Effects of dexmedetomidine on postoperative delirium and expression of IL-1, IL-6, and TNF-α in elderly patients after hip fracture operation

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Abstract

Background: Postoperative delirium (POD) is a common surgical complication in elderly patients. This study investigated the effects of dexmedetomidine on POD and inflammatory factors in elderly patients with hip fracture.

Methods: The randomized, double-blind, controlled trial enrolled patients aged ≥65 years who underwent operation for hip fracture in the Department of Anesthesiology in Beijing JiShuiTan Hospital from October 2016 to January 2017. The patients were divided into the DEX group and the NS group and were intravenously infused with dexmedetomidine or an equal volume of normal saline, respectively. After surgery, the incidence of delirium at postoperative day 1 (T1), day 2 (T2) and day 3 (T3) were assessed using the Ramsay score and Confusion Assessment Method (CAM) delirium scale. Interleukin (IL)-1, IL-6 and tumor necrosis factor (TNF)-α concentrations in the venous blood of the two groups of patients were detected at T0 (before surgery), T1 and T3.

Results: Data from 218 patients were analyzed with 110 patients in the DEX group and 108 in the NS group. Dexmedetomidine decreased POD incidence (18.2% vs. 30.6%, P=0.033). Compared to T0, all three inflammatory factors increased at T1 and then decreased at T3 and changes with time were significant (all P<0.001). IL-6 (P<0.001) and TNF-α (P=0.003) levels were lower in the DEX group, but IL-1 levels were similar. The rate of adverse events was similar in the two groups.

Conclusions: Dexmedetomidine reduced the incidence of POD in elderly patients with hip fracture at an early stage, and reduced short-term IL-6 and TNF-α concentrations.

Background

Postoperative delirium (POD) is an acute confusion that occurs after an operation, characterized by disturbance of consciousness, declined ability to maintain and divert attention, and memory impairment [1]. Depending on the criteria for diagnosis, the patient population, and the surgical procedure the incidence of POD ranges from 10-70% [2]. Alongside the unpleasant experience of POD for the patient, its occurrence also causes other problems. In hospitalized elderly patients, mental disorders such as delirium are associated with increased hospitalization stay, dementia, morbidity and mortality [3]. As the population age increases the requirement for surgical procedures in elderly patients increases. For example, the incidence of hip fractures has been increasing, and surgical treatment has become the major treatment method for elderly patients with hip fracture [4]. POD is also considered to be the most common surgical complication of elderly patients with hip fractures [5-7]. In patients undergoing hip fracture surgery, general anesthesia or subarachnoid (spinal) anesthesia show similar rates of POD [8].

The occurrence of POD is usually associated with a variety of factors, such as advanced aged, preoperative multi-system diseases, medications used in anesthesia, massive blood loss during the operation and pain stimulation [9]. One suggested mechanism for POD is overexpression of inflammatory responses due to surgical stress leading to the production of proinflammatory cytokines in the brain [10].

The resulting neuroinflammation can damage the brain tissue, thereby causing POD. This theory is supported by expression of peripheral inflammatory markers in delirium including C-reactive protein, tumor necrosis factor alpha (TNF-α), and interleukin (IL)-1 and IL-6 [11-14]. Therefore, decreasing the expression of inflammatory factors during the perioperative period may be of great importance for protecting the brain.

Dexmedetomidine (DEX) is a highly selective α2-receptor agonist which provides sedation, analgesia and anxiety relief [15]. As an α2-adrenergic receptor agonist DEX can also reduce the systemic inflammatory response and regulate the immune system by inhibiting the central sympathetic nervous system [16]. Moreover, it can activate anti-apoptotic signaling pathways to play protective effects on damaged cells in multiple organs including the brain [17, 18].

A number of studies have demonstrated that DEX can reduce the risk of delirium in elderly patients after surgery [9, 19-21], but few studies have investigated related changes in inflammatory factors. One study has shown that the mechanism of DEX may be correlated with its inhibition of inflammatory responses in addition to hypoxemia, analgesia and sleep improvement [9]. Preclinical experimental models have shown that DEX can inhibit central inflammatory responses, and reduce the production of peripheral serum TNF-α [22]. Therefore, investigation of the role of DEX in reducing the incidence of POD in elderly patients undergoing surgery for hip fracture alongside levels of inflammatory markers may provide more of an insight into the prevention of POD with DEX.

This trial aimed to investigate the effects of intraoperative sedation by intravenous application of DEX on POD of elderly patients with hip fracture. Moreover, the inflammatory responses alongside the occurrence of POD were explored by detecting expression changes of serum TNF-α, IL-1 and IL-6 at different time points after surgery.

Methods

Patients

This prospective, randomized, double-blind, controlled trial was approved by the Institutional Review Board of the Beijing Jishuitan Hospital (Approval No.: 201606-09), and the patients signed written informed consent. The registration number of the clinical experiment was: ChiCTR-OON-16008691. Our study enrolled elderly patients with hip fracture treated in the Department of Anesthesiology, Beijing Jishuitan Hospital from October 2016 to January 2017.

The inclusion criteria were: 1) patients with hip fracture undergoing operation; 2) patients aged 65-90 years; 3) American Society of Anesthesiologists (ASA) physical status scale grade I-III [23].

The exclusion criteria were: 1) patients with a history of psychosis or of long-term psychotropic medication use (dementia, schizophrenia), history of chronic analgesic use or history of alcohol abuse; 2) patients with preoperative mini-mental state examination (MMSE [24]) score of ≤23, which was assessed

at 1 day before surgery (T0); 3) patients who were illiterate; 4) patients with hearing and visual impairments as well as those who had any cerebrovascular accidents such as stroke or transient ischemic attack (TIA) within 3 months; 5) patients with severe infection; 6) patients with communication barriers who could not complete the cognitive function test.

A computer-generated random number scheme was used to assign the patients into two groups, the DEX group (n=110) and the normal saline (NS) group (n=108).

The patients and researchers (responsible for data recording and analysis, Confusion Assessment Method (CAM [25]) delirium scale assessment and POD diagnosis) were blinded to the groups, but the anesthesiologists knew about the medication of the patients.

Anesthetic management

Patients in both groups underwent proximal femoral nail anti-rotation (PFNA), cannulated screw fixation, hemi-arthroplasty, or total hip arthroplasty (THA). The surgical procedures were perfomred according to standard procedures. The operations for all patients were performed by the same attending physicians (vice-senior physicians) with 5-10 years of surgical experience.

The anesthetic management was the same for both groups of patients except for the administration of DEX. Electrocardiogram (ECG), arterial blood pressure (ABP), heart rate (HR) and pulse oxygen saturation (SpO_2) results were monitored after the patients entered the operating room. The patients were in supine position, and a portable ultrasound unit (WISONIC CLOVER 60VET) with a 4-12 MHz Convex array probe was used to identify the femoral artery, femoral nerve and fascia. The puncture point was at the point 2 cm towards the caudal side from the point of 1/3 length externally along the line between the anterior superior iliac spine and the pubic tubercle. The in-plane needle approach was applied. After the nerve block needle reached the fascia iliaca compartment, 30 ml of 0.4% ropivacaine was injected. Twenty minutes after nerve block, the patients were assisted by 3 physicians into the spinal anesthesia position, thus the diseased side was on the top, and a subarachnoid block was performed in the lateral position. The puncture point was in the L3-4 gap, and 12 mg of 0.5 ropivacaine was injected through the subarachnoid space after the puncture was successful; otherwise, puncture was performed between L2-3. General anesthesia was performed if spinal anesthesia failed. Etomidate (0.3 mg/kg) was used in general anesthesia, sufentanil (0.1 μg/kg) was used for induction, and rocuronium (0.6 mg/kg) was also applied. After successful intubation, a ventilator was connected to control breathing. Propofol was continuously pumped in and sevoflurane anesthesia was inhaled during the operation to maintain the anesthesia. Anesthesia depth was maintained by continuous pumping in 2% sevoflurane and propofol. Dexmedetomidine (0.5 μg/kg/h) was intravenously infused 30 minutes before the start of anesthesia in the DEX group, and was continuously infused at 0.3 μg/kg/h during the operation. The same volume of normal saline was administrated for the NS group. The medication was discontinued 30 min before the end of surgery. Self-controlled analgesia was performed by administrating patient controlled intravenous analgesia (PCIA), and sufentanil combined with flurbiprofen ester immediately after the operation.

Data collection

Demographics and medical history of the patients in both groups were recorded, including gender, age, ASA grade, body mass index (BMI), education level, type of fracture, type of anesthesia, surgical procedure, operation time and comorbidities.

Primary endpoint

The primary endpoint was the incidence of POD, which was assessed using the Chinese version of the Richmond Agitation Sedation Scale (RASS) [26] and the CAM Scale at the first postoperative day (T1), the second postoperative day (T2), and the third postoperative day (T3).

CAM assessment was performed for patients with RASS of >-4. The diagnostic criteria for positive CAM [25] was as follows: (1) acute onset, and fluctuation of the disease condition; (2) distracted attention; (3) thinking disorder; (4) changes of consciousness. If patients showed characteristics of points 1 and 2 and any one of 3 and 4, then CAM was considered positive.

Patients with positive CAM at any time point during the follow-up period were diagnosed by a psychiatrist or psychologist based on the Diagnostic and Statistical Manual of Mental Disorders 5 (DSM-5) [27]. Delirium was diagnosed if the following 5 items were satisfied based on DSM-5: (1) Attention deficit disorder; (2) acute onset and repeated changes of symptoms; (3) combined with cognitive impairment; (4) standards (1) and (3) cannot be explained by existing neurological diseases, and arousal disorder was excluded; (5) it can be seen from medical history, physical examination or laboratory tests that it was direct physiological consequences of general physical conditions.

Two trained individuals in our department conducted the assessment of POD, and they were also blinded to the grouping.

Secondary endpoints

Biochemical tests

Five ml of venous blood from the side without infusion was extracted at 9:00 in the morning at T0, T1 and T3, and was centrifuged at 4000 r/min for 10 min. The serum was separated and stored at -80 °C. Before assay, all samples were thawed to room temperature and mixed by gentle swirling or inversion. All sera were assayed on the same day to avoid inter-assay variation. Plasma IL-1, IL-6 and TNF-α levels were measured by an enzyme-linked immunosorbent assay (ELISA) kit from Bender MedSystems (GmbH, Vienna, Austria). The ELISA methods were basically the same involving a two antibody sandwich ABC-ELISA method. The first antibody was anti-human TNF-α, IL-1, or IL-6 monoclonal antibody and the second antibody was a monoclonal antibody containing biotin. Enzyme-labelled streptavidin was bound to the biotin, o-phenylenediamine was added, and the mixture turned yellow. At this time, sulfuric acid was added, and the color became darker. The optical density (OD) value was measured at 492 nm and

the concentrations of TNF-α, IL-1, and IL-6 were proportional to OD value. Concentration of TNF-α, IL-1, or IL-6 in the specimen were calculated by plotting a standard curve.

The antibodies used in this procedure have no known cross-reactivities with other cytokines. The lowest detectable limits of IL-1β, IL-6, and TNF-α, were 1.5 pg/mL, 5 pg/mL, and 1.7 pg/mL, respectively.

NRS scores

Postoperative pain was assessed at T1, T2 and T3 according to a numeric rating scale (NRS), where “0” means no pain at all and “10” means extremely serious pain. Patients with a NRS score of ≥4 after the operation were intravenously injected with 40 mg of parecoxib sodium for analgesia in both groups.

Adverse events

Invasive artery blood pressure (systolic (SBP), diastolic (DBP), mean arterial pressure (MAP)), HR, ECG, and SpO_2 were routinely monitored during the operation. The number of intraoperative adverse reactions including hypertension, hypotension, bradycardia and tachycardia were recorded. Tachycardia was defined as heart rate >100 bpm; bradycardia was defined as heart rate <60 bpm; hypertension was defined as systolic pressure >160 mmHg or 20% of baseline; hypotension was defined as systolic pressure <90 mmHg or 20% of baseline. Patients with bradycardia were administrated with 0.1-0.3 mg of atropine, and patients with hypotension were intravenously injected with 4 ug of norepinephrine or intravenously infused at 200 ug/h.

Statistical analysis

The incidence of postoperative delirium in a comparable patient population of a previous study was 28% [4]. We; therefore, assumed that the incidence of delirium would be reduced by one third in the DEX group in this trial. With significance set at 0.05 and power set at 80%, the sample size required to detect differences was 196, calculated with Pass 11.0 software (NCSS, LLC. Kaysville, Utah, USA). Taking into account a loss-to-follow-up rate of about 6%, we planned to enroll 208 patients.

Continuous data with normal distribution were expressed as means ± standard deviation (SD) and analyzed by independent t test, and those with non-normal distribution were expressed as medians (interquartile range) and analyzed by the Mann-Whitney u test. Categorical variables were expressed as frequencies and percentages and analyzed with chi-square analysis or Fisher exact test. Repeated measurement analysis of variance was used to analyse levels of inflammatory factors. Statistical analyses were done on SPSS Statistics for Windows (version 22.0; IBM Corp., Armonk, New York, USA) with two-tailed tests wherever appropriate and $P<0.05$ were considered as statistical significant. The Clinical Research Ethics Committee from Beijing Jishuitan Hospital was involved in overseeing the data.

Results

Patient inclusion

A total of 402 patients were assessed for eligibility. 162 patients were excluded based on the inclusion criteria established for this trial or because they declined to participate. The remaining 240 patients were randomly assigned to the DEX group or NS group. Among these patients, data for 22 patients were not analyzed due to transferring to other hospitals after operation (n=14, 6 in the DEX group and 8 in the NS group) or they withdrew consent (n=8, 4 in each group). The remaining 218 patients were included in the data analysis, 110 in the DEX group and 108 in the NS group (Figure 1).

Demographics and medical history

There were no significant differences between the two groups in demographics including age, gender, BMI, education level, ASA grade, comorbidities, and type of fracture, anesthesia, surgical procedure, and operation time (all P>0.05) (Table 1).

Incidence of POD and NRS scores

There was a lower incidence of POD at T1 in the DEX group than in the NS group (14.55% vs. 26.85%, P=0.025) and in total POD in the DEX group than in the NS group (18.18% vs. 30.56%, P=0.033). However, the POD incidence decreased in both groups and was similar between them at T2 (3.64% vs. 4.63%, P=0.747) and T3 (1.82% vs. 2.78%, P=0.682). NRS scores were similar between the two groups at T1, T2 and T3 (all P>0.05) (Table 2).

Inflammatory markers

The changes in inflammatory markers in the two groups are shown in Figure 2 and Table 3. In both groups, all three markers showed an initial increase at T1 and then decreased at T3. The IL-1 serum concentration changes were similar in both groups and remained above the T0 level at T1 and T3 while both groups showed a significant difference with time (P<0.001). The serum IL-6 concentration was increased at T1 and T3 compared to T0. However, the DEX group showed lower serum IL-6 concentrations than the NS group at T1 and T3 (P<0.001).

In both groups, serum TNF-α concentration increased at T1 and T3. However, the DEX group showed lower TNF-α concentrations than the NS group at T1 and T3 (P=0.003) (Table3).

Adverse events

In total 102 adverse events were recorded 44 in the NS group and 58 in the DEX group. These included tachycardia, bradycardia, hypertension, and hypotension the rates were similar in the two groups (all P>0.05) (Table 4).

Discussion

The aim of this trial was to investigate the effects of DEX on POD and level of inflammatory factors in elderly patients undergoing surgery for hip fractures. Data from 218 patients were analyzed with 110

patients in the DEX group and 108 in the NS group. DEX decreased POD incidence to 18.2% from 30.6% in the NS group. IL-1, IL-6, and TNF-α serum levels all increased one day after surgery and then decreased on the third day after surgery. The DEX group IL-6 and TNF-α levels were lower than in the NS group, but IL-1 levels were similar. The rate of adverse events was similar. These results show that DEX reduced the incidence of POD in elderly patients with hip fracture at an early stage and reduced the short-term increases in IL-6 and TNF-α concentrations post-surgery.

Our results suggest that intravenous administration of dexmedetomidine during surgery significantly reduces the incidence of delirium in elderly hip fracture. This result agrees with numerous other studies that have also shown reduced rates of POD in elderly surgical patients [9, 19-21]. However, by monitoring the serum inflammatory cytokines IL-1, IL-6, TNF-α of the patients in this trial at different time points, we also aimed to investigate the expression of postoperative inflammatory cytokines with DEX administration and the occurrence of POD. Fewer studies have undertaken investigation of cytokines during DEX treatment to prevent POD. A study of 354 patients >65 years of age undergoing laparoscopic major non-cardiac surgery under general anesthesia found that POD was reduced and IL-6 levels were significantly lower at 1 h and 24 h when DEX was administered as a bolus before surgery and by infusion from induction of anesthesia to the end of surgery [28]. For 40 patients undergoing robot-assisted laparoscopic radical cystectomy and ileal conduit diversion, the levels of TNF-α, NSE and IL-6 in the DEX group were significantly lower than in the control group one- and five-days after operation [29]. In young patients combined usage of DEX and sufentanil was investigated to treat POD after general anesthesia [30]. The results showed that levels of IL-6, and TNF-α decreased 1h to 8h after surgery. When the results of these studies and our results are taken together there is a suggestion that there might be a relationship between inflammatory factors and POD. In our study on the 1st day after surgery, the levels of IL-1, IL-6, TNF-α were relatively high, and the incidence of POD was also relatively high (26.85% and 14.55%). On the 3rd day, level of IL-1, IL-6, TNF-α were lower, and incidence of POD dropped to 2.78% and 1.82%. However, further studies are needed to investigate whether there is a direct correlation between POD and cytokine levels.

The pathological mechanism of POD is still unclear, and it may be caused by multiple factors. However, inflammatory responses and neuroinflammation seem to be the main cause. Therefore, DEX, as α-receptor agonist, can prevent the occurrence of POD. Elderly patients with hip fractures often have agitation during surgery due to trauma and the discomfort caused by their positioning, especially patients receiving intramedullary needle fixation. The sedative effect of DEX can reduce the patient's agitation during the operation. There is some concern that application of DEX has many potential side effects, including elevated blood pressure, decreased heart rated and inhibition of cardiac conduction system. For elderly patients with hip fracture, it has been suggested that DEX should be administered in the lowest possible doses for the shortest possible time. In our experiment, the initial dose was 30 ug for elderly patients with hip fracture, the infusing dose was 0.2 ug/kg/h, and medication was discontinued 10 min before the end of the operation. In respect to safety, our data revealed that DEX -induced bradycardia and hypotension were not significantly increased, possibly because of the very low doses that were used.Nevertheless, the hemodynamic-stabilizing property of DEX may be beneficial. Stable heart rate and

mean arterial pressure can reduce myocardial oxygen consumption, thus this property contributes to the decrease in the incidence of cardiac events for high-risk patients [31].

There were several limitations in this study. Firstly, this was a single centre study and there might be selection bias. Secondly, inflammatory indicators were measured at only three time points, but blood specimens were not collected before anesthesia and immediately after anesthesia. Thirdly, the follow-up time was short (only 3 days after surgery), which was mainly because hospitalization of the patients was short, and blood samples could not be obtained effectively after discharge.

Conclusion

Dexmedetomidine reduced the incidence of POD of elderly patients after surgery for hip fractures. Dexmedetomidine also significantly alleviated the increase in short-term IL-6 and TNF-α levels. Dexmedetomidine may benefit patients by reducing the incidence of early POD and offering a better short-term recovery for elderly patients receiving hip arthroplasty.

List Of Abbreviations

POD: Postoperative delirium; CAM: Confusion Assessment Method; IL: Interleukin; IL-6TNF and tumor necrosis factor; ASA: Anesthesiologists; TIA: transient ischemic attack; PFNA: proximal femoral nail anti-rotation; THA: total hip arthroplasty; ECG: Electrocardiogram; ABP: arterial blood pressure; HR: heart rate; PCIA: patient controlled intravenous analgesia; BMI: body mass index; RASS: Richmond Agitation Sedation Scale; ELISA: enzyme-linked immunosorbent assay; OD: optical density.

Declarations

Ethics approval and consent to participate

This prospective, randomized, double-blind, controlled trial was approved by the Institutional Review Board of the Beijing Jishuitan Hospital (Approval No.: 201606-09), and the patients signed written informed consent.

Consent for publication

Not applicable

Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests

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Authors' contributions

WZ and TW contributed conception and design of the study; WZ and GW organized the database; WZ performed the statistical analysis; MY, WZ and TW wrote the first draft of the manuscript; TW, YZ, YY, and MY wrote sections of the manuscript. All authors contributed to manuscript revision, read and approved the submitted version.

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Tables

Table 1. Demographics and medical history of patients in both groups

Characteristics	NS group (N=108)	DEX group (N=110)	P-value
Age (years)	79.14±6.79	78.46±6.42	0.451
Gender (male)	34 (31.48%)	34 (30.91%)	1.000
BMI (kg/m$^{2)}$	23.40±2.20	23.95±2.84	0.111
Education level (years)	0.731		
< 5	80 (74.07%)	79 (71.82%)	
5-8	26 (24.07%)	30 (27.27%)	
> 8	2 (1.85%)	1 (0.91%)	
ASA grade	0.622		
I	9 (8.33%)	7 (6.36%)	
II	76 (70.37%)	74 (67.27%)	
III	23 (21.30%)	29 (26.36%)	
Operation time (min)	60.00 (40.00-70.00)	60.00 (40.00-70.00)	0.890
Comorbidities			
Hypertension	57 (52.78%)	58 (52.73%)	1.000
Diabetes	21 (19.44%)	30 (27.27%)	0.172

Heart failure	9 (8.33%)	17 (15.45%)	0.105
Lung infection	1 (0.93%)	5 (4.55%)	0.223
Chronic bronchitis	9 (8.33%)	9 (8.18%)	1.000
Atrial fibrillation	5 (4.63%)	7 (6.36%)	0.575
Arrhythmia	3 (2.78%)	5 (4.55%)	0.739
Anesthesia	0.399		
Spinal anesthesia	87 (80.56%)	93 (84.55%)	
Combined spinal-epidural anesthesia	17 (15.74%)	16 (14.55%)	
General anesthesia	4 (3.70%)	1 (0.91%)	
Type of fracture	0.582		
Femoral neck fractures	52 (48.15%)	45 (40.91%)	
Intertrochanteric fracture	54 (50.00%)	62 (56.36%)	
Subtrochanteric fractures	2 (1.85%)	3 (2.73%)	
Surgical procedure	0.454		
PFNA	54 (50.00%)	50 (45.45%)	
Cannulated screw fixation	29 (26.85%)	24 (21.82%)	
Hemi-arthroplasty	14 (12.96%)	21 (19.09%)	

THA	11 (10.19%)	15 (13.64%)

Abbreviations: NS= normal saline, DEX= dexmedetomidine, BMI= body mass index, ASA= American Society of Anesthesiologists physical status scale grade, PFNA= proximal femoral nail anti-rotation; THA= total hip arthroplasty.

Table 2. Incidence of POD and NRS scores after surgery

	NS group (N=108)	DEX group (N=110)	P-value
POD			
T1	29 (26.85%)	16 (14.55%)	0.025
T2	5 (4.63%)	4 (3.64%)	0.747
T3	3 (2.78%)	2 (1.82%)	0.682
Total	33 (30.56%)	20 (18.18%)	0.033
NRS			
T1	2.00 (2.00-3.00)	2.00 (2.00-3.00)	0.748
T2	1.00 (1.00-1.00)	1.00 (1.00-1.00)	0.862
T3	1.00 (1.00-1.00)	1.00 (1.00-1.00)	0.509

Abbreviations: POD= postoperative delirium, NS= normal saline, DEX= dexmedetomidine, NRS= numeric rating scale, T1= 1 day after surgery, T2= 2 days after surgery, T3= 3 days

after surgery.

Table 3. Levels of IL-1, IL-6 and TNF-α

	NS group (N=108)	DEX group (N=110)	F(group)/P-value	F(time)/P-value	F(group*time)/P-value
IL-1					
T0	5.19±0.67	5.10±0.71	*F*=0.075	*F*=1226.917	*F*=0.532
T1	10.88±1.51	11.05±1.87	*P*=0.784	*P*<0.001	*P*=0.588
T3	7.99±1.27	7.99±1.31			
IL-6					
T0	22.94±5.39	23.71±5.83	*F*=36.520	*F*=2804.130	*F*=36.593
T1	105.15±16.18	89.04±10.83	*P*<0.001	*P*<0.001	*P*<0.001
T3	63.26±22.08	55.36±16.31			
TNF-α					
T0	4.35±0.73	4.40±0.78	*F*=7.980	*F*=72.608	*F*=5.340
T1	5.37±0.85	4.93±0.91	*P*=0.003	*P*<0.001	*P*=0.024
T3	4.47±0.89	4.19±0.92			

Abbreviations: NS= normal saline, DEX= dexmedetomidine, T0= 1 day before surgery, T1= 1 day after surgery, T3= 3 days after surgery, IL= interleukin, TNF= tumor necrosis factor.

Table 4. Intraoperative adverse events

	NS group (N=108)	DEX group (N=110)	P-value
Tachycardia	6 (5.56%)	10 (9.09%)	0.317
Bradycardia	16 (14.81%)	18 (16.36%)	0.753
Hypertension	14 (12.96%)	22 (20.00%)	0.162
Hypotension	8 (7.41%)	8 (7.27%)	0.970

Abbreviations: NS= normal saline, DEX= dexmedetomidine.

Figures

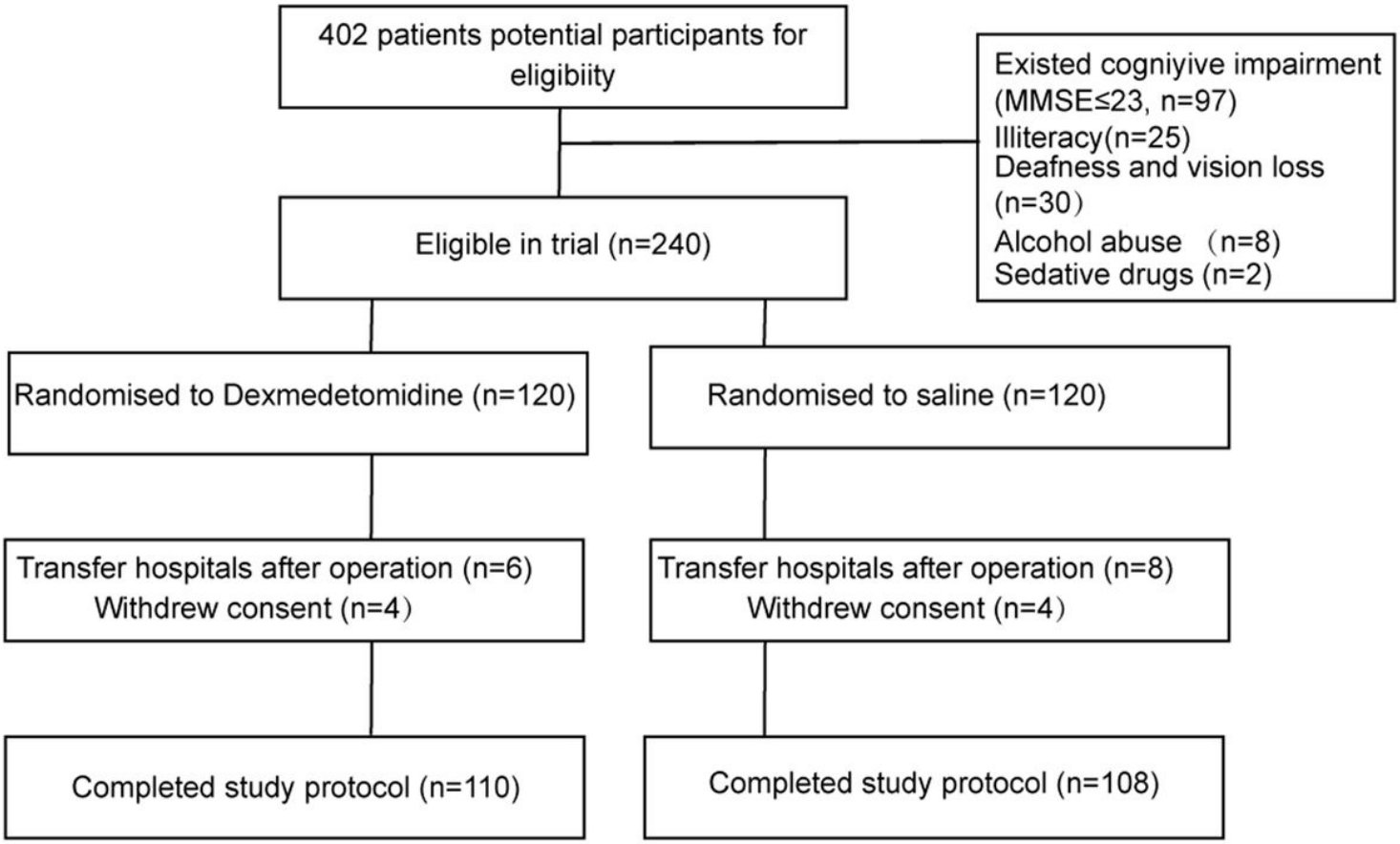

Figure 1

Flow chart of study inclusion, randomization, and follow up.

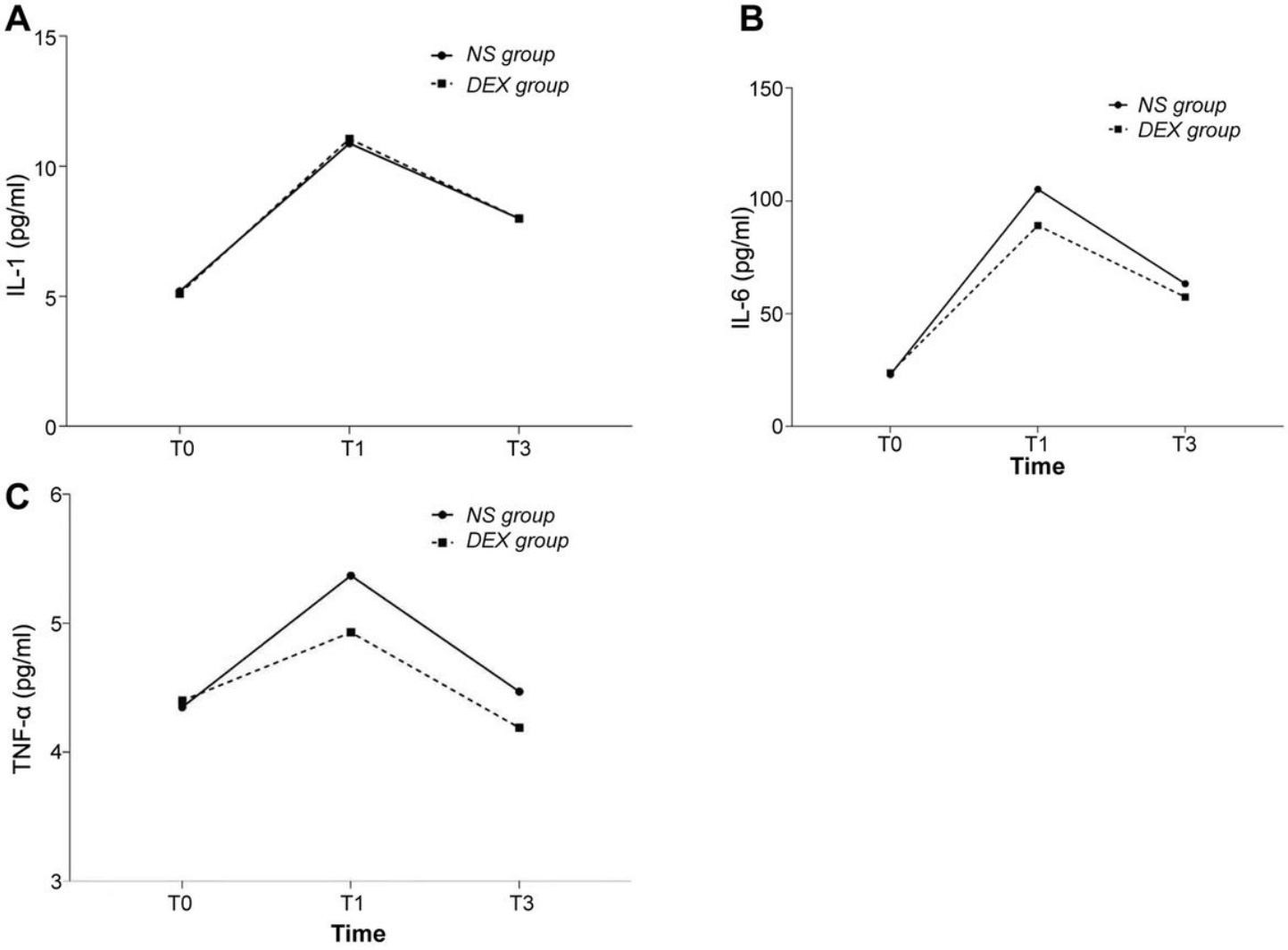

Figure 2

Change in interleukin (IL)-1, IL-6 and tumor necrosis factor (TNF)-α levels over time.