischemic pain, and cancer pain; however, its mechanism of analgesia is still unclear [13]. Dexmedetomidine reduces catecholamines release in nerve endings and causes a biphasic response after IV administration; an initial vasoconstriction, followed by a delayed vasodilation [14]. The overall effects on the respiratory system when combined with other anesthetic drugs are minimal [12]. Moreover, it has been increasingly used as an adjuvant during anesthesia because of its anesthetic and opioid sparing benefits improving quality of recovery [15].

This study aims to compare between the effects of dexmedetomidine and fentanyl infusion on stress response and on perioperative pain control in patients undergoing elective laparoscopic surgeries under general anesthesia.

2. Methods

This prospective randomized double-blinded comparative clinical trial was conducted at the Department of Anesthesia, Faculty of Medicine, Ain Shams University Hospitals. The study population included 82 adult patients (Fig. 1) of both genders undergoing elective laparoscopic surgery under general anesthesia lasting for no more than 2 h, aged between 18–65 years, with American Society of Anesthesiologists (ASA) physical status grade I and II, and body mass index (BMI) 18.5–29.9 kg/m^2. Exclusion criteria were anticipated difficult intubation, history of myocardial, pulmonary, or endocrine diseases, diabetes mellitus, hepatic or renal impairment, and drug abuse or opioid addiction, surgical complication, and failure of laparoscopy. Participants were randomly allocated to two equal-sized groups by simple randomization using 82 opaque sealed envelopes, 41 for each group indicating group assignment to either dexmedetomidine (Group D) or fentanyl (Group F). The study drug syringes were prepared by an independent anesthesiologist, covered, and labeled by a randomization number. This anesthesiologist was not involved in the anesthetic management or the perioperative data collection. Drug administration and intraoperative data recording were performed by another independent anesthesiologist who was blinded to the syringe content, and postoperative data were recorded by a trained nurse who was blinded to the patients grouping.

All patients were subjected to the routine pre-anesthesia assessment and instructed on how to rate their postoperative pain intensity from 0 to 10 on a horizontal line which read “no pain” at the 0 end, and “worst imaginable pain” at the other end at 10.

The study drugs were diluted to a concentration of 4 μg/mL; 200 μg of dexmedetomidine or 200 μg of fentanyl were diluted to 50 mL with normal saline. In the pre-anesthesia room, all patients were monitored for baseline HR, MAP, and arterial oxygen saturation (SpO_2) readings. IV access was secured with a 20 G cannula, and a blood sample for fasting blood glucose and serum cortisol level was collected (T0). The prepared drug was administered IV over 10 min prior to anesthesia induction. Group D (n = 41) received IV dexmedetomidine 1 μg/kg (precedex, Hospira Inc, Rocky Mount, NC, USA) as a loading dose over 10 min prior to induction, followed by 0.2–0.7 μg/kg/h till 10 min before the end of surgery. Group F (n = 41) received IV fentanyl 1 μg/kg (fentanyl hameln, manufactured by Sunny Pharmaceuticals under license of hameln Pharmaceuticals, Germany) as a loading dose over 10 min prior to induction, followed by 0.2–0.7 μg/kg/h till 10 min before the end of surgery.

In the operating room, all participants were monitored by electrocardiography, non-invasive blood pressure, pulse oximetry, and capnography. They were all given IV ringer solution according to the standard fluid replacement regimen, IV granisetron 1 mg (Em-Ex, Amoun Pharmaceuticals, Cairo, Egypt), and famotidine 20 mg (antodine, Amoun Pharmaceuticals, Cairo, Egypt). After 3 min of preoxygenation, anesthesia was induced with IV lidocaine 1 mg/kg (debocaine 2%, Sigma-Tec Pharmaceuticals, Cairo, Egypt), propofol 2 mg/kg (propofol 1%, Fresenius Kabi, Germany), and atracurium 0.5 mg/kg (atracurium hameln, manufactured by Sunny Pharmaceuticals under license of hameln Pharmaceuticals, Germany) to facilitate endotracheal intubation. Laryngoscopy was performed using a Macintosh laryngoscope blade, and intubation was done with a cuffed endotracheal tube of appropriate size after 3 min of bag mask ventilation with 100% oxygen. Laryngoscopy duration and number of attempts were recorded.

Anesthesia was maintained on closed circuit ventilator (GE carestation 620, Anesthesia machine, General Electric Healthcare, Madison, Wi, USA) with fresh gas flow 2 L/min, 50% of oxygen in air, isoflurane (isoflurane AIT, batch number, Arab Company, Cairo, Egypt) maintaining a minimum alveolar concentration of 1.0 using gas analyzer adjusted to age, and 0.1 mg/kg atracurium every 20 min. Volume-controlled mechanical ventilation parameters were set to maintain end tidal CO_2 between 35–40 mmHg. IAP was maintained at 12–15 mmHg. IV infusion of the study drugs was continued at 0.2–0.7 μg/kg/h during the operation till 10 min before the end of surgery. No local anesthetic was infiltrated at surgery port sites. HR and MAP were recorded every 15 min, and 5 min post-extubation. After establishment of spontaneous respiration, residual effect of muscle relaxant was reversed by 0.05 mg/kg neostigmine and 0.02 mg/kg atropine. Once extubated, another blood sample was drawn from all participants for blood glucose and serum cortisol levels (T1). The normal reference range for cortisol was 4.3–22.4 μg/dL for 6–12 AM.

Tachycardia and hypertension were described as 20% increase in HR and MAP respectively from their baseline values, and the highest dose of infusion drugs failed to correct this hemodynamic response. A rescue dose of IV fentanyl 0.5 μg/kg was given to correct these changes with a maximum dose of 1 μg/kg given throughout the surgery duration. If tachycardia or hypertension were resistant to correction despite this regimen, end of study decision was made for this subject. Bradycardia was described as HR $<$55 beats/min and was managed with IV atropine 0.4 mg and repeated if needed. Hypotension was described when MAP dropped to more than 20% of its baseline value and was treated with IV ephedrine 5 mg and repeated if needed.

All patients were given IV paracetamol 1 g (perfalgan, Bristol-Myers Squibb Pharmaceuticals, Middlesex, United Kingdom) every 8 h postoperatively for the first 24 h and

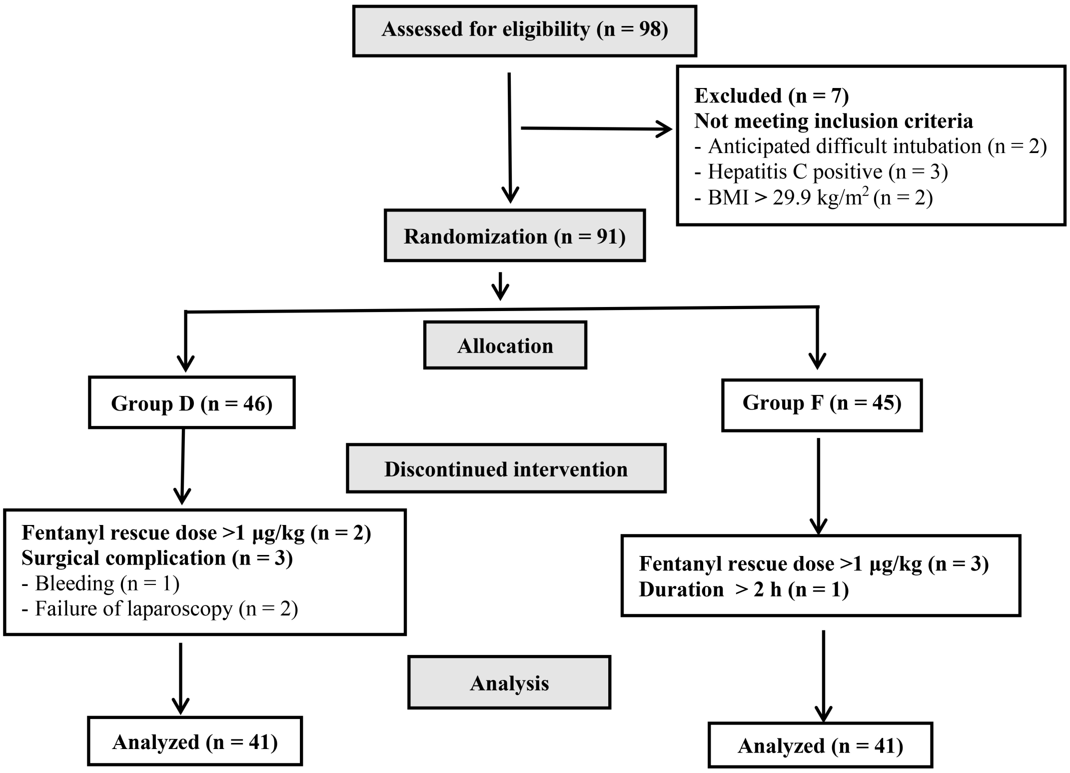

FIGURE 1. Consort flow chart of the study.

continued to be monitored by a qualified nurse for their HR, MAP, and SpO_2 at the post-anesthesia care unit (PACU). Pain was assessed by the VAS pain score upon arrival at the PACU, at 5 and 15 min, every 30 min for 2 h, then every 2 h for 4 h. Patients with a VAS score >4 were given IV morphine 0.05 mg/kg, and the time of the first dose needed was recorded (estimated as the time from the end of anesthesia to the time of the first requested postoperative analgesia or a VAS score of >4). The total dose of morphine consumed in 24 h was recorded as well. A third blood sample was collected 4 h after extubation from all patients for blood glucose and serum cortisol levels measurement (T2).

2.1 Data collection

Age, gender, BMI, type and duration of surgery, and duration and number of laryngoscopy attempts were recorded. Primary outcome was postoperative morphine consumption in 24 h. Secondary outcomes were HR and MAP (baseline, at 1 and 5 min post-intubation, every 15 min till the end of surgery, and 5 min post-extubation), blood glucose and serum cortisol levels pre-anesthesia (T0), immediately after extubation (T1), and 4 h after extubation (T2), postoperative VAS pain score (arrival at the PACU, at 5 and 15 min, every 30 min for 2 h, and then every 2 h for 4 h), total intraoperative rescue dose of fentanyl, time to the first analgesic request postoperatively, as well as number and percentage of patients who did not need any postoperative morphine in 24 h.

2.2 Sample size and statistical analysis

Sample size calculation was based on an expected 20% difference in postoperative morphine consumption between the two groups. Using G power software for sample size calculation, we assumed a large effect size difference (Cohen's d coefficient = 0.8), setting power at 90% and α-error at 0.05, the calculated sample size needed to detect a statistically significant difference between the two groups regarding postoperative morphine consumption was found to be at least 35 patients per group. Collected data were fed to the computer and analyzed using IBM SPSS software package version 20.0 (IBM Corp, Armonk, NY, USA). Qualitative data were described using number and percent. The Kolmogorov-Smirnov test was used to verify the normality of distribution. Quantitative data were described using range (minimum and maximum), mean, standard deviation (SD), and median. Significance of the obtained results was judged at the 5% level. The used tests were Chi-square test for categorical variables, to compare between different groups; Fisher's Exact or Monte Carlo correction for chi-square, when more than 20% of the cells have expected count less than 5; Student *t*-test for normally distributed quantitative variables, to compare between two studied groups; analysis of variance (ANOVA) with repeated measures for normally distributed quantitative variables, to compare between more than two periods or stages; Post Hoc test (Bonferroni adjusted) for pairwise comparisons; and Mann Whitney test for abnormally distributed quantitative variables, to compare between two studied groups.

TABLE 1. Comparison between the two studied groups according to demographic data.

	Group D (n = 41)		Group F (n = 41)		Test of Sig.	p
	No.	%	No.	%		
Gender						
Male	11	26.8	11	26.8	$\chi^2 = 0.000$	1.000
Female	30	73.2	30	73.2		
Age (years)						
Mean ± SD	40.27 ± 9.40		37.76 ± 13.18		t = 0.994	0.324
BMI (kg/m^2)						
Mean ± SD	26.10 ± 3.25		27.44 ± 2.95		t = 1.968	0.053
Surgery Type						
DL	6	14.6	4	9.8	$\chi^2 = 1.166$	$^{MC}p = 0.924$
LC	20	48.8	23	56.1		
LFP	3	7.3	3	7.3		
LHP	4	9.8	5	12.2		
LOC	8	19.5	6	14.6		
Surgery Duration (min)	65.49 ± 23.58		70.24 ± 23.82		U = 741.0	0.354
Laryngoscopy						
Attempts	1.02 ± 0.16		1.05 ± 0.22		U = 820.0	0.559
Duration (s)	10.80 ± 3.77		10.44 ± 4.04		U = 741.5	0.349
Total dose of the study drug (µg)						
Mean ± SD	96.85 ± 19.04		103.96 ± 18.54		t = 1.713	0.091

Quantitative data was expressed using Mean ± SD.
t: Student t-test; U: Mann Whitney test; χ^2: Chi square test; MC: Monte Carlo; p: p value for comparing between the two studied groups. BMI, body mass index; DL, diagnostic laparoscopy; LC, laparoscopic cholecystectomy; LFP, laparoscopic fundoplication; LHP, laparoscopic hernioplasty; LOC, laparoscopic ovarian cystectomy.

3. Results

This prospective randomized double-blinded comparative clinical trial included a total of 82 patients, who were randomized into either the dexmedetomidine group (D) or the fentanyl group (F), with 41 participants in each group.

3.1 Demographic data

Demographic data (Table 1) showed no significant difference between the two groups.

3.2 Hemodynamic changes

Both HR and MAP decreased significantly in Group D (Figs. 2, 3) at 5 min post-extubation (77.07 *vs.* 86.05 beats/min; p = 0.021 and 90.63 *vs.* 98.1 mmHg; p = 0.022).

3.3 Blood glucose and serum cortisol levels

Blood glucose levels were comparable in both groups at baseline and immediately after extubation, but they showed a decrease in Group D with 0.006 p value at 4 h post-extubation. As for the serum cortisol level, it was significantly less in Group D immediately after extubation (24.42 *vs.* 32.7 μg/dL; $p < 0.001$), and at T2 (21.05 *vs.* 28.42 μg/dL; p = 0.001) (Table 2).

3.4 Perioperative analgesic consumption

As shown (Table 3), the percentage of patients who needed fentanyl rescue doses was 14.7% and 26.9% in Group D and F respectively. The time to the first analgesic request was longer in Group F (39.85 min) than in Group D (29.63 min). Both findings were statistically insignificant. The total dose of postoperative morphine consumption in 24 h was significantly less in Group D (2.49 *vs.* 3.98 mg; p = 0.003), yet not clinically significant. However, the percentage of patients who did not need any postoperative morphine was significantly higher in Group D than in Group F (41.5% *vs.* 19.5%; p = 0.031).

3.5 Visual analogue scale

The VAS pain score recordings showed persistent lower values in Group D than in Group F at all time intervals, with a significant decrease upon arrival into the PACU (p = 0.002), at 60 min, and until 4 h postoperatively with a p value < 0.001 at 120 min postoperatively (Fig. 4).

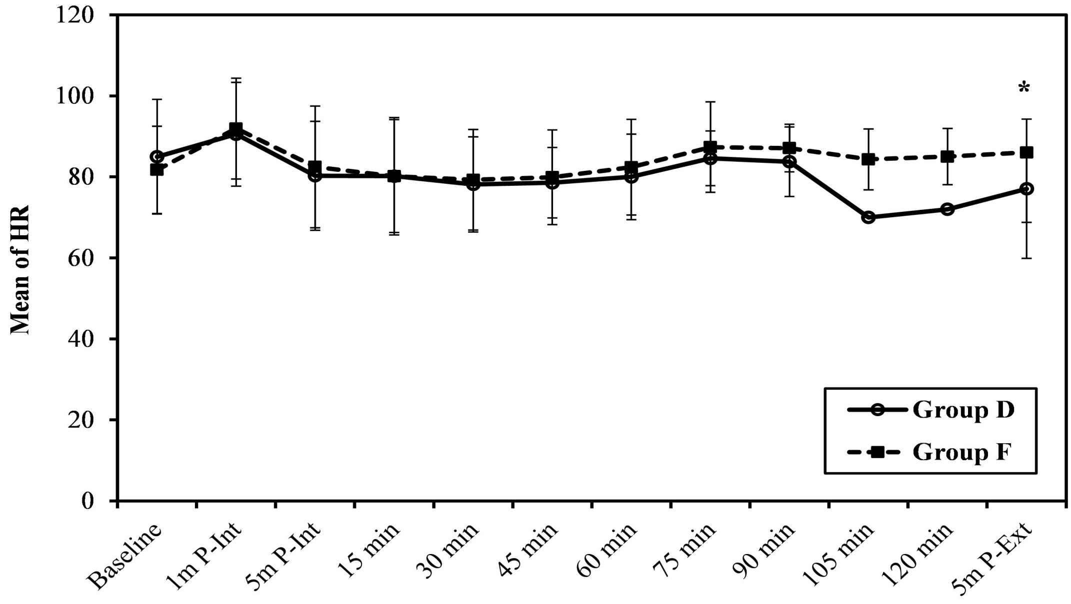

FIGURE 2. Comparison between the two studied groups according to HR (beats/min). *: Statistically significant at $p \leq 0.05$; HR, heart rate; P-Int, post-intubation; P-Ext, post-extubation.

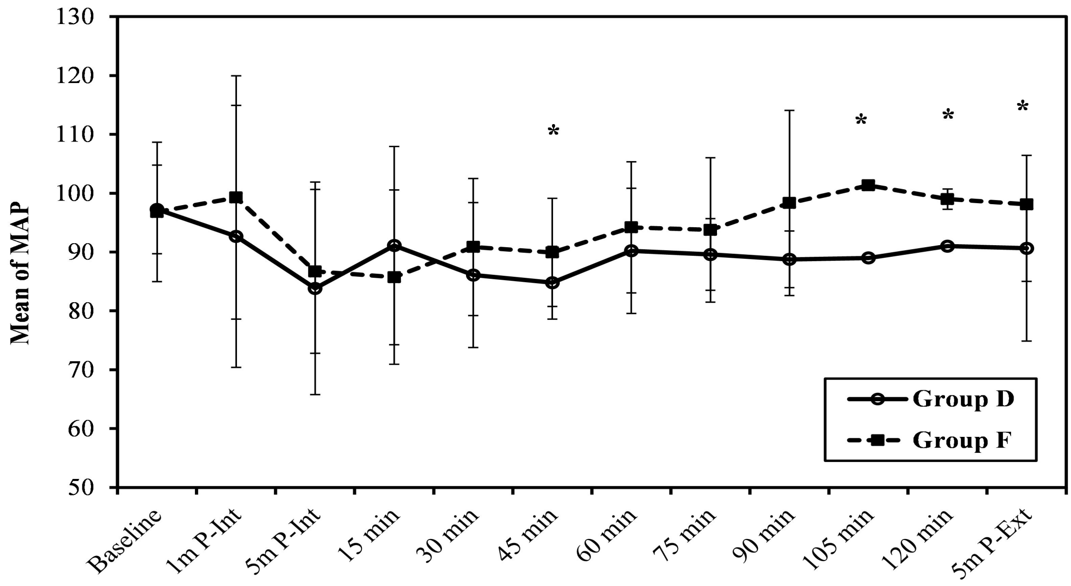

FIGURE 3. Comparison between the two studied groups according to MAP (mmHg).*: Statistically significant at $p \leq 0.05$; MAP, mean arterial pressure; P-Int, post-intubation; P-Ext, post-extubation.

4. Discussion

In this study, the perioperative pain was better controlled with dexmedetomidine. Group D had a lesser percentage of patients who needed intraoperative fentanyl rescue doses (14.7% *vs.* 26.9%), less postoperative morphine consumption in 24 h (mean of 2.49 ± 2.27 mg *vs.* 3.98 ± 2.35 mg in Group F), higher percentage of patients who did not need any postoperative morphine (41.5% *vs.* 19.5% in Group F), and finally less VAS scores were recorded upon arrival at PACU, at 60 and 90 min, 2 and 4 h postoperatively. However, it had a shorter duration to the first analgesic request (29.63 *vs.* 39.85 min in Group F). Dexmedetomidine has been tested as an anesthetic adjuvant or for its role in multimodal analgesia. In our study, it was administered as a single intraoperative analgesic in pursuit of minimal opioids consumption, or complete avoidance.

Noteworthy that we used lidocaine during anesthesia induction at a dose of 1 mg/kg, which might have affected the results, since lidocaine has an analgesic and stress response depressing action through blocking sodium channels and inhibiting G protein and N-methyl-D-aspartate receptors [16].

Chilkoti *et al.* [17] concluded that IV dexmedetomidine infusion at a dose of 0.5 μg/kg/h starting 15 min before induction until the end of surgery in laparoscopic cholecystectomy was an effective analgesic. The drug demonstrated a significant reduction in the analgesic consumption for 24 h postopera-

TABLE 2. Comparison between the two studied groups according to blood glucose and plasma cortisol levels.

	Group D (n = 41)	Group F (n = 41)	t	*p*
Blood glucose (mg/dL)				
T0	100.30 ± 19.02	97.05 ± 11.99	0.938	0.352
T1	149.50 ± 23.65	156.20 ± 17.84	1.460	0.148
T2	104.20 ± 13.00	113.10 ± 15.47	2.813*	0.006*
Serum cortisol (μg/dL)				
T0	13.18 ± 6.35	14.74 ± 5.58	1.189	0.238
T1	24.42 ± 7.38	32.70 ± 12.32	3.693*	<0.001*
T2	21.05 ± 7.90	28.42 ± 11.76	3.331*	0.001*

Data was expressed using Mean ± SD.
*t: Student t-test; p: p value comparing between the two groups; *: Statistically significant at p ≤ 0.05. T0, pre-anesthesia; T1, immediately after extubation; T2, 4 h post-extubation.*

TABLE 3. Comparison between the two studied groups according to perioperative analgesic consumption.

Perioperative analgesic consumption	Group D (n = 41)		Group F (n = 41)		Test of Sig.	*p*
	No.	%	No.	%		
Number of times the patients needed a fentanyl rescue dose						
None	35	85.4	30	73.2		
Once	2	4.9	4	9.8	$\chi^2 = 1.841$	$^{MC}p = 0.421$
Twice	4	9.8	7	17.1		
Time to the 1st analgesic request (min)	29.63 ± 46.78		39.85 ± 56.42		U = 705.5	0.203
Total analgesic dose in 24 h (morphine in mg)	2.49 ± 2.27		3.98 ± 2.35		U = 531.0*	0.003*
Patients who did not need any morphine in 24 h	17	41.5	8	19.5	$\chi^2 = 4.661$*	0.031*

Quantitative data was expressed using Mean ± SD.
*U: Mann Whitney test; χ^2: Chi square test; MC: Monte Carlo; p: p value for comparing between the two studiedgroups; *: Statistically significant at p ≤ 0.05.*

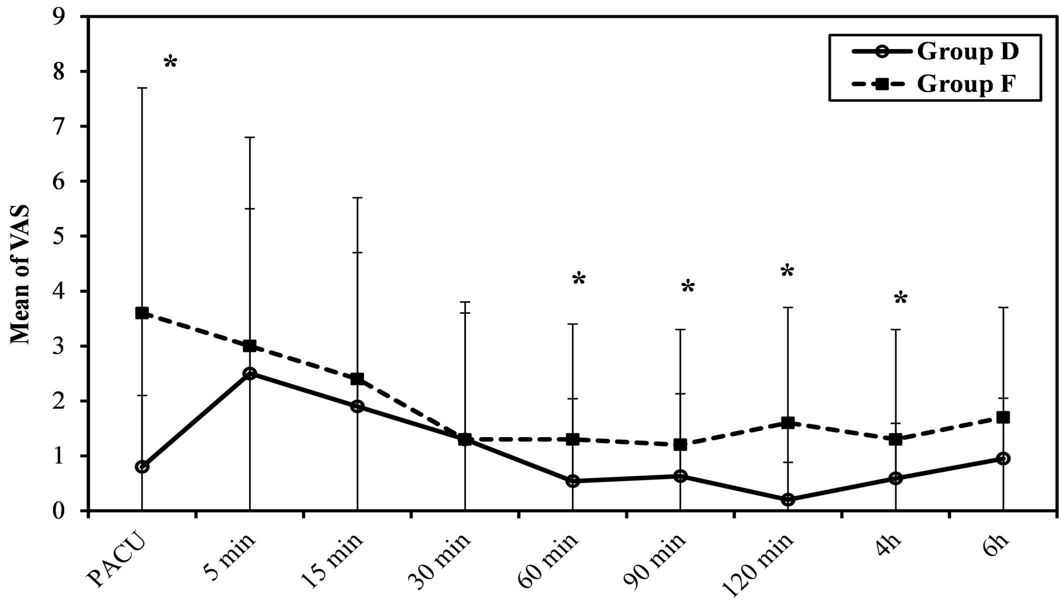

FIGURE 4. Comparison between the two studied groups according to VAS. *: Statistically significant at $p \leq 0.05$. VAS, visual analogue scale.

tively, and in the mean VAS pain score in the initial 15 min compared to the placebo group [17]. In the current study, the VAS score was significantly low for a longer period of time in Group D without administering opioids, while Chilkoti *et* *al*. [17] had routinely administered morphine at anesthesia induction, and diclofenac for 48 h postoperatively. Intraoperative 0.5 μg/kg/h dexmedetomidine infusion as an adjuvant to dexketoprofen in laparoscopic cholecystectomy demonstrated to be safe and effective for improving analgesia during and after elective laparoscopic cholecystectomy, significantly reduced postoperative morphine consumption, and prolonged the time to the first analgesia request. Dexketoprofen was given as a premedication and as a routine postoperative analgesia together with paracetamol [18]. In another randomized trial on patients undergoing radical resection for rectal carcinoma, a significant decrease in morphine consumption during the first 24 h was observed with dexmedetomidine administration and was accompanied by lower plasma cortisol levels at 6 and 24 h postoperatively compared with the control group [19]. A prospective randomized trial by Sharma et al on 100 laparoscopic cholecystectomy surgeries showed that perioperative dexmedetomidine as a part of multimodal analgesia significantly reduced the postoperative analgesic requirement, with lower VAS and better patient satisfaction scores compared to IV paracetamol. This is in accordance with the current study results particularly that no other analgesics were concurrently given by Sharma *et al*. [20]. Ter Brugen *et al*. [21] performed a meta-analysis on dexmedetomidine as a single sedative for short diagnostic and therapeutic procedures compared to three other sedatives (propofol/midazolam/short acting opioid). The study included a total of 1993 patients from 35 studies. Pain scores were 31% lower, and HR as well as MAP were also significantly lower for dexmedetomidine administration compared with placebo, propofol, midazolam, and opioid [21].

Regarding the hemodynamic stress response, dexmedetomidine caused a significant decrease in HR and MAP in Group D after extubation (p = 0.021 and 0.022 respectively). Similar to our study, patients undergoing elective laparoscopic surgeries had hemodynamic changes that were better controlled with dexmedetomidine than with fentanyl [22, 23]. In a study by Mishra *et al*. [22], the effect of dexmedetomidine was compared to fentanyl in 100 patients undergoing laparoscopic surgeries. They were given 1 μg/kg of IV dexmedetomidine over 10 min followed by 0.04–0.05 μg/kg/min as maintenance during surgery, while fentanyl group received 2 μg/kg followed by 0.02–0.03 μg/kg/min. Similar to the current study, hemodynamic changes during intubation were significantly better controlled with dexmedetomidine, although the maintenance dose in the present study was less for both drugs [22]. It is not clear to us why Mishra *et al*. [22] used this high maintenance dose. In a randomized trial by Vaswani *et al.* [23], IV premedication with dexmedetomidine 0.5 μg/kg as a loading dose over 10 min prior to induction in elective laparoscopic surgeries followed by 0.2–0.7 μg/kg/h infusion till surgery is over had a significant attenuating effect on hemodynamic stress response compared to fentanyl infusion. They used a lower loading dose compared to the present study; however, their patients received IV tramadol at anesthesia induction and received a local anesthetic infiltration at the surgery port sites [23]. Similar to our study, dexmedetomidine also had better postoperative hemodynamic stability than fentanyl and remifentanil in patients undergoing elective laparoscopic hysterectomy in a randomized study comparing the three drugs. However, in contrast to the current study, all groups demonstrated a similar pain control effect. A single dose of IV ketorolac 30 mg was given to all patients at the end of surgery [24]. During propofol-based anesthesia for laparoscopic cholecystectomy, dexmedetomidine loading dose at 1 μg/kg and intraoperative infusion at 0.6 μg/kg/h provided stable intraoperative hemodynamics and reduced propofol requirement for induction, as well as maintenance, without compromising recovery profile [25]. A systematic review and meta-analysis of 10 trials revealed that dexmedetomidine, compared to esmolol, is a more effective agent for attenuating the hemodynamic response to tracheal intubation [5].

As for the endocrine stress response, our study demonstrated that the increase in blood glucose (p = 0.006) and serum cortisol levels (p = 0.001) was less in Group D compared to Group F 4 h post-extubation. Similarly, the increase in serum cortisol levels was reduced with dexmedetomidine administration for patients undergoing cardiac valve replacement, where it was given as loading at 1 μg/kg followed by maintenance at 0.5 μg/kg/h. Sufentanil was administered during induction and maintenance of anesthesia [26]. Administering dexmedetomidine by Kim *et al.* [27] immediately after anesthetic induction at 0.4 μg/kg/h, without a loading dose, in major spine surgeries reduced stress hormone release; however, reduction in cortisol level was not of statistical significance [27]. The lower dose of dexmedetomidine which Kim *et a*l. [27] used may explain this insignificance, although they administered remifentanil infusion at induction and throughout the surgery duration. Shamim *et al.* [9] examined dexmedetomidine effect on stress response at two different doses in laparoscopic pyeloplasty; 1 μg/kg as loading followed by 0.7 μg/kg/h as maintenance in one group, and 0.7 μg/kg as loading followed by 0.5 μg/kg/h as maintenance in the other group. Fentanyl 1 μg/kg was repeated every 30–40 min. Blood glucose levels at postintubation and at extubation, as well as serum cortisol levels at postintubation, during mid-surgery, and 2 h post-extubation were all less in dexmedetomidine groups compared to the control group [9]. In the present study, despite fentanyl was given only as a rescue dose for a maximum of 1 μg/kg throughout the surgery duration, the stress response was still less with dexmedetomidine. In contrast to the current study, dexmedetomidine presented no effect on intraoperative hyperglycemia when compared to a placebo in elderly patients undergoing major non-cardiac surgery for which anesthesia was induced and maintained by propofol and sufentanil infusion. Dexmedetomidine was given as a loading dose of 0.6 μg/kg over 10 min pre-anesthesia followed by an infusion at 0.5 μg/kg/h till 1 h before surgery ends [28]. This contradiction to the current study may be attributed to the surgery type, the lesser loading dose, and the earlier discontinuation of dexmedetomidine in Li *et al.*'s [28] trial.

Our study has some limitations. Firstly, it did not include patients with comorbidities, who may benefit the most from opioid-free anesthesia. Secondly, the study examined only one part of the stress response; glucose and cortisol levels, whereas the stress response actually consists of metabolic, hormonal, and immunological responses. Finally, the study included different types of laparoscopic surgeries, and lidocaine was used during anesthesia induction, which may have affected the outcome.

5. Conclusions

This study supports IV dexmedetomidine administration as a sole intraoperative analgesic agent for adult patients without comorbidities undergoing elective laparoscopic surgeries based on its ameliorating effect on the surgical stress response, the postoperative pain, and the perioperative analgesic consumption. Further studies are needed to evaluate dexmedetomidine effect on other surgical stress response markers like epinephrine, norepinephrine, circulating interleukins, and tumor necrosis factor.

AUTHOR CONTRIBUTIONS

BBG designed the research study. MG performed the research, collected the data, and wrote the manuscript. WMAE, DME and RHM analyzed the data. All authors read and approved the final manuscript.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

The work was approved by the Ethics Committee of Ain Shams University Hospitals (FMASU MD 334/2017). Prior to undergoing surgery, patients signed a consent for participation in the study.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

REFERENCES

[1] Robba C, Cardim D, Donnelly J, Bertuccio A, Bacigaluppi S, Bragazzi N, *et al*. Effects of pneumoperitoneum and Trendelenburg position on intracranial pressure assessed using different non-invasive methods. British Journal of Anaesthesia. 2016; 117: 783–791.

[2] Buia A, Stockhausen F, Hanisch E. Laparoscopic surgery: a qualified systematic review. World Journal of Methodology. 2015; 5: 238–254.

[3] Prior SL, Barry JD, Caplin S, Min T, Grant DA, Stephens JW. Temporal changes in plasma markers of oxidative stress following laparoscopic sleeve gastrectomy in subjects with impaired glucose regulation. Surgery for Obesity and Related Diseases. 2017; 13: 162–168.

[4] Kundu S, Weiss C, Hertel H, Hillemanns P, Klapdor R, Soergel P. Association between intraabdominal pressure during gynaecologic laparoscopy and postoperative pain. Archives of Gynecology and Obstetrics. 2017; 295: 1191–1199.

[5] Li Z, Xu L, Zheng J, Wang Q. Comparison of intravenous dexmedetomidine versus esmolol for attenuation of hemodynamic response to tracheal intubation after rapid sequence induction: a systematic review and meta-analysis. BioMed Research International. 2019; 2019: 6791971.

[6] Atkinson TM, Giraud GD, Togioka BM, Jones DB, Cigarroa JE. Cardiovascular and ventilatory consequences of laparoscopic surgery. Circulation. 2017; 135: 700–710.

[7] Marana E, Colicci S, Meo F, Marana R, Proietti R. Neuroendocrine stress response in gynecological laparoscopy: TIVA with propofol versus sevoflurane anesthesia. Journal of Clinical Anesthesia. 2010; 22: 250–255.

[8] Finnerty CC, Mabvuure NT, Ali A, Kozar RA, Herndon DN. The surgically induced stress response. Journal of Parenteral and Enteral Nutrition. 2013; 37: 21S–29S.

[9] Shamim R, Srivastava S, Rastogi A, Kishore K, Srivastava A. Effect of two different doses of dexmedetomidine on stress response in laparoscopic pyeloplasty: a randomized prospective controlled study. Anesthesia, Essays and Researches. 2017; 11: 1030–1034.

[10] Rawal N. Current issues in postoperative pain management. European Journal of Anaesthesiology. 2016; 33: 160–171.

[11] Beleña JM, Núñez M, Vidal A, Anta D. Randomized double-blind comparison of remifentanil and alfentanil in patients undergoing laparoscopic cholecystectomy using total intravenous anesthesia. Journal of Anaesthesiology Clinical Pharmacology. 2016; 32: 487–491.

[12] Kaye AD, Chernobylsky DJ, Thakur P, Siddaiah H, Kaye RJ, Eng LK, *et al*. Dexmedetomidine in Enhanced Recovery after Surgery (ERAS) protocols for postoperative pain. Current Pain and Headache Reports. 2020; 24: 21.

[13] Zhao Y, He J, Yu N, Jia C, Wang S. Mechanisms of dexmedetomidine in neuropathic pain. Frontiers in Neuroscience. 2020; 14: 330.

[14] Talke P, Anderson BJ. Pharmacokinetics and pharmacodynamics of dexmedetomidine-induced vasoconstriction in healthy volunteers. British Journal of Clinical Pharmacology. 2018; 84: 1364–1372.

[15] Geng ZY, Liu YF, Wang SS, Wang DX. Intra-operative dexmedetomidine reduces early postoperative nausea but not vomiting in adult patients after gynaecological laparoscopic surgery: a randomised controlled trial. European Journal of Anaesthesiology. 2016; 33: 761–766.

[16] Rekatsina M, Theodosopoulou P, Staikou C. Effects of intravenous dexmedetomidine versus lidocaine on postoperative pain, analgesic consumption and functional recovery after abdominal gynecological surgery: A randomized placebo-controlled double blinded study. Pain Physician. 2021;24: E997–E1006.

[17] Chilkoti GT, Karthik G, Rautela R. Evaluation of postoperative analgesic efficacy and perioperative hemodynamic changes with low dose intravenous dexmedetomidine infusion in patients undergoing laparoscopic cholecystectomy—a randomised, double-blinded, placebo-controlled trial. Journal of Anaesthesiology Clinical Pharmacology. 2020; 36: 72–77.

[18] Bielka K, Kuchyn I, Babych V, Martycshenko K, Inozemtsev O. Dexmedetomidine infusion as an analgesic adjuvant during laparoscopic cholecystectomy: a randomized controlled study. BMC Anesthesiology. 2018; 18: 44.

[19] Zhang YS, Jin LJ, Zhou X, Liu Y, Li Y, Wen LY. Effect of dexmedetomidine on stress reactions and cellular immune function of patients in perioperative period following radial resection for rectal carcinoma. Journal of Biological Regulators and Homeostatic Agents. 2018; 32: 139–145.

[20] Sharma R, Gupta R, Choudhary R, Singh Bajwa SJ. Postoperative analgesia with intravenous paracetamol and dexmedetomidine in laparoscopic cholecystectomy surgeries: a prospective randomized comparative study. International Journal of Applied and Basic Medical Research. 2017; 7: 218–222.

[21] Ter Bruggen FFJA, Eralp I, Jansen CK, Stronks DL, Huygen FJPM. Efficacy of dexmedetomidine as a sole sedative agent in small diagnostic and therapeutic procedures: a systematic review. Pain Practice. 2017; 17: 829–840.

[22] Mishra LS, Singh V, Raw BK, Kumar S. A randomised control study of dexmedetomidine versus fentanyl as an anaesthetic adjuvant to general anaesthesia in laparoscopic surgeries. International Journal of Scientific Research. 2020; 9: 77–79.

[23] Vaswani JP, Debata D, Vyas V, Pattil S. Comparative study of the effect of dexmedetomidine vs. fentanyl on haemodynamic response in

patients undergoing elective laparoscopic surgery. Journal of Clinical and Diagnostic Research. 2017; 11: UC04–UC08.

[24] Choi JW, Joo JD, Kim DW, In JH, Kwon SY, Seo K, *et al*. Comparison of an intraoperative infusion of dexmedetomidine, fentanyl, and remifentanil on perioperative hemodynamics, sedation quality, and postoperative pain control. Journal of Korean Medical Science. 2016; 31: 1485–1490.

[25] Khare A, Sharma SP, Deganwa ML, Sharma M, Gill N. Effects of dexmedetomidine on intraoperative hemodynamics and propofol requirement in patients undergoing laparoscopic cholecystectomy. Anesthesia Essays and Researches. 2017; 11: 1040–1045.

[26] Wu H, Tang J, Pan J, Han M, Cai H, Zhang H. Effects of dexmedetomidine on stress hormones in patients undergoing cardiac valve replacement: a randomized controlled trial. BMC Anesthesiology. 2020; 20: 142.

[27] Kim MH, Lee KY, Bae SJ, Jo M, Cho JS. Intraoperative dexmedetomidine attenuates stress responses in patients undergoing major spine surgery. Minerva Anestesiologica. 2019; 85: 468–477.

[28] Li CJ, Wang BJ, Mu DL, Wang DX. The effect of dexmedetomidine on intraoperative blood glucose homeostasis: secondary analysis of a randomized controlled trial. BMC Anesthesiology. 2021; 21: 139.

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