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A Study on Effect of Intravenous Infusion of Dexmedetomidine in General Anesthesia on Perioperative Analgesic Requirements

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Abstract

Background: Dexmedetomidine is an alpha-2 receptor agonist having sympatholytic properties which provides very good hemodynamic stability during surgery without any adverse effect on respiration. But its anti-nociceptive property has not been studied much. *Aim:* To study the effects of intra operative infusion of dexmedetomidine on perioperative analgesics requirement, sedation and recovery characteristics in patients undergoing laparoscopic surgery. *Material and Methodology:* Total 50 subjects posted for elective laparoscopic surgery were selected and divided in group D and C, 25 in each. D group subjects were given an initial loading dose of dexmedetomidine 1 g/kg IV over 10 min before the induction of anesthesia, followed by continuous infusion at 0.6μg/kg/hr. while Group C patients received equal amount of 0.9% saline intraoperative. Requirement of analgesic in postoperative period was estimated along with visual analog score, sedation score and recovery characteristics. *Results:* In D group 20 out of 25 subjects required either one or two doses of analgesic while in C group 19 out of 25 subjects required either three or four doses ($P<0.05$). Duration of analgesia was 8.32±1.55 hours in D group while 1.20±0.35 hours among C group ($P<0.05$). Among D group Statistical significant increase in sedation score at 10 minutes (4.57±0.38) postoperative till 24 hours postoperative(1.10±0.64) was found as compared to the group C [3.94±0.55 (10 minutes); 1.44±0.49 (24 hours)]. Modified post anesthetic discharge score was 12.25±1.35 and 9.49±1.39 among D and C group subjects respectively ($P<0.05$). *Conclusion:* Dexmedetomidine provides excellent analgesia. It induces sedation but do not alter recovery.

Keywords: Dexmedetomidine; Analgesia; Laparoscopy; Visual Analog Score.

Introduction

Alpha-2 adrenergic receptor agonists and opioids act by different mechanisms and thus their combination produces a synergistic analgesic effect without increasing the respiratory depression that is often associated with opioid use. Furthermore, the opioid-sparing effect is generally associated with a reduction in adverse effects such as nausea and vomiting. Therefore, α2-AR agonists have been found to be particularly useful in perioperative conditions.

Alpha-2 agonists like dexmedetomidine reduces the requirements of an anesthetic agent and they possess sympatholytic properties so provide good hemodynamic stability during the intraoperative period [1]. Dexmedetomidine blunts hypertensive responses associated with surgical Stimulation. It also decreases level of plasma epinephrine and nor epinephrine during perioperative period [2,3]. Dexmedetomidine blunts hypertensive responses associated with surgical Stimulation [4].

These properties make dexmedetomidine favorite in general anesthesia. In addition patients treated with dexmedetomidine were discharged earlier [5]. Analgesic effect of dexmedetomidine is quite different from opioids and it can replace opioids in general

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anesthesia [6,7,8]. So we decided to evaluate analgesic property of dexmedetomidine.

Material and Methodology

Present double blind prospective study was conducted on 50 patients aged 35 to 65 years with American Society of Anesthesiologists (ASA) status of 1 and 2 and scheduled for laparoscopic surgery at our Hospital. Patients were randomized into 2 groups, Group C and Group D using computer generated random numbers with 1:1 allocation ratio.

Written informed consent from each subject and approval of institutional ethics committee was taken before starting the study. Following subjects were excluded from the study:

- Patients using α2-adrenergic receptors antagonists or any other antihypertensive drugs.
- Patients having dysrhythmia by ECG.
- Body weight more than 100 Kg.
- Height less than 150 cm.
- Heart rate <50/min, first or second- or third degree heart block.
- Patients having cardiac dysfunction, hepatic or renal disease.
- Patient's refusal.

All the patients underwent a detailed pre anesthetic check-up and were explained entire procedure. They were electively kept nil by mouth for at least 6 hours before surgery. After the patient was shifted to the theatre, standard monitors like ECG,

NIBP, and pulse oximetry were applied. Entropy was also connected. Initial values of heart rate (HR), saturation (SPO_2), blood pressure (NIBP), response entropy (RE) and state entropy (SE) were noted. Intravenous line secured with one 18 gauge cannula and another 20 gauge for infusion of study drug in all the patients and intravenous fluid 6-12ml/kg/hr was started. All patients received ondansetron 0.15 mg/kg, glycopyrrolate 0.004 mg/kg and fentanyl 1 μg/kg IV as premedication. The study medication [dexmedetomidine 1μg/kg in 50 ml 0.9% NS] was prepared by anesthetist not involved in this study. Normal saline was similarly prepared in similar prescribed format for standardization. Appropriate labels were allotted and attached beforehand. Both labeled solution received by the particular patients with allocated random serial numbers, over 10min after premedication. Then, Patients were induced with propofol 1.5 - 2 mg/kg and vecuronium 0.1 mg/kg IV after pre oxygenated with 100% oxygen for 5 minutes using Bain's circuit. All patients were intubated with appropriate sized cuffed endotracheal tube. Anaesthesia was maintained by sevoflurane with dial setting of 0.8 to 1.5% in 50:50 nitrous oxide and oxygen mixture. The patients were mechanically ventilated using circle system to keep the EtCO2 between 35 and 45 mm Hg. Group D patients received continuous infusion at 0.6μg/kg/hr by a syringe infusion pump and similarly Group C patients received 0.9% normal saline as placebo. In each case, the mean arterial blood pressure (MAP) was maintained within normal range. Any shoot up in Mean arterial blood pressure rise 20% above baseline was treated by raising the dial setting of sevoflurane concentration upto 2% and IV nitroglycerin 5 mcg/min continuous IV infusion and titrated accordingly. Patients in whom MAP decreased>20% below baseline were treated with ephedrine 10 mg IV and reduction of the end-tidal sevoflurane concentration to 0.5% and IV fluids. Bradycardia (heart rate< 45 bpm) was treated with atropine 0.5-1 mg IV. Additional boluses of vecuronium 0.05 mg/kg IV were administered to maintaining muscle relaxation while surgery after assessment of neuromuscular function with train-of-four. Analgesia in form of fentanyl up to 1μg/kg IV was given based on RE reading. Our aim was to maintain both RE and SE in the range of 40-60. Intra abdominal pressure was maintained between 13-15 mm of Hg through the surgery. Total amount of fentanyl consumed by each patient was recorded. Dexmedetomidine infusion was stopped at 10min before the end of surgery.

Upon completion of surgery, each patient was extubated when they were able to follow verbal commands. All subjects were transferred to the postoperative care unit (PACU), where they were monitored for vitals and received nasal O_2 supplementation. Degree of pain was determined by 11 point 'visual analog scale (VAS) [9]. VAS measures severity of pain ranging from 0(no pain) to 10(worst pain imaginable). In this method patient decides how severe pain he/she is having and accordingly suggest numbers between 0-10. It was explained to the patients that this score will be used after the end of surgery to assess their pain.

Diclofenac sodium 2mg/kg IV was administered for rescue analgesia as a bolus dose if the pain score at rest remained higher than 3. Sedation levels were also recorded using the 'Ramsay sedation scale [10].'

VAS and RSS was recorded at following time intervals postoperative. 10min, 30min, 60min, 90min,

120 min, 6hr, 12hr, 18hr, 24hr. Recovery characteristics were assessed using modified post anesthetic discharge scoring system [11] (0 to 15) at 20 minutes after tracheal extubation.

Emergence time [12] was measured as the time interval between discontinuation of Sevoflurane and the time to open eyes spontaneously or on verbal commands.

Extubation time [12] was measured as the time interval between sevoflurane discontinuation and extubation. Extubation was carried out only when patient had spontaneous breathing, obeyed verbal commands and moved their limbs.

Each Observer who recorded data was blinded with respect to patients' group allocation.

Statistical Analysis

Results obtained from the study were expressed in mean ± SD, for non-parametric data Chi square test and for numeric data 'T' test was applied. "*P*" value less than 0.05 was considered as statistically significant. Statistical analysis was done with GRAPH PAD software (version 7.0 San Diego, USA).

Sample size was calculated using MedCalc software version 11.5.0.0. (MedCalc Software bvba, Acacialaan 22, 8400 Ostend, Belgium) Based on minimum mean difference of 25% in parameters with α =0.05 and β =0.20, sample size for each group was estimated at 22 with 80% power of study.

Results

Both the groups were comparable for demographic data and characteristics of surgery and no significant difference were found in these parameters (*P*>0.05) [Table 1]. However intraoperative fentanyl consumption was less among D group (65.89 ± 9.56) as compared to C group (136.22±14.56) (P<0.05) [Table 1]. All the subjects in the both the groups required rescue analgesia during postoperative period.

However, those who were given dexmedetomidine intraoperative needed significantly lesser number of doses of analgesic (*P*<0.05).

In D group majority of subjects 20/25 required either one or two doses of analgesic while in C group majority 19/25 required either three or four doses. This difference was statistically significant. (*P*<0.05) [Table2]. VAS was also significantly less throughout postoperative period among D group as compared to C group (*P*<0.05) [Table 3].

Duration of analgesia was longer among D group individuals compared to their counterparts. First dose of rescue analgesic among D group patients needed after 8.32 hours postoperative while only after 1.20 hours among C group (*P*<0.05) [Table 4].

Sedation was more among D group (*P*<0.05) [Table 5], but recovery was also better in dexmeditomidine administered group.(*P*<0.05) [Table 6].

Table 1: Demographic profile intraoperative fentanyl consumption of the Dexmedetomidine (D group) and Control (C group) Groups

Parameter	D group (n=25) (mean ± SD)	C group (n=25) (mean ± SD)	P value
Age (years)	45.32 ±6.05	44.96 ± 6.35	0.83
Weight (Kg)	61.28 ± 7.06	62.05 ± 6.57	0.69
Sex (male: female)	11:14	12:13	0.86
ASA I/ ASA II	12:13	11:14	0.56
Duration of surgery(min)	150.16 ±11.93	151.82 ± 12.40	0.63
Intraoperative fentanyl consumption (µg)	65.89 ± 9.56	136.22 ± 14.56	<0.0001

Table 2: Diclofenac (rescue analgesic) requirement among study groups during postoperative period (up to 24hours)

		D group	C group
Number of patients required rescue analgesia		25	25
Number of Doses (n=25)	0	0	0
	1	8	1* (S)
	2	12	5* (S)
	3	4	10* (S)
	4	1	9* (S)

*P<0.05

Table 3: Postoperative visual analogue score (VAS)

Timings (postoperative)	D Group VAS (mean ± SD) (n=25)	C Group VAS (mean±SD) (n=25)
10min	0 ± 0	1.52 ± 0.71
30min	0.28 ± 0.54	2.56 ± 1.12*
60min	0.32 ± 0.62	2.84 ± 0.98*
90min	0.68 ± 1.10	3.64 ± 1.28*
120min	1.64 ± 1.50	2.44 ± 1.29*
6hr	2.32 ± 1.85	5.44 ± 1.32*
12hr	3.96 ± 0.73	4.88 ± 0.67*
18hr	2.64 ± 1.35	4.88 ± 1.05*
24hr	4.28 ± 0.89	5.44 ± 1.42*

*P<0.05

Table 4: Comparison of time after which 1st dose of rescue analgesia given in both the groups postoperative

	D group (n=25)	C group (n=25)
Time to 1st dose of rescue analgesia given in postop period postoperative. (mean value in hours)	8.32 ±1.55 hrs	1.20 ± 0.35hrs*

*P<0.05

Table 5: Postoperative Ramsay sedation score (RSS)

Timings (postoperative)	D Group (mean ± SD) (n=25)	C group (mean ± SD) (n=25)
10min	4.57 ± 0.38	3.94 ± 0.55*
30min	4.37 ± 0.19	3.84± 0.27*
60min	4.08 ± 0.57	2.25± 0.52*
90min	3.48 ± 0.58	2.39± 0.35*
120min	2.60 ± 0.52	2.10± 0.20*
6hr	2.59 ± 0.62	1.55± 0.49*
12hr	1.86 ± 0.48	1.12± 0.44*
18hr	1.21 ± 0.48	1.38± 0.35*
24hr	1.10 ± 0.64	1.44 ± 0.49*

*P<0.05

Table 6: Recovery characteristics

	Group D (n=25)	Group C(n=25)
Emergence time (min)	9.86 ± 1.15	10.19 ± 2.20
Extubation time (min)	11.15 ± 1.39	11.85 ± 2.05
Modified post anesthetic discharge score	12.25 ± 1.35	9.49 ± 1.39*

*P<0.05

Discussion

Primary outcome from our study is need of fentanyl intraoperative, diclofenac sodium as rescue analgesia postoperative and visual analog score remained less among the patients who were given dexmedetomidine intraoperatively.

Our findings are similar to study done by Gurbet A. et al. [13] and Khaled Taha [14], where they proved intraoperative administration of dexmedetomidine reduces postoperative morphine requirement. Another study done by Nevriye salman et al. [15] also showed total number of doses of rescue analgesic reduces with dexmedetomidine usage.

The results we got have been proved in various animal and human studies. Experiments with thermal pain models in animals by Kayser V et al. [16] and Hall JE et al.[17] have shown that systemic administration of clonidine or dexmedetomidine has significant analgesic effects. However, conflicting results were documented in one study in an experimental model of secondary hyperalgesia, where volunteers who received clonidine at a dose sufficient to cause sedation experienced no analgesia [18].

Arain*et al.* [19] compared the efficacy of dexmedetomidine with morphine for postoperative analgesia. They observed similar pain scores in both the groups but the morphine group had escalated requirement of morphine by 66% to have an analgesic effect. Venn *et al.* [20] administered dexmedetomidine after the end of cardiac and general surgery andinvestigated the postoperative effects of drug in 119 patients. They found dexmedetomidine had an analgesia-sparing effect and decreased need for rescue sedation. Anxiolytic and analeptic properties of α2-agonists explains postoperative analgesia [21].

We also found that need of 1st dose of rescue analgesic was delayed with intraoperative dexmedetomidine use (Table 4).

Dexmedetomidine did cause some amount of sedation, but It did not cause any delay in recovery of the patient from anesthesia in fact recovery was better among D group. The sedation was also not that severe so as to warrant any interference from our side.

These results in our study were similar to one study of D.P. Bhattacharjee, Sushil Nayek et al [22]. Where they noticed dexmedetomidine induces sedation but do not affect recovery time. KN Gopal Krishna et al. [12] also found recovery is better in Dexmeditomidine administered group. However In another study of Toni Uhrich et al [23]. It was found that small dose of dexmedetomidine infusions caused sedation, impairment of memory and psychomotor performance.

Conclusion

From the study it is conclusive that dexmedetomidine infusion during laparoscopic surgery significantly reduces intraoperative fentanyl consumption and the amount of rescue analgesic that patients require to remain comfortable postoperative. Dexmedetomidine produces some amount of sedation in the patients, but the sedation was not significant enough to delay recovery from anesthesia.

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