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Research Article

Continuous Dexmedetomidine Infusion Reduces Postoperative Cognitive Dysfunction and Postoperative Pain in Patients Undergoing Laparotomy Surgery: Single-Blinded, Randomized Controlled Trial

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ABSTRACT

Background: Postoperative cognitive dysfunction (POCD) is a major concern in anesthesia, leading to increased morbidity and longer hospital stays. Our study aimed to evaluate the efficacy of target-controlled infusion (TCI) dexmedetomidine in reducing the incidence of POCD following laparotomy surgery.
Methods: A single-blinded, randomized controlled trial involving 107 patients aged >18 years old undergoing laparotomy surgery was conducted. Patients were randomly assigned to 54 patients in Group D (TCI dexmedetomidine with a target plasma of 1 ng/ml) and 53 patients in Group I (sevoflurane at 0.8% concentration).
Results: Our study showed subjects whose anesthesia was maintained by TCI dexmedetomidine had a lower chance of developing POCD (p=0.043) and experienced less pain at 12 hours (p=0.049) and 24 hours (p=0.049) in the postoperative period, compared to the control group. There were no significant differences between both groups in intraoperative MAP (p=0.290) and HR (p=0.453).
Conclusion: Maintaining anesthesia using Conox®-guided TCI dexmedetomidine reduces the incidence of POCD and postoperative pain in laparotomy patients who underwent general anesthesia.

Introduction

Postoperative cognitive dysfunction (POCD) affects all age groups and can lead to increased morbidity and more extended hospital stays [1]. It occurs in 25.8% of elderly patients (>60 years old) [2]. Postoperative cognitive impairment is influenced by factors such as older age, types of anesthesia, and major surgery [3–5].

Early screening of cognitive impairment is one of the secondary prevention measures included in the comprehensive geriatric assessment (CGA) to improve the quality of life, especially in older adults following major surgery [6-7]. Various examinations can be carried out to diagnose POCD. The Edmonton Frailty Scale

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(EFS), Administrative Risk Analysis Index (RAI-A), and Clinical Risk Analysis Index (RAI-C) were preoperative frailty tests that have a cognitive domain. EFS has been reported to be the best predictor for postoperative complications. However, the EFS cognitive domain only includes the clock drawing test. Therefore, its use in detecting mild cognitive impairment is limited [7]. Mini-Mental State Examination (MMSE) is widely used to detect POCD because it is simple and easy to use [8].

Target-controlled infusion (TCI) is a computer-guided intravenous drug administration technique that regulates drug administration based on pharmacokinetics, reducing side effects and providing controlled induction and fast recovery time [9]. It maintains stable hemodynamics and sedation and reduces the risk of postoperative cognitive impairment [10–12]. TCI has overtaken inhalational agents, which previously had been the classic anesthesia drug for the elderly [13].

Dexmedetomidine reduces POCD by inhibiting the increase in proinflammatory cytokines IL-6 and TNF-α, and its anti-inflammatory activity contributes to its protective effect [14]. Previous studies found that dexmedetomidine reduced POCD incidence in non-cardiac [15] and cardiac surgery [16].

Therefore, the goal of this study was to specifically investigate if using TCI dexmedetomidine to maintain anesthesia in laparotomy surgeries reduces the incidence of POCD compared to inhalation anesthesia by sevoflurane. Subsequently, we also assessed the perioperative hemodynamics and postoperative pain between the two groups.

Methods

A single-blind, randomized, controlled trial was conducted at a tertiary referral teaching hospital from January to February 2024. The study protocol was approved by the institutional ethical research committee (registry number 0295/UN14.2.2.VII.14/LT/2024) on January 3, 2024. All patients provided written informed consent to be included in this study.

This study included patients aged ≥18 years and older who underwent laparotomy surgery under general anesthesia and who were identified with American Society of Anesthesiologists (ASA) physical status I to III. Exclusion criteria included a history of allergies to anesthetic drugs, impaired consciousness, neurocognitive, psychiatric, mental, or cerebrovascular disorders, sick sinus syndrome, hypoalbuminemia, massive bleeding, and liver and kidney diseases.

We employed the consecutive sampling method and randomized the patients into two groups using a permuted block randomization technique available online (https://www.sealedenvelope.com/simple-randomiser/v1/lists). The patients were blinded to the group allocation. An independent statistician generated the random allocation sequence, enrolled the patients, and assigned the patients to interventions. The anesthesiologist opened the sealed envelope containing the intervention allocation just before the induction of anesthesia and surgery.

General anesthesia for subjects in Group D was maintained by target-controlled infusion (TCI) dexmedetomidine (Dyck mode) with a target plasma of 1 ng/ml, and for Group I by inhalation anesthesia using sevoflurane at 0.8% concentration.

Mini-Mental State Examination by telephone (MMSE-T) was performed 12-24 hours before surgery to evaluate preoperative cognitive function [17]. All patients of both groups were fasted for eight hours prior to surgery. In the operating room, standard ASA monitoring was attached to all subjects. The depth of anesthesia was monitored using Conox® (Fresenius Kabi, Bad Homburg, Germany). Conox® is a non-invasive monitoring tool for the depth of anesthesia and the analgesic effects of patients undergoing anesthesia. An arterial line was properly placed per the institution's guidelines, followed by intravenous Ringer's lactate administration.

Anesthesia induction started with fentanyl 2 µg/kg and TCI propofol (Schnider's model) [18] with a target effect of 2 µg/ml. Subsequently, atracurium 0.5 mg/kg was administered to facilitate intubation. In group D, anesthesia was maintained by TCI propofol (Schnider's model) with a target effect of 2 µg/ml combined with TCI dexmedetomidine (Dyck mode) with a target plasma of 1 ng/ml. In Group I, sevoflurane at 0.8% concentration was used to maintain anesthesia. Intraoperative hemodynamic parameters were measured at 5 min, 30 min, 1 hour, and 2 hours. The Conox® monitor shows two parameters: quantum consciousness index (qCON) and quantum nociception index (qNOX). A qCON value of 40-60 indicates adequate anesthesia depth. During the intraoperative period, qCON was maintained at 40 to 60 in group D. If the qCON value was less than 40, the TCI propofol dose was lowered, and if the qCON value was more than 60, the TCI propofol dose was increased. The qNOX is also maintained at 40-60 in both groups. Additional fentanyl 0.5 µg/kg was administered if the qNOX value was more than 60. Fentanyl 0.5 µg/kg was also additionally administered when systolic (SBP), diastolic blood (DBP), and mean arterial pressures (MAP) remained >20% from baseline or heart rate (HR) was >100 bpm. Atracurium 0.1 mg/kg is administered intraoperatively every 30 minutes in both groups. Postoperatively, both groups also received intravenous fentanyl at 0.25 µg/kg/24 hours and oral paracetamol 10 mg/kg every eight hours. Postoperative pain was evaluated at 1, 12, and 24 hours using the visual analogue scale (VAS). MMSE-T was performed again at 48 hours and 30 days after the surgery. The primary outcome of the study was postoperative cognitive function assessed by MMSE-T. POCD was defined as a decrease in the

MMSE-T score of ≥2 points from the preoperative assessment [19]. Secondary outcomes were intraoperative hemodynamics (SBP, DBP, MAP, HR) and postoperative VAS.

Descriptive data were presented as mean and standard deviation for normally distributed data or median and interquartile range (IQR) otherwise. Categorical variables were presented in proportion. We employed the Kolmogorov-Smirnov test to test for normality. The independent t-test was used for normally distributed data to compare intraoperative hemodynamics, postoperative pain, and anesthesia depth in both groups, and the Mann-Whitney test was used for non-normally distributed data. Furthermore, the chi-square test was used to identify significant correlations between POCD and anesthesia depth. Logistic regression was employed to calculate the odds ratio (OR). Data analysis was done using SPSS for Windows 25.0 (IBM Corp., Armonk, NY, USA). A p-value of <0.05 was considered statistically significant.

Results

The study included 112 patients, where 56 patients were enrolled in both groups, while 18 were excluded (Figure 1). During the follow-up, two patients in Group D and three in Group I refused to participate. Fifty-four patients in Group D and 53 patients in Group I were analyzed. The mean age of the subjects was 52.9±14.7 years in Group D and 57.6±13.1 years in Group I. Meanwhile, the total intraoperative propofol (600 [50-1800] vs 600 [50-1500] mg) and fentanyl (175 [50-300] vs 200 [50-300] µg) in Groups D and I, respectively (Table 1).

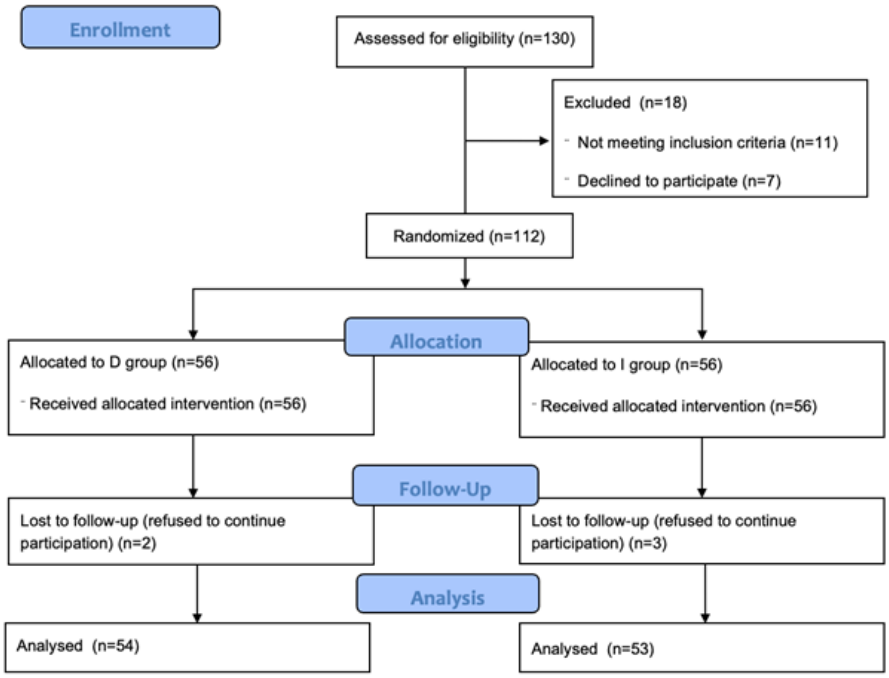

Figure 1- CONSORT flowchart

Table 1- Demographic data.

Variables	Group D	Group I
Age (years), mean±SD	52.9±14.7	57.6±13.0
Gender, n (%)		
Male	42 (53.2)	37 (46.8)
Female	12 (42.9)	16 (57.1)
BMI (kg/m2), median (IQR)	23.4 (3.9)	23.2 (4.3)
ASA physical status, n (%)		
I	11 (20.4)	14 (26.4)
II	24 (44.4)	19 (35.8)
III	19 (35.2)	20 (37.7)
Total intraoperative propofol requirements (mg), median (IQR)	600 (755)	600 (755)
Total intraoperative fentanyl requirements (µg), median (IQR)	175 (50)	175 (50)

Group D: TCI dexmedetomidine with target plasma of 1 ng/ml; Group I: Sevoflurane at 0.8% concentration; SD: Standard Deviation; BMI: Body Mass Index; ASA: American Society of Anesthesiologists; IQR: Interquartile Range

The median (IQR) preoperative MMSE score was 22 points in both groups (p = 0.817, (Table 2). Moreover, the second and third MMSE assessments at 48 hours and 30 days after surgery showed similar results in both groups (21 points, p=0.024). In this study, as per the preset definition, ten patients experienced POCD (2 patients in Group D and 8 in Group I, p = 0.043). Furthermore, using TCI dexmedetomidine during general anesthesia guided by a Conox® monitor reduced postoperative pain at 12-hour (p=0.049) and 24-hour (p=0.049) postoperative periods. Additionally, our subset analysis in the geriatric age group (i.e., ≥65 years old) found no significant differences in postoperative pain between the two groups (p=0.238).

Meanwhile, we found no significant differences in intraoperative hemodynamic instability between the groups in terms of SBP (p=0.755), DBP (p=0.304), MAP (p=0.290), and HR (p=0.453). These insignificances were also consistently shown at other preset time points (Figure 2).

Finally, a cross-tabulation table (Table 3) showed that there is no correlation between the depth of anesthesia (measured by Conox® monitor) and the incidence of POCD (p=0.402, OR=0.39). Conversely, we did find a correlation between the use of TCI dexmedetomidine and the incidence of POCD (p=0.403, OR=4.62 [CI95%=0.93-22.89]).

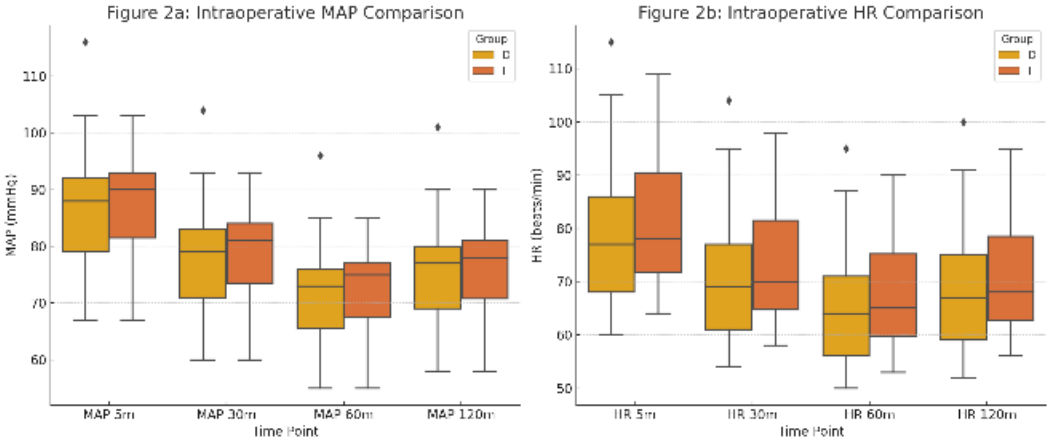

Figure 2- Mean arterial pressure (MAP, 2a) and heart rate (HR, 2b) comparison between the two groups.

Table 2- Observed variables in the study groups.

Variables	Group D	Group I	P value
MMSE-T, median (IQR)			
Preoperative	22 (2)	22 (1)	0.817*
48-hour postop	21 (0)	21 (0)	0.024*
30-day postop	21 (0)	21 (0)	0.024*
Anesthetic depth, n (%)			
40 – 60	53 (98.1)	49 (92.5)	0.163†
<40	1 (1.9)	4 (7.5)	
POCD in all ages, n (%)			0.043†
Yes	2 (3.7)	8 (15.1)	
No	52 (96.3)	45 (84.9)	
POCD in ≥65 years old, n(%)			0.238‡
Yes	0 (0)	3 (18.8)	
No	12 (100)	13 (81.2)	
Visual analogue scale			
1-hour postop, n (%)			
0			0.540†
1	36 (66.7)	37 (69.8)	
2	14 (25.9)	12 (22.6)	
3	3 (5.6)	1 (1.9)	
12-hour postop, n (%)	1 (1.9)	3 (5.7)	
0			0.049†
1	15 (27.8)	27 (50.9)	
2	36 (66.7)	24 (45.3)	
	3 (5.6)	2 (3.8)	

24-hour postop, n (%)			0.049†
0	15 (27.8)	27 (50.9)	
1	36 (66.7)	24 (45.3)	
2	3 (5.6)	2 (3.8)	

MMSE-T: Mini-Mental State Examination by telephone; IQR: interquartile range; POCD: Postoperative Cognitive Dysfunction; *Mann-Whitney test; †Chi-square test; ‡Fisher's exact test.

Table 3- Correlation between depth of anesthesia and TCI dexmedetomidine usage with POCD.

Variables	POCD, n (%)		P value	OR (CI95%)
	Yes	No		
BIS, n (%)			0.402	0.39
40 – 60	9 (90)	93 (95.9)		(0.04-3.84)
<40	1 (10)	4 (4.1)		
TCI Dex, n (%)			0.043	4.62
Yes	2 (3.7)	52 (96.3)		(0.93-22.89)
No	8 (15.1)	45 (84.9)		

BIS: anesthetic depth; TCI: target-controlled infusion; POCD: Postoperative Cognitive Dysfunction; OR: odds ratio

Discussion

This study compared the incidence of POCD in patients undergoing laparotomy surgery under general anesthesia guided by a Conox® monitor. We demonstrated that the dexmedetomidine group had a lower incidence of POCD (3.7%) compared to the inhalational anesthesia group (15.1%). The postoperative pain at 12 and 24 hours was also significantly lower in the dexmedetomidine groups. Finally, we found no significant difference in intraoperative hemodynamics between the two groups.

We utilized the Conox® monitor to monitor the depth of anesthesia. The Conox® monitor displays real-time feedback on qCON and qNOX indices derived from various physiological parameters, mainly electroencephalography (EEG) signals and frontal electromyography [20]. As a tool based on processed-EEG (p-EEG), it quantifies the depth of anesthesia on a numerical scale, with higher qCON values indicating a deeper level of anesthesia and lower values suggesting lighter anesthesia or potential awareness [20]. Compared to the conventional sedation assessment scores, which are assessed subjectively, p-EEG provides objective and real-time information on the depth of anesthesia [21]. A previous study reported that qCON significantly correlated with the Richmond Agitation Sedation Scale (RASS) [22]. Furthermore, another EEG-based index, called the bispectral index, has been shown to significantly correlate with the Ramsay Sedation Scale (RAS) [23] and consciousness level [24]. Previous studies have emphasized the importance of deep anesthesia in reducing the incidence of POCD [25–27]. Also, a recent meta-analysis outlined the benefit of monitoring the depth of anesthesia in reducing POCD incidence [28].

In a previous study, we reported an 8.3% incidence of POCD [29]. However, that study recruited only elderly patients aged >60 years old, while our present study included a more extensive age range (>18 years old). Our study demonstrated that the incidence of POCD at 48 hours and 30 days postoperative was 9.3%. It is important to note that none of these were carried out in a large number of subjects. This incidence is somewhat similar to previous studies [2, 30–32]. In our subset analysis, in which we funnelled the subjects to the geriatric population, we found no significant differences in the incidence of POCD between the two groups. The modest number of subjects in this age group may cause this.

Our study showed subjects whose anesthesia was maintained by TCI dexmedetomidine had a lower chance of developing POCD compared to those maintained by sevoflurane (p=0.043). Previously, a study reported that the incidence of POCD in dexmedetomidine was significantly lower than in those who received normal saline [15]. Similarly, reports showed that patients who received dexmedetomidine showed higher postoperative MMSE and MoCA scores than those who received normal saline up to seven days postoperatively [16, 33]. Dexmedetomidine alleviates stress response and reduces catecholamine release, resulting in reduced surgery and anesthesia stress, all suspected to play a role in the development of POCD [34]. Dexmedetomidine is suggested to protect the central nervous system by decreasing intracerebral catecholamines during trauma. Its neuroprotective effects involve modulating proapoptotic and antiapoptotic proteins and inhibiting excitatory neurotransmitter glutamate [35]. Dexmedetomidine administration during laparoscopic cholecystectomy reduced proinflammatory cytokines and POCD incidence compared to saline administration [36]. Furthermore, while dexmedetomidine has been proposed to reduce the risk of POCD, further studies are needed to understand the exact mechanism [35].

Our study found no significant difference between the two groups in intraoperative MAP (p=0.290) and HR (p=0.453). This is essential because impaired hemodynamics suggest more stress hormone release, which may cause further deterioration in the cerebral vasculature. A previous study found that

dexmedetomidine increases the incidence of bradycardia [37], although this was dose dependent. Additionally, other studies reported that dexmedetomidine significantly reduced MAP and HR in laparoscopic cholecystectomy [38-39].

Dexmedetomidine's hemodynamic effects during anesthesia are linked to the sparing effects of anesthetic drugs, as it reduces the anesthetic dose needed to maintain adequate depth of anesthesia. Previous studies have shown that it is superior to clonidine [32] and midazolam [35]. Dexmedetomidine influences hemodynamics by reducing the activity of the sympathetic nervous system. Although it sometimes produces transient hypertension during loading doses, which is associated with the initial peripheral vasoconstrictive effect, treatment is generally not necessary [40]. It is well-established that α2-receptors are extensively dispersed throughout the cerebral vasculature [41-42]. This vasoconstrictive feature may primarily occur at the level of the pial arterioles, the smaller-caliber cerebral arteries located distal to the circle of Willis [41]. Additionally, activation of intrinsic noradrenergic neural pathways projecting to the microvasculature of the central nervous system from the locus coeruleus may play a role [41,43]. Furthermore, investigations in humans and animals have revealed significant cerebral vasoconstrictive effects of dexmedetomidine.

While our study found no significant difference in postoperative pain at 1 hour after the surgery, it showed a significant difference in VAS results at 12- and 24-hour post-surgery (both at p=0.049). Previously, a trial reported that dexmedetomidine resulted in lower VAS scores at 24 and 48 hours postoperatively but not at 72 hours [33]. Another trial [37] reported that the VAS score at 20 minutes and 2, 6, 12, and 24 hours after laparoscopic cholecystectomy was lower in subjects receiving dexmedetomidine than in those receiving normal saline. However, this pain-alleviating feature was reported as not dose-dependent [44].

Limitation

Our study has several limitations. First, the small number of subjects limited its extrapolation to the general population, requiring further studies. Second, the study did not analyze quantitative inflammatory indicators, which hindered the objective evaluation of the inflammatory process and thus led to the lack of the anti-inflammatory impact of dexmedetomidine. Additionally, our dataset contains a limited number of subjects who were >65 years old. While POCD may occur at any age, its incidence increases in the older age group. Therefore, future studies in higher-risk populations are still needed. Finally, the cognitive domain of MMSE is limited. Consequently, it may not be the best tool to diagnose POCD. As no single tool has been established to assess POCD objectively, further studies in this field are also required.

Conclusion

We conclude that maintaining anesthesia using Conox®-guided TCI dexmedetomidine reduces the incidence of POCD in laparotomy surgery patients who underwent general anesthesia. Moreover, it reduces postoperative pain at 12 and 24 hours, resulting in similarly stable hemodynamics compared to inhalational anesthesia by sevoflurane. Further research involving more subjects and using other cognitive function assessments (e.g., biomarker measurement) to detect POCD is needed.

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