Dexmedetomidine might improve postoperative cognitive dysfunction in older patients undergoing pulmonary surgery

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Abstract

Background

The effect of dexmedetomidine on cognitive function after various surgeries were reported, however no consensus is made on pulmonary surgery. In this study we aimed at investigating the effect of dexmedetomidine anesthesia on postoperative cognitive function (POCD) in pulmonary surgery.

Methods

A prospective randomized placebo-controlled study was conducted with blinded to patients. The study was performed on 60 patients (29 in the dexmedetomidine group; 31 in the placebo group). Dexmedetomidine-group patients received dexmedetomidine (1 μg/kg, i.v.) and Placebo-group patients received an equal volume of physiologic (0.9%) saline for 20 min before anesthesia induction. Cognitive function was evaluated using Montreal Cognitive Assessment (MoCA) 1 day before surgery, as well as on postoperative day (POD)1, POD3 and POD7. The regional cerebral oxygen saturation (rSO_2) was monitored continuously by near-infrared spectroscopy before anesthesia.

Results

The MoCA score between the two groups was significantly different on POD1 (Dex 26.4 ± 0.73 vs Placebo 25.5 ± 0.96, $p < 0.001$) and POD3 (Dex 27.1 ± 0.79 vs Placebo 26.6 ± 0.80, $p = 0.032$). In detail, attention and orientation scores were increased in the dexmedetomidine group on POD1 and POD3. The rSO_2 between the dexmedetomidine group or placebo group was not significantly different (Dex 64.9 ± 2.73 *vs.* Placebo 64.3 ± 3.29, $p = 0.483$), and no significant difference was found before drug administration and after regaining consciousness (Dex 63.5 ± 2.52 *vs.* Placebo 64.2 ± 3.22; $p = 0.390$).

Conclusion

We showed, for the first time, that dexmedetomidine (1.0 μg/kg) could reduce the risk of POCD and might not decrease rSO_2. Hence, dexmedetomidine could be employed in pulmonary surgical procedures, especially for older patients facing high risk of delirium.

Background

Postoperative cognitive dysfunction (POCD) is a condition in which consciousness, cognitive function, memory, and orientation decline after surgery. POCD is caused by postoperative neurological disorders due to various factors, including cerebral hypoxia or the side-effects of anesthesia as one of the most important pathophysiological mechanism. POCD is related closely to the trauma experienced from a

surgical procedure, and can impair the prognosis and quality of life. POCD prevalence ranges from 16–62% in patients undergoing repair of hip fracture [1–3]. In particular, older patients are vulnerable to memory disturbances and other types of cognitive impairment after surgical procedures [4].

Dexmedetomidine is an alpha-2 agonist. It is a sedative and analgesic agent that has been licensed recently in the USA as intensive care unit (ICU) sedation ≤ 24 h after surgery [5]. Its use has been linked to reduced postoperative delirium, stress, and inflammatory responses and, thus, improved protection of the nervous system [6–8]. A few studies on cognitive function in volunteers or patients who received dexmedetomidine have been published. They showed that preoperative administration of dexmedetomidine could protect cerebral blood vessels effectively, improve cognitive dysfunction and damage to attentional network function, and increase postoperative quality of life [9]. The effect of dexmedetomidine on cognitive function after various surgeries were reported[10, 11], however no consensus is made on pulmonary surgery.

Studies have indicated that dexmedetomidine causes a reduction of cerebral blood flow (CBF) in humans [11, 12]. Drummond and colleagues showed that dexmedetomidine caused a dose-related reduction in CBF and cerebral metabolic rate (CMR) in healthy individuals [13]. Furthermore, an increasing number of studies carried out in anesthetized dogs have indicated that the reduction in CBF was not accompanied by a simultaneous reduction of CMR [14–18]. It was reported that regional hemoglobin oxygen saturation (rSO_2) and CBF velocity are comparably preserved during sedation using dexmedetomidine or propofol, but did not clearly point out the effect of dexmedetomidine on rSO_2, which is an indication of the actual regional cerebral oxygen supply and raised concern whether postoperative cognitive function would be affected. Dexmedetomidine might have a dual role in the perioperative period of patients who have undergone pulmonary surgical procedures.

In this study we investigated the effect of dexmedetomidine on rSO_2 to test whether cerebral blood supply was affected, and we aimed at investigating the effect of dexmedetomidine anesthesia on postoperative cognitive function (POCD) in pulmonary surgery.

Methods

Study protocol

We carried out this prospective randomized, placebo-controlled trial in Beijing Tuberculosis and Thoracic Tumor Research Institute (Beijing, China). The study protocol was approved by the local Clinical Research Ethics Committees (2017[10]). Written informed consent was obtained from all individuals participating in the trial. Our study adheres to CONSORT guidelines and the CONSORT checklist was submitted as supplementary files. The trial was registered before patient enrollment at clinical trials.gov (ChiCTR1800015610; principal investigators: Tao Liu and Taijun Luo; date of registration: 11 April 2018).

Sixty-one patients who underwent an elective pulmonary surgical procedure were included from May to November 2018. Patients were excluded if they: had cerebrovascular disease, arrhythmia, sinus bradycardia, ischemic heart disease, history of obstructive sleep apnea, or known allergy to dexmedetomidine; were taking medication for mental disorders; had neurologic disease previously (e.g., stroke, seizures, dementia); had memory impairment.

Pulmonary resections, including wedge resection, lobectomy, bilobectomy, sleeve-lobectomy and pneumonectomy were selected on the basis of tumor location. Video-assisted Thoracoscopic Surgery was first choice and thoracotomy were performed when necessary. Unilateral pulmonary collapse was routinely performed in pulmonary surgeries for better surgical view and operation.

Grouping and drug administration

During the study period, patients were divided randomly into a placebo group and dexmedetomidine group using a computer-generated random-number table. Included patients were assigned randomly to receive dexmedetomidine or physiologic (0.9%) saline. In an emergency (e.g., unexpected, rapid deterioration in clinical status), an anesthesiologist could adjust or interrupt infusion of the study drug if indicated. Both the enrolled patients and the physicians in charge of POCD evaluation were blinded to the group allocation.

Study drugs (dexmedetomidine hydrochloride (200 μg/2 mL) and physiologic saline (2 mL)) were provided as clear aqueous solutions in identical 3-mL bottles (Jiangsu Heng rui Medicine, Jiangsu, China). Dexmedetomidine hydrochloride was diluted with physiologic saline to 50 mL (i.e., final concentration = 4 μg/mL) before administration. Premedication or sedation was not given to any participant. Patients breathed room air during the entire experiment.

Peripheral intravenous access was secured. Perioperative monitoring comprised electrocardiography, pulse oximetry, and continuous monitoring of arterial blood pressure (*via* a 20-G catheter inserted into the radial artery). The primary outcome is postoperative cognitive function and the second outcome is designed as rSO2 evaluation. The Bispectral Index (BIS), peripheral oxygen saturation (SpO_2), rSO_2, mean arterial blood pressure (MAP) and heart rate (HR) were secondary outcome, and were acquired at baseline before patients received dexmedetomidine or physiologic saline.

After SpO_2, MAP, and HR at baseline had been recorded, patients in the dexmedetomidine group received dexmedetomidine (1 μg/kg), whereas patients received physiologic saline (0.25 mL/kg) in the placebo group, as recommended in other studies [19, 20]. This dose ensured that patients in both groups received an equal dose of physiologic saline regardless of randomization. Drug solutions were prepared by an anesthesiologist and the volume maintained at 50 mL. Dexmedetomidine or physiologic saline was infused by a micro-pump for >20 min before the induction of anesthesia. Parameters were also monitored after patients regained consciousness. Demographic details (e.g., age, sex, weight, height) were also noted. Data were recorded by an investigator blinded to the study protocol and only attending anesthetist were required to guarantee quality control of the study.

Cognitive function

Cognitive assessment was undertaken using the Montreal Cognitive Assessment (MoCA). The MoCA was developed to screen for mild or more serious cognitive dysfunction. The score of the MoCA ranges from 0 to 30, and is divided into seven subsets: visuospatial/executive; attention; abstraction; naming; memory; language; orientation. A MoCA score ≤25 is considered to denote cognitive impairment. Neuropsychologic evaluations were undertaken by a trained clinical anesthetist blinded to the study protocol. Evaluations were made at 1 day before surgery, as well as at postoperative day (POD)1, POD3, and POD7.

rSO_2 monitoring

rSO_2 was monitored continuously by near-infrared spectroscopy (NIRS) before anesthesia (EGOS-600A; Enginmed, Beijing, China)[21], which provided continuous, non-invasive, real-time measurement of cerebral oxygenation[22]. This cerebral oximeter has two channels (right and left), which automatically registers which sensor is connected, and uses sensor-dependent algorithms for rSO_2 calculation . The variable of brain oxygenation was defined as the mean value of oxygen saturation of the right and left sides of the brain. The BIS is a commonly used tool to measure the sedation level. A BIS-monitoring electrode (BIS™ Quatro; Aspect Medical Systems, Norwood, MA, USA) was placed on the forehead of the patient after careful cleaning of the skin according to manufacturer instructions. Then, an electrode was attached to a BIS monitor (BIS EEG Vista™; Aspect Medical Systems) which provided continuous, real-time surveillance.

Sample size

Based on MoCA detected between the two groups in a pilot study, the mean value was 26 in the dexmedetomidine group and 24 in the placebo group. Hence, the size of the group sample needed to reach 23 for each group to achieve 90% power to detect a difference between these two groups, with an alpha of 0.05 using a two-sided two-sample *t*-test. Considering the prospects of inadequate cases and exclusion, we planned to enroll 30 cases for each group.

Statistical analyses

The independent Student's *t*-test was used to compare the mean value between the dexmedetomidine group and placebo group at different times. $p < 0.05$ was considered significant. Statistical analyses were carried out using SAS v9.4 (SAS Institute, Cary, NC, USA).

Results

Sixty-one patients fulfilled the inclusion criteria. Finally, 29 patients in the dexmedetomidine group and 31 patients in the placebo group completed the study, and their data were employed for statistical analyses (Fig. 1). Patient characteristics in the two study groups were similar (Table 1). Significant differences were not observed in demographic data or the American Society of Anesthesiologists functional class

between the two groups. Changes in rSO_2, the BIS, MAP, HR and SpO_2 during pulmonary surgical procedures in the two groups were recorded (Table 2).

Table 1
Demographic parameters of patients

Variable	Placebo Mean(SD)	Dexmedetomidine Mean (SD)	*P*
Age (years)	68.5 (2.34)	68.1 (2.60)	0.352
Male/female	15/16	16/13	0.599
BMI (kg/m^2)	23.18 (2.60)	22.45 (3.14)	0.333
ASA class (I/II)	22/7	25/6	0.653
BMI: body mass index; ASA: American Society of Anesthesiologists			

Table 2
Changes in BIS, rSO_2, MAP, HR and SpO_2 during pulmonary surgery in the two groups

Parameter	Group	Baseline	After regaining consciousness
		Mean (SD)	Mean (SD)
BIS	Dexmedetomidine	97.0 (0.57)	96.8 (0.60)
	Placebo	96.9 (0.40)	96.9 (0.40)
	p	0.300	0.565
rSO_2	Dexmedetomidine	64.9 (2.73)	63.5 (2.52)
	Placebo	64.3 (3.29)	64.2 (3.22)
	p	0.483	0.390
MAP	Dexmedetomidine	95.4 (6.92)	93.9 (7.42)
	Placebo	95.9 (7.75)	95.0 (6.59)
	p	0.784	0.544
HR	Dexmedetomidine	81.1(12.89)	66.9 (13.29)
	Placebo	80.4(10.57)	76.8 (9.46)
	p	0.831	0.001
SpO_2	Dexmedetomidine	97.4 (0.74)	97.5 (0.74)
	Placebo	97.6 (0.72)	97.7 (0.74)
	p	0.383	0.317

BIS: Bispectral Index; rSO_2: regional oxygen saturation; MAP: mean arterial pressure; HR: heart rate; SpO_2: peripheral oxygen saturation.

The rSO_2 between the dexmedetomidine group or placebo group was not significantly different (Dex 64.9 ± 2.73 *vs*. Placebo 64.3 ± 3.29, p = 0.483), and no significant difference was found after the patient regained consciousness (Dex 63.5 ± 2.52 *vs*. Placebo 64.2 ± 3.22; p = 0.390) before drug administration and after regaining consciousness, and no hypoxia was found among the patients (Table 2).

We assessed the depth of sedation using the BIS. No significant difference was found between the value at baseline and after regaining consciousness between the two groups (97.0 ± 0.57 *vs*. 96.9 ± 0.40, p = 0.300; 96.8 ± 0.60 *vs*. 96.9 ± 0.40, p = 0.565).

The two groups had a similar hemodynamic profile (Table 2). The HR in the dexmedetomidine group after regaining consciousness was significantly lower than that of the placebo group (66.9 ± 13.29 *vs*. 76.8 ±

9.46, p = 0.001). The MAP in the dexmedetomidine group was not significantly different between two groups, and nor were with the BIS or SpO_2.

The MoCA score between the dexmedetomidine group and placebo group was compared at different time points. The MoCA score between two groups was significant elevated in Dex group on POD1 (26.4 ± 0.73 vs 25.5 ± 0.96, p < 0.001) and POD3 (27.1 ± 0.79 vs 26.6 ± 0.80, p = 0.032). No significantly difference of MoCA scores were found between the two groups on POD7. (Table 3).

Table 3
Change in the MoCA score to assess mild cognitive impairment in the two groups

Time point	Dexmedetomidine	Placebo	*P*
	Mean (SD)	Mean (SD)	
Baseline	27.8(0.80)	27.9 (0.84)	0.511
POD1	26.4(0.73)	25.5 (0.96)	< 0.001
POD3	27.1 (0.79)	26.6 (0.80)	0.032
POD7	27.8 (0.72)	27.6 (0.68)	0.32

In comparison with the detailed categories of the MoCA score (Table 4), the attention score was increased in the dexmedetomidine group on POD1 (5.03 ± 0.50 *vs*. 4.58 ± 0.56, p < 0.05) and POD3(5.14 ± 0.44 vs. 4.96 ± 0.48, p < 0.05), and we noticed that attention score in placebo group was deteriorated on POD1 and POD3 compared with preoperative baseline value. We found significant decrease in memory score in both groups without intergroup differences, and memory score would recover on POD7. The orientation score was also improved in the dexmedetomidine group on POD1 (5.27 ± 0.70*vs*. 4.23 ± 0.72, p < 0.05)and POD3(5.48 ± 0.57 *vs*. 5.06 ± 0.51, p < 0.05).

Table 4
Comparison of detailed categories of the MoCA score

Parameter		T0	T1	T3	T7
Visuospatial/	D	4.68 ± 0.47	4.59 ± 0.50	4.62 ± 0.49	4.72 ± 0.45
Executive	P	4.61 ± 0.50	4.58 ± 0.49	4.67 ± 0.47	4.64 ± 0.50
Attention	D	5.20 ± 0.43	5.03 ± 0.50	5.14 ± 0.44	5.20 ± 0.41
	P	5.12 ± 0.34	**4.58 ± 0.56^{ab}**	**4.96 ± 0.48^{ab}**	5.03 ± 0.40
Abstraction	D	1.72 ± 0.45	1.69 ± 0.47	1.75 ± 0.43	1.79 ± 0.41
	P	1.81 ± 0.40	1.74 ± 0.44	1.84 ± 0.30	1.87 ± 0.34
Naming	D	2.93 ± 0.26	2.83 ± 0.38	2.86 ± 0.35	2.89 ± 0.31
	P	2.97 ± 0.18	2.87 ± 0.34	2.84 ± 0.37	2.90 ± 0.30
Memory	D	4.58 ± 0.50	**4.03 ± 0.56^{b}**	**4.07 ± 0.70 ^{b}**	4.48 ± 0.51
	P	4.64 ± 0.48	**4.19 ± 0.65^{b}**	**4.35 ± 0.61 ^{b}**	4.54 ± 0.51
Orientation	D	5.72 ± 0.45	5.27 ± 0.70	5.48 ± 0.57	5.62 ± 0.49
	P	5.74 ± 0.44	**4.23 ± 0.72^{ab}**	**5.06 ± 0.51^{ab}**	5.61 ± 0.56
Language	D	2.93 ± 0.26	2.89 ± 0.31	2.86 ± 0.35	2.83 ± 0.38
	P	2.96 ± 0.18	2.94 ± 0.25	2.93 ± 0.24	2.90 ± 0.30
D: Dexmedetomidine group; P: placebo group					
T0: preoperative; T1: postoperative day-1; T3: postoperative day-3; T7: postoperative day-7.					
a: significant difference between the dexmedetomidine group and placebo group, $p < 0.05$.					
b: significant difference between the postoperative Tx and T0 (preoperative baseline value), $p < 0.05$.					

Discussion

No study has evaluated the impact of dexmedetomidine on POCD in older patients undergoing pulmonary surgery patients, which makes this study the first report filling the blank of protective function of dexmedetomidine in in this specific surgical subtype. Some studies have shown that dexmedetomidine caused a dose-related reduction in CBF and CMR, but our study proved no effect of dexmedetomidine on rSO_2 [13, 23], which suggested that the worries about rSO2 declining thus resulted in POCD could be unnecessary.

To evaluate the effect of dexmedetomidine on rSO_2, it is very important to obtain the precise value of rSO_2. Cerebral oxygen saturation using NIRS has been widely used to monitor the relative change in the oxidative status of the brain. However, NIRS data requires careful interpretation because rSO_2 can be affected by age, hemoglobin concentration, bleeding, and transfusion [19, 20]. We controlled the variables that influence rSO_2, including the type of anesthetic used and oxygen inhalation, which boosted the robustness of our findings.

The secondary key finding of the present study was that a reduction in rSO_2 in the dexmedetomidine group was not significantly lower than that of the placebo group. Dexmedetomidine can act directly on selective α_2-adrenoreceptors in cerebral vessels, which can cause vasoconstriction and decrease CBF [24], Gao and colleagues found that dexmedetomidine (1 μg/kg) administration for 15 min before the surgical incision decreased cerebral oxygen saturation during single-lung ventilation [25]. A series of studies demonstrated that a decline in rSO_2 was correlated significantly with POCD as assessed by the Mini-Mental State Examination [26, 27]. Casati and coworkers designed a multicenter, randomized, prospective trial to estimate the efficacy of using rSO_2 monitoring during abdominal surgery[28]. They found that cerebral desaturation occurred intraoperatively and was correlated positively with a decline in cognitive status, however, was not observed during pulmonary surgery. The mechanisms behind that need further exploration including liver metabolism, but we demonstrated that rSO_2 does not decrease in pulmonary surgery even after a long duration of single-lung ventilation, which suggested that dexmedetomidine does not appear to have a negative role in POCD with regard to pulmonary surgery.

The MoCA score was calculated on POD1, POD3 and POD7. The MoCA score in the dexmedetomidine group were significantly higher than that in the placebo group at POD1 day and POD3. The prevalence of POCD was significantly lower in the dexmedetomidine group than that in the placebo group at POD1 day and POD3. Solanki and Goyal showed that DEX can reduce the incidence of nerve injury after transient ischemia in rats[29]. However, the specific mechanisms of the organ-protective effects of DEX are still unclear. Patients receiving dexmedetomidine were less likely to experience delirium than patients receiving midazolam, propofol or remifentanil. It has been suggested that dexmedetomidine treatment intraoperatively can significantly reduce the prevalence of delirium and POCD in both normal older patients and older patients with amnestic mild cognitive impairment, which suggests that it may be an effective option for POCD prevention. In our study, attention and orientation were significantly different between the two groups, a finding that is in accordance with the observation of a reduction in delirium within 1 week when patients stayed in the ICU. Hence, we propose the possible benefit of dexmedetomidine for patients likely to be admitted to the ICU postoperatively owing to the increased incidence of perioperative delirium.

Dexmedetomidine is an α_2-adrenoreceptor agonist that calms, reduces pain, and inhibits the activity of the sympathetic nervous system, but also can inhibit the inflammatory response and stress response, reduce neuronal toxicity and apoptosis, and promote brain protection through synapse formation and

neurotrophic nutrition [30]. Zeng and colleagues showed that dexmedetomidine can affect expression of proinflammatory factors and reduce the inflammatory response in blood vessels by activating the corresponding signaling pathways [31]. We suppose that the protective effect of dexmedetomidine on cerebral blood vessels may also have been manifested in a reduction of the level of proinflammatory factors in cerebral blood vessels, which thereby reduced the level of inflammation in the brain tissues of patients.

Our study had two main limitations. First, we did not measure cerebral autoregulation, alterations in which may have affected the brain's response to dexmedetomidine. Second, because it would have involved collection of additional blood samples, the serum concentration of dexmedetomidine was not monitored. Further large-scale multicenter studies should be designed to compensate for this inadequacy.

Conclusions

We showed, for the first time, that a loading dose of dexmedetomidine (1.0 μg/kg) could reduce the risk of POCD and might not decrease rSO_2. Hence, dexmedetomidine could be employed in pulmonary surgical procedures, especially for older patients facing high risk of delirium.

Abbreviations

Dex dexmedetomidine

BIS Bispectral Index

rSO $_2$ regional cerebral oxygen saturation

NIRS near-infrared spectroscopy

SpO $_2$ peripheral oxygen saturation

MAP mean arterial blood pressure

HR heart rate

Declarations

Ethics approval and consent to participate

The study protocol was approved by the local Clinical Research Ethics Committees (2017[10]). Written informed consent was obtained from all individuals participating in the trial.

Consent to publish

All authors confirm the Consent to publish.

Availability of data and materials

All authors confirm the availability of data and materials.

Competing interests

All authors have no competing interests to declare

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Authors' Contributions

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Figures

Figure 1

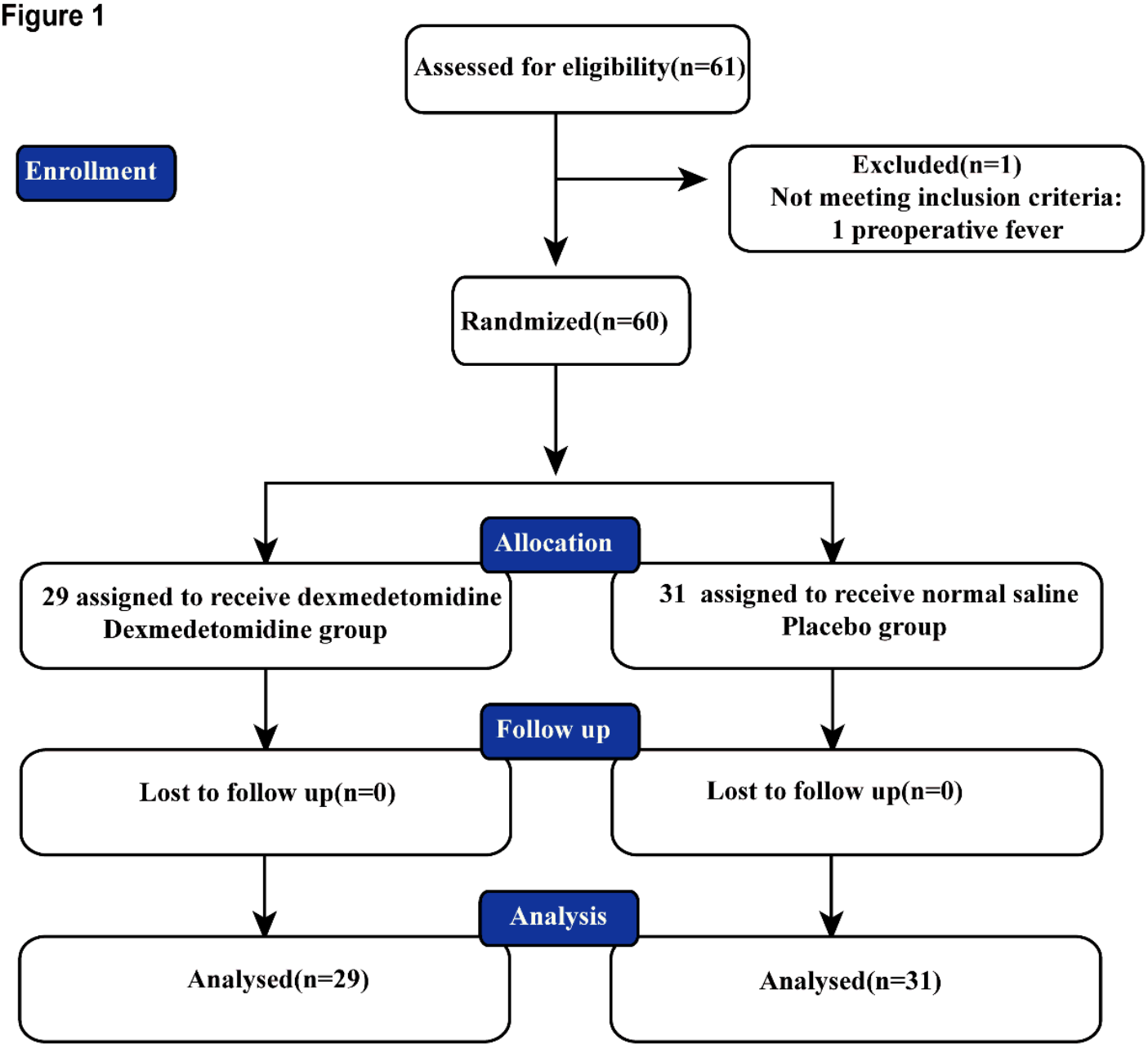

Figure 1

CONSORT diagram showing patient allocation

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- CONSORT2010Statementsubmitted.pdf