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Effect of Different Doses of Dexmedetomidine on Stress Response and Emergence Agitation after Laparoscopic Cholecystectomy: Randomized Controlled Double-Blind Study

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Abstract

Background: Emergence agitation (EA) may develops during recovery from general anesthesia. It causes confusion, disorientation, and unpredictable behaviours. Surgical stress response activates the sympathetic nervous system and increase the release of catabolic hormones leading to prolonged hospital stay.

Objectives: We designed this study to assess the effect of different doses of intra-operative dexmedetomidine infusion on surgical stress response, emergence agitation and postoperative outcome.

Study design: A controlled double-blind study was conducted using a computer-generated randomization scheme.

Setting: The study was conducted in Assiut University Hospitals, Assiut, Egypt.

Methods: 90 patients scheduled for laparoscopic cholecystectomy were randomly assigned into three equal groups to receive intraoperative dexmedetomidine infusion over 20 minutes before end of surgery. Group I received 1 μg/kg, group II received 0.75 μg/kg and group III received 0.5 μg/kg.

Results: We found that dexmedetomidine (0.5, 0.75 or 1 μg/kg) can decrease the incidence of EA when infused 20 minutes before skin closure in laparoscopic cholecystectomy in adults. Lower agitation scores, pain scores, cortisol and glucose levels were observed during the first 2 hours postoperatively with no serious complications.

Limitations: First, we think a larger number of patients may be needed to detect better comparison between different doses of dexmedetomidine in preventing EA and monitor possible complications. Second, we did not take in mind any other preoperative predisposing factors that may affect the incidence of EA especially anxiety or smoking. Finally, we did not use any monitoring for depth of anesthesia which has an important factor in the incidence of emergence agitation.

Conclusion: We conclude that low doses of dexmedetomidine infusion (0.5 μg/kg) over 20 minutes before skin closure are effective as higher doses (0.75 and 1 μg/kg) to decrease stress response and incidence of emergence agitation in laparoscopic cholecystectomy in adults with less adverse effects.

Keywords: Dexmedetomidine; Stress; Emergence agitation; Laparoscopic cholecystectomy

Introduction

Emergence agitation (EA) may develop during recovery from general anesthesia. It causes confusion, disorientation, and unpredictable behaviors [1]. It is more common in children than adults [2]. Serious complications may occur as a result of agitation such as bleeding, self extubation, removal of catheters, hypoxia or even aspiration [3]. The exact etiology and sequence of EA in adults are not well-cleared yet [4].

Tissue injuries during surgeries can lead to stress response [5]. Surgical stress response activates the sympathetic nervous system and increases the release of catabolic hormones. Changes in heart rate, blood pressure and cortisol levels also may occur [6]. Prolonged hospital stay may be the result of all these events [7].

The highly selective alpha-2 receptor agonist; Dexmedetomidine; has many anti-stress, sedative and analgesic actions [8]. It decreases surgical stress response and leads to better stable hemodynamic properties [9]. Dexmedetomidine decreases the postoperative supplemental analgesic requirements and pain intensity. Information about dexmedetomidine and EA is limited especially in adult patients [10].

Objectives

We designed this study to assess the effect of different doses of intraoperative dexmedetomidine infusion on the surgical stress response and general anesthesia. Also, we evaluated the effect of these doses on the post-anesthetic emergence agitation, quality of recovery after surgery, postoperative analgesic requirements and complications.

Methods

Eligibility

This study was carried out after approval from our Faculty Ethical Committee (ref. no. IRB00008718). Clinical trials registration was approved under this number NCT02917018. All patients were informed with complete information about the anesthesia and analgesia techniques that would be provided to them. A written informed consent was obtained from each patient before entry in this study.

Sample size calculation

It is based on the pilot study, where the incidence of surgical stress response in laparoscopies is found to be more than 70% and intervention that can cause 25% reduction in this incidence will be interesting. With a power of 90% and type I error of 5%, 27 patients were required to be in each group (α=0.05 and β=90%), but to avoid possible loss of samples (dropouts) during the study, the number of patients in each group is increased to 30.

Study design

A controlled double-blind study was conducted on 90 patients scheduled for elective laparoscopic cholecystectomy. They were randomly allocated using a computer-generated randomization program into three equal groups to receive intraoperative infusion of dexmedetomidine (Precedex, 100 µg/ml, Hospira, Inc., Rocky Mount, IL, USA). Access to the randomization codes was only available to one anesthesiologist. Group I received 1 µg/kg, group II received 0.75 µg/kg and group III received 0.5 µg/kg diluted to 50 ml NaCl 0.9% by syringe pump over 20 minutes before end of surgery. The study drugs and randomization were prepared by the second anesthesiologist while drug administration and observations were done by the first anesthesiologist.

Inclusion criteria

ASA I-II, Age 20 to 60 years, both sex and Laparoscopic cholecystectomy under general anesthesia

Exclusion criteria

Any cardiac disease, diabetes, reactive upper airway disease, known allergies to dexmedetomidine, cognitive disorders, renal insufficiency or hepatic dysfunction. Chronic use of analgesics, cortisone or drugs known to interact with dexmedetomidine.

Preoperative assessment and preparation: The day prior to surgery, all patients underwent pre-anesthetic check-up including detailed history, general & systemic examination and weight measurement.

Anesthetic technique

With no premedication, all patients received pre-oxygenation by O_2 100% for 3-5 minutes and intravenous access was secured. NaCl 0.9% 4 ml/kg/h were infused intraoperatively. General anesthesia was induced by fentanyl 1 µg/kg, propofol 2 mg/kg and nimbex (cisatracurium) 0.15 mg/kg. Endotracheal intubation then was inserted using oral ETT of appropriate size under direct laryngoscopy and secured at the angle of the mouth. Sevoflurane inhalational anesthetic (2-4 %) in 100% oxygen and nimbex 0.03 mg/kg were used for maintenance of anesthesia. The lungs were mechanically ventilated to keep intra-operative $EtCO_2$ between 35-40 mmHg.

Intraoperative monitoring: Routine monitors including ECG, non-invasive blood pressure, pulse oximetry and $EtCO_2$ were recorded every 5 minutes during the intraoperative 20 minutes of the study drug administration. Bradycadia (heart rate<60 beat/minute) was treated with IV atropine 0.5 mg. Hypotension (mean arterial blood pressure<60 mmHg) was treated with IV ephedrine 5 mg increments. Durations of anesthesia, sevoflurane % and duration of surgery were recorded.

At the end of surgery and stoppage of sevoflurane inhalation, neostigmine 0.04 mg/kg and atropine 0.02 mg/kg were used for muscle relaxant reversal (Time 0 in the emergence process), patients were extubated and transferred to the PACU for recovery and monitoring.

Assessment in PACU: Routine monitoring was continued during staying in the PACU. During emergence, the level of agitation was evaluated using the Ricker Sedation-Agitation Scale "RSAS" [11]. The maximum level of agitation was recorded for each patient at time 0, 5, 10, 20, 30, 60, 90 and 120 minutes.

Emergence agitation was defined when RSAS ≥ 5. Dangerous agitation was defined when RSAS=7 and it was treated with fentanyl 1 µg/kg.

Duration of stay in PACU was recorded. Criteria for discharge from PACU were applied according to the modified Aldrete scoring system. A score ≥ 9 was required for discharge [12].

Postoperative analgesia: The 10 points Visual Analogue Scale (VAS) for pain measurement was used to assess the severity of postoperative pain. Score 0 indicated no pain and score 10 indicated severe pain. If VAS ≥ 4, rescue analgesia was indicated. Perfalgan (perfalgan_, paracetamol 1000 mg. UPSA laboratories, France) infusion was used as supplemental analgesia. The first dose and the total amount in 24 hours of perfalgan were recorded. Patient's satisfaction was also recorded at the end of the first 24 hours postoperatively.

Blood sampling: All blood samples (2 ml each sample) were venous and obtained from peripheral vessels (antecubital vein) away from the limb infused with fluids. Samples were withdrawn 20 minutes pre-operatively, 20 minutes after skin incision, just after skin closure and 2 hours after end of surgery. The blood samples were centrifuged at 3500 × g for at least 10 minutes and then serum samples were collected for cortisol level analysis. Blood glucose levels were also recorded at the same times.

Statistical analysis

Statistical analysis was conducted with SPSS version 20 (SPSS Inc., Chicago, IL, USA) for Windows. Quantitative data were compared using One-way ANOVA and Student's t-test. Qualitative data were

analyzed using the Chi-square test. P-values <0.05 were considered statistically significant.

Results

90 patients were enrolled in our study and randomly allocated into 3 equal groups of 30 patients each. There was no statistically significant difference with respect to Patients' characteristics (age, sex, weight, BMI, duration of anesthesia, duration of surgery and time to extubation) between the three study groups (Table 1).

Variable		Group I	Group II	Group III	P value
		(n=30)	(n=30)	(n=30)	
Age (years)		32.71 ± 13.30	36.31 ± 11.18	33.56 ± 13.19	NS
Sex					
	Male	11	16	13	NS
	Female	19	14	17	
Weight (kg)		65.18 ± 10.77	65.72 ± 11.09	63.64 ± 10.95	NS
BMI		23.89 ± 3.20	24.28 ± 3.10	23.55 ± 3.41	NS
Duration of Anesthesia (minutes)		80.22 ± 19.95	78.91 ± 20.86	80.50 ± 20.16	NS
Duration of Surgery (minutes)		71.15 ± 20.37	69.82 ± 21.09	70.44 ± 20.71	NS
Time to extubation after end of surgery (minutes)		9.11 ± 2.77	8.97 ± 3.10	8.90 ± 3.09	NS
Data were expressed as mean ± SD and numbers.					

Table 1: Patients' characteristics of the three study groups.

There was no statistically significant difference between the three study groups during the whole intraoperative and 2 hours postoperative periods regarding heart rate, mean arterial blood pressure, oxygen saturation or $EtCO_2$.

We noted slight insignificant reduction in heart rate and mean arterial blood pressure than the pre-infusion readings.

Emergence agitation scoring (RSAS)

We noted decrease incidence of agitation in our patients. It occurred only in 3 (10%) cases in the group I, in 3 cases (10%) in group II and in 5 cases (16.7%) in group III. The RSAS was 4.03 ± 1.49 in group I, 4.11 ± 1.35 in group II and 4.42 ± 1.05 in group III.

There was no statistically significant difference between the three study groups as regarding the incidence or the scoring of emergence agitation in the recovery room (Table 2).

Pain scoring

Patients in the three study groups recorded low VAS pain scores through the postoperative 2 hours in the recovery room. VAS was 3.79 ± 1.93 in group I, 3.64 ± 2.01 in group II and 3.75 ± 2.12 in group III. There was no statistically significant difference between the three study groups as regarding VAS pain scoring (Table 2).

Patients in group I stayed in the PACU for 42.32 ± 7.15 minutes while patients in group II stayed in PACU for 40.58 ± 8.03 minutes and patients in group III stayed in PACU for 43.19 ± 7.10 minutes with no statistically significant difference between the three groups (Table 2).

Variable	Group I	Group II	Group III	P value
	(n=30)	(n=30)	(n=30)	
Incidence of agitation in PACU (no.)	3 (10%)	3 (10%)	5 (16.7%)	0.098
RSAS	4.03 ± 1.49	4.11 ± 1.35	4.42 ± 1.05	0.127
VAS	3.79 ± 1.93	3.64 ± 2.01	3.75 ± 2.21	0.108
Duration of stay in PACU (minutes)	42.32 ± 7.15	40.58 ± 8.03	43.19 ± 7.10	0.116
Data were expressed as no. percentages, mean ± SD.				

Table 2: Postoperative Emergence Agitation and Pain Scoring.

Supplemental analgesia

12 (40%) patients in group I required supplemental analgesia during the first 24 hours postoperatively while 15 (50%) patients in group II and 14 (46.7%) patients in group III required supplemental analgesia with no statistically significant difference between the three groups (Table 3). Regarding the time of 1st analgesic requirement and the total amount of supplemental analgesia, there were no statistically significant differences between the three groups (Table 3). 21 patients in group I, 20 patients in group II and 17 patients in group III were satisfied with the results of our study (Table 3).

Regarding serum cortisol and blood glucose levels, there were no statistically significant differences between the three study groups (Tables 4,5). These levels were increased after surgical skin incision and

decreased at the end of surgery with drug infusion indicating the effect of dexmedetomidine in decreasing stress response related to surgery.

Variable	Group I (n=30)	Group II (n=30)	Group III (n=30)	P value
No. of patients need analgesia	12 (40%)	15 (50%)	14 (46.7%)	NS
Time of first analgesia (hours)	4.17 ± 1.12	4.90 ± 1.33	4.51 ± 1.62	NS
Total amount of Perfulgan in first 24 hours (grams)	28.31 ± 3.65	29.82 ± 3.99	29.79 ± 4.03	NS
Patients' Satisfaction				
Yes	21 (70%)	20 (66.7)	17 (56.7)	NS
No	9 (30%)	10 (33)	13 (43.3)	
Data were expressed as numbers, percentages, mean ± SD.				

Table 3: Supplemental Analgesia and Patients' Satisfaction.

Variable	Group I (n=30)	Group II (n=30)	Group III (n=30)	P value
20 minutes preoperatively	92.57 ± 4.32	90.88 ± 4.91	89.96 ± 5.20	0.184
20 minutes after skin incision	232.13 ± 17.65	235.29 ± 19.14	234.66 ± 19.61	0.093
Just after skin closure	190.83 ± 14.77	193.25 ± 15.39	190.12 ± 15.01	0.101
2 hours after end of surgery	188.45 ± 11.27	190.76 ± 14.50	191.02 ± 11.16	0.237
Data were expressed as mean ± SD.				

Table 4: Serum cortisol level changes in the three study groups.

Variable	Group I (n=30)	Group II (n=30)	Group III (n=30)	P value
20 minutes preoperatively	88.36 ± 6.71	90.84 ± 7.52	91.90 ± 7.81	0.085
20 minutes after skin incision	127.58±27.46	130.13±28.70	128.67 ± 28.59	0.104
Just after skin closure	120.33 ± 11.96	121.00 ± 11.58	121.51 ± 11.30	0.099
2 hours after end of surgery	121.64 ± 15.32	120.54 ± 16.06	120.72 ± 16.13	0.113
Data were expressed as mean ± SD.				

Table 5: Blood glucose level changes in the three study groups.

There were no serious complications noted throughout the whole conduct of our study. Few cases of nausea, vomiting, headache, hypotension or bradycardia were recorded and treated promptly (Table 6).

Variable	Group I (n=30)	Group II (n=30)	Group III (n=30)	P value
Nausea & Vomiting	6 (20%)	7 (23.3%)	6 (20%)	NS
Bradycardia	1 (3.3%)	0 (0%)	0 (0%)	NS
Hypotension	2 (6.7%)	0 (0%)	0 (0%)	NS
Headache	4 (13.3%)	5 (16.7%)	2 (6.7%)	NS
Data were expressed as numbers, percentages.				

Table 6: Postoperative complications in the three study groups.

Discussion

Emergence agitation (EA) can be defined as a transient condition of agitation, may occur during recovery from general anesthesia. Surgical stress response may have a role in EA pathogenesis [13]. Surgeries closed to diaphragm usually decrease the vital capacity, movement of the diaphragm and respiratory functions especially in PACU [14]. Many contributing factors can affect the incidence of EA and a lot of studies tried to discover these factors [15].

We found that dexmedetomidine (0.5, 0.75 or 1 μg/kg) can decrease the incidence of EA when infused 20 minutes before skin closure in laparoscopic cholecystectomy in adults. Lower pain scores were recorded during the first 2 hours postoperatively then supplemental analgesics were prescribed when needed.

Dexmedetomidine has anxiolytic, analgesic and sympatholytic effects through activation of α2 receptors in CNS, decreasing the neuronal activities and enhancing the vagal activities [16]. The α2 agonists have a clear role on CVS as they inhibit the release of catecholamines by vasoconstrictive effect augmentation [17].

Emergence from general anesthesia is equal to the stress of laryngoscopy. The effect of sudden decrease of anesthetic depth and rapid increase in catecholamines levels may lead to serious complications. Dexmedetomidine leads to a smooth transition from sudden cessation of anesthesia and the recovery [18].

One study concluded the intraoperative infusion of dexmedetomidine (0.4 μg/kg/hr) until extubation can decrease the incidence of EA after nasal surgeries in adults without increasing complications or delaying extubation [19]. Another study found dexmedetomidine can reduce EA after anesthesia in adults by about 46% [20].

Some investigators evaluated the effect of dexmedetomidine (0.1 or 0.3 μg/kg) on EA. They found the better results with the 0.3 μg/kg dose [21]. It has anesthetic-sparing, anxiolytics and analgesic effect with no respiratory depressant effect [22].

When dexmedetomidine was administered 0.3 or 0.5 μ/kg post-induction in the pre-school children, reduced incidence and severity of emergence agitation after sevoflurane anesthesia were observed. No delayed recovery or hemodynamic instability was associated with the smaller dose [23].

According to our observations, we did not find any serious hemodynamic changes throughout our study period. One case of slight bradycardia and two cases of hypotension were found insignificantly and easily corrected. Cortisol and glucose levels showed increased

readings after start the operative maneuver then these levels decreased at the end of drug infusion and end of surgery.

Some studies showed the higher doses (0.5 or 1 μg/kg) of dexmedetomidine can decrease the incidence of EA after sevoflurane inhalation but can affect the hemodynamics of the patients [24]. Another study used different doses of dexmedetomidine (0.1-10 μg/kg/h) but there was a higher incidence of hypotension and bradycardia especially in large doses [25].

Use of dexmedetomidine 0.4 μg/kg as a bolus injection within 30 minutes after general anesthesia induction can stabilize the patient's heart rate and blood pressure during emergence after thyroid gland surgery and also decreases awakening and extubation times [26].

We used smaller doses of dexmedetomidine infusion to avoid rapid changes in hemodynamics. Stress response in anesthetized patients can lead to autonomic or endocrine disturbance. Hemodynamic changes are usually unpredictable [27]. Cortisol level is widely used as the marker of surgical stress response [28]. A dose-dependent decrease in heart rate and arterial blood pressure occurred with dexmedetomidine, and decrease of sympathetic nervous activity was observed through the recorded levels of norepinephrine in plasma [29].

A previous research reported that dexmedetomidine use can significantly reduce the circulating catecholamines and also can decrease the blood pressure and the heart rate [30]. Another researcher found the pretreatment with dexmedetomidine 1 μg/kg attenuated (but did not totally abolish) the cardiovascular and stress response responses to laryngoscopy and tracheal intubation after induction of general anesthesia [31].

Conclusions

We conclude that low doses of dexmedetomidine infusion (0.5 μg/kg) over 20 minutes before skin closure are effective as higher doses (0.75 and 1 μg/kg) to decrease stress response and incidence of emergence agitation in laparoscopic cholecystectomy in adults with less adverse effects.

Limitations

First, we think a larger number of patients may be needed to detect better comparison between different doses of dexmedetomidine in preventing EA and monitor possible complications. Second, we did not take in mind any other preoperative predisposing factors or premedication that may affect the incidence of EA especially anxiety or smoking. Finally, we did not use any monitoring for depth of anesthesia which has an important factor in the incidence of emergence agitation.

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