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Intraoperative dexmedetomidine infusion might help to preserve the cognitive function of geriatric patients undergoing arthroscopic shoulder surgery

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ABSTRACT

Objectives: This study tried to evaluate the impact of dexmedetomidine (DXM) infusion provided during sevoflurane (SEV) anesthesia on cognitive function (CF) of elderly patients undergoing elective arthroscopic shoulder surgeries.

Patients & Methods: A total of 140 patients were randomly allocated into Groups S and D. All patients received SEV (0.5–1 MAC) with placebo or DXM (0.6 μg/kg/h) infusions, respectively. CF was evaluated preoperatively, 48-h, 1-wk, and 2-wk postoperative (PO) using the Montreal Cognitive Assessment Test and Mini-Mental State Examination (MMSE). The study outcome is the frequency and severity of PO cognitive dysfunction (POCD).

Results: At 48-h PO, the frequency of normal CF and scorings were significantly decreased compared to preoperative findings, but were significantly higher in group D. At 1-wk PO, the frequency of normal CF and scores increased in both groups with significant difference in favor of group D, but differences were significantly lower than in preoperative measures. At 2-wk PO, 79.3% of patients regained their normal CF, with significantly higher frequency and score for group D, and the difference compared to preoperative data was insignificant in group D, but it was significant in group S. At 48-h, scorings were positively related to using DXM but were negatively related to age, obesity, and PO analgesia. Regression analysis defined old age as negative and the use of DXM as positive predictor for high scores.

Conclusion: SEV anesthesia induced reversible short-term POCD. Coupling of DXM infusion with SEV anesthesia decreased the frequency and scores of POCF and fastened resumption of normal CF.

1. Introduction

Postoperative cognitive dysfunction (POCD) is a common central nervous system complication that predominantly affects elderly patients with high incidence after cardiac surgery with cardiac bypass [1]. Multiple perioperative independent factors; women, presence of mental illness, diabetes mellitus, dyslipidemia, aortic stenosis, type of surgery, especially cardiac surgery are risk factors for POCD [2–4]. In addition to its health risks, POCD consumes a huge part of resources through extended hospital stays, higher costs, and workforce dropout [5].

Sevoflurane (SEV) is one of the most widely used anesthetics for surgery for its advantages of easy and rapid induction and emergence from anesthesia, but unfortunately, SEV is one of the main causes of POCD [6]. However, animal studies reported insignificant differences between SEV and isoflurane, another commonly used inhalational anesthetic (IA), on cognitive function (CF) [7,8]. Another animal study detected acute neuronal apoptosis in neonatal mice exposed to isoflurane or sevoflurane and found that the impact was more pronounced with isoflurane [9].

Propofol total intravenous anesthesia (TIVA) was tried to replace IA to guard against POCD; however, the results of comparative trials are discrepant. A meta-analysis showed SEV was a risk factor for the emergence of delirium compared to propofol-based TIVA during various surgeries but not intracranial surgery [10]. Another study reported an insignificant difference in the incidence of PO delirium between anesthesia maintenance with a volatile agent and propofol-based TIVA [11].

Unfortunately, effective prevention methods remain elusive; experimental studies have shown that melatonin has an alleviating effect on SEV-induced cognitive deficits [7], vitamin D supplementation improves anxiety and enhances learning ability and long-term memory after SEV anesthesia [12], and metformin was found to reduce SEV-induced neurogenesis damage and neurocognitive defects [13].

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1.1. Hypothesis

The present study suggested the implementation of dexmedetomidine (DXM) infusion during induction of anesthesia may ameliorate the SEV impact on CF.

1.2. Objectives

The present study targets to evaluate the impact of DXM infusion on CF of elderly patients undergoing elective arthroscopic shoulder surgeries (ASS) under SEV maintenance anesthesia

1.3. Design

Prospective comparative multicenter study.

1.4. Setting

Anesthesia, Pain & ICU departments, Faculty of Medicine, Menoufia & Ain Shams Universities.

1.5. Ethical considerations

The study protocol was approved by the departmental committee before start of case collection at Jan 2021 and was approved by the Local Ethical Committee, Menufea University after the end of case collection and evaluation of CF at the last follow-up visit of the last case operated up on at 1–24/ANET3.

1.6. Patients

Patients over 60 years old who assigned for elective ASS were evaluated for demographic data: age, gender, height, weight, and calculation of body mass index (BMI) as weight divided by height in meter square. The presence of associated morbidities, indications for other elective or emergency surgery, ASA grade, and the presence of contraindication for general IA or allergy to the drugs to be used were reported. Patients underwent routine preoperative lab investigations and radiological workups.

1.7. Exclusion criteria

The presence of neurological or psychiatric disorders, previous cerebrovascular stroke, cardiac surgery, or manipulation of carotid vessels, the presence of uncontrolled diabetes mellitus or hypertension, chronic renal impairment, hepatic disorders, coagulopathies, and refusal to sign the written consent were the exclusion criteria. Patients who missed or had other surgical procedures during follow-up were also excluded from the study.

1.8. Inclusion criteria

Patients older than 60 years with ASA grade of I-III, assigned for elective ASS, available for follow-up, and were free of exclusion criteria were enrolled in the study.

1.9. Sample size

A previous study compared POCD after SEV anesthesia versus propofol TIVA during cancer resection for 110 patients per group and detected insignificant differences in the frequency of patients who developed POCD: 29.1% vs. 27.3%, respectively [14]. Thereafter, a similar comparative study included 83 women divided into two groups and detected affection of all items evaluating the neurocognitive function with varied extent between SEV inhalational anesthesia and propofol TIVA, but differences were insignificant [15]. The study's null hypothesis is the significant reduction of the extent of POCD after SEV anesthesia in conjunction with DXM infusion in comparison to the use of SEV alone. Considering that females are more vulnerable to POCD [2], the current study evaluated the proposed regimen for anesthesia of patients undergoing ASS, especially females. To achieve a study power of 80%, using the G*Power (Version 3.1.9.2) computer system for sample size calculation [16] with an effect size of 0.20, α-error factor of 5%, the required sample size to assure the reliability of the null hypothesis was calculated using the F-test model, to be 70 patients per group.

1.10. Randomization & grouping

Using a computer-generated random number sequence in a 1:1 ratio with the dropping of odd numbers, patients were categorized into two groups; Group S & Group D. Group titles were printed into cards that were enclosed in sealed envelopes and patients were asked to choose a closed envelope and present it to the anesthetist in charge. Categorization and grouping were performed by one of the authors: Salah MA.

1.11. Blindness

Assessment of cognitive function before and after surgery was the duty of an author, Helwa A, who was blinded by the type of infusion used. The preparation of intraoperative (IO) infusions and provision of anesthetic procedure was the duty of another author, El-Henawy T, who was blinded by the results of the preoperative assessment of CF. The interpretation of the results was conveyed by the 3rd author; Salah MA who was blinded by the Pre and PO assessments of CF.

1.12. Preparation of IO infusions

Using masked saline bottles, DXM infusion was prepared to provide patients of Group D with 0.6 µg/kg/h, while patients of Group S received an infusion of plain saline in masked bottles.

1.13. Anesthetic technique

Anesthesia was induced by propofol 1–2 mg/kg, fentanyl 1 µg/kg, and atracurium 0.5 mg/kg. DXM and placebo infusions were applied at a rate of 0.6 µg/kg/h infusion during anesthesia. Tracheal intubation was aided by gentle tracheal pressure and an endotracheal tube measuring 6.5 mm was inserted. After intubation of the trachea, the lungs were ventilated with 100% O_2 in the air using a semi-closed circle system. Anesthesia was maintained with sevoflurane 0.5–1 MAC and top-up doses of atracurium if needed. Ventilation was controlled with a tidal volume of 6–8 ml/kg, and the ventilatory rate was adjusted to maintain an end-tidal carbon dioxide (pa_{CO2}) of 32–35 mmHg. The muscle relaxant was reversed using neostigmine 0.05 mg/kg with atropine 0.01 mg/kg.

1.14. Intraoperative monitoring

(1) Continuous IO non-invasive monitoring for mean arterial pressure (MAP) and heart rate (HR) until the end of surgery. HR and MAP measures were recorded preoperatively, after intubation, every 30-min till the end of surgery and after extubation

(2) Duration of surgery and development of IO complications were recorded.

1.15. Postoperative monitoring

(a) HR and MAP measures were determined at PACU admission, 1-h, 2-h, 4-h thereafter and every 4-h till discharge.

(b) Postoperative (PO) pain data

- All patients received PO analgesic protocol including paracetamol 1-g every 8 h and ketorolac 30 mg every 12 h.

- The numeric rating scale (NRS) was used to assess pain severity at PACU transfer and hourly for 4 h and at 8-h and 12-h PO. A higher score on NRS score indicated worse pain sensation and a score of ≥ 4 indicated the need for receiving rescue analgesia.[17]

- Pain was evaluated during rest with the upper limb supported by the shoulder suspensor.

- Duration of PO analgesia was defined as the time elapsed between PACU admission and the 1st request for rescue analgesia.

- Rescue analgesia was provided as nalbufin 5–10 mg depending on the previous data documented by **Seol et al**.[18], (2003) who used a combination of fentanyl (600 mg) and nalbufin (60 mg) for patient-controlled intravenous analgesia (PCIA) and reported an insignificant difference in analgesic efficacy and side effects between fentanyl alone or this combination. Aslo, **Wang et al**.[19], (2022) found sufentanil combined with nalbuphine for PCIA provided superior analgesia compared with sufentanil alone after CS. Rescue analgesia was repeated whenever the NRS score was ≥4 up to a maximum dose of 100 mg. The frequency of need for rescue analgesia and the total doses of nalbuphine used to abolish pain were registered.

(c) The frequency of PO adverse events: PO sedation was assessed at PACU admission, 30-min, 1-h, and 2-h thereafter using the 6-point modified Ramsey sedation scale (RSS) [20]. PO nausea and vomiting (PONV) was evaluated using a 0–3 point scale for nausea; no, mild, moderate, and severe nausea, and 0–2 points for vomiting; no, one and >1 attack [21]. Ondansetron (Zofran); 4 mg IV dose as previously documented [22] was given and repeated according to PONV severity. Hypotension, bradycardia, respiratory depression, and the need for ICU transfer were recorded.

1.16. Evaluation of cognitive function

Cognitive function was evaluated preoperatively, 48-h, 1-wk, and 2-wk PO during attendance at the orthopedic clinic for follow-up using:

(1) Montreal cognitive assessment (MoCA) test: MoCA is a 7-domain 30-point questionnaire evaluating executive/visuospatial function [5 points], naming [3 points], attention [6 points], language [3 points], abstraction [2 points], recall [5 points], and orientation [6 points] through answering 11 questions with a higher score indicates normal CF. MoCA test result was interpreted as follows: 25–30 points indicate normal CF; 18–25 indicate mild CD, 10–17 points indicate moderate, and a score <10 indicates severe CD[23].

(2) Mini-Mental State Examination (MMSE) is a 5-domain 30-point questionnaire for evaluation of orientation, registration, attention/calculation, recall, and language. MMSE score of 25–30 indicates normal CF, 21–24 indicates mild CD, 10–21 indicates moderate CF, and score <9 indicates severe CD.[24]

1.17. Statistical analysis

Inter-group differences were evaluated using a paired t-test, and intra-group differences were evaluated using the one-way ANOVA test. The chi-square test was used to assess the differences in the percentage of data. Correlation between MMSE score at 48-h PO and perioperative data was examined using Pearson's correlation analysis. Regression analysis was used to determine the predictor for obtaining normal CF as assessed by MMSE. The Receiver Operating Characteristic (ROC) curve was conducted to assure the predictability of correlated variates for regaining normal CF as judged by the area under the curve (AUC) and its significance concerning the area under the reference line (AUC $= 0$). The optimum cutoff point for significance was $p < 0.05$. Statistical analyses were conveyed using IBM® SPSS® Statistics software (Version 22, 2015; Armonk, USA).

1.18. Study outcomes

(1) The primary outcome is the frequency and severity of POCD in patients of both groups.

(2) Secondary outcomes included:
  - PO analgesic efficacy of IO infusion was judged by the PO duration of analgesia and the frequency and dose of nalbuphine used.
  - The frequency and severity of PO adverse effects need for ICU admission, and duration of PO hospital stay.
  - The ability of the perioperative findings to be used as predictors for the oncoming CF.

2. Results

The preliminary evaluation included 153 patients; 5 patients had other indications for surgical interference, 4 patients had neuropsychiatric disorders and 2 patients refused to participate, while 140 patients were randomly divided into two study groups (Figure 1).

There were insignificant differences between patients' enrolment data as shown in Table 1.

Duration of surgery ranged between 50 and 90 min with insignificant difference between both groups. Preoperative hemodynamic measures showed insignificant differences between both groups, while HR and
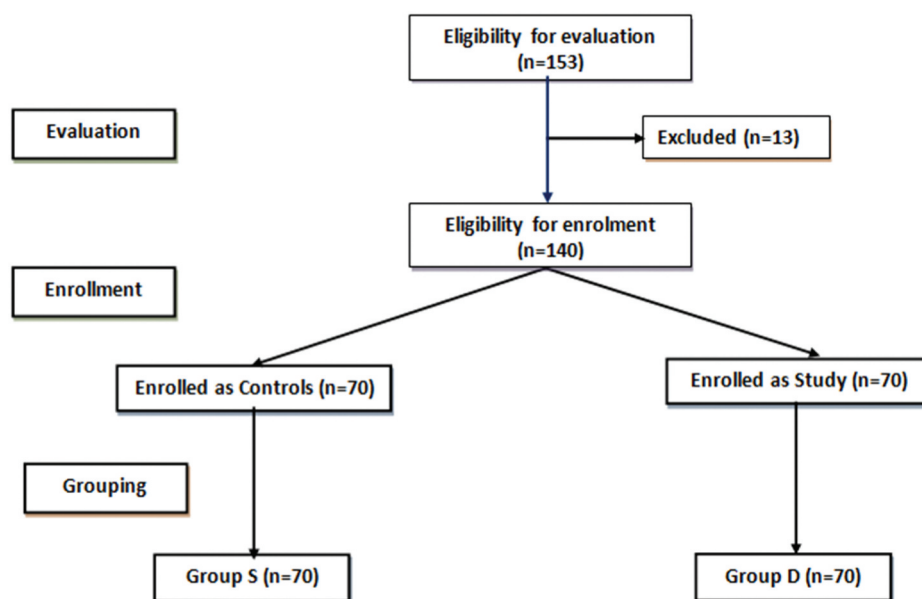

Figure 1. Study flow chart.

Table 1. Baseline data of patients from both groups.

		Group S ($n = 70$)	Group D ($n = 70$)	P value
Age (years)		65.5 ± 3.5	65 ± 4	0.431
Gender	Males	27 (38.6%)	20 (28.6%)	0.210
	Females	43 (61.4%)	50 (71.4%)	
BMI (kg/m^2)	Overweight	34 (48.6%)	27 (38.6%)	0.232
	Obese	36 (51.4%)	43 (61.4%)	
	Mean (± SD)	30 ± 1.6	29.9 ± 1.8	0.650
ASA	Grade I	21 (30%)	16 (22.8%)	0.581
	Grade II	38 (54.3%)	40 (57.1%)	
	Grade III	11 (15.7%)	14 (20%)	
Co-morbidities	Yes	5 (7.1%)	8 (11.4%)	0.382
	No	65 (92.9%)	62 (88.6%)	

Table 2. The finding detected during surgery for patients from both groups.

Parameters		Group S (n=70)	Group D (n=70)	P value
Duration of surgery (minutes)		64 ± 10.7	66.5 ± 8	0.118
HR (beats/min)	Preoperative	79.4 ± 4.4	79 ± 6.5	0.673
	After intubation	87.2 ± 3.9	84.8 ± 4.7	0.0012
	30-min IO	73.7 ± 6.2	71 ± 6.4	0.012
	60-min IO	74.7 ± 5.1	72.5 ± 5	0.010
	After extubation	81.6 ± 6	79.3 ± 5	0.015
MAP (mmHg)	Preoperative	83.7 ± 3.9	83.1 ± 4.1	0.377
	After intubation	89.5 ± 4.2	87.7 ± 4.5	0.017
	30-min IO	78.6 ± 3.1	76.5 ± 5.2	0.0045
	60-min IO	76.1 ± 6	73.3 ± 5.8	0.006
	After extubation	81.2 ± 5.7	79.3 ± 4.7	0.034

MAP measures estimated during surgery, were significantly lower in patients of group D in comparison to that of patients of group S. No IO complications were encountered in patients of both groups (Table 2)

At the time of PACU admission and till 8-h PO, HR measures were significantly lower in patients of group D than corresponding measures in patients of group S, while at the 12th PO hour, the difference was insignificant despite being lower in patients of group D. Similarly, MAP measures since PACU admission till 4-h PO were significantly lower in patients of group D, but at the 8th and 12th hours after surgery, MAP measures were non-significantly lower in patients of group D., NRS pain scores at time of PACU admission were non-significantly lower in patients of group D than group S. Then, pain scores started to increase progressively in all patients but were significantly lower in patients of group D than group S till 3-h PO, while at the 8th PO hour, pain scores were significantly
(p = 0.034) higher in group D. At the 4th and 12th hour PO, the difference in pain scores was insignificant. The average 12-h PO pain score was significantly

(p < 0.001) lower in patients of group D than in group S. Thirty patients did not request rescue PO analgesia; 8 in group S and 22 in group D with significant (p = 0.015) intergroup difference. The duration till the 1st nalbufin request was significantly (p = 0.0003) longer, and the total nalbufin consumed dose was significantly (p = 0.037) lower as shown in Table 3.

The frequency of patients who had RSS of two increased progressively in group D, but decreased progressively in patients of group S with insignificant differences between both groups at 30-min and 120-min PO, while the frequency of patients who had RSS of two was significantly (p = 0.039) higher in group D at 60-min PO. No patient had respiratory depression or vomiting, and admission to ICU was not required. Regarding other adverse events, the differences between both groups were insignificant in favor of group D (Table 4).

Preoperative MoCA score showed an insignificant difference between the enrolled patients and all patients had a normal cognitive function, but about 56.4% of patients (n = 79) had a preoperative score of <28 with an insignificant

Table 3. Hemodynamic and pain data reported during postoperative course for patients from both groups.

Parameters	Time		Group S (n = 70)	Group D (n = 70)	P value
HR (beats/min)	At PACU		83.8 ± 4.5	82 ± 5.6	0.037
	1-h PO		84.9 ± 4	82.7 ± 5.7	0.009
	2-h PO		85.5 ± 5.3	83.4 ± 4.9	0.015
	4-h PO		86.5 ± 4.9	84.3 ± 6.2	0.022
	8-h PO		86.2 ± 5.5	84.4 ± 4.4	0.034
	12-h PO		87.4 ± 5.3	86.9 ± 5	0.109
MAP (mmHg)	At PACU		85.1 ± 4.6	82.9 ± 5.5	0.011
	1-h PO		84.1 ± 5.7	81.3 ± 6.8	0.009
	2-h PO		82.9 ± 5.3	81.1 ± 4.3	0.029
	4-h PO		83.5 ± 4.7	82 ± 4.2	0.048
	8-h PO		83.9 ± 4.2	82.6 ± 4.8	0.089
	12-h PO		86.1 ± 4.7	84.7 ± 5.2	0.095
NRS pain scores	At PACU		0.86 ± 0.73	0.67 ± 0.63	0.109
	1-h PO		1.29 ± 0.82	0.89 ± 0.6	0.0013
	2-h PO		1.81 ± 0.92	1.33 ± 0.74	0.0008
	3-h PO		2.46 ± 0.96	1.83 ± 0.8	<0.001
	4-h PO		2.59 ± 1.38	2.49 ± 0.9	0.612
	8-h PO		2.03 ± 1.56	2.56 ± 1.36	0.034
	12-h PO		1.64 ± 1.34	1.76 ± 1.61	0.719
	Average score		1.81 ± 0.37	1.63 ± 0.46	<0.001
PO analgesia	Times of requests	No	8 (11.4%)	22 (31.4%)	0.015
		One	57 (81.5%)	45 (64.3%)	
		Two	5 (7.1%)	3 (4.3%)	
	Duration till 1st request (h)		6.4 ± 3.2	8.5 ± 3	0.0003
	Total dose of nalbufin (mg)		10.4 ± 1.4	9.7 ± 2.2	0.037

Table 4. The reported postoperative adverse events affected patients from both groups.

Parameters	Time		Group S (n = 70)	Group D (n = 70)	P value
Ramsey sedation score (after PACU transfer)	30-min	RSS = 2	29 (41.4%)	38 (54.3%)	0.128
		RSS = 3	41 (58.6%)	32 (45.7%)	
	60-min	RSS = 2	37 (52.9%)	49 (70%)	0.037
		RSS = 3	33 (47.1%)	21 (30%)	
	2-h	RSS = 2	42 (60%)	44 (62.9%)	0.728
		RSS = 3	28 (40%)	26 (37.1%)	
PO hypotension			4 (5.7%)	7 (10%)	0.346
PO bradycardia			5 (7.1%)	9 (12.9%)	0.259
PO nausea	Score = 0		65 (92.9%)	67 (95.7%)	0.467
	Score = 1		5 (7.1%)	3 (4.3%)	
Total incidence of adverse events			14 (20%)	19 (27.1%)	0.319

difference between both groups. At 48-h PO, 37 patients (26.4%) showed POCD with significantly (p = 0.013) lower incidence among patients of group D. However, the frequency of patients who had POCD was significantly higher in group S (p < 0.001) and group D (p = 0.0014) in comparison to preoperative frequency. Similarly, the mean value of MoCA score at 48-h PO was significantly (p < 0.001) lower in both groups compared to the preoperative score with significantly (p = 0.0001) lower score of patients of group S than group D. At the end of the 1st week PO, CF started to improve and 32 patients (22.9%) had POCD with significantly (p = 0.016) lower incidence, but significantly (p = 0.032) higher mean score with than without DXM. At the 2-wk PO visit, six patients (8.6%) of group D still had mild POCD, while 19 patients (27.1%) of group S had PCOD with significantly (p = 0.0066) lower incidence of POCD among patients of group D. The frequency of patients who had normal CF was significantly lower in group S (p = 0.00002) and group D (p = 0.012) in comparison to preoperative frequencies. Also, the mean value of the MoCA score was significantly (p = 0.0004) lower in group S, but insignificantly (p = 0.495) lower in comparison to their respective mean preoperative score (Table 5, Figure 2).

Evaluation of preoperative CF using MMSE defined 11 patients (7.9%) had mild CD with insignificant difference between both groups. The frequency of patients who had normal CF was significantly decreased at 48-h PO in comparison to preoperative frequency in both group S (p < 0.001) and group D (p = 0.0005) with significantly (p = 0.022) higher frequency among patients of group D. Similarly, MMSE score was decreased significantly (p < 0.001) compared to preoperative score of patients of both groups, but was significantly (p = 0.0011) higher for patients of group D than group S. At 1-wk PO, the frequency of patients who had normal CF increased in both groups with significantly (p = 0.014) higher difference in favor of group D, but in comparison to preoperative frequencies, normal CF was still significantly lower in patients of group S (p < 0.001) and group D (p = 0.001) in comparison to preoperative frequency. For the MMSE score, it was still significantly lower in both groups S & D (p < 0.001 & 0.00003, respectively) but was significantly (p = 0.0043) lower in group S than group D.

At 2-wk PO, 111 patients (79.3%) regained their normal CF with significantly (p = 0.018) higher frequency among group D than group S. In comparison to preoperative frequencies, the difference in group S was still

Table 5. Postoperative findings on Montreal Cognitive Assessment for patients from both groups.

| Time				Group S (n = 70)	Group D (n=70)	P value
Preoperative	Normal CF			70 (100%)	70 (100%)	-
	Score (Mean ± SD)			27.3 ± 1.6	27.2 ± 1.5	0.707
48-PO	Quality of CF	Normal		45 (64.3%)	58 (82.9%)	0.034
		CD	Mild	13 (18.6%)	9 (12.9%)	
			Moderate	8 (11.4%)	3 (4.2%)	
			Severe	4 (5.7%)	0	
	Significance vs. preoperative			<0.001	0.0014	
	Score	Mean ± SD		22.5 ± 5.4	25.4 ± 2.7	0.0001
		Significance vs. preoperative		<0.001	<0.001	
1-wk PO	Quality of CF	Normal		48 (68.6%)	60 (85.7%)	0.015
		CD	Mild	13 (18.5%)	9 (12.9%)	
			Moderate	9 (12.9%)	1 (1.4%)	
	Significance vs. preoperative			<0.001	0.0046	
	Score	Mean ± SD		24.3 ± 4.9	25.8 ± 2.7	0.032
		Significance vs. preoperative		<0.001	0.0002	
2-wk PO	Quality of CF	Normal		51 (72.9%)	64 (91.4%)	0.0066
		CD	Mild	13 (18.5%)	6 (8.6%)	
			Moderate	6 (8.6%)	0	
	Significance vs. preoperative			0.00002	0.012	
	Score	Mean ± SD		25 ± 4.2	27 ± 1.9	.0004
		Significance vs. preoperative		0.0004	0.495	
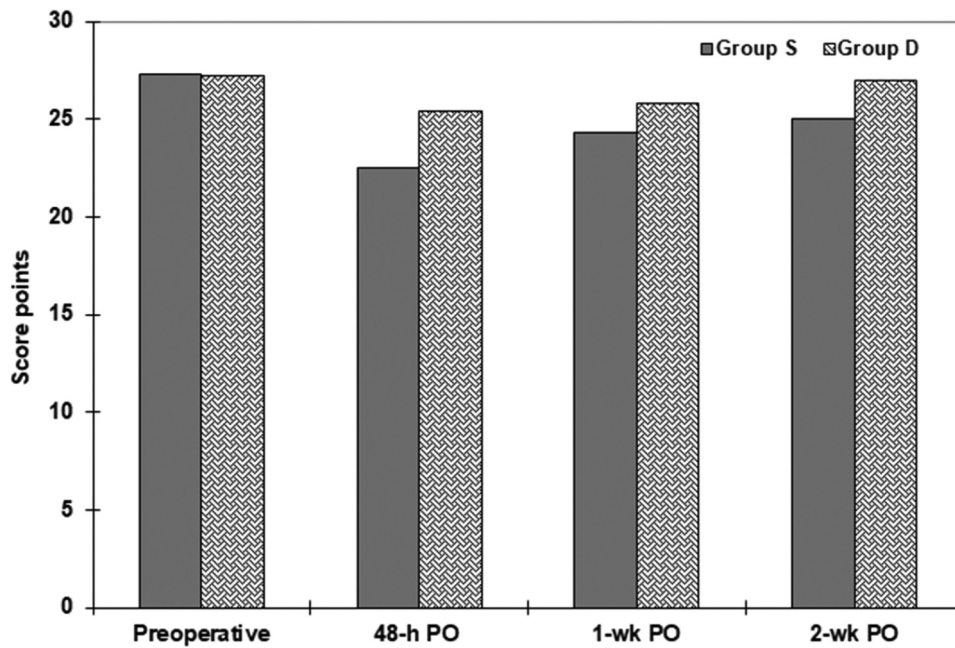
Figure 2. Mean value of MoCA score determined in the studied groups.

significant (p = 0.0022) but was insignificant (p = 0.507) in group D. Similarly, the MMSE score was significantly (p = 0.048) higher in group D with insignificant (p = 0.100) difference versus preoperative score, while in group S the score was significantly (p = 0.038) lower than preoperative score (Table 6, Figure 3).

Correlation analysis of the calculated CF scorings at 48-h PO showed a positive significant correlation with the use of DXM infusion but showed negative significant correlations with age, BMI, and the dose used of PO nalbufin. The correlation between the CF scorings with female gender was negative and significant in the case of MoCA, but insignificant in the case of MMSE. MMSE scores showed a negative significant correlation with the

frequency of PO adverse events, but the relation with MoCA was negatively insignificant. CF scorings were negatively correlated with operative time and PO pain score, but the relation was insignificant (Table 7).

The perioperative data significantly correlated with CF scorings were evaluated using the Regression analysis that defined old age as negative and the use of DXM as positive predictors for high scores on patients' CF evaluation using MoCA or MMSE (Table 8).

ROC curve analysis defined old age as a significant sensitive predictor for POCD with MMSE < 25 (AUC = 0.254 ± 0.113; p = 0.042; 95% CI: 0.032–0.475), while defining the use of DXM infusion as a significant specific predictor (AUC = 0.761 ± 0.063;

Table 6. Mini-mental state examination findings of patients from both groups.

| Time			Group S (n = 70)	Group D (n = 70)	P value
Preoperative	Quality of CF	Normal	65 (92.9%)	64 (91.4%)	0.061
	Dysfunction	Mild	5 (7.1%)	6 (8.6%)	
	Score (Mean ± SD)		25.9 ± 1.7	26.5 ± 2	0.707
48-PO	Quality of CF	Normal	23 (32.9%)	39 (55.7%)	0.022
	Dysfunction	Mild	28 (40%)	20 (28.6%)	
		Moderate	19 (27.1%)	11 (15.7%)	
		Significance vs. preoperative	<0.001	0.0005	
	Score	Mean ± SD	21.4 ± 3.9	23.5 ± 3.5	0.0011
		Significance vs. preoperative	<0.001	<0.001	
1-wk PO	Quality of CF	Normal	30 (42.9%)	47 (67.1%)	0.014
	Dysfunction	Mild	27 (38.5%)	17 (24.3%)	
		Moderate	13 (18.6%)	6 (8.6%)	
		Significance vs. preoperative	<0.001	0.001	
	Score	Mean ± SD	23.2 ± 3.6	24.8 ± 2.7	0.0043
		Significance vs. preoperative	<0.001	0.00003	
2-wk PO	Quality of CF	Normal	50 (71.4%)	61 (87.1%)	0.018
	Dysfunction	Mild	14 (20%)	8 (11.5%)	
		Moderate	6 (8.6%)	1 (1.4%)	
		Significance vs. preoperative	0.0022	0.507	
	Score	Mean ± SD	25 ± 3	25.9 ± 2.1	.048
		Significance vs. preoperative	0.038	0.100	
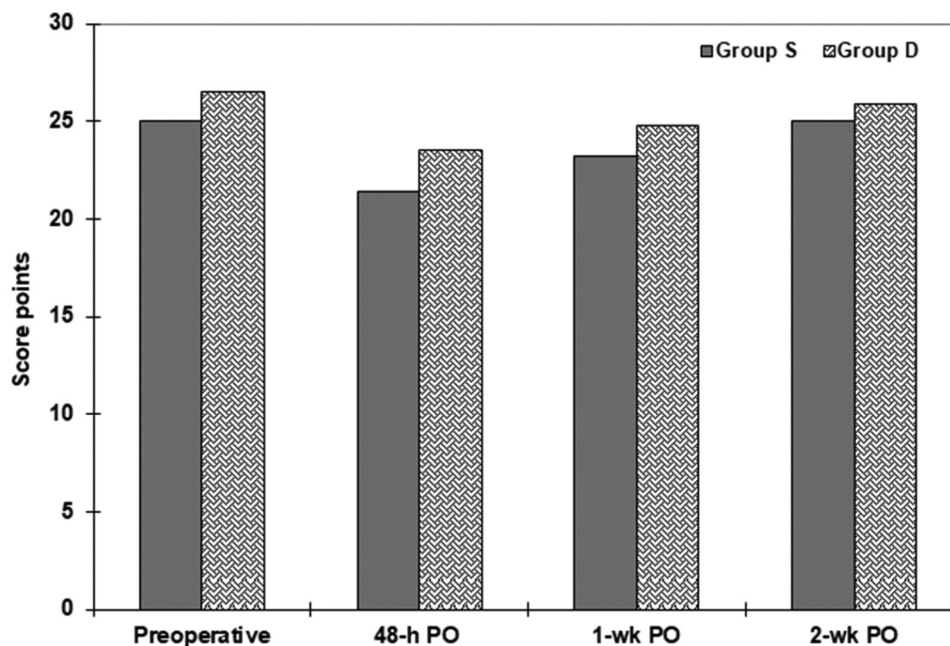
Figure 3. Mean value of MMSE score determined in the studied groups.

Table 7. Correlation analysis of the relation between cognitive function scorings and perioperative data.

	MoCA score		MMSE score	
	"r"	P	"r"	P
Age	−0.338	<0.001	−0.304	<0.001
Female gender	−0.235	0.005	−0.057	0.504
BMI	−0.267	0.001	−0.179	0.034
ASA grade	0.002	0.985	−0.132	0.119
The use of DXM infusion	0.282	0.001	0.288	0.001
Operative time	−0.099	0.244	−0.164	0.052
PO pain score	−0.131	0.122	−0.151	0.075
The used dose of PO nalbuphine	−0.246	0.003	−0.257	0.002
The frequency of adverse events	−0.133	0.117	−0.195	0.021

$p = 0.031$; 95% CI: 0.637–0.885) for achieving normal CF with MMSE of >25 (Figure 4). Also, ROC curve analysis predicted MMSE = 28 as the uppermost value of MMSE score at 48-h PO with the use of DXM infusion (AUC = 0.759 ± 0.069; $p = 0.049$; 95% CI: 0.625–0.894), while excluded age (AUC = 0.472 ± 0.150; $p = 0.831$; 95% CI: 0.178–0.766) as predictor for achieving MMSE = 28 (Figure 5).

Table 8. Regression analysis for the correlated perioperative data with CF scorings.

Parameters	Model-4 β	Model-4 P	Model-3 β	Model-3 P	Model-2 β	Model-2 P	Model-1 β	Model-1 P
MoCA scoring								
Age	−0.280	<0.001	−0.305	<0.001	−0.321	<0.001	−0.338	<0.001
Female gender	−0.228	0.003	0.249	0.001	excluded			
BMI	−0.192	0.011			excluded			
The use of DXM infusion	0.280	<0.001	0.288	<0.001	0.288	<0.001	0.276	0.001
Dose of PO nalbuphine			Excluded					
Frequency of adverse events			Excluded					

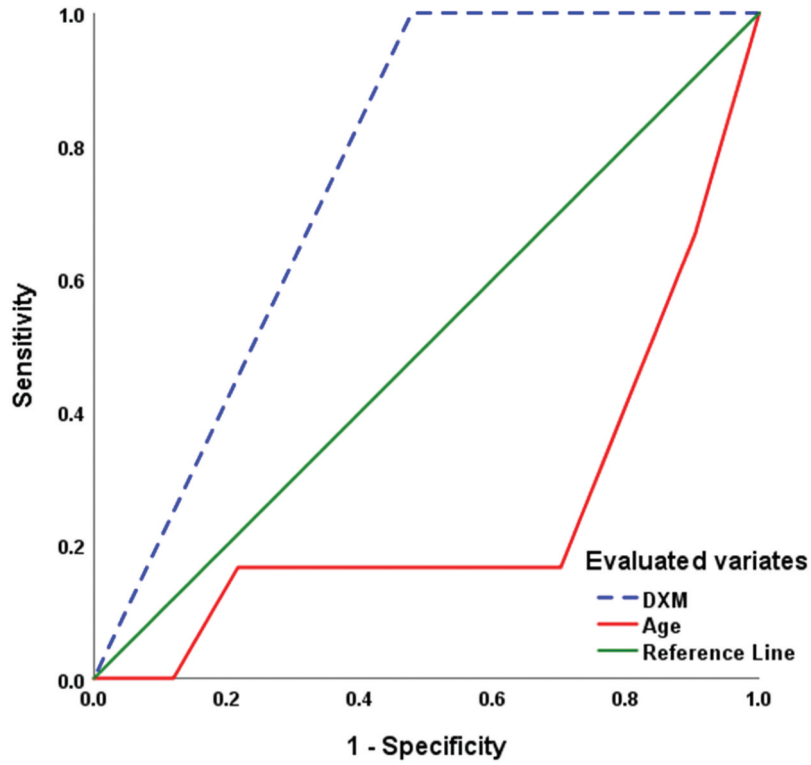| Parameters	Model-2 β	Model-2 P	Model-1 β	Model-1 P
MMSE scoring				
Age	−0.286	<0.001	−0.269	0.001
Female gender	Excluded		Excluded	
BMI	Excluded		Excluded	
The use of DXM infusion	0.296	<0.001	0.304	<0.001
Dose of PO nalbuphine	Excluded		Excluded	
Frequency of adverse events	Excluded		Excluded	

Figure 4. ROC curve analysis to define the predictive value of old age and the use of DXM infusion to predict the lowermost value of normal CF at 48-h PO (MMSE=25).
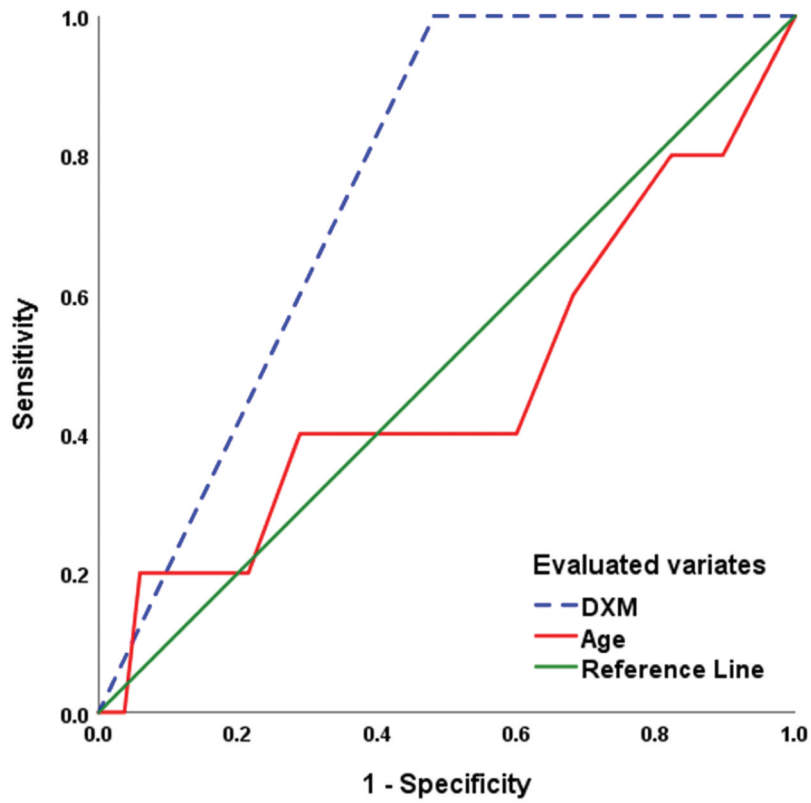

Figure 5. ROC curve analysis to define the predictive value of old age and the use of DXM infusion to predict the uppermost value for normal CF at 48-h PO (MMSE=25).

3. Discussion

Evaluated CF at 2-wk after surgery showed an insignificant difference in comparison to preoperative evaluation both as frequency and score in patients who received DXM infusion as adjunctive to SEV inhalational anesthesia (IA) with a significant difference in comparison to patients who received SEV alone. This outcome assured the null hypothesis of the study that perioperative use of DXM might be a decisive statement for the preservation of CF of geriatric patients going to receive IA.

In line with the reported ameliorative effect of DXM on PO cognitive dysfunction (POCD), multiple animal and clinical studies assured the obtained outcomes; animal models' studies found perioperative DXM did only significantly reduce the incidence of POCD, but also improved PO neurocognitive function mostly through activation of the PI3K/Akt signaling pathway via acting on the α_2 adrenergic receptor to inhibit the massive release of high mobility group protein B1 (HMGB1) and reduces its binding with Toll-like receptor-4 leading to inhibition of release of inflammatory mediators especially TNF-α, IL-1β [25]. Moreover, extracellular HMGB1 was found to impair the stability of T regulatory cells, decrease its expression of cell surface marker molecules, and inhibit the secretion of the anti-inflammatory cytokine leading to an intensified autoimmune process; however, DXM was found to alleviate these effects [26]. In addition to the downregulating effect of DXM on HMGB1 release and action, DXM was also found to decrease the rate of apoptosis in the hippocampus [27].

Clinically, a review of recent literature assured the positive effects of DXM on CF, especially for PO neurocognitive (NC) disorders and found DXM may help improve POCD, particularly for PO acute events and delayed NC recovery [28]. Regarding geriatric patients, a review of the literature documented the enhanced early recovery of CF in old aged patients undergoing abdominal surgery with the intraoperative use of DXM [29]. Moreover, another review of trials evaluating CF of elderly patients who underwent non-cardiac surgery under various anesthetics and adjuvants found sufentanil and DXM was ranked as the top in reducing the incidence of POCD by 87.4% and 81.5%, respectively [30].

Furthermore, recent randomized comparative clinical studies supported the superiority of DXM as a neuroprotective drug, where **Chawdhary et al**. [31] reported that DXM is anesthetic sparing and in combination with bispectral index-guided monitoring for titrating the depth of anesthesia is an invaluable tool for reducing POCD than propofol and **Yoo et al**. [32] in a placebo comparative study detected significant difference in the Mini-Cog© score over time in favor of DXM and found the probability of perioperative CD decreased by 0.48 times on day-3 after SEV/DXM anesthesia for geriatric patients.

Also, **Racman et al**. [33] reported significantly lower incidence of delayed NC recovery and better cognitive outcomes on procedural sedation with DXM compared to propofol. Additionally, **El-Ghazaly et al**. [34] found intravenous injection of a DXM bolus before induction of anesthesia is associated with the lowest incidence of delirium and CD after isoflurane anesthesia in comparison to pre-induction injection of ketamine or placebo and Regression analysis revealed reduction of PO delirium and CD by 32% and 62%, respectively, with DXM than placebo, while ketamine increased the risk by 3-fold and 4.5 times, respectively, than placebo.

Concerning the impact of SEV on CF and the benefit of DXM as an adjuvant, in a similar comparative study, **Zhang et al**. [35] found SEV anesthesia for old-aged patients resulted in a higher incidence of POCD compared to those received combination of SEV and DXM and found that DXM alleviates POCD through decreasing plasma levels of TNF-α and IL-6. **Neimark et al**. [36] documented that sevoflurane anesthesia for old-aged patients who underwent laparoscopic cholecystectomy developed moderate POCD during early PO observation. **Zeng et al**. [30] through a meta-analysis documented that DXM significantly reduced the incidence of POCD in comparison to SEV

As previously documented that understanding the mechanism of SEV-induced POCD may allow its prevention and treatment [37]; SEV was found to activate microglia and induce apoptosis in hippocampus through overexpression of the peroxisome proliferator-activated receptor gamma [38] and induce imbalanced cytoplasmic calcium homeostasis through activation of NMDA receptors leading to necroptosis of hippocampus neurons which affects cognitive performance in aged mice [39]. On the contrary, DXM was found to increase the number of microglia and alleviate SEV-induced upregulation of proinflammatory cytokines' levels, overexpressed purinergic ionotropic-4 receptor and NOD-like receptor protein-3 in the hippocampus, leading to amelioration of CD [40]. Also, DXM improved POCD by targeting the CCAAT/enhancer-binding protein-β to activate the c-Jun N-terminal kinase/p-38 signaling pathway and inhibiting microglial M1 polarization-mediated inflammation in the central nervous system [41]. Further, DXM was found to exert its neuroprotective effect through the upregulation of expression of microRNA miR-204-3p resulting in suppressed expression of F-box/LRR-repeat protein 7 in tissues with subsequent alleviation of neuroinflammation [42].

However, the obtained results showed an interesting finding that despite the reported SEV-induced CD, 32.9% of patients of group S had normal CF at 48-h PO, and this may suggest individual vulnerability for CD on SEV

exposure. Furthermore, by 2-wk post-exposure to SEV, about 40% of affected patients regained their normal CF, thus indicating the transitory nature of SEV-exposure CD. Similarly, a meta-analysis detected a comparable effect regarding the occurrence of short-term POCD after inhalation versus intravenous anesthesia for old-aged patients undergoing non-cardiac surgery [43] and **Karakurt et al**. [44] found MMSE at 1-h after SEV was significantly lower than preoperative and 24-h PO scores but was comparable to TIVA.

Such observation may be explained according to the result of the recent experimental work that found SEV exposure of aged rats induced overexpression of sestrin2, which is stress-inducible gene and exerts neuroprotective effects against brain injury, overexpressed sestrin2 in hippocampus alleviated SEV-induced CD through inhibition of SEV-induced inflammasome activation, production of pro-inflammatory factors, oxidative stress, and neuronal apoptosis [45]. Additionally, sestrin2 counteracts SEV-induced CD through enhanced mitochondrial function and mitophagy through sestrin2-mediated activation of SIRT1, which is a nuclear NAD-dependent deacetylase [46].

4. Conclusion

SEV anesthesia induced reversible short-term POCD. Using IO infusion of DXM during SEV anesthesia decreased the frequency and scores of POCD and allowed faster resumption of normal CF.

4.1. Limitation

The study limitation is the short-term follow-up for these old-aged patients who found repeated attendance at the orthopedic clinic is tedious

4.2. Recommendation

Similar comparative studies of DXM-based versus propofol-based TIVA to establish the preservative effect of DXM for CF after major surgeries, especially when high-risk patients are recommended.

List of Abbreviation

ASS	Arthroscopic shoulder surgeries
AUC	Area under the curve
BMI	Body mass index
CF	Cognitive function
DXM	Dexmedetomidine
HR	Heart rate
IA	Inhalational anesthetic
IO	Intraoperative
MAP	Mean arterial pressure
MMSA	Mini-Mental State Examination
MoCA	Montreal cognitive assessment
NRS	Numeric rating scale
PCIA	Patients-controlled intravenous analgesia
PO	Postoperative
POCD	Postoperative cognitive dysfunction
PONV	Postoperative nausea and vomiting
ROC	Receiver Operating Characteristic
RSS	Ramsey sedation scale
SEV	Sevoflurane
TIVA	Total intravenous anesthesia

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