Clinical Investigation

Dexmedetomidine ameliorates monitored anaesthesia care

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ABSTRACT

Background and Aims: Monitored anaesthesia care (MAC) is meant for procedures under local anaesthesia. Various drugs have been used for this purpose. The recently introduced alpha2 agonist, dexmedetomidine provides "conscious sedation" with adequate analgesia and minimal respiratory depression. Hence, the safety and efficacy of two doses of dexmedetomidine for sedation and analgesia were evaluated. **Methods:** A total of 90 patients were distributed in three groups of 30 each: Dexmedetomidine 0.5 μg/kg (DL), dexmedetomidine 1.0 μg/kg (DH) and normal saline (C). The initial loading dose was followed by maintenance infusion of 0.2-0.7 μg/kg/h of dexmedetomidine or equivalent volume of saline. Study drug was started at least 15 min before placement of local anaesthesia. Drugs were titrated to a target level of sedation (=3 on Ramsay sedation scale [RSS]). Midazolam 0.02 mg/kg for RSS < 3 and fentanyl 0.5 μg/kg were supplemented as required. The statistical analysis was performed using Chi-square test and mean and anova analysis. **Results:** In groups DL and DH fewer patients required supplemental midazolam, 56.7% (17/30) and 40% (12/30), compared with control, where 86.7% (26/30)needed midazolam supplements. $P = 0.000$. Both groups DL and DH required significantly less fentanyl (84.8 and 83.9 μg) versus control (144.2 μg). There was significantly increased ease of achieving and maintaining targeted sedation and analgesia in both dexmedetomidine groups when compared with placebo ($P = 0.001$). Adverse events observed with dexmedetomidine were bradycardia and hypotension. **Conclusions:** Dexmedetomidine in the doses studied was considered safe and effective sedative and analgesic for patients undergoing procedures under MAC.

Key words: Conscious sedation, dexmedetomidine, monitored anaesthesia care, respiratory depression

INTRODUCTION

Monitored anaesthesia care (MAC)[1] is a specific anaesthesia service for optimum care, comfort and safety of patients undergoing surgical procedures under local anaesthesia. Various drugs have been used for sedation and analgesia for such procedures viz. opioids, benzodiazepines, propofol,[2,3] etc. Most of these drugs have been associated with significant respiratory depression or delayed recovery period which is very undesirable for the patient as well as for the surgeon; in addition it increases in anxiety and stress level of the anaesthesiologist to manage the patient. The centrally acting alpha2 adrenergic agonists are being used now-a-days as an adjuvant to local anaesthetic agents during MAC. Clonidine and dexmedetomidine are commonly used drugs of this class. Dexmedetomidine has advantage of providing "conscious sedation" with adequate analgesia and no respiratory depression.[4] In addition, it has a sympatholytic effect thereby attenuating stress response to surgery and better haemodynamic stability.[5] All these beneficial effects make it most suitable for MAC. Thus, in this randomised, double-blind study, we evaluated the safety and efficacy of two doses of dexmedetomidine for sedation of patients undergoing surgical procedures under MAC.

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METHODS

This prospective, randomised, double-blind placebo controlled study was conducted after obtaining approval by the hospital ethical committee. Written informed consent was obtained from all the patients undergoing the study, scheduled for elective surgeries requiring MAC. Surgeries/procedures were expected to last at least 30 min and included general, plastic and otorhinolaryngological surgeries.

The inclusion criteria were, ASA Grade I/II, weight 40-80 kg, age 18-60 years and the exclusion criteria were patients with cardiac disease, congenital disorders, patients on psychotropic drugs; weight >20% of ideal body weight, significant systemic disorders, and patients with known sensitivity to local anaesthetics, opioids orbenzodiazepines, Patients on antihypertensives, antianxiety and sedative drugs or those who had received alpha 2 agonists or. unwilling to the procedure were also excluded from the study.

The sample size for this study was calculated based on power of 90% with a two sided error of 5% based on a difference of two in patient's satisfaction and sedation scores between groups. The number of patients required in each group to demonstrate this difference between groups was 30. A total of 90 patients were randomly divided in three groups of 30 each to: Group DL 0.5μg/kg – low dose dexmedetomidine group, group DH 1 μg/kg – high dose dexmedetomidine group, group C saline-control group. Allocation of the group to the patients was randomised, based on chit method. Baseline heart rate, blood pressure, respiratory rate, oxygen saturation were recorded and these parameters were continuously monitored throughout the study period. An 18 gauge intra venous cannula was placed on the dorsum of either hand. Patients were preloaded with 500 ml 0.5% dextrose in normal saline. Initial loading dose was followed by a maintenance infusion of 0.2-0.7 μg/kg/h of dexmedetomidine. 15 min before giving local anaesthetic injection, the respective initial loading doses of 0.5 or 1.0 μg/kg of dexmedetomidine or placebo diluted in 50cc normal saline were administered over 10 min. Both the person noting observations and one administering the drug were blinded to these groups. The initial loading dose was followed by a maintenance infusion beginning at a rate of 0.6 μg/kg/h and titrated to 0.2-1 μg/kg/h so as to maintain Ramsay sedation scale (RSS) score[6] to 3. 15 min after starting study drug, patients were assessed for level of sedation using the RSS (scores = 3) and any patient having a score <3 received intravenous (IV) midazolam in 0.02 mg/kg doses, repeated until RSS score was = 3. Total dose of rescue midazolam and number of patients requiring it were also noted in each group. Pain was assessed on visual analogue scale (VAS) of 0-10 from no pain to worst pain.[6] Target was to achieve score of 3 or less. IV fentanyl 0.5 μg/kg boluses and repeated as necessary, could be given if a patient expressed a pain score of >3 during study drug infusion and >4 in the post anaesthesia care unit (PACU). Total dose of rescue fentanyl and number of patients requiring it in each group were also noted. At any time, if clinically indicated, the patient could be converted to an alternative sedative or anaesthetic techniqueand the study drug discontinued. RSS scores and all standard vital signs were recorded every 5 min throughout the study drug infusion, before the administration of any rescue midazolam or fentanyl and every 15 min throughout the procedure. Study drug was discontinued when the patient left the operating room. Subjects remained in the PACU for a minimum of 1 h after discontinuation of study drug. Vital signs were recorded every 5 min for the first 15 min, then every 15 min for the next 45 min. The sedation and pain scores were assessed every 15 min while the patient was in the PACU. After transfer to the PACU, the patient's level of anxiety was assessed using the anxiety assessment scores range from 0 (no anxiety) to 10 (extreme anxiety).[6] Patients were discharged when the modified Aldrette score[6] was >9. Patients satisfaction and surgeon's satisfaction was assessed on a seven point Likert scale.[6] The primary criteria of efficacy was the percentage of patients not requiring midazolam for rescue sedation based on achieving and/or maintaining RSS score 3. Other criteria included the total amount of rescue midazolam, total amount of fentanyl required for pain control and incidence of post-operative nausea and vomiting in the PACU. Safety was evaluated by monitoring adverse events and cardiac haemodynamic variables. Protocol-defined relative changes in arterial blood pressure (30% or more change from the baseline, which was determined as the average of three measurements 3 min apart). Bradycardia was defined as heart rate <60/min.[7] Absolute respiratory depression (defined as respiratory rate of <8 or oxygen saturation of <90%) were also assessed.

Statistical analysis of quantitative data comparing each group of dexmedetomidine versus control for the total amount of required rescue doses of midazolam and fentanyl were performed separately

using mean and ANOVA test. The qualitative study scales RSS for sedation, VAS for pain and number of patients requiring rescue doses were analysed using Chi-square test. The demographic data was analysed by the standard deviation. $P < 0.05$ were considered to be statistically significant.

RESULTS

The study groups were comparable in patient characteristics, type of surgical procedure and duration of surgery [Table 1].

Significantly more patients required rescue doses of midazolam in the group C (26/30) as compared to dexmedetomidine groups DL (17/30) and DH (12/30) respectively [Figure 1a]. Furthermore, the total rescue dose of midazolam was significantly higher in the control group when compared to groups DL and DH ($P = 0.00$) [Table 2]. There were however no significant differences in number of patients requiring midazolam and total dose of midazolam between groups DL and DH ($P = 0.382$).

The number of patients requiring rescue doses of fentanyl [Figure 1b] was higher in group C (25/30) as compared to the groups DL (18/30) and DH (11/30), so also the total dose of fentanyl was higher in group C ($P = 0.011$). There were no significant differences in group DL and DH ($P = 0.914$) [Table 2].

Desired RSS was achieved in more number of patients in groups DL and DH as compared to group C ($P = 0.001$) however there was no significant difference between both groups DL and DH ($P = 0.63$) [Figure 2a].

Similarly, desired VAS score was achieved in more number of patients in groups DL and DH as compared to group C ($P = 0.0001$) which was highly significant, but there was no difference among groups DL and DH ($P = 0.99$) [Figure 2b].

Bradycardia was observed in 3 (10%) patients in DH group 2 (6.7%) patients each in DL and control group. However, atropine was not required in any patient. Respiratory depression was seen in 2 (6.7%) patients in group C and none in groups DL and DH. Total 4 (13.4%) patients in DH group had hypotension whereas 2 (6.7%) each in DL and control group [Table 3].

In PACU, the sedation scores were higher in more number of patients in group C as compared to groups DL and DH ($P = 0.006$) which was statistically significant. However, there were less significant difference in groups DL and DH ($P = 0.04$) [Figure 3a].

In PACU, VAS score <3 was achieved in more number of patients in group C than groups DL and DH ($P = 0.0001$). This was statistically highly significant. Similarly, more number of patients in groups DL achieved VAS score <3 as compared to group DH ($P = 0.003$). This was statistically significant [Figure 3b].

Patient satisfaction on seven point Likert scale was better in groups DL and DH as compared to group C ($P = 0.03$). No significant difference was seen betweenth groups DL and DH ($P = 0.94$).

So also the surgeon satisfaction in terms of patient cooperation and better operative field on seven point Likert scale was better in groups DL and DH as compared to group C ($P = 0.06$). However, there was no significant difference between groups DL and DH ($P = 0.667$).

Modified Aldrette score of 9 or more was achieved in more number of patients in groups DL and DH as compared to group C ($P = 0.0001$) however no

Table 1: Demographic data and nature of surgeries

Group	DL	DH	C
Mean age±SD (years)	33.13±9.04	33.26±8.65	33.96±8.94
Mean weight±SD (kg)	54.30±10.87	52.24±11.45	52.52±8.60
Sex incidence (male/female)	18/12	21/9	16/14
Nature of surgeries			
General surgery	12	14	12
ENT	10	12	11
Plastic surgery	8	4	7
Duration of surgeries (mean±SD) min	63.16±22.34	68±24.79	65.67±25.55

SD – Standard deviation, ENT – Ear nose throat surgery

Table 2: Mean total doses of rescue midazolam and fentanyl

Group	Mean total dose of midazolam (mean±SD) mg	Mean total dose of fentanyl (mean±SD) ug
DL	1.28±2.3	84.8±30.15
DH	0.87±1.1	83.9±33.8
C	3.88±2.15	144.2±41.56
	P=0.000	*P*=0.011
	P=0.382	(*P*=0.914)

The *P* value written in brackets denotes the comparison between both dexmedetomidine groups. SD – Standard deviation

Table 3: Intra operative adverse events

Adverse events	DL (%)	DH (%)	C (%)
Hypertension	1 (3.3)	0	1 (3.3)
Hypotension	2 (6.6)	4 (13.3)	2 (6.6)
Tachycardia	0	0	3 (10)
Bradycardia	2 (6.6)	3 (10)	2 (6.6)
Respiratory depression	0	0	2 (6.6)

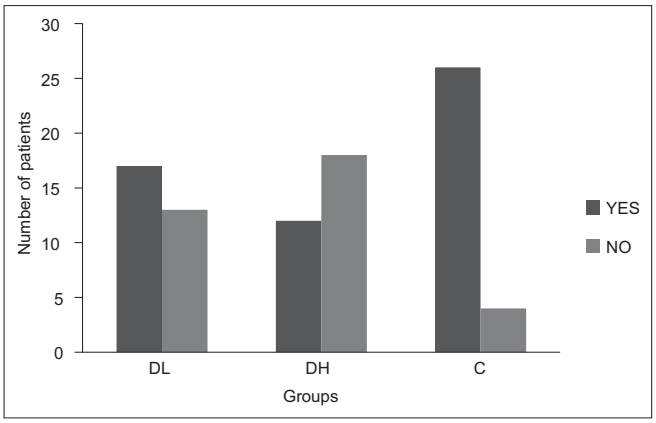

Figure 1a: Number of patients requiring midazolam

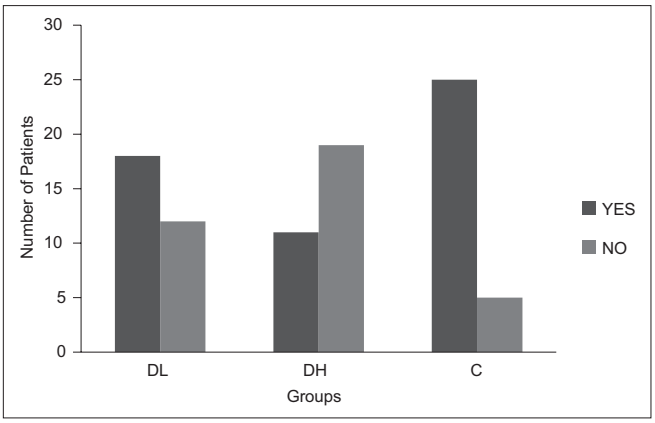

Figure 1b: Number of patients requiring fentanyl

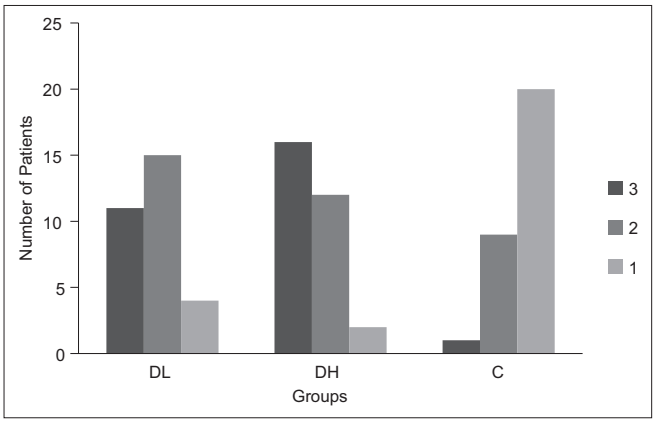

Figure 2a: Ramsay sedation scores in three groups

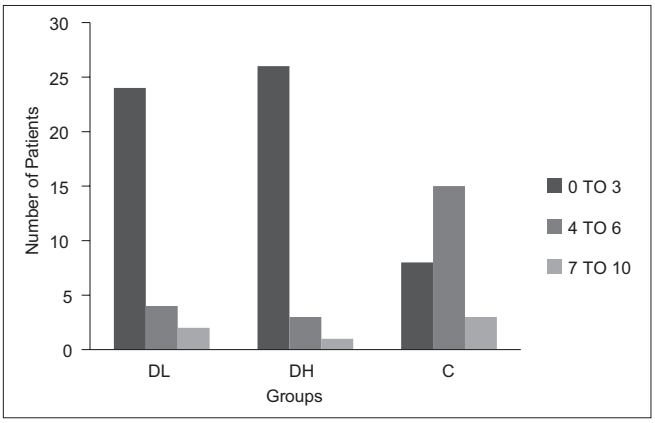

Figure 2b: VAS for Pain in three groups

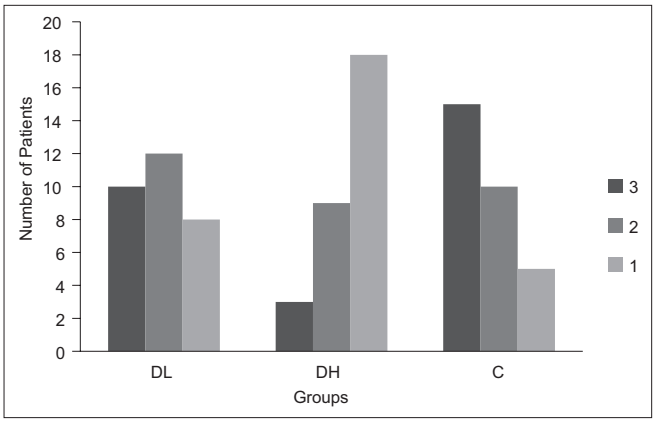

Figure 3a: RSS In PACU in three groups

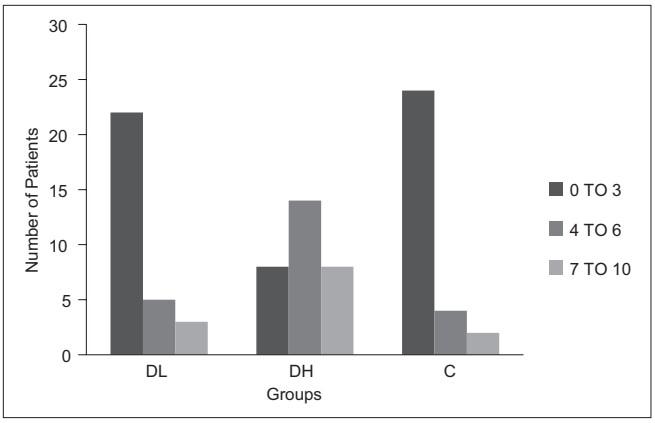

Figure 3b: VAS In PACU in three groups

significant difference was noted in groups DL and DH (P = 0.99). None of the patients had nausea or vomiting.

DISCUSSION

MAC is emerging as a special modality by virtue of which, procedures that required patients to stay overnight in a hospital are now performed safely in outpatient suites.[1] It combines IV sedation, anxiolysis and analgesia with local anaesthetic infiltration or nerve blocks. Ideally, there should be minimal physiological disturbances and recovery should be rapid. American Society of Anaesthesiologists recommends continuous monitoring of vital signs viz. heart rate, blood pressure arterial oxygen saturation, capnography etc.[8] Since, there is lack of airway control, proper selection of drugs and titration of doses is essential so as to minimize respiratory depression.

Various agents have been used to provide sedation during MAC viz. propofol, benzodiazepines and opioids.[2,3] Use of propofol was associated with over sedation and disorientation, benzodiazepines with confusion, opioids with respiratory depression and desaturation. Thus, there has been continuous search of a safer alternative and alpha2 adrenergic agonist clonidine was tried. A newer drug of this class, dexmedetomidine provides sedation and analgesia without respiratory depression. It has a novel property of providing "conscious sedation",[4] i.e. patient can be aroused any time during the procedure only to go to sleep again. The sleep produced by dexmedetomidine mimics natural sleep.[9] Moreover, it has an impressive pharmacological profile with a shorter half-life (2 h) as compared to midazolam (3-4 h) and a wider margin of safety.[10] Besides sedation, it also produces analgesia via acting on substantia nigra and locus coeruleus.[11] All these characteristics make dexmedetomidine an ideal agent during MAC.

In this study, dexmedetomidine in two different loading doses, was found to be safe and effective for sedation and analgesia in patients undergoing surgical procedures under MAC. Significantly fewer patients in both the groups DL and DH required supplemental midazolam or fentanyl for sedation and analgesia respectively, the mean total dose of rescue midazolam used to achieve or maintain the targeted sedation level was significantly lower in both the groups DL and DH as compared to group C.[12] Similarly, the total rescue dose of fentanyl required in groups DL and DH was less than in group C. This may be because dexmedetomidine acts at the spinal cord and locus coeruleus to produce analgesia and sedation thereby reducing the requirement of opioids and benzodiazepines respectively. However, no significant differences were observed in groups DL and DH. Our observations are similar to Candiotti *et al*.[13]

Desired RSS was achieved in more number of patients in groups DL and DH as compared to group C ($P = 0.001$) however, there was no significant difference between both the groups DL and DH ($P = 0.63$) [Figure 2a]. Similarly, desired VAS score was achieved in more number of patients in groups DL and DH as compared to group C ($P = 0.0001$) which was highly significant but there was no difference among groups DL and DH ($P = 0.99$) [Figure 2b]. This finding confirms that dexmedetomidine is an effective analgesic which is in accordance with studies by Ebert *et al*. and Dere *et al*. Its analgesic action is probably due to its action at the spinal cord and locus coeruleus. Respiratory depression was observed in a larger number of patients in group C than in groups DL and DH. Bradycardia and hypotension were seen in more patients in group DL/DH than group C. This was supposed to be due to sympatholytic effects of dexmedetomidine. Similar observations were done in a study by Anand *et al*.[14]

In this study, we observed that dexmedetomidine does not cause respiratory depression in the recommended doses. Similar results were obtained in other studies.[15,16]

Recovery conditions were better in groups DL and DH than group C. This may be because lower doses of midazolam were required in groups DL/DH. There was better patient and surgeon satisfaction in groups DL and DH as compared to group C. Similar findings were observed by Kumari *et al*. while comparing midazolam and clonidine.[6]

In PACU, greater VAS scores could be achieved in the control group than dexmedetomidine groups which is contrary to findings by Candiotti *et al*. This may be due to larger doses of fentanyl required for rescue analgesia in group C.

Limitations of our study were that a wide variety of surgical procedures were included in the study and capnography was not used. Moreover, pain is a subjective sensation and there can be individual variations in terms of pain threshold.

There is a scope for conducting the study with the use of Bispectral index monitor and patient controlled analgesia.

CONCLUSION

Dexmedetomidine in the doses studied was cfound to be a safe and effective sedative and analgesic for patients undergoing procedures under MAC, and the requirement of fentanyl and midazolam were reduced. It does not cause respiratory depression, nausea and vomiting in the doses used and provides better recovery conditions and better patient and surgeon satisfaction. It ameliorates MAC and there are less chances of bradycardia and hypotension at 0.5 μg/kg dose as compared to a higher loading dose.

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