

Serial Blood Glucose Level Estimation to Assess the Attenuation of Metabolic and Hemodynamic Stress Responses with Dexmedetomidine Infusion during Laparoscopic Surgery - A Randomized Control Study

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Abstract

Background: Laparoscopic surgery under general anaesthesia activates the neurohumoral stress responses thereby causing release of significant amount of catecholamines into the tissue. We hypothesized that intraoperative dexmedetomidine infusion would attenuate the metabolic and hemodynamic changes during laparoscopic surgery which could be assessed by estimating the serial blood sugar level. **Subjects and Methods:** Sixty adult consenting patients undergoing laparoscopic surgery were enrolled. Patients were randomized into two equal groups of 30 patients each. Patients of Group D received loading dose of dexmedetomidine 1µg/kg over 10 min, followed by dexmedetomidine infusion at rate of 0.5µg/kg/h while patients of Group C received equal volume of normal saline. Primary end points were changes in heart rate, blood pressure, electrocardiogram, emergence time and serial blood glucose levels. Any adverse effects related to dexmedetomidine or anesthetic technique, were noted as secondary outcome. **Results:** Patients of Group D showed comparatively lower intraoperative heart rate and mean arterial blood pressure with no significant changes in cardiac rhythm. The blood glucose concentration showed 20% increase after surgery in patients of Group D versus 35% increase in patients of Group C, with statistically significant difference. The emergence time in patients of Group C was significantly lower when compared to patients of Group D. **Conclusion:** Dexmedetomidine infusion has effectively attenuated the metabolic and hemodynamic changes during laparoscopic surgery with inherent advantages of analgesia, sedation and anaesthetic sparing effects.

Keywords: Dexmedetomidine, Laparoscopic surgery, Metabolic and Hemodynamic stress response, Pneumoperitoneum.

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Introduction

Laparoscopic surgery leads to several pathophysiological changes due to pneumoperitoneum which manifested by hemodynamic changes of hypertension and tachyarrhythmia, metabolic changes of hyperglycaemia and neurohumoral changes by increased levels of catecholamines.^[1] Adaptation of these stress responses during laparoscopic surgery is of high relevance to the anaesthesiologists. Moreover, surgical patients are inevitably anxious due to their underlying fears which reflect the stress of the circumstances. The choices of premedication and anesthetic techniques would influence these responses by modulating the pathophysiological pathways.^[2]

The therapeutic armamentarium to offset these stress responses during laparoscopic surgeries includes a wide diversity of pharmacological agents to improve outcome which include high doses of opioid analgesics, α_2 -adrenergic agonist, beta adrenergic blockers and vasodilators. Dexmedetomidine, α_2 adrenergic agonist, is used as an anesthetic adjuvant to attenuate the intraoperative hemodynamic response by reducing the nociceptive transmission and decreasing the norepinephrine concentration in serum. It also provides anxiolysis, sedation, and analgesia without any respiratory depression. It simultaneously potentiates the effects of general anesthetic agents and suppress the sympatho-adrenal response to noxious stimuli of laryngoscopy and laparoscopic surgery.^[3-6]

The objective of this prospective randomized double blind control study was to evaluate the clinical efficacy of dexmedetomidine infusion to attenuate the metabolic and hemodynamic changes during laparoscopic surgery by analysing the perioperative serial blood glucose levels and hemodynamic changes.

Subjects and Methods

After approval of the protocol by the Institutional Ethical Committee, written informed consent was obtained from all patients. The study was conducted on sixty otherwise healthy adult patients of American Society of Anaesthesiologist (ASA) physical status I and II of either gender, aged 28-58 years, weighing less than 65 kg, and scheduled for elective laparoscopic surgery under general anesthesia.

Patients with history of any cardiac or respiratory disease, hypertension, obesity (BMI >24kg/m²), hepatic or renal dysfunction, endocrinal or metabolic disorders, or were receiving medications which affect sympathetic response or hormonal secretions, were excluded from the study. Complicated surgeries of more than 2 h, patients with anticipated difficult airway or refused to participate, were also excluded from the study.

Randomization schedule

Patients were randomized into two study groups by computer generated random number table, each receiving a sealed opaque envelope of study medication. Patients of Group D received loading dose of dexmedetomidine 1µg/kg over 10 min, followed by dexmedetomidine infusion at rate of 0.5µg/kg/h and patients of Group C received an equal volume of saline. The study was conducted in double-blind manner by use of coded syringe.

Anesthetic Technique

All selected patients were given tablet Alprazolam 0.25 mg and tablet Ranitidine 150 mg orally the night before surgery and were kept fasting for 6 hour prior to surgery. They were operated during morning hours to minimize variability in the secretion of hormones.

On the day of surgery, they received premedication of glycopyrrolate 0.2 mg intramuscularly 30 min prior to induction of anesthesia. On arrival to operation theatre, Multipara monitor was attached and vital parameters of heart rate, systemic blood pressure, peripheral oxygen saturation (SpO₂) and electrocardiogram (ECG) were monitored continuously. Patients of Group D (n = 30) received loading dose of dexmedetomidine 1µg/kg over 10 min, followed by dexmedetomidine infusion at rate of 0.5µg/kg/h and patients of Group C (n = 30) were given equal amount of saline solution, in double blind manner.

All patients received ondansetron (4 mg), midazolam (2 mg) and fentanyl (2µg.kg⁻¹) before induction of general anesthesia. After preoxygenation, the anesthesia was induced with propofol (1%) till loss of verbal command and total dose of propofol for requirement for induction was noted. Tracheal intubation was facilitated by vecuronium 0.1 mg kg⁻¹ and anaesthesia was maintained with isoflurane and 60% nitrous oxide in oxygen. The patient were mechanically ventilated using close circuit with a tidal volume of 8 ml/kg,

respiratory rate of 12 breaths/min and I: E ratio of 1:2 in volume-controlled mode. Five minutes after abdominal insufflation by carbon dioxide, the lung mechanics were adjusted to maintain normocapnia (EtCO₂ value of 35-40 mm Hg) and intra-abdominal pressure was maintained between 12 and 15 mm Hg throughout the surgery. The degree of muscle relaxation was maintained using the train-of-four ratio of <25% with supplemental doses of vecuronium bromide (0.05 mg).

Intraoperative assessment and management

Patients were assessed for changes in the heart rate and blood pressure prior to premedication, before induction, after intubation and after pneumoperitoneum, followed by at every 5 min interval till end of surgery and post extubation. Intraoperatively, any bradycardia or tachycardia, hypotension or hypertension was managed by adjusting the infusion rate of dexmedetomidine and dial concentration of isoflurane to maintain systolic blood pressure within 20% of preoperative value.

All infusions and isoflurane were discontinued 10 min prior to end of surgery and surgeon administered 20 mL of ropivacaine 0.2% in the peritoneum through trocar in all patients. The residual neuromuscular blockade was antagonized with appropriate doses of neostigmine (0.05 mg/kg) and glycopyrrolate (0.01mg/kg). Ventilation was continued to eliminate isoflurane until signs of awaking appeared.

Patients were extubated after achieving signs of adequate reversal and patients were able to obey simple commands. Emergence time, defined as the interval between the discontinuation of anaesthetics to response of eye opening to verbal command, was recorded. All patients received ketorolac 30 mg intravenously at the end of surgery for postoperative analgesia.

Patients were transferred to post-anesthesia care unit and monitored for any respiratory depression, hemodynamic changes, nausea/vomiting, shivering or any other drug or technique related adverse effects.

Blood samples were analysed by using Glucometer (Abbott Optium Xceed) for blood glucose level preoperatively, at 30 min after start of surgery and then after at 150 min (2.5 h) of surgery.

Study population size

The sample size was calculated for purposive sampling in consultation with statistician who computed that approximately 23 patients should be included in each group to ensure the power of study 80% and alpha error of 0.05 with confidence limit of 95% for detecting reduction by at least 20% in enhanced hemodynamic and metabolic parameters. The final sample size was set at 60 patients for better validation of results.

Statistical analysis

The obtained data are expressed as mean and standard deviation (SD), considering the latter as the best predictor. The results were analyzed using Stat Graphic Centurion for windows, (Stat point technologies INC, Warrenton, Virginia). Patient's characteristics and operative data was compared using unpaired t-test and Chi-square test. Differences in blood glucose levels were analysed by using

student's t-test. A 'p' value of <0.05 was considered to indicate statistical significance.

Results

One twenty adult patients were selected for elective laparoscopic surgery were screened, out of which, sixty patients were excluded due to not meeting the inclusion criteria (48) or declined to participate (12), thus only 60 patients were randomized to the treatment with dexmedetomidine infusion (n-30) or placebo (n-30). There was no protocol deviation and data of all patients were included for statistical analysis.

Patients in both groups did not differ with respect to patient's characteristics, biochemical and procedure related data. The induction dose of propofol was significantly less in patients of Group D as compared to Group C (1.67±0.34 mg/kg) versus (2.13±0.49 mg/kg), respectively. [Table 1]

In the present study, the rise in mean heart rate and blood pressure after intubation at 1st, 2nd, 3rd, and 5th min, was significantly lower in patients of dexmedetomidine group as compared to control group. In patients of both groups, there was increase in blood pressure and heart rate after intubation compared to baseline but in patients of dexmedetomidine group, blood pressure came to baseline after 3 min of intubation. Mean heart rate also increased in both groups compared to baseline but it came back to baseline at 5 min in patients of dexmedetomidine group. Hemodynamic parameters recorded at specified timings during the study are shown in Table -2 and 3.

In patients of Group D, the hemodynamic changes were more stabilized intraoperatively when compared to patients of Group C. Patients of Group D needed lesser amount of isoflurane (dial concentration at 0.6 to 1) to maintain the systolic blood pressure as compared to patients of Group C where dial concentration of isoflurane was kept at 1 to 1.5 to maintain the desired level of blood pressure.

Blood glucose levels were significantly increased during the laparoscopic surgery and remained increased postoperatively in patients of both groups. This postoperative increment was significantly more pronounced in patient of Group C (127.13±25 versus 117.46±21 mg/dl; P<0.05). [Table -4]

The emergence time was significantly lesser in patients of control group. Respiratory rate and peripheral oxygen saturation (SpO₂) were comparable with no episode of desaturation at any time. No significant anesthesia or surgical complications occurred during the study.

Table 1: Demographic Data.

Parameters	Group D	Group C	P value
Age (years)	43.29 ± 8.3	45.31 ± 6.7	0.09
Weight (kg)	59.4 ± 7.8	60.21 ± 6.3	0.08
Gender (M/F)	12/18	13/17	0.69
ASA status I/II	21/09	19/11	0.61
Duration of Surgery (min)	96.8 ± 21.3	105 ± 18.4	0.06
Propofol for induction (mg/kg)	1.67 ± 0.34	2.13 ± 0.49	*0.045

Data are expressed as Mean ± SD or as absolute numbers, *p value is statistically significant

Table 2: Changes in heart rate during anesthesia

Heart rate (beats/min)	Group D	Group C
Base line	84.23 ± 7.28	85.61 ± 10.39
After premedication	71.92 ± 8.65	79.43 ± 6.81
After induction	69.43 ± 7.45	74.27 ± 8.75
After intubation	77.83 ± 8.13	87.36 ± 9.15
After pneumoperitoneum	79.78 ± 9.21	93.72 ± 7.39
Intraoperative period	73.2 ± 10.4	84.78 ± 11.34
Post extubation	87.4 ± 12.36	97.15 ± 12.17

Data are expressed as mean ± SD;

Table 3: Changes in systolic blood pressure during anesthesia.

SBP (mm Hg)	Group D	Group C
Base line	123.4 ± 17.3	127.2 ± 11.5
After induction	102.7 ± 6.5	112.5 ± 7.4
After intubation	115.8 ± 2.8	135.8 ± 2.8
After pneumoperitoneum	117.5 ± 6.2	128.4 ± 5.6
Intraoperative period	99.71 ± 5.3	116.77 ± 4.1
60 min	99.62 ± 2.7	118.74 ± 6.3
Post extubation	112.43 ± 15.7	133.37 ± 14.6

Data are expressed as mean ± SD; SBP- systolic blood pressure

Table 4: Perioperative blood glucose concentration (mg/dl)

Time/Groups	Group D	Group C	P value
Preoperative (Baseline)	89.8 ± 23	93.2 ± 14	0.62
Intraoperative after 30 min	128.4 ± 16	125.7 ± 17	0.57
Postoperative after 150 min (2.5 h)	119.7 ± 24	129.3 ± 19	0.039*

*P value is statistically significant

Discussion

Normally, the nervous and endocrine system act simultaneously to precise fluctuations in blood pressure and ensure to maintain it at an appropriate level. Laryngoscopy and laparoscopy is associated with increased blood pressure, heart rate and plasma catecholamine concentrations which could be attenuated by opioids, alpha 2-adrenergic agonist, beta-adrenergic blocking agents, vasodilators and local anesthetic agents.

Normotensive patients can develop sympathetic over activity due to pain, light plane of anesthesia and hypercapnea during intraoperative period. This adrenergic response is caused by nociceptive pathways and humoral mediators, originating from the surgical site and are detrimental in elderly and hemodynamically compromised patients.

In the present study, premedication with intravenous dexmedetomidine before induction of anesthesia has attenuated the hemodynamic response of heart rate and blood pressure of intubation and laparoscopic surgery but could not totally abolish the metabolic and hemodynamic stress responses. In spite of hemodynamic effects of pneumoperitoneum, variations of blood pressure and heart rate never outdid more than 16% of baseline which could be attributed to the known sympatholytic effects of the dexmedetomidine.

Dexmedetomidine regulates the autonomic and cardiovascular systems by acting on blood vessels to modulate the heart rate and blood pressure by inhibiting norepinephrine release. Many studies have investigated the effects of dexmedetomidine before induction of anesthesia and reported significant reduction in heart rate and blood pressure.^[7,8]

Bhattacharjee et al evaluated the efficacy of dexmedetomidine in patients undergoing laparoscopic surgery, by observing the significantly lower mean arterial pressure and heart rate in patients of dexmedetomidine group. They concluded that dexmedetomidine has improved the intra and postoperative hemodynamic stability without prolongation of recovery.^[9]

Gupta K et al studied the 60 patients of comparable demographic profile and concluded that premedication with dexmedetomidine at a dose of 1µg/kg attenuated the adverse hemodynamic stress response of laryngoscopy and exhibited linear hemodynamic pharmacokinetics in the dosages range of 0.5 to 1µg/kg.^[10]

Masoodi T et al did a study on 60 adult patients, scheduled for elective laparoscopic surgery and concluded that dexmedetomidine infusion in doses of 0.6 µg/kg/h after the loading dose of dexmedetomidine (1µg/kg), was significantly more effective for attenuating the hemodynamic changes of laryngoscopy, tracheal intubation and pneumoperitoneum during laparoscopic cholecystectomy. The hemodynamic results of present study were in agreement of their study.^[11]

Bakhamees HS et al studied the effects of dexmedetomidine on morbidly obese adult patients undergoing laparoscopic gastric bypass by giving 0.8µg/kg bolus of dexmedetomidine, followed by dexmedetomidine infusion in dose of 0.4 µg/kg/h. They concluded that the intraoperative infusion offered a better control of intraoperative and postoperative hemodynamics.^[12]

Blood glucose levels have been shown to correlate with catecholamine levels in surgical trauma patients.^[13] The characteristic metabolic effect of surgical stress led to greater activation of neuroendocrine response and hepatic gluconeogenesis under perioperative conditions, which corresponds to hemodynamic changes and postoperative pain. There is strong correlation between hyperglycaemia and poor outcome. Bessey et al have suggested that increased circulating concentration of catecholamine, glucagon and cortisol can evoke the changes in carbohydrate metabolism which do occur immediately surgical trauma.^[14]

Poldrman JAW et al did their study on patients with type II diabetes mellitus, undergoing major abdominal surgery or cardiothoracic surgery and did the continuous glucose monitoring (CGM) to improve perioperative treatment without increasing the risk of hypoglycaemia. They treated all patients according to same algorithm, targeting for a plasma glucose of 72-180 mg/dl and concluded that intravenous continuous glucose monitoring did not improve intraoperative glycaemic control compared with hourly point-of-care measurement, when targeting for glucose between 72 and 180 mg/dl.^[15]

In the present study, serial blood sugar levels were measured at specific time interval, and we found increased blood glucose concentration during and after surgery in patients of both groups due to metabolic response to surgical trauma. This increment in blood glucose level was more pronounced in patients of control group than in patient who were receiving intraoperative dexmedetomidine infusion.

Dexmedetomidine has sedative and analgesic sparing effects via central actions in the locus coeruleus and in the dorsal horn of the spinal cord. In the present study, the induction

dose of propofol to produce loss of consciousness and verbal command, was significantly lower in patients of dexmedetomidine group.

Several studies concluded that perioperative use of dexmedetomidine is associated with a significant decrease in the consumption of inhalational agent and analgesia in dose dependent manner.^[16,17] Isoflurane depresses the excitable tissues at all levels of nervous system by interacting with neuronal membranes, resulting in a decreased release of neurotransmitters and transmission of impulses as well as general depression of excitatory post synaptic responsiveness.^[18]

In the present study, isoflurane was used as main anaesthetic agent and its requirement was also reduced to maintain the anaesthetic depth. Synergism between isoflurane and dexmedetomidine was observed in the present study.

Schcinim B et al concluded from their study that dexmedetomidine not only attenuated the sympatho-adrenal responses to intubation but also reduces the need for thiopentone and preoperative fentanyl.^[19]

Dexmedetomidine was associated with significant longer emergence time and time to total recovery from anesthesia. In the present study, the emergence from anesthesia was slower but smooth in patients of dexmedetomidine group.

In the present study attempts were done to standardize anesthetic and postoperative pain management to avoid influence on glucose metabolism of patients, so the alterations in postoperative glucose metabolism presumably were the consequences of surgical trauma. Attenuation of metabolic and hemodynamic stress responses to surgery might enable laparoscopic surgeries in obese, hypertensive and cardiac compromised patients for improving their outcome.

Conclusion

There was effective attenuation of metabolic and hemodynamic stress responses of laparoscopic surgeries by dexmedetomidine infusion, which was assessed by analysing the perioperative serial blood glucose levels and hemodynamic changes. Dexmedetomidine offered many inherent advantages of analgesia, sedation and anesthetic sparing effect and patients showed longer but smooth emergence from anaesthesia.

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