Original Article

Substitution of propofol for dexmedetomidine in the anaesthetic regimen does not ameliorate the post-operative cognitive decline in elderly patients

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ABSTRACT

Background and Aims: Post-operative cognitive dysfunction (POCD) is a poorly understood complication particularly observed in elderly patients, with long-term poor outcome. The randomised study was to compare the incidence of POCD in elderly with bispectral index (BIS)-guided intra-operative use of either dexmedetomidine or propofol with sevoflurane. **Methods:** Eighty-seven patients, planned for non-cardiac surgery under general anaesthesia, were included between June 2017 and March 2018. After exclusion of 7 patients, remaining 80 patients were randomised into dexmedetomidine group and propofol group with 40 patients each. In both the groups, BIS-guided anaesthesia was provided. Cognitive function was assessed by an anaesthesiologist using a battery of neuropsychological tests at baseline pre-operatively, third and seventh day after surgery. The data were entered into a Microsoft Excel spreadsheet and analysis was performed using Statistical Package for Social Sciences (SPSS) version 21. **Results:** Propofol group had a non-significant lower incidence of POCD on third day and dexmedetomidine group showed decreased incidence of POCD on seventh day, accompanied by lower anaesthetic requirement (inhalational as well as intravenous) concomitant with delayed emergence with an acceptable BIS value. **Conclusion:** Dexmedetomidine appeared to be anaesthetic sparing as compared to propofol. BIS monitoring for titrating depth of anaesthesia and hence the anaesthetic exposure is an invaluable tool as compared to routine care anaesthesia for reducing POCD. The patients in both groups did not develop significant POCD until the seventh post-operative day.

Key words: Bispectral index, dexmedetomidine, elderly, neuropsychological tests, post-operative cognitive dysfunction, propofol

INTRODUCTION

Post-operative cognitive dysfunction (POCD) has a significant impact on patient's post-operative recovery. As the mechanism of POCD is poorly understood, prevention and early identification remain the cornerstone of management.

POCD involves impairment of memory, concentration and information processing. Several factors related to POCD include physical status, electrolytic and immune disorders; alcoholism, drugs and advanced age.[1] Hospital admission causes stress due to noise, lights and immobilisation. Similarly, anxiety by sleep deprivation, pain and removal from family environment may contribute to POCD. The metabolic

and endocrine responses to surgical stress have been related to POCD.[2]

The Diagnostic and Statistical Manual, 5th edition, defines post-operative neurocognitive disorder as as an overarching term, including post-operative delirium and delayed neurocognitive recovery. It is described as decline in neuropsychological test (NPT) performance from before to after surgery. Reported incidence is 25% 1-week post-surgery and 10% after 3 months.[3] It has preponderance in elderly[3] lasting few days to weeks after surgery.[3]

Dexmedetomidine, being selective α2-receptor agonist, decreases peri-operative pro-inflammatory response and exerts neuroprotective effects, implicated as adjunct to anaesthetic regimen for prevention of POCD.[4] Propofol is selective modulator of inhibitory neurotransmitter (GABA-A) with rapid and clear-headed awakening.[5] Monitoring by bispectral index (BIS) allows titration of anaesthetic delivery and can lower POCD rates,[6] suggesting excessive exposure as a triggering mechanism for POCD.

We designed a study to examine whether intra-operative use of dexmedetomidine or propofol in a combined intravenous plus volatile anaesthetic (sevoflurane) regimen is associated with lower incidence of neurocognitive dysfunction in elderly patients. We hypothesised that analgesic and sedative properties of dexmedetomidine can reduce sevoflurane consumption.

METHODS

This prospective, randomised, open-label, two-arm, controlled clinical study was conducted at an oncology centre between June 2017 to March 2018, after obtaining approval from institutional review board. Inclusion criteria were patients of either sex, age ≥55 years with minimum secondary level education, scheduled for elective non-cardiac surgery [Figure 1] under general anaesthesia, American Society of Anesthesiologists (ASA) status I–III and duration of surgery ≥120 min [Table 1]. Exclusion criteria were pre-operative Mini-Mental State Examination (MMSE) score ≤23, any cognitive impairment, substance abuse, cardiac co-morbidity, history of neurologic deficits (stroke or seizures), unable to comprehend NPTs, significant hearing, language, visual impairment and patient refusal.

Patients were randomly allocated to two groups: group 'P' (Propofol group) who received continuous
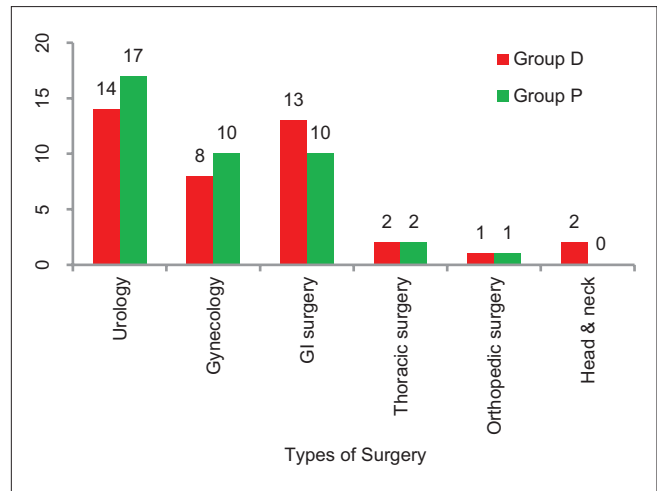
Figure 1: Distribution of surgery types among two groups

propofol infusion along with inhalational air: oxygen (0.4:0.6%) mixture with sevoflurane and group 'D' (dexmedetomidine group), who received dexmedetomidine infusion instead of propofol with same anaesthetic regimen. Online randomisation tool was used (http://www.graphpad.com/qickcalc/randMenu) to randomly assign (first method was selected) patients to groups. Each patient's assignment was entered into a sealed opaque envelope and opened after written informed consent was obtained.

In the preoperative session, information about the study was provided. MMSE score and series of neuropsychological tests[7,8] [Tables 2 and 3] were conducted in pre-operative clinic and on days 3 and 7 post-operatively by an anaesthesiologist. All patients were managed as per institutional protocol.

In the absence of a previous or pilot study, Cohen's effect size (ES) was used to calculate sample size of two samples with a continuous outcome variable. To detect ES of 0.7, minimum required sample size with 80% power of study and two-sided alpha of 5% was 32 patients per group. Allowing for dropouts, sample size taken was 40 per group. We employed the following formula:

$$n \geq \frac{2(z\alpha + z\beta)^2}{(ES)^2}$$

Where Z_α is the value of Z at two-sided alpha error of 5% and Z_β is the value of Z at power of 80%, and ES is effect size.

Categorical variables were presented as number and percentage and continuous variables were presented as mean ± SD and median. Normality of data was

Table 1: Patient characteristics					
	Mean±SD				P
	Group D	Min-max	Group P	Min-max	
Age	66.18±6.58	55-80	64.75±5.89	55-81	0.372
Weight	66.4±7.45	50-78	67.38±12.16	48-96	0.667
Sex (F/M)	12/28	NA	11/29	NA	0.805
ASA (I/II/III)	15/24/1	NA	16/22/2	NA	0.797
MMSE score	26.05±1.18	24-29	26.38±1.27	24-29	0.211
Literacy (G/HS/PG)	16/15/9	NA	18/10/12	NA	0.462
Co-morbidity (no/yes)	15/25	NA	17/23	NA	0.648
Pre-GA (0/1/2)	32/8/0	NA	32/7/1	NA	0.587
Pre-RA (0/1/2)	32/8/0	NA	32/7/1	NA	0.643
GA/GA+RA	24/16	NA	24/16	NA	1

ASA=American Society of Anaesthesiologists; MMSE=Mini-Mental State Examination; G=Graduate; HS=High school; PG=Postgraduate; pre-GA=Previous general anaesthesia; pre-RA=Previous regional anaesthesia; GA=General anaesthesia; RA=Regional anaesthesia

Table 2: Mean±standard deviation for the neuropsychological tests studied		
	Mean±SD	P
	Group D	Group P	
VVLT-0	4.4±1.55	4.58±2.31	0.696
VVLT-3	4.85±1.46	4.92±2.16	0.984
VVLT-7	5.6±1.37	5.95±2.21	0.462
Trail A-0	56.08±13.32	49.65±18.24	0.016
Trail A-3	61.45±16.84	52.4±18.84	0.022
Trail A-7	58.08±15.31	49.65±17.84	0.027
Trail B-0	154.26±43.03	132.21±44.85	0.031
Trail B-3	169.29±41.18	144.53±50.71	0.022
Trail B-7	162.55±36.53	141.9±47.34	0.036
DSST-0	17.62±3.82	19.73±6.41	0.08
DSST-3	16.4±3.33	18.35±6.56	0.099
DSST-7	18.38±3.96	19.6±6.49	0.313
STROOP A-0	33.64±12.55	24.97±11.57	0.001
STROOP A-3	36.18±12.23	29.56±12.75	0.015
STROOP A-7	33.77±11.43	28.44±12.4	0.032
STROOP B-0	103.12±32.23	90.32±45.97	0.073
STROOP B-3	110.5±30.53	94.75±47.63	0.023
STROOP B-7	106.22±30.46	93.4±45.13	0.141

VVLT=Visual verbal learning test; Trail A=Trail making test A; Trail B=Trail making test B; DSST=Digit symbol substitution test; Stroop A=Stroop colour word test A; Stroop B=Stroop colour word test B; 0=Pre-operative session; 3=Third post-operative day; 7=Seventh post-operative day

tested by Kolmogorov–Smirnov test. If normality was rejected, then non-parametric test was used. Quantitative variables were compared using unpaired *t*-test/Mann–Whitney test (when data sets were not normally distributed) between two groups and paired *T*-test/Wilcoxon ranked sum test (for non-parametric data) across follow-up within the group. Qualitative variables were correlated using Chi-square test or Fisher's exact test. A *P* value of <0.05 was considered statistically significant. Statistical analyses were performed with Statistical Package for Social Sciences (SPSS) version 21.0.

All patients were premedicated with 150 mg of oral ranitidine and 8 mg of ondansetron 2 h prior to surgery.

In the operating room, standard ASA monitoring (five lead electrocardiogram (ECG), pulse oximetry [SPO_2] and non-invasive blood pressure) was done. End-tidal carbon dioxide ($EtCO_2$) concentration, BIS (Covidien, Mansfield, MA 02048, USA) and nasopharyngeal temperature were monitored. Anaesthesia was induced in both groups with fentanyl 2 μg/kg, morphine 0.1 mg/kg, induction dose of propofol (2 mg/kg) and neuromuscular blocking agent (atracurium 0.5 mg/kg). All patients were intubated and mechanically ventilated. Anaesthesia was maintained with fresh gas flow of 2.0 l with air: oxygen (0.4:0.6%) mixture and BIS (maintained 40–60)-guided anaesthesia titrated with sevoflurane and either an intravenous (IV) infusion of propofol 80–100 μg/kg/min or dexmedetomidine 0.5–0.7 μg/kg/h. Analgesia was provided with intermittent boluses of fentanyl (maximum of 0.5–2 μg/kg) and morphine (0.05–0.1 mg/kg) intravenously and/or as epidural analgesia (morphine 3 mg ± bupivacaine 0.25% bolus and/or bupivacaine 0.1% infusion). Patient's heart rate (HR), mean arterial pressure (MAP), $EtCO_2$ and end-expiratory sevoflurane concentration (exp. sevo.) were monitored. Intra-operative MAP ≤70 mmHg, HR ≤50/min and SPO2 ≤90% were recorded. At the end of surgery mean total dosage of propofol (262.35 mg) or dexmedetomidine (95.4 μg) used, sevoflurane uptake, consumption (retrieved at the end of the anaesthetic procedure from the logbook of Draeger Primus® anaesthesia workstation) and total duration of anaesthesia were noted. Neuromuscular blockade in all patients was reversed with inj. neostigmine 0.05 mg/kg + inj. glycopyrrolate 0.01 mg/kg of and trachea extubated. The time from end of anaesthesia until eye opening and response to verbal commands was noted for each patient [Figure 2]. Patients with epidural catheter received morphine 0.3–0.5 mg/h and patients without epidural were given morphine 3 mg

Table 3: Neuropsychological tests

Tests	Description of test
MMSE score	It consists of tests of orientation (to time and place), memory (immediate and short-term), calculation, language, visual spatial awareness, concentration and attention
VVLT	It tests secondary memory performed in two steps. Step I: Showing patient placard with 20 pictures for time period of 30 s with instructions to carefully memorise it, in order to answer questions towards the end of session. Step II: Patient is asked to reproduce the list of pictures towards the end of session (after 20 min). The dependent variable is the number of pictures recalled, measuring learning ability and memory retrieval
DSST	It measures speed of processing of general information and involves a code within which every digit corresponds to a letter. The patient is asked to enter the correct code in the corresponding blank box. The dependent variable is the number of digits correctly coded in 90 s
Trail making tests	It tests dexterity and ability to combine tasks and is done in two parts. Part A is a page with 24 numbered circles and involves drawing lines connecting the numbers, in increasing sequential order. Part B is a page with circles containing letters A-L and 12 numbered circles intermixed and randomly arranged and involves connecting the circles by drawing lines between numbers and letters in a sequential order. The time needed to do each part is measured in seconds
Stroop colour word test	It involves a card displaying 32 stimuli; names of the colours are printed in incongruously coloured ink. The dependent variables are the time taken in seconds to identify the colour name (part 1) and the time taken in seconds to read the colour of printing ink (part 2); errors in both parts are noted. This test examines the patient's selective attention, mental speed and interference susceptibility

MMSE=Mini-Mental State Examination; VVLT, Visual verbal learning tests; DSST=Digit symbol substitution test

every 4 h and on demand to achieve visual analogue scale <3 at rest for 48 h and subsequently non-opioid analgesics. NPTs were conducted on post-operative days 3 and 7. Patients who did not perform well on NPTs, were contacted telephonically, reassured and advised proper follow-up.

Primary outcome measure was diagnosis of POCD and its incidence based on NPT, with results utilising 'individual change approach' in which each patient acts as its own control.

We chose to analyse test results using 1 standard deviation (SD) rule. A previous study (Van Dijk *et al*) on cognitive decline analysing NPT results found incidence of cognitive dysfunction after CABG has previously been overestimated. On reassessing their data, they reported decreased incidence of POCD at 3 months from 14–28% to 7.7%.[9] Also in absence of control group, 1 SD rule shows less false positives than 20% rule. This explains the lower rates of POCD found when 1 SD rule is used.[10] Hence, we decided to define POCD as decline in performance

equalling to or more than 1 SD from a pre-operative score in two or more NPT for exploratory analysis.

The results for various NPTs were calculated as follows:
1. For VVLT and DSST, we calculated mean ± SD and patients were classified as having POCD if their test performance was less than calculated value.
2. For TRAIL making and STROOP colour tests, we calculated mean ± SD and patient was labelled as having POCD if required time was more than calculated value.

Secondary outcome measures were to assess sevoflurane consumption in relation to POCD, time to eye opening and response to verbal commands after recovery from anaesthesia.

RESULTS

Eighty-seven patients under general anaesthesia (duration of ≥120 min) were assessed. Seven patients were excluded based on exclusion criteria. Two patients from group D and one from group P were unable to perform Trail B test, and one patient from each group was unable to complete Stroop B test pre and post-operatively and were excluded for these tests [Figure 3].

Upon assessment, it was found that the incidence of POCD on third post-operative day in group D and group P was 32.5% and 22.5%, respectively ($P = 0.31$), and on seventh post-operative day, it was 20% and 27.5%, respectively ($P = 0.43$) [Figure 4]. Dexmedetomidine group showed non-statistically significant decreased incidence of POCD on seventh day as compared to propofol group.

Propofol group patients had clear-headed recovery profile as measured by time (in s) to eye opening (6.82 vs. 6.18; *P* value 0.11) and response to verbal command (in s) following extubation (190.12 vs. 147.93; *P* value 0.01) with a more stable and easily titrable haemodynamics as evidenced by decreased incidence of hypotension (17.5% vs. 10% between group D and group P; *P* value 0.51) and episodes of BIS <40 (10% vs. 5%; *P* value 0.67 between group D and group P).

DISCUSSION

The finding of our study was that replacing dexmedetomidine with propofol in an anaesthetic
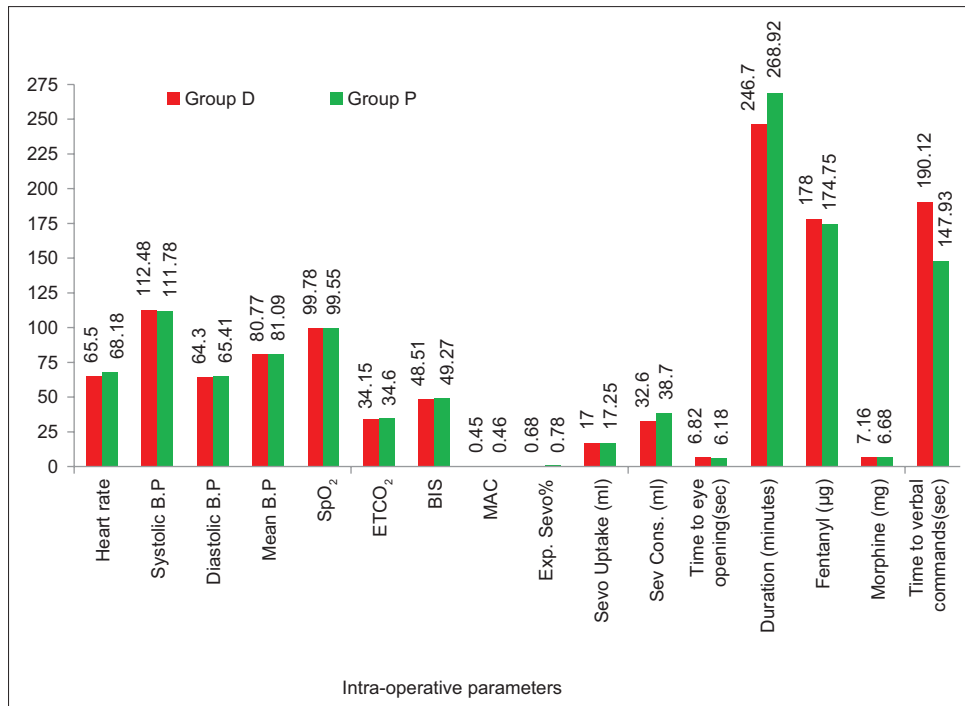
Figure 2: Intra-operative parameters. Haemodynamic parameters (HR – heart rate, BP – blood pressure, SPO$_2$ – oxygen saturation, ETCO$_2$ – end tidal carbondioxide), BIS – bispectral index, MAC – minimum alveolar concentration, Sevo – sevoflurane, V/C – verbal command. Exp. Sevo – expiratory sevoflurane concentration, duration – duration of anaesthesia in minutes, reaction time – time to eye opening after reversal of anaesthesia
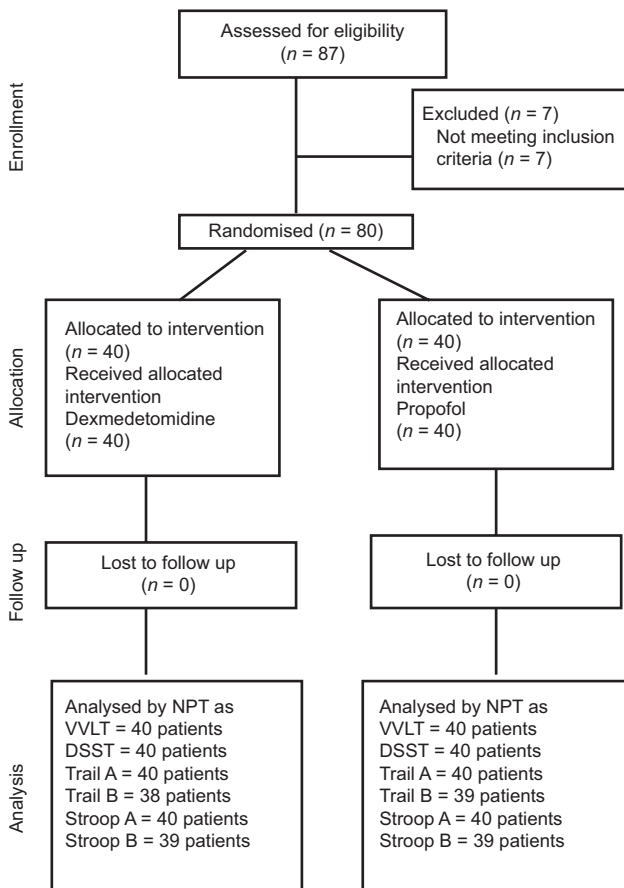

Figure 3: Consort flow diagram

regimen does not result in a lower rate of POCD. By assessing POCD with 'individual change approach' and taking 1 SD rule in 2 or more NPTs as a diagnostic criterion, with dexmedetomidine, the incidence of POCD decreased on the seventh post-operative day, possibly as a result of a reduced sevoflurane consumption (group D 32.6 ml vs. group P 38.7 ml; *P* value 0.11) and by reduced expiratory sevoflurane concentration (group D 0.68% vs. group P 0.76%; *P* value 0.01) with an acceptable range of BIS values (48.6 vs. 49.3; *P* value 0.52).

Increased life expectancy and comorbidities expose an increasing number of elderly patients to anaesthesia and surgery, and hence risk of POCD. Patients develop reduced functional status and lose their ability for independent decision-making,[8] old age being an independent and non-modifiable risk factor.[2] Our study also focused on elderly patients, and large number (42.5%) were 60–70 years old which is similar to other studies.[11]

There were 28.75% females and 71.25% males in our study. We could not confirm female gender to be a risk factor for POCD as reported by Kotekar[8] although it might have been underpowered, given the fewer number of female participants. As per cognitive reserve hypothesis, higher education protects
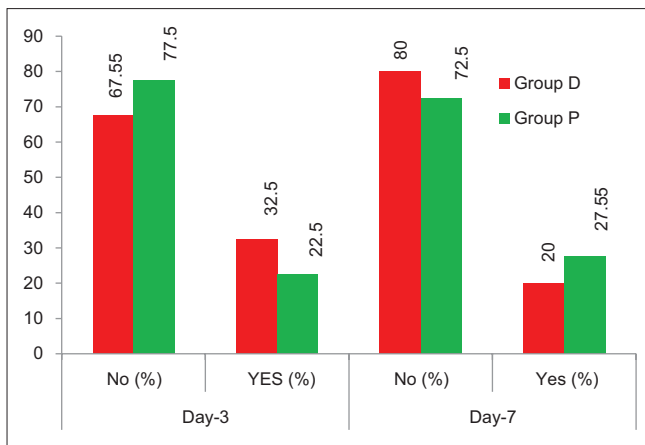
Figure 4: Incidence of POCD at different time points: day 3 POCD on third post-operative day (%), day 7 POCD on seventh post-operative day (%)

against cognitive decline after cardiac surgery.[12] The minimum education for inclusion was secondary level, being more frequent in group D (37.5% vs. 25%), whereas greater number of patients in group P had post-graduate education (30% vs. 22.5%). Despite this difference, group D patients had less incidence of POCD and performed better in various NPTs at post-operative day 7, suggesting possibly the protective role of dexmedetomidine in POCD.

We chose not to use benzodiazepines as an unnecessary confounder, although studies report that they do not play a role in cognitive dysfunction.[13,14] The type of GA has been examined as a contributing factor for POCD. Cai and co-workers[15] investigated the association between Apo lipoprotein E4 and POCD in elderly by comparing total intravenous anaesthesia with the general inhalational anaesthesia (GA). They found that GA group had a significant decrease in post-operative MMSE scores. Our study showed decreased uptake and consumption of sevoflurane with reduced end tidal (ET) sevoflurane concentration, to achieve an acceptable BIS value in group D, with decreased incidence of POCD. The mean of percentage ET sevoflurane for group D was 0.68% and for group P – 0.78% (*P*-value 0.01). The study by Mohamed *et al.*[16] showed anaesthetic and analgesic sparing effect of dexmedetomidine, with prolonged extubation and orientation times in dexmedetomidine group. Sevoflurane uptake and consumption were lesser in group D as compared to group P (17 ml vs. 17.25 ml; *P* value 0.91 and 32.6 ml vs. 38.7 ml; *P* value 0.11, respectively) suggesting anaesthetic sparing effect vis-à-vis more time to respond to verbal command (190.12 s vs. 147.93 s; *P* value 0.01) and time to eye opening (6.82 s vs. 6.18 s; *P* value 0.11). However, our study could not determine analgesic sparing effect of dexmedetomidine which was comparable (178 µg vs. 175 µg of fentanyl; *P* value 0.82 and 7.16 mg vs. 6.68 mg of morphine; *P* value 0.44 for group D and group P, respectively). The study by Song[17] showed that BIS monitoring decreases maintenance requirements of inhalational anaesthetic (sevoflurane and desflurane) by 30–38% and time to verbal responsiveness were 30–55% shorter in the BIS-titrated (vs. control) group. The study[18] comparing the effect of end-tidal anaesthetic concentration and BIS monitoring on recovery profile (time to eye opening, time to extubation and time to name recall) of patients receiving desflurane anaesthesia concluded that both are comparable with better recovery profile than standard group. The study by Gan TJ[19] showed maintenance requirement of i.v. hypnotics titrated with BIS monitoring decreased propofol use (22% reduction) with improved recovery. Our study showed non-statistically significant (*P*-value 0.91) lesser requirement of inhalational agent sevoflurane in group D as compared to group P. The time to verbal commands was less in propofol group as compared to the dexmedetomidine group.

Intra-operative data revealed that HR, blood pressure, SPO_2, $ETCO_2$, BIS and MAC were comparable between two groups. However, hypotension (MBP ≤70 mmHg) and BIS ≤40, although statistically non-significant (*P* = 0.51 and 0.67, respectively), were numerically more frequent in group D patients (17.5% vs. 10% and 10% vs. 5%, respectively), as was the use of vasopressors (IV ephedrine bolus and/or norepinephrine infusion).

Intragroup comparison of performance of NPTs between third and seventh day revealed no significant difference. VVLT, signifying learning ability and memory retrieval, showed improvement on seventh day in both group D and group P. On measurement of speed of processing of general information (DSST), though not statistically significant, group D performed better and showed improvement on seventh day. The study[20] also showed hastened recovery of psychomotor function by Trieger dot and DSST with intravenous dexmedetomidine infusion as adjuvant. Similarly, selective attention, mental ability and interference susceptibility, as assessed by Stroop A test, showed better performance by group D on seventh day, whereas both groups showed a decline in the Trail B test results, testing dexterity and ability to combine tasks. The study demonstrated non-statistically significant reduced

incidence of POCD in dexmedetomidine group on seventh day post-operatively in comparison to group P (20% vs. 27.5%; *P* value 0.43), which is consistent with a study by Chen *et al.*[11] During emergence from anaesthesia, group D patients had more prolonged time to extubation, eye opening and response to verbal commands (190.12 s vs. 147.93 s; *P* value 0.01). None of the patients developed major anaesthetic or surgical complications including delirium.

The estimated incidence cannot be inferred to general population, as patients not fulfilling the criteria were excluded. Intermediate term (30 days) NPT follow-up could not be performed. Many abilities besides our chosen NPTs remained untested. Lastly, concentrations of anti-inflammatory cytokines indicative of brain injury were not measured.

CONCLUSION

Dexmedetomidine infusion as adjuvant to inhalational anaesthesia in non-cardiac surgeries decreased the incidence of POCD on seventh post-operative day as compared to propofol (statistically not significant) and not on third post-operative day. Patients receiving dexmedetomidine had lesser consumption of sevoflurane (as compared to patients receiving propofol) as well as mean expiratory sevoflurane concentration which may be a contributing factor. The 'neuroprotective and anaesthetic sparing' effects of dexmedetomidine may protect against POCD in elderly patients. Further studies are warranted to establish the role of dexmedetomidine in pathogenesis and prevention of POCD.

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Conflicts of interest
There are no conflicts of interest.

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