The Effect of Dexmedetomidine on Haemodynamic Changes, Extubation Time and Sedation during Laparoscopic Hysterectomy

ABSTRACT

Background and Aim Suppression of deleterious effect of pneumoperitoneum is a very important goal of laparoscopic surgeries. Dexmedetomidine is a highly selective α2-adrenoceptor agonist that causes centrally mediated reduction of sympathetic nervous system activity and lead to sedation and analgesia. The aim of our study was to evaluate the effect of dexmedetomidine on haemodynamic response of intraoperative events like laryngoscopy, endotracheal intubation, pneumoperitonieum and extubation time, and sedation during and after laparoscopic hysterectomy.

Methods A prospective, randomised and double blind study was done on 50 female patients, undergoing laparoscopic total hysterectomy. All patients were randomly allocated into two groups; group D (dexmedetomidine) and group C (normal saline). Group D received inj dexmedetomidine 1 µg/kg, diluted in 50 ml of normal saline over 15 min of duration and 0.4 µg/kg/h infusion was started till the pneumoperitoneum continues. Group C patients receive normal saline infusion. Parameter recorded was heart rate (HR), systolic blood pressure (SBP), diastolic blood pressure (DBP), mean blood pressure (MAP), SPO2 and ETCO2. Assessment of sedation was done at extubation than every 15 min for 2 h by Ramsay sedation score (RSS).

Results Among haemodynamic profile, mean arterial pressure and HR after drug administration were significantly lower in perioperative period, particularly at intubation and extubation time in dexmedetomidine (group D) as compared with controls (group C). The extubation time was significantly lower in the dexmedetomidine groups than in the control group. No significant change was seen in the sedation score in both the groups.

Conclusion Dexmedetomidine use during laparoscopic hysterectomy leads to attenuation of hemodynamic response to pneumoperitonium and decrease in extubation time with no change in sedation level of the patients.

KEYWORDS dexmedetomidine, laparoscopic hysterectomy, pneumoperitonium

INTRODUCTION

All the laparoscopic surgeries have several advantages, at the same time the procedure is not free from risk. Pneumoperitonium creation leads to deleterious changes in cardiovascular, respiratory and acid base balance systems1. Haemodynamic changes are caused by release of catecholamine, vasopressin, carbon dioxide absorption and due to the position of the patients2,3. Release of vasopressin and catecholamine causes sympathetic nervous system stimulation, leads to increase in both mean blood pressure (MAP) and systemic vascular resistance (SVR). Further rise in MAP and SVR are caused by Trendelenburg and lithotomy positions. Trendelenburg position causes redistribution of blood from extremities to heart and lithotomy causes rise in SVR4,5.

To prevent and control these changes, several methods and pharmacological agents have been introduced. Amongst pharmacological agents, nitroglycerine, opioids, beta blocker, esmolol, gabapentin, pregablin, clonidine and dexmedetomidine are mostly used to provide haemodynamic stability during intraoperative period6–13.
Dexmedetomidine was introduced in 1999 for use in human; it is an imidazole derivative and a α₂-adrenergic receptor agonist with eight times more specific action than clonidine, produces sedative, analgesic and sympatholytic effects. It has been used to blunt haemodynamic response of pneumoperitoneum by decreasing sympathetic tone during laparoscopic surgeries and maintains blood pressure and heart rate (HR). It also diminishes the requirement of analgesic during operation. It provides sedation without any respiratory depression.

The first aim of our study was to evaluate the effect of dexmedetomidine on haemodynamic response of intraoperative events like laryngoscopy, endotracheal intubation, pneumoperitoneum and extubation during laparoscopic hysterectomy. The second aim was to compare the extubation time and third aim was to observe the effect on sedation and adverse effect due to dexmedetomidine.

MATERIAL AND METHODS

A prospective, randomised and double blind study was conducted after taking written informed consent from the patients and the approval of institutional ethical committee. The study was conducted at Rama Medical College, Mandhana, Kanpur, Uttar Pradesh from January 2015 to December 2015. After routine preanaesthetic checkup (PAC) and investigation, a total number of 50 female patients of American Society of Anesthesiologist (ASA) grade I and II posted for laparoscopic hysterectomy under general anaesthesia were included in this study.

Exclusion criteria were >70 years, patient with body mass index more than 35, previous abdominal surgery, known asthmatics, ischaemic heart disease, hypertension, left ventricular dysfunction, atroventricular conduction disturbances, decreased autonomic control, medication like clonidine, methyl dopa, phenetoin, benzodiazepine, monoamine oxidase inhibitors (MAO) and who required transfusion during surgery.

A total number of 50 patients were randomly divided into two groups; group D (dexmedetomidine) and group C (control). The group and name of patients were coded and concealed till the statistical analysis of the results was completed. Randomisation was done with block randomisation method with black sealed envelopes by anaesthetists who were not involved in anaesthetic management of patients and collection of data, both bolus infusion and maintenance infusion of study solution were prepared by nurses who were not involved in the study.

Patients were taken inside the operation theatre (OT) and five lead electrocardiograms (ECGs), noninvasive blood pressure (NIBP), pulse oximetry (SPO₂) and end tidal carbon dioxide (ETCO₂) monitoring were attached to the patients (monitor GE-D-FPD 15-00). Different parameters were recorded: HR, systolic blood pressure (SBP), diastolic blood pressure (DBP), MAP, SPO₂ and ETCO₂. Intravenous access is secured and intravenous fluid (IVF) was started (crystalloids). Premedication done with injection (inj) pantoprazole, inj glycopyrolate 0.02 mg/kg, inj fentanyl 1.5 µg/kg was given. Patients of group D received inj dexmedetomidine 1 µg/kg, diluted in 50 ml of normal saline over 15 min duration. Then inj dexmedetomidine 0.4 µg/kg/h infusions was started till the pneumoperitoneum continues. Patients of group C receive 50 ml normal saline infusion for 15 min and infusion of normal saline till pneumoperitoneum ceases. All patients were induced with inj propofol 2 mg/kg and inj succinylcholine 1.5 mg/kg. After endotracheal intubation, anaesthesia was maintained with nitrous oxide, oxygen (70:30) and inj vecuronium bromide 0.15 mg/kg bolus, and one forth of bolus dose as maintenance over every 20 min (Datex–Ohmeda S5 Avance). Infusion of intermittent inj fentanyl 0.5 µg/kg was given in every patient after 1 h. ETCO₂ was maintained between 35 and 45 mm Hg and intra abdominal pressure not more than 14 mm Hg.

Infusion of test drug were switched off at the end of pneumoperitoneum. Inj paracetamol 1 g IV infusion was given in every patient for post operative pain relief. Reversal of residual neuromuscular blockade was done with inj neostigmine 0.5 mg/kg and inj glycopyrolate 0.02 mg/kg. After extubation, all patients were shifted to recovery unit where patients were assessed for sedation by Ramsay sedation score (RSS). Measurement of different parameters were done at baseline, 10 min after infusion of test drug infusion, just before induction, 1 min after endotracheal intubation, before pneumoperitoneum, than every 15 min, 1 min after extubation and 15 min after extubation. Extubation time was defined from the closer of study solution infusion to the extubation. Assessment of sedation was done at extubation than every 15 min for 2 h by RSS. All patients were observed for adverse effects like bradycardia, tachycardia, hypotension and hypertension (>25% or <25% of baseline values), RSS >4 and SPO₂ <90%.

STATISTICAL ANALYSIS

Statistical analysis of continuous data with normal distribution is given as mean ± S.D. Comparisons were performed with Student’s t test or Mann–Whitney tests or X²-test or with Fisher’s exact test, when appropriate. Propensity score matching analysis was performed to select background-matched patients to the dexmedetomidine group. P < 0.05 was considered statistically significant.

RESULTS

A total number of 50 female patients were enrolled in the study. Patients of both the groups were compared with respect to age, weight, duration of surgery, change in HR, MBP, extubation time and change in sedation.
score after extubation for 120 min. Demographic variables and duration of surgery were comparable in both the groups with no statistical significance (Figs. 1, 2).

Among haemodynamic variable, mean baseline HR was almost similar but after 10 min, before, after intubation, at CO₂ insufflations, during intraoperative period and 15 min after extubation; there was a significant rise in HR was seen in group C, whereas HR in group D was more stable (P < 0.05) (Table 1).

MBP was also comparable in both group C and D with loading dose and ongoing infusion of dexmedetomidine. MAP fell significantly in group D and there was not many changes are seen during intubation and extubation; in group C, there was significant rise in MAP seen during endotracheal intubation and extubation (P < 0.05) (Table 2).

Duration of extubation time in group D (4.18 ± 3.24) was significantly less as compared to group C (4.18 ± 3.24) (P < 0.05).

Sedation score after extubation for 2 h in group D was 4.01 at extubation that came to 1.32 after 2 h and in group C it was 3.45 at extubation that reduced to 1.12 after 2 h. That was statistically insignificant (P > 0.05) (Fig. 3).

No adverse events occur in our study in both the groups.

**DISCUSSION**

In our study, we observed the effect of dexmedetomidine on haemodynamics during laparoscopic hysterectomy patients. During laproscopic surgeries, because of pneumoperitoneum, there was a release of vasopressin and neurophysin. Plasma concentration of epinephrine, norepinephrine and rennin was also increased

Dexmedetomidine is a stereoisomer of medetomidine, with chemical formula 4-[(1S)-1-(2,3-imethylphenyl)ethyl]-1H-imidazole, is a highly selective α₂-adrenergic receptor (AR) agonist with a relatively high ratio of α₂/α₁-activity (1620:1 as compared to 220:1 for clonidine).

Centrally, α₂-AR agonists cause analgesia and sedation by inhibition of substance P release in the nociceptive pathway at the level of the dorsal root neuron and by activation of α₂ AR in the locus coeruleus. Suppression of activity in the descending noradrenergic pathway, which modulates nociceptive neurotransmission, terminates propagation of pain signals, leading to analgesia.

In the spinal cord, activation of both α₁, C and α₂-ARs, situated in the neurons of superficial dorsal horn especially lamina II, directly reduces pain transmission by reducing the release of pronociceptive transmitter, substance P and glutamate from primary afferent terminals, and by hyperpolarising spinal interneurons via G-protein-mediated activation of potassium channels. Postsynaptic activation of central α₂-ARs results in sympatholytic effect leading...
to hypotension and bradycardia, an effect judiciously used to attenuate the stress response of surgery\textsuperscript{23-26}, so to summarise dexmedetomidine act like a break and decrease central sympathetic outflow response by acting on all three \( \alpha_2 \) receptors, \( \alpha_2A, \alpha_2B \) and \( \alpha_2C \) present in brain (vasomotor center and locus ceruleus) and spinal cord lead to suppression of norepinephrine release from brain and substance P from spinal cord lead to bradycardia, hypotension and analgesia with minimal respiratory depression.

Varying concentration of dexmedetomidine has been studied but most of the study used loading dose of 1 mcg/kg over 15 min than infusion of 0.2–0.5 mcg/kg/h as maintenance. In this study, we also used loading dose and maintenance dose at 0.4 mcg/kg/h, because dose more than 0.4/\( \mu \)g/kg may lead to excessive sedation and delayed extubation. Different studies showed similar results.

Use of dexmedetomidine infusion intraoperatively reduced required dose of propofol and fentanyl to maintain required state of anaesthesia and reduced dose of morphine and better recovery.

Stress response of intubation is attenuated with dexmedetomidine, in group D patient’s HR after intubation changes from 71.84 to 74.93 at the same time in group C; it was 95.82–102.38, similarly MAP in group D changes from 67.14 to 71.14 and in group C from 79.14 to 89.42 mm Hg. Different studies showed similar results as in our study.

Studies showed that dexmedetomidine decreases the circulating catecholamines up to 90% which lead to sympatholysis and haemodynamic stability. It significantly attenuates responses to noxious stimuli, increases intraoperative cardiovascular stability out of which most of the effects are concentration dependent\textsuperscript{16}. Similar observation was shown in our study that after CO\textsubscript{2} insufflations and after 1 min of extubation, there was stable haemodynamics seen in group D as compared to group C. Mean HR after CO\textsubscript{2} insufflations and after 1 min of extubation in group C was 89.45 and 89.92, and in group D it was 64.38 and 59.75. MAP after CO\textsubscript{2} insufflations and after 1 min of extubation in group C was 81.94 and 87.15, and in group D it was 64.87 and 66.33 mm Hg.

Dexmedetomidine exerts its sedative and anxiolytic effects through activation of \( \alpha_2 \) receptors in locus ceruleus, a major site of noradrenergic innervations in CNS. The locus ceruleus has been implicated as a key modulator for a variety of critical brain functions, including arousal and sleep anxiety. The sedation produced by \( \alpha_2 \)-adrenoceptors agonists unlike that produced by traditional sedatives such as benzodiazepine and propofol does not depend primarily on activation of GABA system. Dexmedetomidine produces a ‘co-operative form’ of sedation, in which patients easily gets transition from sleep to wakefulness and task performance when aroused. Cognitive integrity was well preserved in patients receiving dexmedetomidine\textsuperscript{17}.

Study with dexmedetomidine alone\textsuperscript{18} and in comparison with midazolam–fentanyl\textsuperscript{19} in a concentration of 0.2 \( \mu \)g/kg/h showed that the good sedation level could be achieved with dexmedetomidine. We used dexmedetomidine 0.4 \( \mu \)g/kg/h infusion and the results of our study were comparable to the results of the above studies.

### CONCLUSION

Dexmedetomidine 1 \( \mu \)g/kg as bolus over 15 min and 0.4 \( \mu \)g/kg/h infusion during intraoperative duration leads to better maintenance of haemodynamics during intraoperative period particularly during laryngoscopy, endotracheal intubation, CO\textsubscript{2} insufflation and at extubation. There was significant decrease in extubation time with use of dexmedetomidine. There was no significant change in sedation score with use of dexmedetomidine. We do not encounter any adverse effect due to dexmedetomidine.

### REFERENCES

Dexmedetomidine is in laparoscopic hysterectomy