Original Article

Time course of psychomotor recovery after intravenous dexmedetomidine infusion as a part of balanced anaesthetic technique: A randomised, double-blind study

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ABSTRACT

Background and Aims: Dexmedetomidine is a drug that is being widely used as an adjuvant to anaesthesia because of its unique pharmacodynamic and pharmacokinetic properties. We aimed to assess the recovery of psychomotor function from balanced anaesthesia including intravenous dexmedetomidine infusion as adjunct. **Methods:** Ninety American Society of Anesthesiologists I and II patients were randomised to group D ($n = 45$), to receive 1 μg/kg of dexmedetomidine loading dose over 10 min, with maintenance infusion of 0.5 μg/kg/h, and group S ($n = 45$), to receive an equal volume of 0.9% normal saline. Objective parameters were recovery of psychomotor function assessed by Trieger dot test (TDT), digit symbol substitution test (DSST) and intraoperative opioid requirement. the total fentanyl used intraoperatively in the two groups. Statistical analysis was performed using unpaired Student's t-test, Chi-squareor Fisher's exact test. **Results:** Psychomotor recovery assessed by TDT showed statistically significant early recovery in group D compared with group S. This was seen in the maximum distance of dots missed at 30 min, 60 min, 90 min and 120 min as well as in the average distance of dots missed at identical time points. Similarly, DSST revealed early recovery at 30 min (12.4 ± 5.3 vs. 10.4 ± 3.9 $P = 0.04$) postoperative interval but not at other time intervals. There was significant decrease in the intraoperative opioid requirement in group D compared with group S. **Conclusion:** The addition of dexmedetomidine to balanced anaesthetic technique significantly hastened the psychomotor recovery compared with placebo.

Key words: Balanced anaesthetic, dexmedetomidine, digit symbol substitution, psychomotor recovery, Trieger dot

INTRODUCTION

Postoperative readiness for discharge is consistent with the recovery of psychomotor function after undergoing surgery under general anaesthesia. Psychomotor function has been evaluated by a wide variety of tests with the most commonly used being pen and pencil test like Trieger dot test (TDT) and digit symbol substitution test (DSST). Recovery of psychomotor function assessed by these tests indicates the recovery from anaesthesia.

Dexmedetomidine has analgesic and sedative properties which does not cause respiratory depression.[1] Hypoxic and hypercapnic ventilator drives are also preserved with this drug. Addition of dexmedetomidine as an adjuvant to a balanced anaesthetic technique

decreases perioperative opioid consumption and has also been shown to minimise the requirement of inhalational agent.[2-5] Dexmedetomidine has an elimination half-life of 2 h which makes it ideally suited for short and intermediate duration, as well as for day care surgery.

Various studies have shown that psychomotor function has been preserved with dexmedetomidine when it is used for sedation. However, no studies have been done evaluating the psychomotor recovery wherein dexmedetomidine has been used as a part of the balanced anaesthetic technique.

We hypothesised that postoperative psychomotor recovery from anaesthesia would be better if dexmedetomidine is used as an adjunct to the balanced anaesthetic technique. Hence, this study was designed to assess the recovery of psychomotor function from balanced anaesthesia with intravenous (IV) dexmedetomidine infusion as an adjunct compared with placebo in patients undergoing elective surgery under general anaesthesia with anticipated duration less than 3 h.

METHODS

This study was conducted in a tertiary care hospital after obtaining approval from Institute Ethics Committee (Human Studies, JIPMER, IEC no: No.JIP/IEC/2014/1/216, 03.03.2014) during the period of March 2015 to January 2016. This study was registered in Clinical Trials Registry-India (CTRI/REF/2015/02/008532). The study followed the guidelines laid down in Declaration of Helsinki (2013).

A total of 90 patients (American Society of Anaesthesiologists physical status 1 or 2) in the age group of 18–50 years scheduled for elective surgery under general anaesthesia with anticipated duration of less than 3 h were included in the study after obtaining informed and written consent [Figure 1]. Patients with known history of psychiatric illness, chronic drug or alcohol abuse, known hypersensitivity to drugs used, family history of malignant hyperthermia, pregnant and breastfeeding women, hypertensive patients not on any treatment or those treated with alpha- or beta-blockers, patients on concurrent sedative medications and patients who refused to consent were excluded from the study. Participants were then allocated to receive either dexmedetomidine infusion (group D) or saline infusion (group S) by
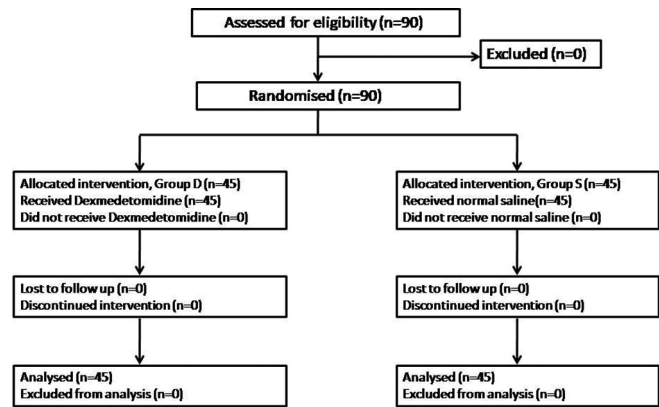

Figure 1: CONSORT diagram of the study

computer-generated random sequencing done by an independent clinician. This was forwarded directly to another clinician who was also not involved in the study. All drugs for administration, including matching placebos for both arms, were prepared by the same clinician in the operating room. Sealed envelopes with randomisation codes were made for the purpose of patient allocation into groups. On the day of surgery, before induction, patients were allocated into two groups by opening sealed envelopes with the randomisation codes inside.

On the day before surgery, psychomotor function of the patient was assessed with the TDT and DSST. Both the tests were done thrice to familiarise it to the patient, and the fourth test was taken as the baseline psychomotor evaluation for that patient. TDT consists of joining 40 dots with a line to form a figure within a time limit of 60 s. It was analysed by number of dots missed (NDM), maximum distance of dots missed (MDDM) and average distance of dots missed (ADDM).

DSST consists of matching digits with their corresponding symbol within a time limit. The digits along with the corresponding symbols were located in a legend given at the top of the page. Nine such digits were assigned symbols in the legend. It was analysed by the number of digits correctly matched with the corresponding symbols within 90 s. To avoid practice factor obscuring results in this test particularly, a new set of arrangement of digits were given to patient, every time.

All participants were premedicated with famotidine 20 mg and tab. diazepam 0.1 mg/kg per orally on the night before surgery. They were administered famotidine 20 mg, diazepam 0.1 mg/kg and

metoclopramide 10 mg per orally in the morning on the day of surgery.

After shifting the patient to the operation theatre, baseline and continuous recording of electrocardiogram, haemodynamic parameters [heart rate and non-invasive blood pressure (BP)] and oxygen saturation (SpO_2) were performed using a multiparameter monitor. All the participants were administered midazolam (30 µg/kg), fentanyl (2 µg/kg) IV and were induced with propofol to achieve state entropy of 40. After ensuring adequacy of mask ventilation, vecuronium (0.1 mg/kg) was administered in both the groups and trachea was intubated after 3 min. Dexmedetomidine was diluted to 2 µg/ml in a total volume of 50 mL and was blinded against an identical volume of saline. After intubation, all participants received an IV loading dose of 0.5 mL/kg of either the study or control medication over 10 min and a maintenance IV infusion of 0.25 mL/kg/h. This ensured that the dose of dexmedetomidine received by every patient in group D was 1 µg/kg bolus (over 10 min), followed by an infusion dosage of 0.5 µg/kg/h. Owing to the dilutions that we had worked out (as stated above), this dosage was well-blinded by providing an identical volume (per kg body weight) of saline placebo in group S. The infusions were continued in both the groups upto the initiation of skin closure. Anaesthesia was maintained with 60% nitrous oxide in oxygen and sevoflurane whose minimum alveolar concentration (MAC) of sevoflurane was adjusted to maintain an entropy value of 40–60. Vecuronium was administered as 1 mg bolus to maintain muscle relaxation. IV fluid therapy consisted of lactated Ringer's solution as per standard protocols.

Supplemental fentanyl was given as clinically indicated [After ensuring adequate depth of anaesthesia, 1 µg/kg of fentanyl was administered for 20% increase in heart rate or systolic blood pressure (SBP) from baseline.] Ventilation was adjusted to maintain end-tidal carbon dioxide within a normal range of 35–40 mmHg. Fentanyl was not administered within 30 min of the end of surgery. Inhalational agents and infusions were stopped at the time of skin closure.

Hypotension, defined as SBP less than 90 mmHg, was treated with mephentermine 6 mg IV and a fluid bolus of 5 mL/kg. Symptomatic bradycardia, defined as heart rate less than 50/min associated with SBP <90 mmHg, was treated with 0.5 mg of atropine. For hypertension and tachycardia, defined by heart rate or BP increase of more than 20% over baseline, fentanyl 1 µg/kg was given and the depth of anaesthesia was reviewed. At the end of the surgery, patients were ventilated with 100% oxygen at a flow rate of 6 L/min. Once patient developed spontaneous breathing efforts, neuromuscular blockade was antagonised with 50 µg/kg of neostigmine and 10 µg/kg of glycopyrrolate. Extubation was performed when adequate spontaneous ventilation and response to verbal commands were established. The anaesthesiologist managing the case was blinded. Ketorolac 30 mg IV was given for postoperative analgesia. TDT and DSST were conducted at intervals of 30, 60, 90 and 120 min after the extubation. The clinician performing the postoperative psychomotor analysis was unaware of the drug that had been administered to the patient. The primary outcome measures assessed were the NDM and the distance (average, and maximum) by which these dots were missed on the TDT, and the scores of the DSST. The secondary outcome measure assessed was the total dosage of fentanyl used intraoperatively between the two groups, which was calculated at the end of the surgical procedure. Sample size was calculated using an *a priori* power analysis which suggested a sample size of 41 patients for each group to provide 80% power at α error of 0.05. This was calculated assuming a mean difference of six dots missed on TDT as being of statistical significance with standard deviation (SD) of 10.[6] We enrolled 45 patients in each group expecting some drop outs from the study. Consecutive sampling technique was used in study. Normality of data was tested using Kolmogorov–Smirnov test. Analysis of the TDT and DSST values between the groups was studied using unpaired Student's *t*-test. The same was also used for comparison of cumulative doses of fentanyl used between the two groups. Categorical data were analysed using Chi-square/Fisher's exact test. Data were analysed by GraphPad Prism 6.

RESULTS

Age, height, weight and body mass index were expressed as mean ± SD. American Society of Anesthesiologists status and gender were expressed as percentages. All these demographic variables were comparable [Table 1]. The type of surgery performed in both the groups was expressed as percentage [Table 1]. Duration of surgery (from skin incision to closure of the incision), duration of anaesthesia (from induction to extubation) and intraoperative entropy values were comparable between the groups [Table 1].

Baseline value of NDM was comparable between the two groups. NDM was lower in group D compared with group S at 30, 60, 90 and 120 min postoperatively although it was not statistically significant [Figure 2a].

Baseline MDDM was comparable between the groups. There was statistically significant reduction in the mean of the MDDM at 30, 60, 90 and 120 min postoperatively in group D compared with group S [(7.3 ± 2.4, 5.6 ± 2.2, 4.3 ± 2.1, 3.3 ± 1.7) mm vs. (8.4 ± 1.5, 6.4 ± 1.45, 5.3 ± 1.4, 4.1 ± 1.4) mm], respectively [Figure 2b].

Baseline ADDM was comparable between the groups. There was statistically significant reduction in the mean of the ADDM at 30, 60, 90 and 120 min postoperatively in group D compared with group S [(3.7 ± 1.3, 2.9 ± 1.0, 2.3 ± 0.9, 1.9 ± 0.8) mm vs. (4.1 ± 0.6, 3.3 ± 0.6, 2.7 ± 0.6, 2.1 ± 0.5) mm], respectively [Figure 2c].

Baseline DSST was comparable between the groups. DSST values were higher in group D compared with group S at the corresponding postoperative time

Table 1: Details of patients, surgery and anaesthesia			
Parameter	**Group D (mean±SD)**	**Group S (mean±SD)**	**P**
Age (years)	34.9±10.6	35.2±10.7	0.88
Gender (M/F)	18/27 (40/60)	20/25 (45.5/55.5)	0.14
Height (cm)	161.7±6.97	163.1±7.1	0.34
Weight (kg)	61.2±9.4	61.9±8.9	0.70
BMI (kg/m^2)	23.3±2.8	23.2±2.9	0.89
ASA PS 1/2 (%)	27/18 (60/40)	25/20 (55.5/45.5)	0.67
Duration of surgery (min)	99.89±35.2	96.56±30.4	0.63
Duration of anaesthesia (min)	113.6±38.06	111.9±31.91	0.82
Highest entropy value	59.8±3.3	60.5±2.9	0.27
Lowest entropy value	35.07±2.7	35.11±5.1	0.96
Type of surgery	**Group D (numbers)**	**Group S (numbers)**	
Laparoscopic cholecystectomy	18	15	
Percutaneous nephrolithotomy	3	6	
Hemi/total thyroidectomy	9	4	
Modified radical mastectomy	6	6	
Hernioplasty	5	3	
Functional endoscopic sinus surgery and modified radical mastoidectomy	4	11	
Total	45	45	

SD – Standard deviation; BMI – Body mass index; ASA – American Society of Anesthesiologists; PS – Physical status
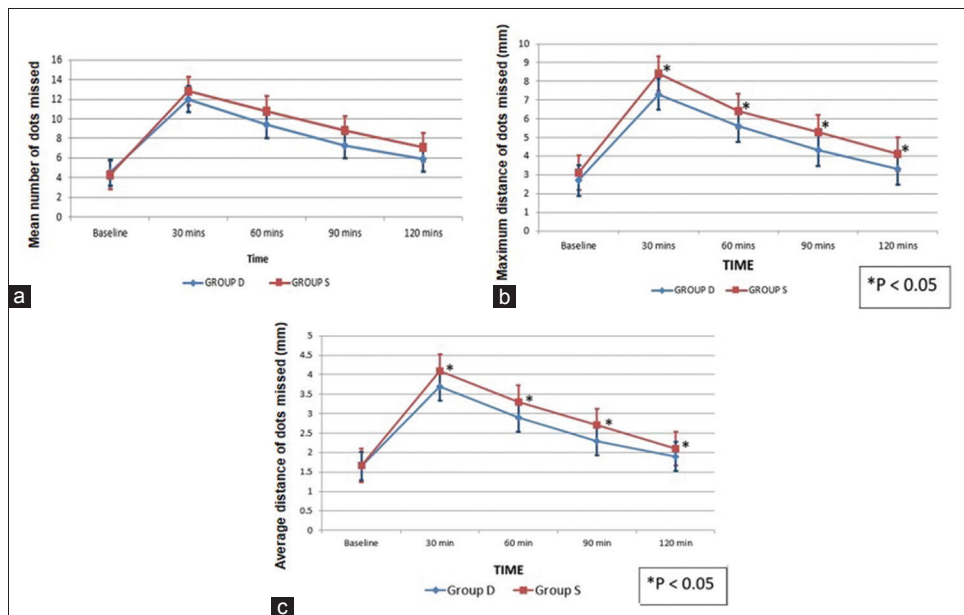

Figure 2: (a) Number of dots missed (NDM) between the groups at various time points. (b) Maximum distance of dots missed (MDM) between the groups at various time points; *statistically significant. (c) Average distance of dots missed between the groups at various time points; *statistically significant

intervals, but it was statistically significant only at 30 min [Figure 3].

There was significantly reduced requirement of cumulative dose of fentanyl in group D when compared with group S (135.8 ± 33.9 μg vs. 194.3 ± 40.0 μg, $P = 0.0001$). Intraoperative fentanyl requirement was reduced by 33% in group D compared with group S [Table 1].

DISCUSSION

The aim of this study was to assess whether the addition of dexmedetomidine improves the psychomotor recovery when used as a component of general anaesthesia. It was demonstrated that addition of dexmedetomidine as a component of balanced anaesthesia significantly improved the postoperative psychomotor recovery. Psychomotor recovery was assessed with TDT and DSST. TDT is a modification of the motor gestalt test.[6] Takayama *et al.* compared the recovery of psychomotor function after total intravenous anaesthesia with propofol–remifentanil and propofol–fentanyl.[7] They assessed the recovery profile with TDT, and TDT was recorded using the same variables, as used by us. They also noted TDT to be more sensitive compared with other tests for assessing the intermediate and late recovery of psychomotor function after general anaesthesia. Our data showed that NDM was lesser in the dexmedetomidine group when compared with the control group which was not statistically significant.

The study results on psychomotor recovery were similar to the findings shown in patients undergoing robotic-assisted laparoscopic radical cystectomy by Ding *et al.*[8] The authors used six neuropsychological tests which included mini-mental state examination,
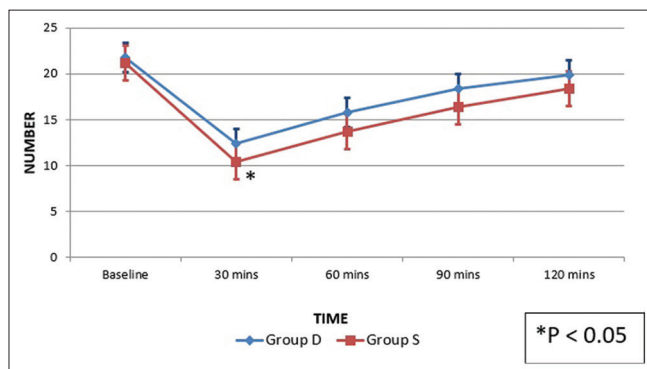
digital span test, digital symbol test, trail making test, words recall test and verbal fluency test. These tests were performed in all patients on the day before surgery, on first and fifth postoperative days to assess cognitive function and its recovery in the postoperative period. They found that cognitive function and psychomotor function recovery were better in patients receiving dexmedetomidine and this was secondary to the decreased neuroinflammatory mediator release in these patients. Alpha-2-adrenergic receptor is a transmembrane G-protein-coupled receptor found extensively in the central nervous system (CNS), peripheral nervous system and autonomic ganglia, and their density is highest in the pontine nucleus, parahippocampal gyrus and locus coeruleus. The main function of dexmedetomidine is to activate alpha-2-adrenergic receptors with high selectivity so that these can have their effect on the locus coeruleus of the CNS, the spinal cord and central and peripheral neurotransmitters to result in sedation and hypnosis, analgesia and antagonism of sympathetic activity, respectively. Dexmedetomidine also displays cerebroprotective effect. It reduces catecholamine levels in serum and improves the neurological and histopathological outcomes, in dose-dependent fashion. During cerebral ischemia reperfusion, dexmedetomidine reduces levels of nitric oxide (NO) and tumor necrosis factor-α and increases the superoxide dismutase activity so that nerve injuries can be avoided. Moreover, dexmedetomidine can minimise vasospasm by inhibiting release of catecholamines in cerebral tissues, which can prevent brain injuries from subarachnoid haemorrhages. Furthermore, dexmedetomidine can avoid damages to hippocampus, thalamus and cortex caused by inhaling isoflurane independently as well as influence the long-term impact of isoflurane on neurocognitive functions. Dexmedetomidine can also provide protection in traumatic brain injuries, the mechanism of which may be related to relieving inflammatory reactions.

In this study, ADDM and MDDM were significantly lesser in the dexmedetomidine group when compared with the control group. This could be explained by the fact that MDDM and ADDM were more subtle indicators of psychomotor performance and that early psychomotor recovery was shown in them before it could be reflected in the NDM. Psychomotor recovery was assessed with DSST also. DSST has been used in numerous studies for assessing psychomotor function.[8-11] DSST showed significant difference

Figure 3: Digit symbol substitution test values between the groups at various time points; *statistically significant

between the groups only at the 30 min interval and it was not significant at the other time intervals.

Disparity between the TDT and DSST results in our study could have been because of the fact that TDT is a pure psychomotor test, whereas DSST involves memory processing and cognitive function apart from assessing psychomotor function.

In this study, the cumulative dose of fentanyl requirement in group D was decreased by 33% compared with group S. The decrease in cumulative dose of fentanyl in group D was probably because of analgesic property of dexmedetomidine. This is consistent with the studies done by Arain *et al.* and Bajwa *et al.*[9,12] Arain *et al.* studied the effect of dexmedetomidine on early postoperative morphine requirement and the time for first analgesic dose in patients undergoing elective inpatient surgery and showed that there was a 66% decrease in the early postoperative morphine requirement as well as significant delay in the demand for the first analgesic dose. Bajwa *et al.* showed that there was more than 50% decrease in the fentanyl and isoflurane requirement in the dexmedetomidine group.

There are a few limitations to this study. At the outset, psychomotor recovery was assessed based on TDT and DSST. These are paper and pencil tests. The disadvantage with these tests is that they have practice effect, that is, improvement in score from baseline with repeated testing. Second, depth of anaesthesia was monitored using entropy and MAC was adjusted accordingly. Entropy does not correlate well with the depth of anaesthesia when the patient is receiving dexmedetomidine. This is because the highly ordered slow waves that are present commonly during sedation with dexmedetomidine do not comply with the depth of anaesthesia. Third, tests for psychomotor analysis were done from 30 to 120 min postoperatively. We should have included 15 and 150 min also as it would have shown a complete trend of early deficit to complete recovery of psychomotor function. Most of the patients in both the groups did not reach their baseline value at the 120-min interval. We should have assessed the time to recover to baseline which would have given us a complete recovery profile. The MAC-sparing effect of dexmedetomidine can be studied in future.

CONCLUSION

The results of this study suggest that the addition of dexmedetomidine to balanced anaesthetic technique significantly hastened the psychomotor recovery compared with placebo and also there was reduction in perioperative fentanyl consumption in dexmedetomidine group.

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Institutional.

Conflicts of interest
There are no conflicts of interest.

REFERENCES

1. Arain SR, Ruehlow RM, Uhrich TD, Ebert TJ. The efficacy of dexmedetomidine versus morphine for postoperative analgesia after major inpatient surgery. Anesth Analg 2004;98:153-8.
2. Ohtani N, Kida K, Shoji K, Yasui Y, Masaki E. Recovery profiles from dexmedetomidine as a general anesthetic adjuvant in patients undergoing lower abdominal surgery. Anesth Analg 2008;107:1871-4.
3. Lee YY, Wong SM, Hung CT. Dexmedetomidine infusion as a supplement to isoflurane anaesthesia for vitreoretinal surgery. Br J Anaesth 2007;98:477-83.
4. Shin HW, Yoo HN, Kim DH, Lee H, Shin HJ, Lee HW. Preanesthetic dexmedetomidine 1 μg/kg single infusion is a simple, easy, and economic adjuvant for general anesthesia. Korean J Anesthesiol 2013;65:114-20.
5. Patel CR, Engineer SR, Shah BJ, Madhu S. The effect of dexmedetomidine continuous infusion as an adjuvant to general anesthesia on sevoflurane requirements: A study based on entropy analysis. J Anaesthesiol Clin Pharmacol. 2013;29:318-22.
6. Newman MG, Trieger N, Miller JC. Measuring recovery from anesthesia – A simple test. Anesth Analg 1969;48:136-40.
7. Takayama A, Yamaguchi S, Ishikawa K, Shinozaki M, Kimura Y, Nagao M, *et al.* Recovery of psychomotor function after total intravenous anesthesia with remifentanil-propofol or fentanyl-propofol. J Anesth 2012;26:34-8.
8. Ding L, Zhang H, Mi W, Wang T, He Y, Zhang X, *et al.* Effects of dexmedetomidine on anesthesia recovery period and postoperative cognitive function of patients after robot-assisted laparoscopic radical cystectomy. Int J Clin Exp Med 2015;8:11388-95.
9. Arain SR, Ebert TJ. The efficacy, side effects, and recovery characteristics of dexmedetomidine versus propofol when used for intraoperative sedation. Anesth Analg 2002;95:461-6.
10. Hall JE, Uhrich TD, Barney JA, Arain SR, Ebert TJ. Sedative, amnestic, and analgesic properties of small-dose dexmedetomidine infusions. Anesth Analg 2000;90:699-705.
11. Cheung CW, Ng KF, Liu J, Yuen MY, Ho MH, Irwin MG. Analgesic and sedative effects of intranasal dexmedetomidine in third molar surgery under local anaesthesia. Br J Anaesth 2011;107:430-7.
12. Bajwa SJ, Kaur J, Singh A, Parmar S, Singh G, Kulshrestha A, *et al.* Attenuation of pressor response and dose sparing of opioids and anaesthetics with pre-operative dexmedetomidine. Indian J Anaesth 2012;56:123-8.