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The Effects of Dexmedetomidine or Remifentanil Continuous Infusion on End-Tidal Sevoflurane Concentration in Patients Undergoing Laparoscopic Cholecystectomies, Monitored by Bispectral Analysis

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Abstract

Background and Objective: Owing to the hemodynamic response to pneumoperitoneum, laparoscopic is not devoid of risk; adjuvants have been used to decrease the dose of volatile agents and their side effects and to blunt the hemodynamic response. This study was designed to compare the effect of dexmedetomidine and remifentanil on sevoflurane expired fraction concentration (EF sevo) in general anesthesia, monitored by BIS. Hemodynamic response, postoperative recovery profile, analgesic requirements and PONV were also recorded.

Patients and methods: General anesthesia induction with propofol 2.5 mg/kg rocuronium bromide 0.6 mgkg and sevoflurane 1-1.5 MAC. Tracheal intubation was performed and patients were mechanically ventilated. Patients were allocated to Groups D or R. Group D (≤ 40) was the dexmedetomidine group, they received dexmedetomidine diluted with 0.9% NaCl to a concentration of 4 ugmL in 50 mL (an initial loading dose of 0.7 ug/kg given for a 10 min period followed by 0.5 ug/kg/h). Group D (n=40) was the dexmedetomidine group, they received dexmedetomidine (Precedex, 200 ug per 2 mL; Abbott, USA) (an initial loading dose of 0.7 ug/kg given for a 10 min period followed by 0.4 ug/kg/h). Group R (n=40) was the remifentanil group and received an intravenous (i.v.) remifentanil (an initial loading dose of 0.7 ug/kg given for a 10 min period followed by 0.2 ug/kg/h). The infusion was stopped 15 min before the end of surgery. sevoflurane concentration adjusted to maintain BIS between 40 and 60. The parameters evaluated (BIS, SBP, DBP, MAP, HR, and EF sevo) were expressed as mean and standard deviation at 15 min before induction, during induction of anesthesia, 15 min later, during pneumperitonium, after release of insufflation and 15 min after release of insufflation.

Statistical analysis: Student's t-test is a test of significance used for comparison of quantitative variables between two groups of normally distributed data, while Mann Whitney's test was used for comparison of quantitative variables between two groups of not normally distributed data. Chi-square test ($\chi 2$) was used to study association between qualitative variables. Whenever any of the expected cells were less than five, Fischer's Exact test with Yates correction was used. P-value of <0.05 was considered statistically significant.

Results: No patients had marked hypotension MAP less than 60 mmHg or bradycardia HR less than 45 in both groups but there were significant decrease in HR and MAP between the two groups during induction, 15 min after induction, during pneumperitonium, aftert release of insufflation and 15 min after release of insufflation, extubation time, spontaneous eye movement, eye movement to verbal stimuli, spontaneous arm movement, purposeful movement and time of discharge to recovery room were significantly lower in group R than group D, However group R showed significantly higher EF sevo 15 min after induc, BSI during insufflation of CO_2, EF sevo during insufflation of CO_2, BSI after release. CO_2, EF sevo after release of CO_2, BSI before end of surgery and EF sevo before end of surgery than group D.

Conclusion: Both dexmedetomidine and remifentanil reduce the anesthetic requirement and depress the hemodynamic response during pneumoperitoneum with more significant decrease in EF sevo in the D group, however dexmedetomidine provides better postoperative analgesia and less incidence of PONV.

Keywords: Bispectral index; Dexmedetomidine; Remifentanil; Sevoflurane

Introduction

Laparoscopic cholecystectomy (LC) procedure is a more preferable technique than open cholecystectomy in the treatment of symptomatic cholelithiasis; [1] it reduces postoperative pain, with faster recovery and more rapid return to normal activities and lesser hospital stay [2].

Several adjuvants have been used to decrease the dose of inhalational agents and to provide better sedation, hypnosis, and analgesia [3].

Dexmedetomidine is a potent alpha-2 adrenoreceptor agonist and reduces the volatile anesthetics requirements. It has beneficial

properties when used in anesthesia as it provides better hemodynamic and adrenergic stability *via* its sympatholytic action, sedation and decreased anesthetic and analgesic consumption without marked ventilatory depression [4]. Remifentanil is an analogue of fentanyl its rapid onset and half time of nearly three to five min make it an easy drug to control for achieving the desired depth of anesthesia and its rapid offset provides optimal analgesia without any delayed recovery [5].

The most common method of titration of volatile anesthetics is the minimum alveolar concentration (MAC) but, this includes chiefly the immobilizing potency (prevention of movement to skin incision in 50% of patients) of the anesthetic agent [6].

The dose of the hypnotic agent used to maintain the patient unconscious is detected by bispectral index (BIS) which is EEG-derived parameter. Many studies have shown that BIS has a great correlation with the brain metabolism and with hypnotic and sedative effects of various anesthetic agents as isoflurane, sevoflurane, midazolam and propofol [7,8].

The aim of this study was to evaluate the influence of either dexmedetomidine or remifentanil continuous infusion on expiratory fraction sevoflurane concentration (EF sevo) during general anesthesia, monitored by bispectral index (BIS).

Methods

After institutional review board approval and written informed consent, 80 ASA I-II patients their ages were between 40 and 50 years old and their weight were between 80 and 90 Kg scheduled for elective Videolaparoscopic cholecystectomy were included in a prospective, randomized, double-blind study and equally divided into two groups, Dexmedetomidine (D group) and Remifentanil (R group). Patients were excluded if they had severe cardiac disease, chronic obstructive lung disease, renal and hepatic insufficiency, endocrine, metabolic or central nervous system disorders, a-2-agonist or antagonist therapy taken, and active upper respiratory infection, those receiving medications known to affect MAC, or having a history of alcohol or drug abuse; and women who were lactating or pregnant. One of the anesthetists participating into the study randomized patients into one of the two study groups, using a computer- generated random number table. Study drugs (dexmedetomidine and remifentanil) were prepared by a nurse without any marks on the syringes. The same nurse who knew the study protocol adjusted the perfused dose and the perfuser's syringe and screen were covered to enable double blindness throughout the operation, and no change of the dose was allowed. The anesthetist blinded to the drug continued with the anesthesia process and recorded the study parameters.

All patients had general anesthesia induction, after previous oxygenation for 3 min, at anesthesia induction with propofol 2.5 mg/kg rocuronium bromide 0.6 mgkg and sevoflurane 1-1.5 MAC. Tracheal intubation was performed and patients were mechanically ventilated with 100% oxygen inspired fraction (FiO_2), 2.5 L/min fresh gas flow and 8 mL/kg tidal volume, with respiratory rate adjusted to maintain ET CO^2 between 35 and 40 mmHg, using circle system with CO_2 absorber.

In this double-blind study, patients were allocated to Groups D or R. Group D («=40) was the dexmedetomidine group, they received dexmedetomidine (Precedex, 200 ug per 2 mL; Abbott, USA) (an initial loading dose of 0.7 ug/kg given for a 10 min period followed by 0.4 ug/kg/h). Group R (n=40) was the remifentanil group and received an intravenous (i.v.) remifentanil (an initial loading dose of 0.7 ug/kg given for a 10 min period followed by 0.2 ug/kg/h). Dexmedetomidine or remifentanil was prepared and administered using a syringe pump (Fresenius-Vial-Pilot A2 perfuser; Homburg, Germany) by the same nurse and the infusion was stopped 15 min before the end of surgery.

Anesthetic depth was controlled by varying sevoflurane concentration to maintain BIS between 40 and 60. Muscle relaxation was achieved by rocuronium bromide 0.3 mgkg for maintenance of neuromuscular blockade but no intraoperative narcotics were used in both groups. During the perioperative period, both groups received i.v lactated ringer solution at 4 mL/kg.

In the operating room, routine monitoring (Cardiocaps/5; Datex-Ohmeda, Helsinki, Finland) included five lead electrocardiogram (ECG), pulse oximeter, non-invasive blood pressure (BP) measurement. Electrodes for monitoring the Bispectral Index (BISTM, model A-2000s; Aspect Medical Systems, Norwood, MA, USA) were attached to the head and an iv. line was sited. End-tidal CO_2 ($ETCO_2$) concentration and end-expiratory concentration of sevoflurane were also recorded (Cardiocaps/5) from the time of anesthesia induction to the time of extubation.

The parameters evaluated (BIS, SBP, DBP, MAP, HR, and EF sevo) were expressed as mean and standard deviation in moments at 15 min before induction, during induction of anesthesia, 15 min later, during pneumperitonium, after release of insufflation and 15 min after release of insufflation. Twenty min before the end of surgery, all patients received, dexamethasone 8 mg, ondansetron 4 mg for the prevention of postoperative nausea and vomiting (PONV). Infusion drugs were turned off 15 min before the completion of surgery and patients were ventilated with 100% oxygen at 5 L/min. Following a spontaneous recovery, a combination of atropine 0.02 mg/kg and neostigmine 0.05 mg/kg was administered i.v. to reverse the neuromuscular block. The endotracheal tube was removed when the patient was fully awake. Patients were kept in the post-anesthesia care unit for 2 h.

Sedation was assessed using Ramsay Sedation Scale (RSS) by a blinded nurse, at 5, 15 and 30 min following tracheal extubation. Pain were assessed using a Visual Analog Scale (VAS) from 0 to 10, where 0 no pain and 10 the worst imaginable pain. The predetermined analgesia level was set as a VAS, 4 and rescue i.v. bolus doses of fentanyl (25 mg) were administered if the initial regimen failed to achieve or maintain this goal or if the patient asked for additional analgesics. The presence of PONV and the need for additional analgesics or antiemetics were recorded.

Statistical analysis of the collected data

Results were collected, tabulated and statistically analyzed by an IBM compatible personal computer with SPSS statistical package version 20 (SPSS Inc. Realesed 2011. IBM SPSS statistics for windows, version 20.0, Armnok, NY: IBM Corp.).

Two types of statistical analysis were done:

a) Descriptive statistics: e.g. was expressed in: Number (No), percentage (%) mean ($\bar{x}$) and standard deviation (SD).

b) Analytic statistics: e.g. 1-Student's t-test is a test of significance used for comparison of quantitative variables between two groups of normally distributed data, while Mann Whitney's test was used for comparison of quantitative variables between two groups of not normally distributed data. 2 Chi-square test ($\chi 2$) was used to study

association between qualitative variables. Whenever any of the expected cells were less than five, Fischer's Exact test with Yates correction was used. P value of <0.05 was considered statistically significant.

We planned a study of a continuous response variable from independent control and experimental subjects with 1 control (s) per experimental subject. In a previous study (Paventi et al.) [9], the response within each subject group was normally distributed with standard deviation 0.7. If the true difference in the experimental and control means is 0.5, we will need to study 36 experimental subjects and 36 control subjects (which we rounded to 40) to be able to reject the null hypothesis that the population means of the experimental and control groups are equal with probability (power) 0.85. The Type I error probability associated with this test of this null hypothesis is 0.05.

Logistic regression was not done as prediction was not an aim of this work , however, the 2 groups were matched at the beginning of the study for gender, age and ASA (Table 1).

Results

Variable	No.	%
Gender		
Male	17	21.3
Female	63	78.8
ASA		
I	58	72.5
II	22	27.5
Mean ± SD		
Age	42.7 ± 3.43	
Weight	88.78 ± 4.13	
Surgical time	85.96 ± 6.11	

Table 1: Socio-demographic data of the studied group.

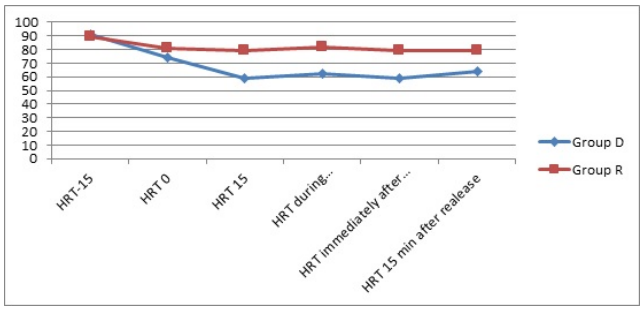

Figure 1: Heart rate (HRT) at different times readings in the 2 studied groups.

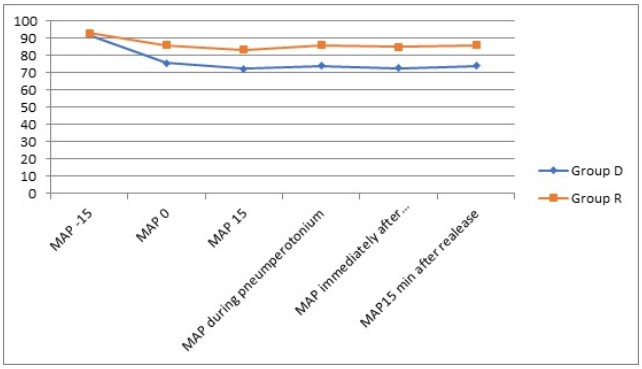

Figure 2: Mean arterial blood pressure (MAP) at different times readings in the 2 studied groups.

No patients had marked hypotension MAP less than 60 mmHg or bradycardia HR less than 45 in both groups but there were significant decrease in HR and MAP between the two groups during induction, 15 min after induction, during pneumperitonium, aftert release of insufflation and 15 min after release of insufflation (Figures 1 and 2).

	Group D (n=40) Mean ± SD	Group R (n=40) Mean ± SD	t-test	P value
Extubation time:	18.80 ± 2.69	4.40 ± 0.90	32.09	<0.001
Spontaneous eye move.	7.57 ± 1.41	2.36 ± 0.65	21.20	<0.001
Eye movement to verbal:	8.92 ± 1.50	3.31 ± 0.76	20.98	<0.001
Spontaneous arm movement:	4.67 ± 0.47	2.46 ± 0.65	17.31	<0.001
Purposeful movement:	6.60 ± 0.81	1.97 ± 0.72	7.86*	<0.001
Time of discharge to recovery room:	21.30 ± 2.78	6.27 ± 0.98	32.16	<0.001
*Mann Whitney test				

Table 2: This table shows that extubation time, spontaneous eye movement, eye movement to verbal stimuli, spontaneous arm movement, purposeful movement and time of discharge to recovery room were significantly lower in group R than group D.

Table 2 shows that extubation time, spontaneous eye movement, eye movement to verbal stimuli, spontaneous arm movement, purposeful movement and time of discharge to recovery room were significantly lower in group R than group D.

	Group D (n=40) Mean ± SD	Group R (n=40) Mean ± SD	t-test	P value

VAS at 5 min	2.05 ± 0.74	1.57 ± 0.63	3.05	0.003
VAS at 15 min	3.32 ± 0.72	4.37 ± 0.49	7.55	<0.001
VAS at 30 min	4.02 ± 0.83	4.90 ± 0.78	5.06	<0.001

Table 3: Mean visual analogue score (VAS) score at different times in both groups.

VAS score at 5 min was significantly higher in group D than group Rhowever it turned to be significantly higher in group R than group D at 15 and 30 min (Table 3).

	Group D (n=40) Mean ± SD	Group R (n=40) Mean ± SD	t-test	P value
Sedation score at 5 min	3.67 ± 0.47	1.50 ± 0.50	19.82	<0.001
Sedation score at 15 min	2.50 ± 0.50	1.07 ± 0.26	15.74	<0.001
Sedation at 30 min	1.22 ± 0.42	1.00 ± 0.00	3.36	0.002

Table 4: Mean sedation score at different times in both groups.

Sedation score was significantly higher in group D than group R at 5 min, 15 min and 30 min (Table 4).

	Group D (n=40) No. %		Group R (n=40) No. %		χ2	P value
Need for analgesia						
No	24	60.0	12	30.0	7.27	0.007
Yes	16	40.0	28	70.0		
Nausea 1 h						
No	36	90.0	31	9	2.29	0.13
Yes	4	10.0	77.5	22.5		
Nausea 2 h						
No	38	2	35	5	0.63*	0.42
Yes	95.0	5.0	87.5	12.5		
Vomiting 1 h						
No	39	1	36	4 10.0	0.85*	0.35
Yes	97.5	2.5	90.0			
Vomiting 2 h						
No	40	100.0	38	2	0.51*	0.47
Yes	0	0.0	95.0	5.0		
*Fisher's Exact test						

Table 5: The need for analgesia and postoperative nausea and vomiting at 1 and 2 hours postoperatively.

The need of analgesia was significantly higher in group R than group D, however nausea and vomiting at 1 and 2 h were not statistically significantly different (Table 5).

	Group D (n=40) Mean ± SD	Group R (n=40) Mean ± SD	t-test	P value
BSI base line	97.97 ± 0.15	97.97 ± 0.15	0.00	1.00
BSI 15 min after induc	50.67 ± 2.41	51.52 ± 3.12	1.36	0.17
EF sevo 15 min after induc	2.00 ± 0.10	2.09 ± 0.16	3.08	0.003
BSI during insuf CO_2	53.55 ± 2.64	55.02 ± 2.09	2.76	0.007
EF sevo during insuf CO_2	1.46 ± 0.15	1.61 ± 0.19	3.97	<0.001
BSI after release of CO_2	53.12 ± 2.66	55.42 ± 2.06	4.32	<0.001
EF sevo after release of CO_2	0.82 ± 0.10	0.92 ± 0.17	2.97	0.004
BSI before end of surgery	54.80 ± 2.38	56.30 ± 1.80	3.17	0.002
EF sevo before end of surgery	0.23 ± 0.07	0.61 ± 0.12	16.29	<0.001

Table 6: BSI and EF sevo at different times in the two groups.

BSI : Bispectral index.

EF sevo : Expiratory fraction of sevoflurane.

Group R showed significantly higher EF sevo 15 min after induc, BSI during insufflation of CO_2, EF sevo during insufflation of CO_2, BSI after release CO_2, EF sevo after release of CO_2, BSI before end of surgery and EF sevo before end of surgery than group D (Table 6).

Discussion

In this study, we compared dexmedetomidine and remifentanyl in hemodynamic stability, the dose of inhalational anesthetics, Recovery parameters and post-operative analgesic requirements in patients undergoing laparoscopic cholecystectomy. This study demonstrates that both drugs blunted the smpathoadrenal responces during surgery, however dexmedetomidine had superior postoperative pain control efficacy and reduced the analgesic requirement and PONV incidence compared to remifentanil. Dexmedetomidine is an ideal sedative as it is a highly selective alpha-2-agonist, with a shorter duration of action than clonidine, [10] it produces a state of hypnosis similar to normal sleep, it doesn't depress the respiration. [11] It has a good analgesic effect by suppression of the nociceptive neurotransmission and inhibition of pain signals propagation. Its sympatholytic effect causes reduction of blood pressure and heart rate; that help in attenuation of the stress response of surgery [12]. It also attenuates the sympathoadrenal effects of tracheal intubation [12]. The ultra-short

acting mu opioids receptor agonist, remifentanil [5] is a potent opioid and has predictable controllability owing to its short half-life and rapid elimination; thus make it has an ultrashort duration of analgesia [13,14].

Some studies [15-17] have shown the role of dexmedetomidine both loading and maintenance dose in reducing the dose of inhalational anesthetics and other studies [18,19] have shown the role of remifentanil in reducing the dose of inhalational anesthetics. In our study, BIS monitoring was allowed for maintaining anesthetic depth within a standard variation to avoid unnecessary deep anesthesia or awareness, we noticed that the sevoflurane requirements were decreased in both groups as the intraoperative BIS-guided sevoflurane alteration led to decrease in the fraction of exspired concentration of sevoflurane (EF sevo). Thus, the EF sevo became significantly lower in group D than in group R 15 min after induction, during pneumperitonium, after release of insufflation and before the end of surgery.

Shin et al. [15] gave preanaesthetic dexmedetomidine 1μg/kg single infusion and found that patients had the end-tidal concentration and total sevoflurane consumption were significantly reduced in dexmedetomidine group more than in control group. Ozcengiz et al. [20] noted in minor surgeries in children that end-tidal sevoflurane concentration was significantly lower in dexmedetomidine group prior to incision, after incision, and after the surgery than in control group. Ohtani et al. [21] made a study in patients undergoing lower abdominal surgeries and found that dexmedetomidine decreased the anesthetic requirements needed to keep BIS of 45 by 20–30%, reducing sevoflurane from 1.1 ± 0.2% to 0.8 ± 0.2% and propofol from 4.4 ± 0.8 mg/kg/h to 3.1 ± 1 mg/kg/h. Keniya et al. 13 found that dexmedetomidine has significant opioid and anesthetic sparing property. It significantly reduces the sympathoadrenal response to tracheal intubation. Ni W et al. [22] showed that remifentanil effectively decreased the sympathetic adrenergic response to CO_2 pneumoperitoneum stimulus, and decreased the end-tidal sevoflurane concentration needed during anesthesia.

In our study the pain stimuli included a small skin incision and the distension of the peritoneum by CO_2 pneumoperitoneum expected to induce a violent sympathetic adrenergic response but both dexmedetomidine and remifentanil are effective to blunt hemodynamic responses all over the surgery.

During the maintenance of anesthesia in group D, we observed significant decrease in HR and MABP values, this is may be due to the combined effect of vasodilatation and myocardial depression with volatile agents. statistically significant hypotension and bradycardia was reported by Patel et al. [23] in patients received dexmedetomidine throughout the intraoperative period with partial blunting of response to intubation and reduction of sevoflurane consumption. While group R showed no significant changes all over the surgery in the hemodynamics. These desirable effects of remifentanil on hemodynamic stability has been shown in previous studies using different doses of remifentanil [24-27].

Our study also showed that patients in group D had a prolonged extubation time than patients in group R. Also Spontaneous eye move, Eye movement to verbal stimli, Spontaneous arm movement, Purposeful movement and Time of discharge to recovery room were more delayed in group D as shown in Table 3 and the postoperative sedation was significant in group D.

Song D et al. [27] found that awakening and extubation times decreased on using of remifentanil (0.05-0.2 μg/kg/min) in obese patients had sevoflurane anesthesia undergoing a laparoscopic cholecystectomy.

Patel et al. [23] in their study observed that postoperatively dexmedetomidine group showed a significant sedation at 2 h compared to control group. Shin et al. reported similar findings [15]. Ebert TJ et al. explained this by the 2 h elimination half-life of dexmedetomidine [11].

In our study as compared to remifentanil, dexmedetomidine also reduced the analgesic requirements; in group D 40% (16 patients) while in group R 70% (28 patients) needed analgesia in the postoperative period. Damian J et al. showed that an alternative analgesic should be given before discontinuation of remifentanil [18]. Previous studies have shown the postoperative analgesic effect of dexmedetomidine [28,29]. and other studies have demonstrated that dexmedetomidine had superior efficacy compared to remifentanil in pain management during a PACU stay [30,31].

Our results showed that PONV incidence was lower in group D; as the incidence of nausea and vomiting during the first 2 h were lower in group than in group R. This was in consistence with Hwang W et al. who compared dexmedetomidine and remifentanil as adjuvants in propofol-based TIVA and found that dexmedetomidine produced more efficient pain control and lesser incidence of PONV [30].

Conclusion

We conclude that any of the two anesthetic techniques are acceptable for in laparoscopic cholecystectomy, both groups are effective in reducing sevoflurane requirement and blunt hemodynamic response during pneumoperitoneum with more significant decrease in EF sevo with dexmedetomidine. Remifentanil provides earlier recovery but with less postoperative analgesia and more incidence of PONV than dexmedetomidine.

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