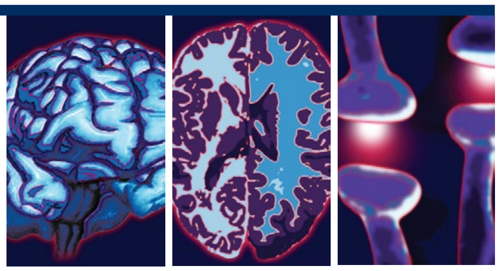

Optimized Anesthesia to Alleviate Postoperative Cognition Decline in Female Middle-Aged Patients Undergoing Laparoscopic Myomectomy: A Pilot Study

Jianhui Liu[1,†,*], Li Cai[2,*], Junjun Yang[1], Gang Guo[3], Heng Wu[4], Yanhong Zhao[1], Xiaoqing Zhang[1]

Abstract

Objective

The purpose of this randomized, single-center study was to clarify the impact of anesthetic regimens for laparoscopic myomectomy on the release of cytokines (interleukin IL-1β, IL-2R IL-6, IL-8, tumor necrosis factor (TNF)-alpha, C-reactive protein (CRP) and to ascertain that whether a combination of intravenous and inhalational anesthesia compared with inhalational anesthesia attenuates the inflammatory response and cognitive impairment.

Methods

We enrolled 90 patients undergoing laparoscopic myomectomy (LM), and allocated them into three groups of 30 to receive high concentration sevoflurane (S group), low concentration sevoflurane with dexmedetomidine (SD) or with propofol (SP) in combine with remifentanil and cis-atracurium. The lungs were maintained normocapnia with mechanically ventilated. If the mean arterial pressure and the heart rate increased by >30% from baseline, remifentanil infusion was adjusted. The depth of anesthesia was modulated to maintain a bispectral index (BIS) of 40-60. Invasive hemodynamic monitoring was used. Serum levels of IL-1β, IL-2R, IL-6 and IL-8, TNF-α, and CRP were measured before anesthesia and 24 h post operation. The neurocognitive tests were administered 1 day before and 7 days post operation. Postoperative complications (including pain, infection, sedation, cardiovascular and neurological events) were surveillance during the first week post operation.

Results

Patients anesthetized with low concentration sevoflurane plus dexmedetomidine had lower levels of IL-6 (p=0.0001) and better cognitive function compared with patients with high concentration sevoflurane postoperatively. There was no POCD occurrence among all the three groups in the 7days follow-up.

Conclusion

LM female middle-aged patients exposured to low concentration sevoflurane plus dexmedetomidine had better cognitive function than patients with high concentration sevoflurane, which might be related to lower release of IL-6 post operation.

Keywords

Laparoscopic myomectomy, Propofol, Sevoflurane, Dexmedetomidine, Neurocognition, Inflammatory cytokines

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Introduction

Postoperative cognitive dysfunction or decline (POCD) is an increasingly recognized phenomenon after major surgery, and is associated with impairment in daily functioning and increased morbidity and mortality [1]. Research found that anesthesia and surgical trauma were main causes of POCD [2]. Evidences have shown that the enhancement of inflammatory response especially in the central nervous system served as a predictive parameter for POCD [3-8]. Clinical studies found that interleukin (IL)-6 might serve as a biomarker of POCD prevention and treatment[9]. Animal studies have demonstrated that volatile anesthetics can induce neuroinflammation, which led to cognitive dysfunction in rodents and even in humans [10,11]. Sevoflurane is widely used for the induction and maintenance of general anesthesia during surgery. It has been reported that sevoflurane has dual effects on cognitive function depending on its concentration and duration *in vitro* and *in vivo* [12,13]. Human studies showed that elderly patients with major surgery under inhalation anesthesia with sevoflurane were more prone to occur POCD than those with intravenous propofol [14]. A recent *in vitro* study showed that the release of proinflammatory cytokines could almost be completely inhibited by propofol treatment [15]. It has also been reported that dexmedetomidine, a highly selective α-2 adrenergic receptor agonist, could prevent POCD due to its neuroprotective effects *via* the suppression of inflammatory cytokines [16,17]. Thus, the use of intravenous dexmedetomidine or propofol during surgery has been shown to suppress inflammatory cytokines perioperatively. However, it is not clear if dexmedetomidine or propofol combined with a low concentration of sevoflurane can be neuroprotective in middle-aged patients. Thus, we hypothesized that intravenous anesthesia combined with a low concentration of inhalational anesthesia could attenuate the inflammatory response compared with a high concentration of inhalational anesthesia. To identify the hypothesis, the incidence of POCD surgery patients and inflammatory cytokines expression were analyzed during sevoflurane alone and sevoflurane with intravenous propofol or dexmedetomidine general anesthesia in middle-aged patients undergoing LM.

Methods and Materials

■ Study design

The protocol for this prospective randomized clinical study were approved and performed following the guidelines of the Shanghai Tongji Hospital Ethics Committee of China. The informed consent was obtained from all subjects and approved by the Institutional Review Board (IRB). (Registration number: ChiCTR-IPR-16010216, Jianhui Liu, 2016/12/21, Shanghai, China). Patients were randomly divided into three groups by using computer-generated simple randomization program (www.random.org): sevoflurane (S group, n=30), sevoflurane plus dexmedetomidine (SD group, n=30), or sevoflurane plus propofol (SP group, n=30). All selected participants were American Society of Anesthesiologists (ASA) grades I or II and 40-60 years of age who had laparoscopic myomectomy under general anesthesia in Shanghai Tongji Hospital from December 2016 to March 2017 **(Figure 1)**.

The exclusion criteria were: (i) A Mini Mental State Examination score <24 (of 30 possible points) was supposed to cognitive impairment from the screening test of overall cognitive status at the initial visit of the patient; (ii) history of drug and alcoholism dependence, neurological or psychiatric diseases (stroke, Alzheimer disease and psychosis); (iii) severe auditory or/and visual disorders; (iv) not willing to abide by the agreement or program; (v) inability to understand the language (Mandarin Chinese); (6) with terminal disease.

■ General anesthesia

After obtaining written informed consent, all participants had general anesthesia. Anesthesia was induced with sufentanil (0.2-0.3 μg/kg), midazolam (0.04-0.05 mg/kg), etomidate (0.3 mg/kg), and *cis*-atracurium (0.15 mg/kg), followed by tracheal intubation. Patients were treated with 35-40 mmHg end-tidal CO_2 and ventilated mechanically constantly. The S group was maintained with 1-1.2 minimal alveolar concentration (MAC) sevoflurane after induction of general anesthesia. The SD group was maintained with 0.5 MAC sevoflurane and administered dexmedetomidine (1 μg/kg) over 10 min then infusion at 0.2-0.5 $\mu g \cdot kg^{-1} \cdot h^{-1}$ dexmedetomidine. The SP group was maintained with 0.5 MAC sevoflurane and administered with a target controlled infusion (TCI) of 2-3 μg/mL (target plasma concentration) propofol. All the groups were infused with remifentanil (0.10-0.20 μg/kg/min) continuously and *cis*-atracurium intermittently as required. Routine monitoring of standard anesthetic care was provided: arterial blood pressure, electrocardiography and oxygen saturation. Bispectral Index (BIS) monitor was used to determine the relative depth of general anesthesia. The BIS value of satisfactory depth of general anesthesia was maintained between 40 and 60. Similar BIS contributed by values among the three groups were maintained to exclude the POCD incidence contributed by the depth of general anesthesia.

Neurocognitive tests

This pilot study consisted of 11 cognitive tests. Each participant underwent the cognitive tests preoperatively 1 day and postoperatively 7 days. It takes about 30 minutes with only the participant and investigator for cognitive tests in a quiet environment. The tests were carried out in Mandarin Chinese. The investigator was blinded to the assigned groups (S, SD, SP). The tests included the Hopkins Verbal Learning Test-Revised Immediate Recall Test (HVLT-R1), HVLT-R Delayed Recall Test (HVLT-R2), Brief Visual Spatial Memory Test-Revised (BVMT-R1), BVMT-R Delayed Recall Test (BVMT-R2), Benton Judgment of Line Orientation Test (JLOT), Forward Digit Span Test (FDST), Backward Digit Span Test (BDST), Symbol-Digit Modalities Test (SDMT), Stroop Effect test, Trail Making Test (TMT), and Verbal Fluency Test (VFT). These tests are widely used in neuropsychology and highly sensitive to different types of cognitive impairments (Table 1).

The change of each individual's test scores relative to baseline were calculated (preoperatively) after 1 week postoperation (ΔX), and subtracted the learning effect (ΔX control). The resulting divided by the standard deviation (SD) of the corresponding changes in the controls (SDΔX control) enabled production of a Z score for each test. Patients with Z scores ≥2 and in individual tests >1.96 were defined as cognitive dysfunction.

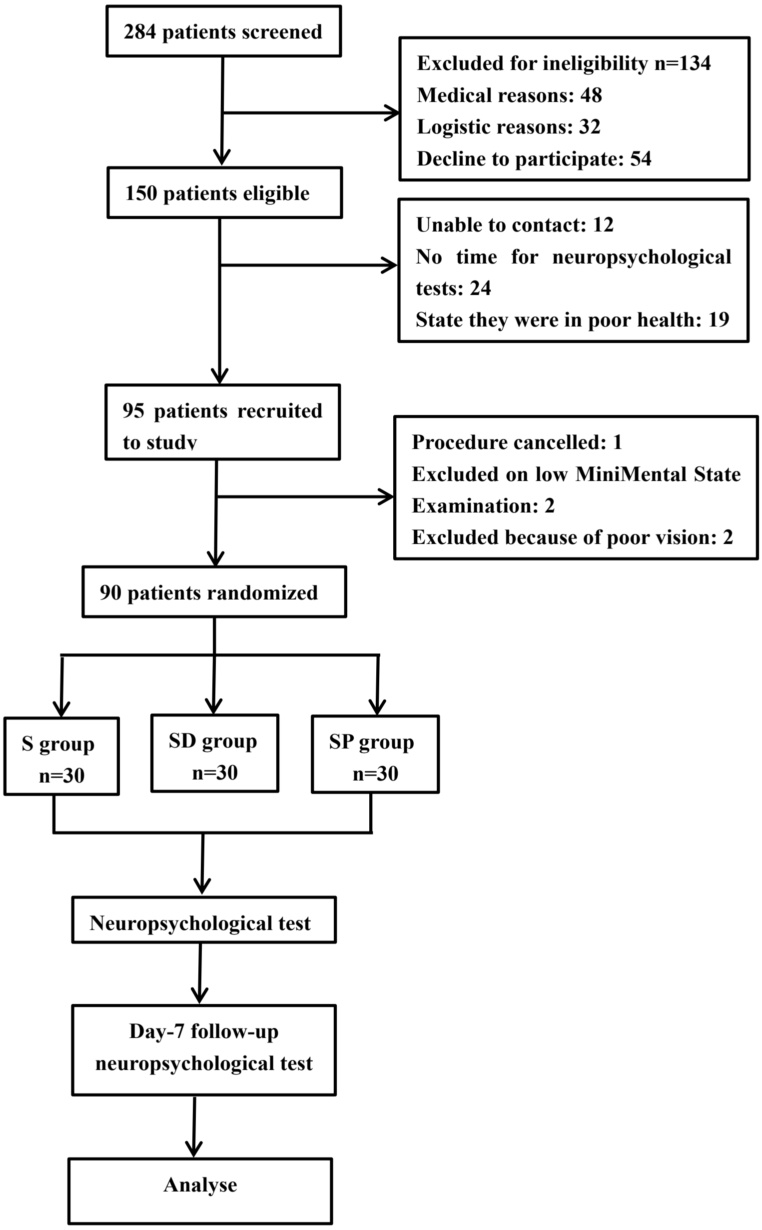

Figure 1: Study flow.

Table 1: Description of neuropsychological tests.

Psychometric test	Description
HVLT	Anterograde verbal learning and memory assessment.
HVLT Delayed Recall Test	Assess delayed verbal learning and memory function.
BVMT	Assessment of visual memory.
BVMT Delayed Recall Test	Assess delayed visual memory function.
TMT	Examine executive functioning and cognitive processing speed.
FSDT	Test measures short-term auditory memory, sequencing, and concentration.
BSDT	Measures working memory and concentration.
SDMT	It measures attention and speed of information processing.
JLOT	It assesses visuospatial ability, requires minimal motor involvement.
STROOP	It measures selective attention, cognitive flexibility and processing speed and it is used as a tool in the evaluation of executive functions.
VFT	Exploration of semantic memory.

Measurement of blood samples

Venous blood at each time-point were used to analysis the expression of C-reactive protein (CRP), IL-1β, IL-6, IL-2R, IL-8, and tumor necrosis factor (TNF-α) as representative systemic inflammatory mediators 24 h preoperatively and postoperatively, respectively. Blood samples obtained from different group were placed in heparin anticoagulant tubes and then plasma samples were separated and stored at −80°C after centrifuged at 2,000 × *g* for 10 min at 4 °C. Plasma levels of the following cytokines were measured: IL-1β, IL-6, IL-2R, IL-8, CRP, and TNF-α (Meikang Biotech).

Statistical Analyses

All data are expressed as the mean ± SEM. Data analysis was performed using EpiData v3.1. Differences among groups were evaluated using the Student's *t*-test and a one-way ANOVA for continuous variables and the $\chi 2$ or Fisher's exact tests for categorical variables. A value of $P < 0.05$ was considered significant. For multiple comparisons among groups, the Bonferroni correction was applied. All statistical analyses were done using SAS v9.1.3 (SAS Institute, Cary, NC, USA).

Results

Study population

Screening of 284 individuals for LM resulted in 90 patients for randomization **(Figure 1)**. Recruitment was slow because of geographic, medical exclusions and a reluctance to have a neuropsychological test. There were no significant differences in height, age, body weight, ASA classification, education, duration of anesthesia and surgery, or estimated blood loss in the each group **(Table 2)**. The postoperative course, including the ramsay score and visual analog scale (VAS) score, and preoperative Mini Mental State Examination score were comparable in all groups.

Cognitive outcome

The dysfunction in attention, memory, and visuospatial skills were evaluated by designed battery of neuropsychological tests. The change in scores of the 11 cognitive tests from all subjects was obtained.

Neuropsychological data of baseline and 7 days of follow-up were measured for the 90 patients with complete and matched test (**Table 3**). The results showed no significant difference in all the neuropsychological tests except that the HVLT-R1 and Digit Span test showed a statistically significant (but probably not a clinically significant) improvement in the SD group. No patients had a Z-score >1.96 in the three treatment groups. However, there was a significant difference in HVLT, Digit Span test in Z score among the three treatment groups from baseline to follow-up **(Table 3)**.

Inflammatory cytokines

The baseline plasma values of the cytokines TNF, IL-2R, IL-1β, IL-6, CRP, and IL-8 were comparable in the three groups **(Table 4)**. However, the concentrations of IL-6 and CRP were increased significantly 24h postoperation in all three groups **(Figure 2A)**. Compared with the S group 24 h after surgery, the IL-6 level was much lower in the SD group **(Table 4** and **Figure 2B)**.

Discussion

POCD may manifest impairment of the working memory, long-term memory and information processing, attention or cognitive flexibility. It can affect the quality of life, social independence and mortality. It may last for weeks or months, there may be no solution in a small proportion of those affected [14].

It has been reported that inhalational anesthetic drugs could lead to neuronal apoptosis in animal models, result in learning ability and memory decline after anesthesia. Sevoflurane, with a low blood/gas ratio is used more widely than other inhalation anesthetics for the induction and maintenance of general anesthesia during surgery with fast onset and recovery and low pungency [18-20]. Studies have shown sevoflurane-induced cognitive impairment or improvement in adult mice [12]. Liu et al. found that inhalation anesthesia might exert dural effects on cognitive function depending on the concentration and duration [13]. Human studies showed that inhalational anesthesia was easier to cause POCD than intravenous anesthesia in elder patients undergoing major surgery [14]. We found that, compared with the sevoflurane group, female middle-aged patients in the sevoflurane plus dexmedetomidine group showed better results in HVLT and the Digit Span test. POCD did not occur in all the three groups, which we speculated that middle-aged female patients were not as sensitive as elderly patients in neuropsychological tests.

Table 2: Demographics of patients.

Variables	S group (n=30)	SD group (n=30)	SP group (n=30)	*P* value
Age (year)	43.71 ± 10.78	46.42 ± 10.76	48.21 ± 10.30	0.448
Gender (Female)	30	30	30	
Height (cm)	158 ± 8.78	160 ± 5.56	159 ± 9.88	0.556
Weight (kg)	60.58 ± 7.34	58.89 ± 10.79	62.88 ± 11.58	0.437
Body mass index	24.3 ± 3.8	23.3 ± 4.5	24.8 ± 5.2	0.563
Education background				0.217
<6 years (%)	0 (0%)	0 (0%)	2 (10.5%)	
6-9 years (%)	5 (29.4%)	6 (31.6%)	2 (10.5%)	
9-12 years (%)	3 (17.6%)	7 (36.8%)	7 (36.8%)	
>12 years (%)	9 (52.9%)	6 (31.6%)	8 (42.1%)	
Hypertension	1	2	2	0.667
COPD	0	0	0	-
Diebetes	0	0	1	0.455
MMSE	29.65 ± 0.79	29.95 ± 0.23	29.79 ± 0.54	0.276
Intraopertivet datas				
Operation duration	116.76 ± 50.37	141.32 ± 52.14	100.79 ± 63.08	0.088
Anesthesia duration	138.82 ± 55.72	168.95 ± 62.02	122.11 ± 64.86	0.067
Bis	41.53 ± 4.63	39.95 ± 7.10	43.21 ± 3.84	0.186
Blood loss	87.06 ± 81.76	116.32 ± 118.00	56.58 ± 68.19	0.146
Postoperative datas				
VAS	3.24 ± 1.30	3.63 ± 1.61	3.47 ± 1.78	0.754
Ramsay score	2.21 ± 0.55	2.35+0.24	2.43 ± 0.67	0.688

The results also show that the plasma concentrations of IL-6 and CRP in all treatment groups were increased after surgery. Meantime, compared with the sevoflurane group, the level of IL-6 protein in the sevoflurane plus dexmedetomidine group was much lower. These results suggested that dexmedetomidine may prohibit IL-6 release. Studies [16] have shown that dexmedetomidine in elderly patients after surgery may provide neuroprotection, but the related mechanism of the nerve protective effect is unclear. It is well-known that anesthesia and surgery trauma, combined with primary disease require surgery and commodities, constitute a source of stress of the patients, which is also considered to be responsible for POCD [2]. The interaction between neuroendocrine and sympathetic nervous systems promotes the release of inflammatory factors, particularly the non-specific inflammatory reaction of the nervous system, which probably promotes POCD development in elderly surgical patients [3-9]. It has been demonstrated that the inflammatory and immunological responses were associated with the central nervous system diseases [21,22]. Anesthetic methods and the anesthetics themselves could also trigger the release of stress hormones and cytokines beside surgery. Cytokine such as IL-1β, IL-6 and TNF-α can cross the blood–brain barrier and cause an inflammatory reaction in the central nervous system by promoting the permeability of brain cells, which affects the functioning of synaptic connections, resulting in damage to cognitive function.

Studies showed that the expression of CRP, TNF-α, IL-6 and IL-1 were increased significantly postoperatively in elderly hip-fracture patients, particularly IL-6 have been observed to increase significantly in mental impaired patients [23,24]. IL-6 plays an important role in synapse formation and high level of IL-6 has been reported to inhibit synaptic function. Hippocampal neurogenesis in the dentate gyrus has been reported to be decreased by 63% in adult transgenic rats overexpressing IL-6 from their astrocytes [25]. Administration of a neutralizing antibody for IL-6 also significantly improves long-term potentiation (LTP) and spatial memory in rats. The influence of IL-6 on LTP generation and its inhibitory effects on learning and memory suggest it is likely to also have a role in POCD [26].

Laparoscopic surgery is considered to be "minor" surgery compared with major traumatic surgical procedures such as open thoracotomy or orthopedic surgery. Kang, *et al.* [27] recently reported that LC can also induce the inflammatory mediator's release. In this pilot study, we also found that IL-6 levels increased less obviously

Table 3: Changes between baseline and 7 days after surgery in neurocognitive function tests.

Variables	S group	SD group	SP group	*P* value
HVLT-R1				
Baseline	21.24 ± 3.78	22.68 ± 4.45	24.47 ± 4.87	0.097
ΔPOD7	0.44 ± 4.69	1.90 ± 3.03	-1.16 ± 2.69	0.034
Z score	-0.34 ± 1.01	-0.02 ± 0.65	-0.68 ± 0.58	0.034
HVLT-R2				
Baseline	7.65 ± 1.80	8.42 ± 3.13	8.84 ± 2.09	0.338
ΔPOD7	0.00 ± 0.97	-0.63 ± 2.63	-0.68 ± 1.38	0.490
Z score	-0.92 ± 0.74	-1.41 ± 2.02	-1.45 ± 1.06	0.490
BVMT-R1				
Baseline	23.82 ± 5.91	26.79 ± 5.81	24.47 ± 5.42	0.263
ΔPOD7	1.38 ± 4.51	-0.05 ± 1.99	0.79 ± 3.49	0.514
Z score	-3.42 ± 2.48	-4.20 ± 1.64	-3.74 ± 1.92	0.514
BVMT-R2				
Baseline	9.35 ± 2.52	10.32 ± 2.45	10.16 ± 1.98	0.424
ΔPOD7	0.38 ± 1.59	-0.58 ± 1.07	-0.16 ± 1.92	0.209
Z score	-0.33 ± 1.22	-1.06 ± 0.82	-0.74 ± 1.48	0.209
TMT				
Baseline	44.94 ± 16.05	48.89 ± 22.15	41.26 ± 15.55	0.441
ΔPOD7	-3.31 ± 3.48	-2.95 ± 9.81	-3.26 ± 7.92	0.988
Z score	0.94 ± 0.31	0.97 ± 0.86	0.95 ± 0.70	0.988
FSDT				
Baseline	4.29 ± 0.85	4.32 ± 0.82	4.05 ± 0.85	0.570
ΔPOD7	-0.19 ± 0.66	0.32 ± 0.67	-0.21 ± 0.42	0.013
Z score	-0.88 ± 0.74	-0.32 ± 0.75	-0.91 ± 0.47	0.013
BSDT				
Baseline	2.41 ± 0.62	2.74 ± 0.73	2.68 ± 0.89	0.400
ΔPOD7	-0.19 ± 0.40	0.21 ± 0.71	-0.32 ± 0.67	0.032
Z score	-0.26 ± 0.56	0.30 ± 1.00	-0.44 ± 0.95	0.032
SDMT				
Baseline	47.29 ± 15.24	42.58 ± 17.09	42.16 ± 17.11	0.569
ΔPOD7	0.19 ± 5.15	2.63 ± 9.11	0.79 ± 7.44	0.601
Z score	0.36 ± 0.61	0.65 ± 1.08	0.43 ± 0.89	0.601
JLOT				
Baseline	16.65 ± 2.15	16.05 ± 2.42	16.79 ± 1.93	0.548
ΔPOD7	0.44 ± 1.86	0.21 ± 1.48	-0.21 ± 1.27	0.449
Z score	0.12 ± 0.97	0.01 ± 0.77	-0.21 ± 0.66	0.449
STROOP				
Baseline	55.24 ± 11.79	58.84 ± 18.25	56.11 ± 14.30	0.754
ΔPOD7	1.44 ± 3.16	-0.32 ± 5.55	1.21 ± 5.90	0.534
Z score	-1.33 ± 0.44	-1.58 ± 0.77	-1.36 ± 0.82	0.534
VFT				
Baseline	19.76 ± 4.59	22.53 ± 7.25	19.58 ± 5.53	0.245
ΔPOD7	0.06 ± 1.98	0.84 ± 2.27	0.84 ± 1.74	0.435
Z score	-0.87 ± 0.51	-0.66 ± 0.59	-0.66 ± 0.45	0.435

in the sevoflurane plus dexmedetomidine than sevoflurane-alone and sevoflurane plus propofol groups, also with better cognitive result. Thus, for middle-aged female patients, we speculate that inhibition of IL-6 release may be important for reduction of the risk of postoperative cognition complications. The possible contributory factors include the age, physical status and concomitant diseases of patients.

Sieber, *et al.* [28] reported that the use of light propofol sedation (BIS >80) reduced the prevalence of postoperative delirium by 50% compared with deep sedation (BIS ≈ 50). The results showed that BIS values were similar among the three groups. So, the observed differences in neurocognitive tests among the three groups were not due to differences in the depth of general anesthesia.

Table 4: Baseline and 24h post operation changes of cytokine data.

Variables		S group	SD group	SP group	*P* value
IL-1β (pg/mL)	Baseline	<5	<5	<5	-
	24h follow-up	<5	<5	<5	-
IL-6 (pg/mL)	Baseline	6.67 ± 3.27	8.03 ± 2.14	7.66 ± 3.22	0.433
	24h follow-up	36.06 ± 17.03	19.93 ± 10.04	39.99 ± 19.39	0.001
TNF-α (pg/mL)	Baseline	6.91 ± 3.11	7.06 ± 2.68	5.58 ± 3.1	0.289
	24h follow-up	7.91 ± 3.77	7.36 ± 3.78	5.97 ± 1.73	0.265
CRP (mg/L)	Baseline	8.12 ± 4.22	8.89 ± 3.24	9.21 ± 3.87	0.337
	24h follow-up	24.20 ± 18.35	18.37 ± 14.14	36.79 ± 19.27	0.163
IL-2R (U/mL)	Baseline	323.63 ± 133.60	355.67 ± 210.46	305.12 ± 120.23	0.554
	24h follow-up	355.63 ± 125.70	370.92 ± 222.16	328.93 ± 125.18	0.796
IL-8 (pg/mL)	Baseline	10.55 ± 5.67	14.33 ± 22.28	13.27 ± 8.98	0.412
	24h follow-up	9.43 ± 3.27	19.77 ± 25.78	10.77 ± 7.35	0.283

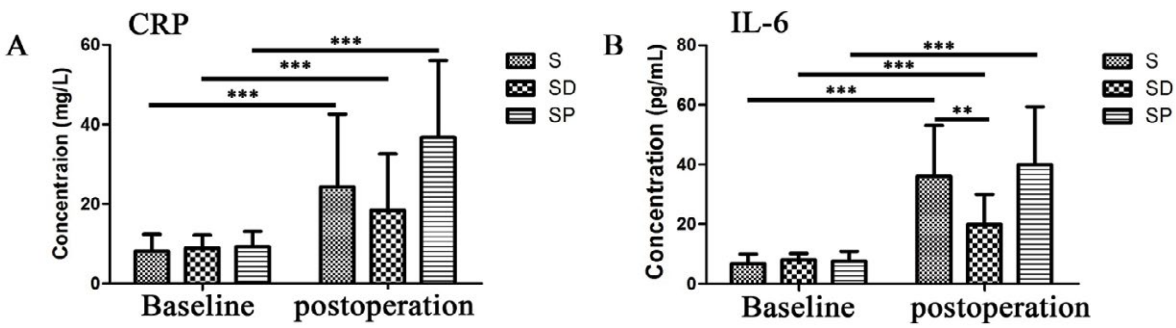

Figure 2: Concentration of IL-6 and CRP at baseline and 24 h after surgery. Expression of CRP and IL-6 was unregulated postoperatively. Relative expression of IL-6 between the S group and SD group was significantly different.
**P<0.01, ***P<0.001.

Pain is another factor that can enhance the systemic inflammatory response and increase serum levels of cytokines [29]. In the study, the possible impact inflammatory response related pain could be ruled out. The difference in the amount of intraoperative remifentanil was not significant among the groups. And the differences in VAS scores and requirements among the groups were also not significant **(Table 2)**.

The limitations of our study were the sample size and the POCD we investigated were restrained to 1 week. It is, therefore, unclear if the altered cognitive function was related to anesthetics. Thus, our research serves as a pilot study to establish a system to further determine the potential differences of sevoflurane only and sevoflurane plus propofol or dexmedetomidine on human cognitive function. Further study will add more subjects and follow-up time.

Conclusion

In this randomized clinical pilot trial, LM female middle-aged patients exposure to low concentration sevoflurane plus dexmedetomidine had better cognitive function than patients with high concentration sevoflurane, which may be related to lower release of IL-6 postoperation.

Highlights

- We selected middle-aged participants with laparoscopic myomectomy under general anesthesia and allocated them to high concentration sevoflurane, low concentration sevoflurane plus dexmedetomidine or plus propofol.
- We detected the inflammatory cytokines and neurocognitive tests pre and post operation in three groups.
- Patients anesthetized with low concentration sevoflurane plus dexmedetomidine had lower levels of IL-6 and better cognitive function compared with patients with high concentration sevoflurane.

Conflict of Interest and Source of Funding

The authors have no conflict of interest to declare pertaining to this work. Our study had no external funding sources. This study was supported by National Natural Science Foundation (81600934), Natural Science Foundation of Shanghai, China (16ZR1432200), Medicine guidance of Science and Technology Commission of Shanghai Municipality (16411967700), awarded to Jianhui Liu. The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

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Conflicts of Interest

We have no financial interest or conflict of interest in association with this work.

Substantial Contribution

Jianhui Liu (design of the work and paper preparation); Li Cai (analysis), Junjun Yang and Yanhong Zhao (acquisition and interpretation of the data); Gang Guo and Heng Wu (drafting the work); Xiaoqing Zhang (design of the work).

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