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Research Article

The effect of Dexmedetomidine on the incidence of postoperative cognitive dysfunction in elderly patients after prolonged abdominal surgery

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KEYWORDS

Dexmedetomidine;
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Abstract *Background:* Postoperative cognitive dysfunction (POCD) in elderly patients is a common complaint after prolonged surgeries. In the present study, we aimed to investigate the effect of intraoperative infusion of Dexmedetomidine on POCD.
Methods: 50 patients aged more than 60 years old undergoing elective abdominal surgery expected to last more than 2 hours were randomized into 2 groups of 25 patients each: those receiving Dexmedetomidine at a dose of 0.4 μg/kg/h, group (A) and those receiving 0.9% normal saline as placebo group (B). All patients underwent neuropsychometric tests (Montreal cognitive assessment and Stroop color word interference tests) the day before the surgery and 24 h after the surgery, and one week postoperatively.
Results: The use of Dexmedetomidine as an adjuvant during Sevoflurane anesthesia did not have significant effect on protection against POCD in one day and one week postoperatively. The anesthetic and analgesic sparing effect of Dexmedetomidine was significantly proved by lower Sevoflurane need and significant lesser amount of total 24 hours postoperative Fentanyl requirements, but with significant prolonged extubation and orientation times in Dexmedetomidine group than placebo group.
Conclusions: The findings of this pilot study suggest that intraoperative use of Dexmedetomidine as an adjuvant in major surgery in elderly patients was not associated with significant protection against POCD.

1. Introduction

Postoperative cognitive dysfunction (POCD) is a common and well known complication after prolonged surgery. Especially the elderly patients are at risk of cognitive dysfunction. But due to the subtle nature of POCD, this complication might be recognized only by the patient's relatives. Thus, neuropsychological testing is necessary for its detection [1]. Early

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cognitive dysfunction may affect the recovery period in several ways. Delayed physical and emotional rehabilitation may delay hospital discharge and return to work. Also, it can interfere with accelerated care programs, which encourage a shorter hospital stay and early independence. These problems may be wrongly attributed to drugs or complications of surgery and anesthesia [2].

Some neuro-pathophysiological studies have suggested that post-operative cognitive disorder (POCD) might even share some mechanisms with Alzheimer's disease through deposition of plasma β amyloid and Tau phosphorylation [3,4].

Dexmedetomidine is a potent and highly selective alpha 2 adrenergic receptor agonist. It provides sedation with modest analgesic and possible anti delirium effects, but with minimal respiratory depression. In addition, the use of alpha 2 agonists has been associated with lower cardiovascular complications in high-risk non-cardiac surgery [5,6]. Taken together, Dexmedetomidine could provide specific advantages over commonly used analgesic and sedative agents for prolonged surgeries.

Besides, Dexmedetomidine's well-established sedative effects on increasing of both in vitro and in vivo evidence indicate that Dexmedetomidine also has a cell-protective effect on nervous tissue under ischemic conditions [7]. Moreover, there is recent evidence suggesting that this effect is mediated by the binding to imidazoline 1-recepors, which are known to be important regulators for cell survival and mediators of neuroprotective effects of many drugs [7–9].

In this randomized double blind pilot study, we aimed to examine whether the intraoperative use of Dexmedetomidine was associated with a lower incidence of neurocognitive dysfunction in elderly patients undergoing elective prolonged abdominal surgery when compared to Placebo.

We also assume that Dexmedetomidine by its analgesic and sedative effect can be adjuvant to inhaled anesthetics and can help in lowering the concentration of inhaled anesthetics and analgesic consumption that added a role in protection from POCD.

2. Methods

This was a pilot, randomized, double-blinded, controlled clinical trial. It was conducted in a tertiary referral hospital (King Faisal Specialist Hospital and Research Center, Jeddah, Saudi Arabia). Ethics approval for this study was provided by the institutional Ethics Committee of the hospital on 18/04/2010. The study was registered with the Australian New Zealand Clinical Trials Registry (ACTRN12613000378729).

Written informed consent was obtained from all patients. 50 patients men and women 25 patients per group, aged 60 years or older, American Society of Anesthesiologists (ASA) physical status classes I to III, scheduled for elective abdominal surgery (expected to be longer than 2 h), hospital stay >48 h, and educable, were included in this study.

All participants were given a written description of their involvement in the research, the neurocognitive test to be made, their rights and how their rights and interests will be protected, particularly in respect of confidentiality, privacy and safety. And all participants are made aware of their ability to withdraw consent and discontinue participation at any time exclusion criteria were patients with high vagal tone (heart rate <60), any arrhythmic disorders, severe ventricular dysfunction (EF $<35\%$), hypovolemic patients, patients with any psychological disorders, preexisting cognitive impairment, alcohol or drug abuse, patients with preexisting CNS deficit, or any neurological symptomatic disorder confirmed by MRI, patients who showed inability or unwillingness to abide by the protocol, inability to follow procedures, or poor comprehension of the language used in the study, and patients with severe visual or auditory handicap.

The patients were randomly allocated to one of two groups, Dexmedetomidine (A) group and a control (B) group, using a computer-generated sequence of random numbers and a sealed envelope technique. Study drugs were prepared by a pharmacist who did not participate in either the intraoperative management or the postoperative care. According to the randomization table, drugs were prepared in unlabeled 50 ml syringes. The unlabeled syringes were filled with normal saline or with Dexmedetomidine. Both the patients and the investigators were blinded to the study drug.

Our primary endpoint was the proportion of patients in each treatment group who was diagnosed to have POCD, while the secondary end points were included the estimation of intraoperative Sevoflurane consumption, Fentanyl consumption, depth of anesthesia, and emergence time. Participants were recruited from the outpatient clinic for anesthesia for preoperative evaluation. The preoperative interview included a medical and surgical history, current medications, alcohol consumption and substance use history, any neurological or psychological disorders, and ASA classification. Echo cardiography in addition to routine laboratory investigation and Electrocardiography was ordered.

2.1. Neuropsychometric evaluation

The baseline cognitive functions were conducted by a trained interviewer who was blinded to patient's allocation, for each patient, a day before surgery and repeated 24 h postoperatively and one week later. The tests used in this study were the following:

(A) Stroop color word interference test, which estimates the directed attention, mental speed and mental control using a booklet consists of 3 basic parts: (1) word page; the s patient reads words of color names (e.g., red, blue) printed in black ink. (2) Color page: the patient identifies colors (e.g., rectangles printed in red or blue). (3) Color-word page; the patient should name the color in which a word is written, while ignoring the printed word. Thus, incongruence between the word's color and identity (e.g., the word "red" presented in green). Lower score indicates higher performance [10,11].

(B) Montreal cognitive assessment test, which is a one page, 30 point test done in approximately 10 min for assessment of attention, memory, abstraction, delayed recall and orientation, with total score of 30, the short-term memory recall task (5 points) contains 2 learning trials of 5 nouns and delayed recall after approximately 5 min. Visuospatial abilities are assessed by a three-dimensional cube copy (1 point) and a clock-drawing task (3 points). Many ways of executive functions are evaluated using an alternation task adapted from the trail-making B task (1 point), a phonemic fluency task

(1 point), and a two-item verbal abstraction task (2 points). Attention, concentration and working memory are evaluated using a sustained attention task (target detection using tapping; 1 point), digits forward and backward (1 point each) and a serial subtraction task (3 points). And language is evaluated using a three-item confrontation naming task with low-familiarity animals (lion, camel, rhinoceros; 3 points), the aforementioned fluency task, and repetition of two syntactically complex sentences (2 points). Finally, orientation to time and place is evaluated (6 points). To keep the learning effects to a minimum, parallel equivalent forms have been used to decrease learning effects [12,13].

2.2. Intraoperative

All patients were monitored by five-lead electrocardiograph, a peripheral pulse oximeter, a noninvasive blood pressure device, a capnograph, airway gas analysis, neuoromuscular monitoring, and nasal temperature sensor. Hypothermia was prevented with a forced air warming blanket, and depth of anesthesia was monitored using a built in Entropy (GE Entropy, GE Healthcare Finland Oy, Helsinki, Finland).

Ten minutes before induction, a blinded study drug bolus infusion was started at 1 μg/kg/h for ten minutes intravenously and then induction was done by a blinded investigator using intravenous injection of Propofol 1–2 mg kg^{-1}, Fentanyl 1–2 μg kg^{-1}, and Rocuronium mg kg^{-1} followed by intubation and controlled mechanical ventilation to maintain end-tidal carbon dioxide at 35 ± 5 mmHg. Anesthesia was maintained using Sevoflurane with oxygen/air inspired gas mixture in a low flow breathing system (FiO_2 = 0.5) Sevoflurane starting with (1–1.5%) and the concentration was titrated 0.1% every 5 min guided by its end tidal concentration to maintain depth of anesthesia using Entropy. Its value should be maintained as close to 45–55 as clinically practical.

Infusion of the blinded drug either Dexmedetomidine (Precedex, Abbott Laboratories, Abbott Park, IL) or 0.9% normal saline at a rate of 0.4 μg kg h by a syringe pump maintained until end of surgery. Fentanyl was infused at a rate of 0.5 μg/kg/h and boluses of Rocuronium 0.2 mg/kg i.v according to the neuromuscular monitoring.

Fentanyl infusion and the study drug infusion were discontinued concomitantly with starting closure of surgical incision. At the end of the surgery, Sevoflurane inhalation was discontinued and local anesthesia infiltration of 0.25% plain bupivacaine was injected by the surgeon around the incision site, concomitant with i.v injection of 10 mg/kg paracetamol and Lornixicam 8–16 mg i.v as a subsequent analgesia. Tracheal extubation after the neuromuscular blockade was reversed with intravenous Glycopyrollate 0.1 mg/kg followed by neostigmine 0.05 mg/kg.

The following collected data were recorded intraoperatively: heart rate, mean arterial blood pressure, fluids intake, blood loss, core temperature, end tidal Sevoflurane, Entropy values every 5 min in first 30 min and then every 15 min, Extubation time, Fentanyl consumption, surgery and anesthesia times, eye opening time, and orientation time.

The patient was transferred to the Post Anaesthesia Care Unit (PACU) and a trained nurse was assigned to start PCA pump (Graseby 3300, Graseby Medical Ltd, Watford, UK) fentanyl, with 50 microgram per ml, and lock out of 6 min. And give 25 μg Fentanyl as boluses as rescue analgesic if numerical rating scale (NRS) > 3. The patients were monitored for hemodynamics, and pain assessment by NRS was done, by asking the patient to verbally rate his level of pain intensity on a numerical scale from 0 to 10 with, (0) representing no pain, and (10) is the other extreme (worst possible pain).

Sedation level was assessed by Ramsay sedation score (patients graded as 1: anxious, 2: oriented and tranquil, 3: respond to commands, 4: brisk response to stimulus, 5: sluggish response to stimulus, 6: no response to stimulus). Patients were considered ready for discharge from PACU when they attained Alderet score reaches 9–10 (Table 1), free of pain, nausea or vomiting. 24 h postoperatively, we recorded NRS on rest and movement, analgesic consumption, and neuropsychological tests, then repeat the neurocognitive tests after one week provided that patient will come to follow up in clinic or stayed at hospital.

We chose to use 1 SD rule to define cognitive dysfunction in each test because it has recently been shown to be associated with fewer false positives results (14). If the two tests were not completed at one time point, assessment for deficit was omitted, as POCD in each patient was defined as two or more abnormal test results.

2.3. The statistical analysis

We accepted a type I error of 0.05 and a type II error of 0.80 for detecting a true difference. A 0.5 or greater difference in independent variables was considered clinically significant. An estimate of standard deviation in independent variables was 1. As a result, we calculated that minimum 23 patients were needed in each group in order to obtain 5% type 1 error and an 80% power of detecting a difference of 0.5 or more. For each group, 25 patients were included to compensate for possible drop-outs. The power calculation was performed with nQuery Advisorw Version 7.0 (Statistical Solutions, Saugus, MA, USA).

Data were statistically described in terms of mean standard deviation (SD), and range, or frequencies (number of cases) and percentages when appropriate. Comparison of numerical variables between the study groups was done using Student *t* test for independent samples in comparing 2 groups when normally distributed and Mann Whitney U test for independent samples when not normally distributed. Within the group, comparison of quantitative data was done using Paired t test for normal data and Wilcoxon Signed Rank test for non-normal data. For comparing categorical data, Chi square (2) test was performed. Exact test was used instead when the expected frequency is less than 5. Within group comparison was done suing McNemar test. p values less than 0.05 was considered statistically significant. All statistical calculations were done using computer program SPSS (Statistical Package for the Social Science; SPSS Inc., Chicago, IL, USA) version 15 for Microsoft Windows.

3. Results

Fifty-eight patients scheduled for elective abdominal surgery expected to last for more than 2 h, participated in this study.

Table 1 Aldert score: criteria for patient discharge from post anesthesia care unit (patient can be discharged from PACU when Aldert score is 9 or 10).

	0	1	2
Activity	Unable to sit	Unable to sit without assistance	Able to sit or stand without assistance
Respiration	Apnea	Depressed from preoperative rate	Same or more than preoperative rate
Circulation	>50% lower than base SBP	20–50% lower	<20% lower
Color	Cyanosis	Pale	Normal
Consciousness	Unresponsive to verbal stimuli	Respond to verbal stimuli	Fully awake

Six patients were excluded on the basis of the exclusion criteria. Two patients, 1 from each group, were excluded after enrollment because of study protocol violations. Of the remaining 50 patients, 25 patients were randomized into Dexmedetomidine group (group A) and a control group (group B).

The two groups were not statistically different for the degree of education, ASA status, duration of anesthesia, the duration of the surgery and the demographic data (Table 2), (except for higher proportion of males in both groups ($p = 0.05$).

When each individual was analyzed by 1 SD rule, the incidence of POCD at 1 day by Montreal cognitive assessment test in either group was 20% (5 patients) nonstatistically significant ($P = 0.99$), while at one week POCD was diagnosed in 24% (6 patients) in group A and 20% (5 patients) in group B, and this was nonsignificant ($P = 0.73$).

Using Stroop color word interference test in group B, there was statistically higher incidence of POCD at 1 day than in group A 80% (20 patients) vs. 16% (4 patients), respectively ($P = 0.00$). Moreover, at one week, there was a decrement in incidence of POCD in both groups, but still statistically significantly higher in group B than group A 40% (10 patients) vs. 8% (2 patients) respectively $P = 0.00$, Table 3.

Within each group comparing incidence of POCD between 1 day and 1 week revealed nonstatistically significant difference in both neurocognitive tests except in Stroop color test in group (B) where there was a statistically significant difference between the two times periods .

The percentage changes of each group for each test are listed in Table 4. There was statistically significant difference in percentage change score between both groups at each time interval. However, all tests in each group changed nonsignificantly with time except in group B in Montreal cognitive assessment test.

Analysis of intraoperative data revealed that patients in group (A) showed increased amount of Sevoflurane need at induction associated with a decline in HR (60 beats/min), followed by stable period and minimal fluctuations around 60 beats/min, trend noted to be at lower values of HR rather than the higher values of group B, which means more hemodynamic stability. Also, group A patients achieved steadiness with no great fluctuations and no hypotensive episodes.

The percentage need of end tidal (ET Sevoflurane) for group (A) was 1.8% at 60 min followed by period of stability till the end of operation at 4 h, when we started to decrease the amount of Sevoflurane for emergence. The Entropy values did not increase proportionately in comparison with group B, and the maximum percentage need of Sevoflurane was 2.2% and associated with marked fluctuations to achieve appropriate depth of anesthesia (indicated by Entropy values).

Intraoperative use of vasopressor (Ephedrine) showed nonsignificant difference in between groups. In addition, intraoperative and PACU requirements of Fentanyl showed nonstatistically significant difference between both groups.

During emergence from anesthesia, patients in group A had more prolonged time for extubation, eye opening, obey order and orientation time than patients in group B.

At PACU, patients in placebo group (B) showed earlier orientation and cooperation by Ramsay sedation score than patients in study (see Fig. 1).

However, patients in group A remained statistically significant tranquilized for more prolonged period (90 min) than patients in group B ($P = 0.00$), Fig. 2.

Table 2 Demographic data, types of operations, and continuous variables are presented as mean ± SD, and categorical variables are presented as frequency (%). M:F, male:Female; *N*, absolute number.

	Group A	Group B
Age (y)	63.92 ± 4.99	67.80 ± 5.37
Anesthesia duration (h)	4.81 ± 2.30	4.44 ± 2.1
M:F	20:5	25:0
ASA 1.2.3	2:4:19	3:6:16
Education level (secondary) *N* (%)	19 (%)	20 (%)
(college) *N* (%)	6 (24%)	5 (20%)
Radical prostatectomy, *N*	0	10
Resection anastomosis, *N*	3	0
Abdominoperineal, *N*	0	5
Adrenelectomy, *N*	0	5
Anterior resection, *N*	4	0
Colectomy, *N*	7	5
Laparotomy, *N*	3	0
Radical cystectomy, *N*	5	0
Hystrectomy, *N*	3	0

Table 3 Proportion of patients with post operative cognitive dysfunction by 1 SD rule in individual tests. *P* value less than 0.05 is considered significant; *P* value less than 0.00 is considered highly significant.

	One day		One day		One week		One week	
	Montreal test	*P* value	Stroop color test	*P* value	Montreal test	*P* value	Stroop color test	*P* value
Group A (n) %	(5/25) 20%	0.99	(4/25) 16%	0.00	(6/25) 24%	0.73	(2/25) 8%	0.00
Group B (n) %	(5/25) 20%		(20/25) 80%		(5/25) 20%		(10/25) 40%	

Table 4 Percentage change for each test. Data are presented as mean ± SD of percentage change from preoperative values, at 1 day and 1 week in Montreal test average decrease in group A and average increase in group B, at 1 day and 1 week in Stroop color test average decrease in group B and increase in group A.

Test	Preoperative	P value between groups	One day	*P* value between groups	One week	*P* value between groups	*P* value across time periods
Montreal group A	25.24 ± 3.05	0.00	−2 ± 3.2	0.00	−0.786 ± 0.4.497	0.000	0.16
Montreal group B	23.60 ± 3.74		2.90 ± 7.159		12.832 ± 18.839		0.00
Stroop color group A	24 ± 4.40	0.09	4.257 ± 8.768	0.02	6.974 ± 9.609	0.001	0.15
Stroop color, group B	20.20 ± 4.62		−4.301 ± 16.288		−2.734 ± 10.601		0.53

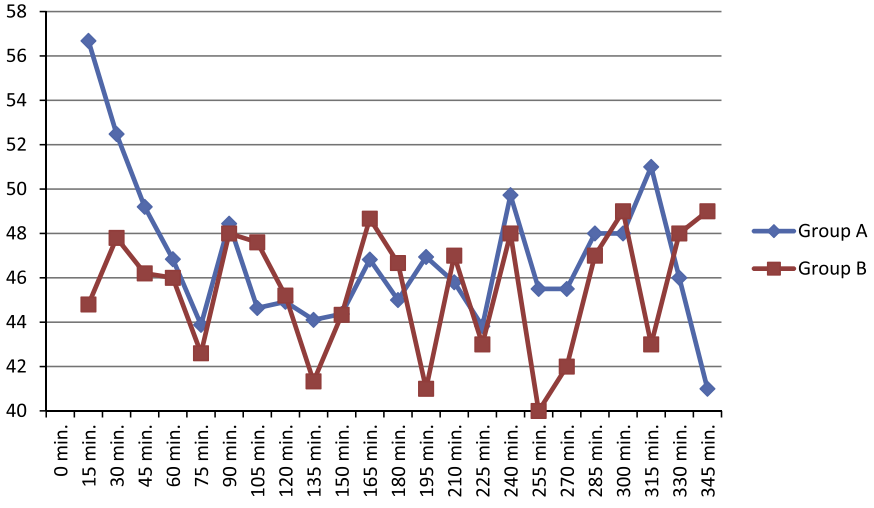

Figure 1 Mean Entropy values between the study groups over the study period.

As noted, there was statistically significant difference between NRS during 24 h at rest in patients of group A with score not exceeding 1.50, while NRS in group B still mild with higher values not exceeding 2. Moreover, NRS during 24 h period at movement were considered significantly lower at group (A) with values less than or equal to 3, in comparison with group (B) with values less than or equal to 4 (see Fig. 3).

Those results correlate with the total 24 h postoperative Fentanyl consumption, in group (A) patients required 290 ± 37.63 μg Fentanyl, compared to 562 ± 214.98 μg Fentanyl consumption in group (B) that indicates statistically highly significant ($p = 0.00$).

4. Discussion

The results of our pilot 2-arm randomized trial demonstrates nonstatistically significant lower incidence of POCD, during one day and one week postoperatively in patients who received Dexmedetomidine. Besides, these patients had stable

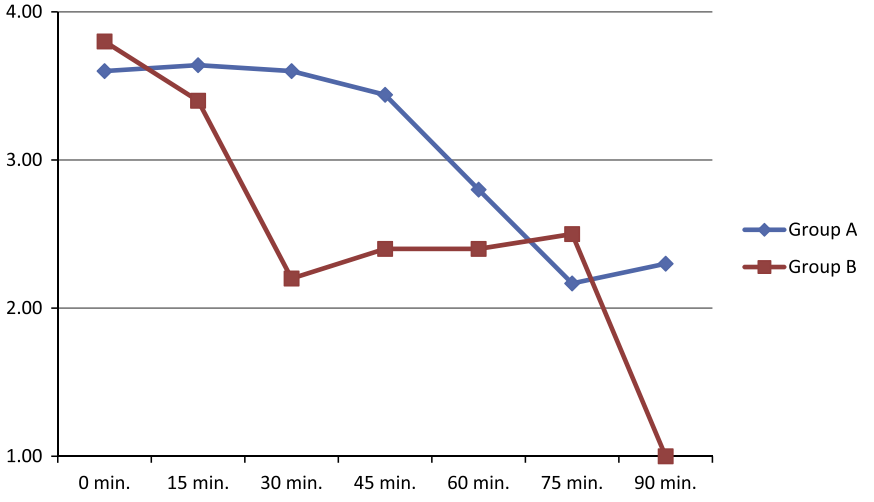

Figure 2 Mean Ramsy sedation score between the study groups over the study period.

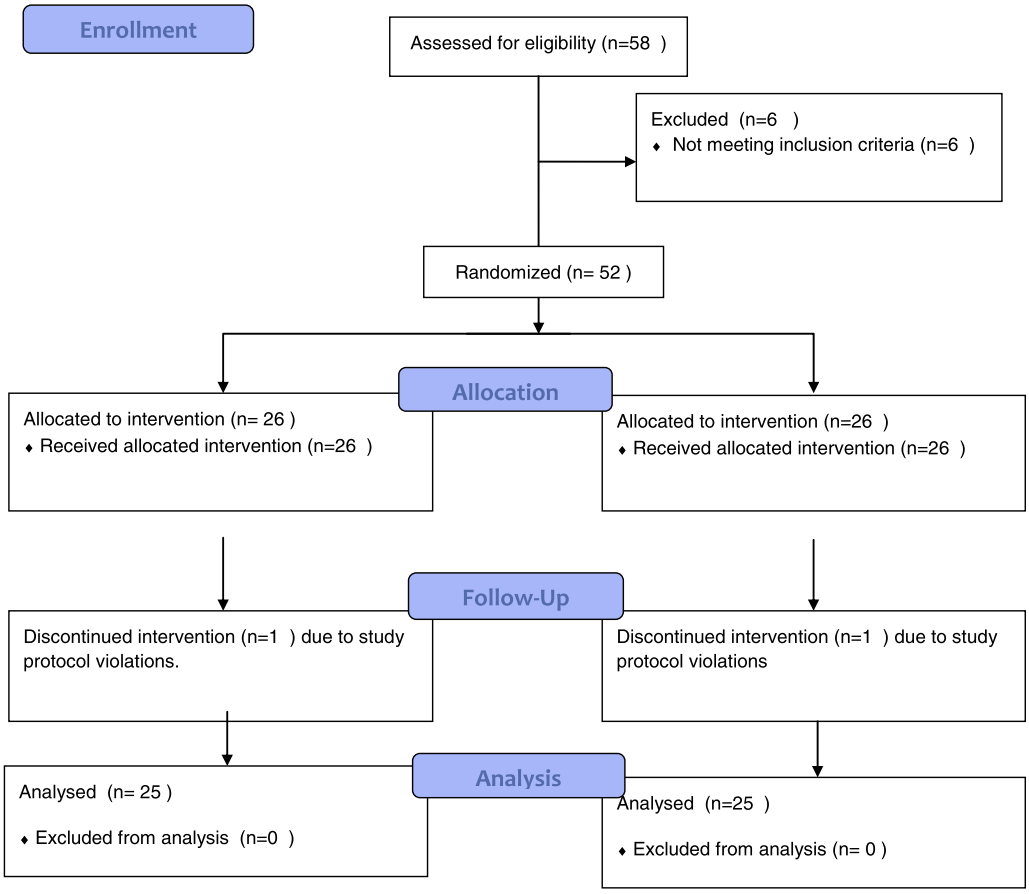

Figure 3 The study flow chart.

hemodynamics, lower anesthetic and analgesic consumption, although concomitant with delayed emergence and prolonged recovery time in PACU.

Changes in cognitive status after surgery may present in the form of delirium or POCD. Delirium is defined as an observational changes that occur in consciousness, with perceptual disturbance, disorganized thoughts and hyper or hypoactive psychomotor activity, whereas in POCD patients exhibiting declines from his own baseline level of performance in one or more neuropsychologic domains [15,16].

POCD often goes unrecognized in the clinical setting although its incidence of occurrence is 19–47% in noncardiac surgery. It is a more persistent problem and is usually detected with neuropsychologic tests [17–19].

In this study, we included patients with higher level of education as according to the cognitive reserve hypothesis. Education level affects susceptibility to POCD and that suggests that a higher level of education seems to protect against decline after cardiac surgery [20]. We also included patients above 60 years old as elderly patients undergoing major surgery are more prone to have POCD as evident in a large well designed study data [21]. We chose to analyze the test results using 1 SD rule. A previous study on cognitive decline after CABG surgery done by Van Dijk et al. used the 20% rule to define the prevalence of POCD. Recently, that group reassessed their data using the 1 SD rule and got the conclusion that the reported incidence of POCD at 3 months decreased from 25% to 10.5% [14].

Also, it had been recently shown that, in the absence of a control group, the 1 SD rule shows less false positives than the 20% rule. This explains the lower rates of POCD found when the 1 SD rule is used to define POCD. For this reason, we decided to use the incidence of POCD as defined by the 1 SD rule for exploratory analysis using logistic regression [18].

Postoperative cognitive dysfunction after prolonged surgery has been the subject of many investigations. Some of these studies have shown some factors associated with POCD, but none have been solely or consistently implicated [22,23]. Yuji study concluded no relationship of Sevoflurane to POCD after cardiac surgery in a study done on 109 patients; his study did not prove that Sevoflurane had preconditioning effect on the brain as on heart to improve the neurological outcome, as suggested by studies done on animal's models [24].

In our study, the use of Dexmedetomidine did not show a protective effect on the development of POCD. The result may be surprising, but if it is true, it contradicts the original assumption that Dexmedetomidine has a neuroprotective effect. And also to the study done by Maldonado et al., who reported that postoperative sedation with Dexmedetomidine was associated with significantly lower rates of postoperative delirium in cardiac surgery (3%) [25].

However, Norimasa and his colleagues studied the recovery profile of both sevoflurane and propofol when Dexmedetomidine was added to both as a general anesthetic adjuvant in patients undergoing lower abdominal surgery. They revealed that the addition of Dexmedetomidine did not affect

postoperative cognitive functions [26]. Moreover, Suleman study concluded Dexmedetomidine used as an adjuvant anesthetic agent in cardiac surgery has no neuroprotective effect against cerebral ischemic injury, by serial measurements of neurons – specific enolase and serum −100B protein, but he recommended larger population than his study sample size (twenty-four patients) [27].

In our study, the use of Dexmedetomidine was associated with hemodynamic stability, lower end-tidal Sevoflurane (around 1.8%) and a stable anesthetic depth detected by Entropy (figure around 46) in Dexmedetomidine group patients that is related to anesthetic sparing effect of Dexmedetomidine and similar to previous studies [28,29]. The extubation and orientation time were significantly prolonged in Dexmedetomidine group than placebo group patients, which was attributed to the sedative effect of Dexmedetomidine. Burcu study [30] revealed different concentrations of Dexmedetomidine infusion failed to facilitate faster emergence, but shorter times than our study that was attributed to prolonged time of infusion.

Postoperative analgesic requirements during 24 h was considered significantly lower in Dexmedetomidine group patients, associated with lower values of NRS at rest and movements. The analgesic sparing effect of Dexmedetomidine would have persisted for up to 24 h postoperatively and also the thymoanaleptic properties of alpha 2 agonists that affect the emotional component of postoperative pain had also a role.

A limitation of our study is that we assessed short term POCD at 1 day and 1 week, a small sample size, and that we could not determine whether the etiology of POCD in postoperative day (1) is different from that at 1 week.

5. Conclusion

This pilot study of POCD in elderly patients after major surgery has shown nonstatistically significant difference in the incidence of POCD in day 1 & first week postoperatively between Dexmedetomidine and placebo group. And we did not prove that Dexmedetomidine infusion can be a helpful adjuvant in general anesthesia to reduce risk of POCD. In spite of its anesthetic–analgesic sparing effect, we recommend a larger population study in the future to prove its role in protection against POCD.

Trial Registery

This study was registered with the Australian New Zealand Clinical Trials Registry (ACTRN12613000378729).

Conflict of Interest

None.

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