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Original Article

Effect of Anesthetic Agents on Cognitive Function and Peripheral Inflammatory Biomarkers in Young Patients Undergoing Surgery for Spine Disorders

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Abstract

Background: Exposure to anesthesia has been postulated to affect the cognitive function by inciting central nervous system inflammation. Hence, we planned to compare the psychometrical effects of anesthetic agents propofol, desflurane, or sevoflurane on postoperative cognitive function and also measure the change in concentration of serum S-100β, interleukin (IL)-6, and tumor necrosis factor (TNF)-α to look for the contribution of systemic inflammation. **Methods:** This was a prospective, double-blind, randomized controlled trial. Intuitional ethical committee approval and consent from patients were obtained. We enrolled 66 patients, allocated into three equal groups to receive either sevoflurane (n = 22), desflurane (n = 22), or propofol (n = 22). Standard anesthesia protocol was followed titrated to a bispectral index of 40–60. Patients with preoperative mini-mental state examination ≤23 were excluded. Each patient was assessed thrice with battery of cognitive tests in preoperative period (baseline), after 72 h (early postoperative cognitive dysfunction [POCD]), after 3 months (delayed POCD) of surgery. Serum levels of IL-6, TNF-α, and S-100β were measured preoperatively and 72 h after surgery. **Results:** Mean scores of various psychometric tests improved slightly in early postoperative period which was not statistically significant ($P > 0.5$). In delayed postoperative period, there was significant improvement in scores as compared to baseline ($P < 0.5$) in all the groups. There was nonsignificant change in the levels of biomarkers S-100β, TNF-α, and IL-6 between baseline and postoperative period in all the groups. **Conclusion:** In young patients, there is no effect of anesthesia on postoperative cognitive functions. There is no association of inflammatory markers with respect to the patient's cognitive status.

Keywords: *Anesthetic agents, biomarkers, cognitive function, inflammation*

Introduction

Cognition is the mental process of perception, memory, and information processing that allows a person to have an organized approach for solving problem and making decision.[1] Any impairment in the abovesaid domains can be termed as cognitive dysfunction. It was first described by Bedford in 1955 as "adverse cerebral effects of anaesthesia" in elderly persons.[2] The first largest study was conducted by international studies of postoperative cognitive dysfunction (ISPOCD) group who reported that people over 60 years have 26% and 10% incidence of cognitive dysfunction 1 week and 3 months after surgery, respectively.[3] Initially, it is thought to be a problem in elderly population; but, subsequent studies reported its occurrence in younger populations after surgery and anesthesia. Chung and Assmann[4] described two cases of young patients who suffered serious traffic accidents shortly after undergoing ambulatory surgery. The effect of anesthesia *per se* on cognitive function depends on the pharmacodynamics and kinetics of the particular agents used. As a rule, the shorter the duration of action of the anesthetic agent, the shorter the duration of cognitive impairment in the immediate postoperative period. Till now, there is no definitive evidence for the assumption that anesthesia itself causes postoperative cognitive dysfunction (POCD).[1] Studies done to arbitrate the effect of various anesthetic agents on the incidence of POCD differed in their results, where some reporting better cognitive scores with intravenous agent like propofol while others suggesting better cognitive scores

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with inhalational agents.[5,6] Exact pathogenesis of POCD is still unclear. It has been postulated that inflammation of the central nervous system (CNS) aggravated by anesthesia and surgery can lead to cognitive deterioration postsurgery.[1,7] Exposure of anesthesia and surgical insult have been associated with the increase in the brain concentration of interleukin (IL)-6, leading to neuronal apoptosis. This might aggravate the release of the pro-inflammatory cytokine tumor necrosis factor (TNF)-α. S-100β protein is generally found in the CNS and is considered as specific for CNS, so when encountered in the systemic circulation, it might suggest damage to blood–brain barrier[8] which may result in postoperative cognitive decline.

In a study by Qiao *et al*.[5] where they compared sevoflurane with propofol for POCD, the authors reported significantly lower cognitive scores in sevoflurane group than in the propofol group in early postoperative day; they also observed that TNF-α and IL-6 levels were significantly higher throughout the first postoperative week in those exposed to sevoflurane than propofol.

We could not find any study comparing the effect of three short acting anesthetic agents – propofol, desflurane, and sevoflurane on cognitive functions. Hence, we planned to compare the psychometrical effects of propofol, desflurane, or sevoflurane on postoperative cognitive function as anesthetic agents for maintenance of anesthesia in young and middle-aged patients undergoing spine surgery of duration ≥ 2 h under general anesthesia. We also planned to measure plasma S-100β protein concentration, IL-6, and TNF-α concentration to look for the contribution of systemic inflammation to POCD.

Methods

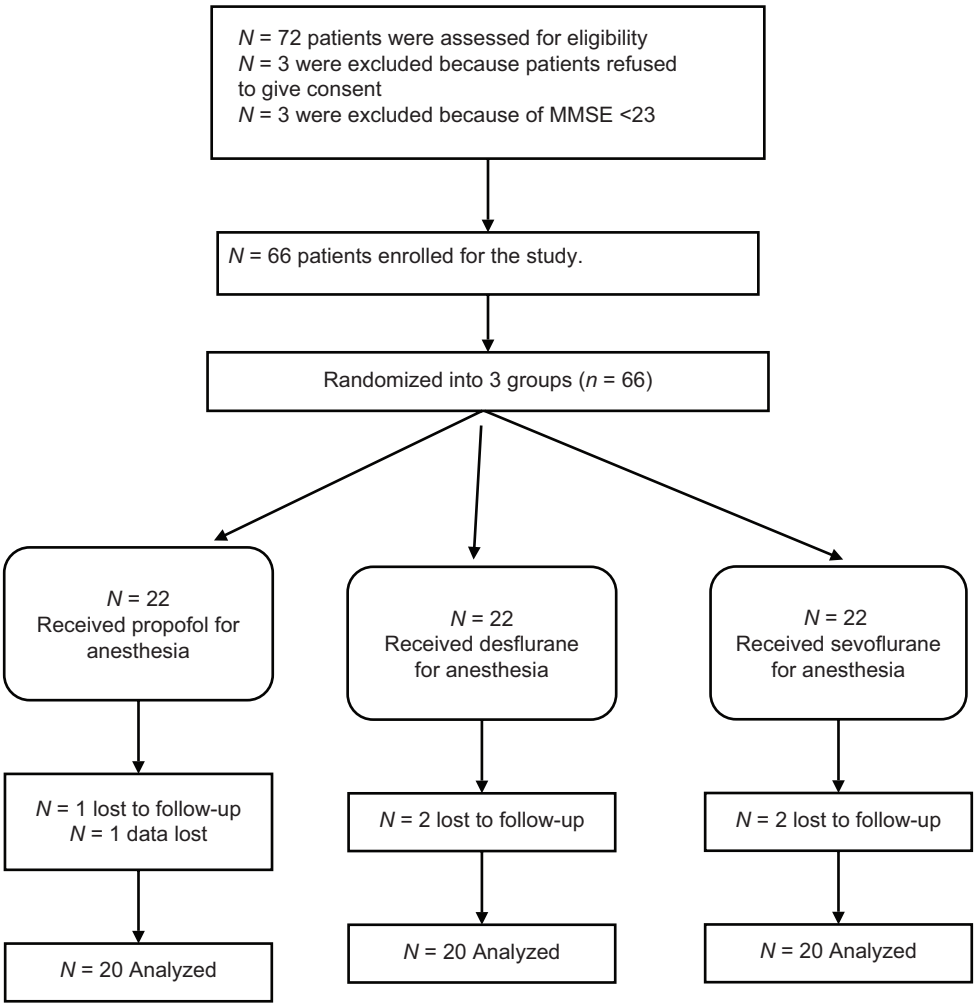
This prospective randomized study got institutional ethics committee approval. Written informed consent was obtained from all the patients. All patients underwent mini-mental state examination (MMSE) test which was used as a screening test to decide whether patient could be included in the study. If MMSE score was ≥23, the patient was included in the study. The following patients were excluded from the study – refusal to consent, cervical spine pathology with upper limb weakness, known psychiatric condition, illiterate, those with significant intraoperative complications, and those who were lost to follow up. Randomization was done by computer-generated random number table, and the random numbers were kept in sequentially numbered opaque envelops. Patients were randomly divided into three groups: Group P (Propofol group), Group S (Sevoflurane group, and Group D (Desflurane group). The group allocation is shown in Flow Chart 1.

A standard anesthesia protocol was followed in each patient. Anesthesiologist anaesthetizing the patient according to the protocol was not involved in the study. All patients were fasted for 8 h according to the standard NPO guidelines (8 h for any solid food and 2 h for clear water). Patients received oral anxiolytic alprazolam (0.25 mg) night before surgery as premedication. Preinduction monitoring included electrocardiogram, noninvasive blood pressure, pulse oximetry (SpO_2), and Bi-spectral index (BIS). Baseline hemodynamic parameters were recorded. Fentanyl was administered intravenously in a dose of 2 μg/kg before induction followed by 2 μg/kg/h as infusion for intraoperative analgesia. Patients in all three groups were induced with Propofol (dose titrated to loss of verbal response) and were intubated after injection vecuronium (0.1 mg/kg) when train of four (TOF) count was zero. Lignocaine 1.5 mg/kg was given 90 s before laryngoscopy to prevent the hemodynamic response to laryngoscopy and intubation. The patients were ventilated with oxygen and air (50:50) by anesthesia workstation (Aestiva 5™ 7900, Datex Ohmeda, USA) to keep the $ETCO_2$ between 35 and 45 mmHg. Propofol, sevoflurane, or desflurane were used to maintain anesthesia according to the group allocation. The dose of anesthetic agents was titrated to keep the BIS value between the confines of 45 and 55. Intra-arterial cannula was put in all the patients for invasive blood pressure monitoring (IBP). Intraoperatively, patients were monitored for heart rate, IBP, SpO_2, neuro-muscular transmission monitoring (NMT), temperature, BIS, and urine output. Hemodynamic parameters, i.e., heart rate and mean arterial pressure were kept between 20% of the baseline value. Toward the end of surgery, fentanyl infusion was discontinued at the beginning of skin closure whereas the maintenance agents were discontinued at the end of skin closure. Toward the end of surgery, local surgical site was infiltrated with bupivacaine 0.25% to provide postoperative analgesia keeping in mind not to exceed dose of bupivacaine more than 2 mg/kg to prevent any toxic side effect. Effect of paralyzing agent was reversed with a combination of neostigmine 50 μg/kg and glycopyrrolate 10 μg/kg when the TOF count was four and TOF percent was 40%. Trachea was extubated when the patients had adequate tidal volume, regular respiration, TOF >90%, and were able to respond to verbal commands. Patients were followed up for 72-h postsurgery. In postoperative study period, all patients received analgesic drugs paracetamol (1 g) 8 hourly and diclofenac (75 mg) 8 hourly; alternately, morphine (0.05 mg/kg) was given as rescue analgesic to maintain the numeric rating scale score <4.

Assessment of cognitive function

Each patient was assessed thrice for cognitive function:

i. In preoperative period to know the baseline values
ii. 4th day of surgery to assess for early POCD
iii. After 3 months of surgery and anesthesia exposure to assess delayed POCD.



Flow Chart 1: Consort diagram

The battery of cognitive tests to assess cognitive functions included the following

i. Montreal cognitive assessment (MOCA) to assess visuospatial/executive functions, naming, attention, language, abstraction, recall (delayed) and orientation
ii. Hopkin's verbal learning test (HVLT) to assess verbal memory. Total number of words recalled during three trials were taken for immediate recall, words recalled after 20 min were taken for delayed recall, and number of true positive words recognized from a set of words were taken as a measure for recognition
iii. Digit span test to assess attention. It consisted of three parts: digit forward, digit backward, and total score
iv. Controlled oral word association test to assess fluency. Score consisted of two domains, total number of words and average words.

Level of biomarkers

The levels of biomarkers: S-100β protein, plasma (IL)-6, and (TNF)-α were assessed. Blood samples were collected in vacutainers before exposure to anesthesia (as baseline values) and 4th day postsurgery (related to early POCD). After allowing the samples to clot at room temperature, the clotted blood in the plain vacutainers were centrifuged at 2000 rpm for 15 min to separate out the serum. Serum was pipetted off into cryovials. All samples were stored at −80°C immediately till analysis. At the end of study, all the samples were analyzed for level of biomarkers using a quantitative ELISA kit (Genxbio Health Sciences Pvt., Ltd.) with precoated antigen wells and a double-antibody sandwich technique.

Data collection

In the preoperative period, data collected were demographic variables (age, sex, ASA status, educational status, and segments of spine involved), battery of cognitive tests to assess the baseline cognitive functions, and the baseline values of the inflammatory biomarkers.

In the intraoperative period, hemodynamics parameters such as heart rate, mean blood pressure, SpO_2, and end-tidal concentration of carbon dioxide were assessed.

In the postoperative period, battery of cognitive tests was repeated on 4th day of surgery to assess early cognition and after

3 months to assess delayed cognition. Furthermore, levels of inflammatory biomarkers were assessed on 4th day of surgery.

Statistical analysis

All observations were recorded in a standardized data collection sheet and analyzed statistically. The statistical analysis was carried out using Statistical Package for Social Sciences (SPSS Inc., Chicago, IL, USA, version 22.0 for Windows). Mean were calculated for all quantitative variables. For measures of dispersion, standard deviation or standard error were calculated. Qualitative or categorical variables were described as frequencies and proportions. Appropriate statistical tests were applied for all variables, and $P < 0.05$ was considered as statistically significant.

Results

In all the three groups, the demographic and intraoperative data such as age, sex, ASA grade, presence or absence of any comorbidities, educational status, segment of spine involved, position during surgery, anesthesia duration, and surgery duration were comparable [Table 1].

Cognitive tests

Montreal cognitive assessment

Preoperative MOCA scores in all groups were comparable (P = 0.294) [Table 2a, b and Figure 1].

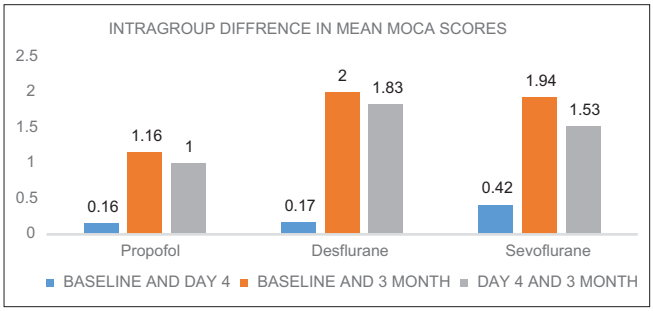


Figure 1: Intragroup difference in mean MOCA scores

At 4th day, mean MOCA score was slightly higher in all the three groups as compared to baseline values. (Propofol – 24.89 ± 3.78, desflurane – 22.72 ± 3.461, and sevoflurane – 23.58 ± 4.538). However, the improvement was not significant statistically. It was also observed that 3 months following surgery, mean scores were improved significantly from baseline value in all the three groups with greater improvement seen in desflurane and sevoflurane group.

Hopkin's verbal learning test

Baseline values in total words were comparable in all the three groups [Table 3a, b and Figure 2]. We found that the scores improved from baseline to day 4 which was not significant in propofol and desflurane group but was statistically significant in sevoflurane group (P = 0.008). Three months following surgery, mean score was improved significantly from baseline value in all the three groups with the highest improvement seen in sevoflurane group. Similarly, delayed recall scores were found to be improved significantly in desflurane and sevoflurane group between baseline and day 4 while assessment at 3 months of surgery revealed significantly higher score in all the three groups. There was no difference in true positive score in any of the groups at any point of time.

Digit span test

We found that mean value of all the three domains in all the groups was comparable at all the time points [Table 4a, b and Figure 3]. In digit forward domain, there was slight improvement in score in all the groups between baseline and day 4 which was not significant; but, there was significant improvement in scores between baseline and 3 months in propofol and sevoflurane group (P = 0.012 and 0.036, respectively) which was not seen in desflurane group. Similarly, in digit backward domain, there was no significant changes between baseline and day 4 in all the groups, whereas there was significant improvement

Table 1: Demographic data and intraoperative parameters

	Propofol	Desflurane	Sevoflurane	*P*
Age (years), mean±SD	37.28±10.35	33.56±11.96	38.58±10.64	0.36[α]
Sex				
Male/female (%)	78/22	78/22	63/37	0.51[β]
Educational status				
<12/>12 years (%)	44/66	67/33	63/37	0.48[β]
ASA status				
ASA1/ASA2 (%)	94/6	89/11	94/6	0.74[β]
Segment of spine involved				
Single/multi (%)	94/6	83/17	89/11	0.65[β]
Position				
Prone/others (%)	94/6	100/0	89/11	0.56[β]
Anesthesia time (min), mean±SD	177.22±35.98	172.22±44.82	181.05±26.85	0.76[α]
Surgical time (min), mean±SD	141.67±35.48	139.44±38.075	142.11±30.29	0.97[α]

$P \leq 0.05$ was considered significant. [α]Data analyzed using One-Way ANOVA, [β]Data analyzed using Pearson Chi-square test. SD – Standard deviation

in scores between baseline and 3 months in all the groups (P = 0.010, 0.048, and 0.004, respectively). In total score domain, there was significant improvement in scores between baseline and 3 months in all the groups (0.000, 0.008, and 0.000, respectively).

Controlled oral word association test

In propofol group, there was slight decrease in scores in both total and average domains between baseline and day 4; but, the difference was not significant whereas in desflurane and sevoflurane group, there was slight improvement which was not significant statistically [Table 5a, b and Figure 4]. In all the groups, there was significant improvement in scores between baseline and 3 months with best score observed in sevoflurane group.

Serum biomarkers

S100b

In all the three groups, there was slight increase in the values of biomarkers levels between baseline and day 4 which was not significant (P = 0.705, 0.682, and 0.892, respectively) [Table 6 and Figure 5].

Interleukin 6

In all the three groups, there was slight increase in the values of biomarkers levels between baseline and day 4 which was not significant (P = 0.279, 0.074, and 0.606, respectively) [Table 6 and Figure 5].

Tumor necrosis factor alfa

In all the three groups, there was slight increase in the values of biomarkers levels between baseline and day 4 which was not significant (P = 0.566, 0.329, and 0.594, respectively) [Table 6 and Figure 5].

Discussion

Cognitive deterioration is a widely debated complication after surgery and exposure to anesthetic agents and POCD after surgery, and anesthesia is considered to affect mostly the elderly patients undergoing longer duration surgery. Patients posted for cardiac surgery under cardiopulmonary bypass also found to have POCD.[9]

Table 2a: Intergroup mean montreal cognitive assessment scores

MOCA (mean±SD)	Propofol	Desflurane	Sevoflurane	*P*
Baseline	24.72±4.07	22.56±3.98	23.16±4.62	0.294
Day 4	24.89±3.78	22.72±3.46	23.58±4.53	0.265
3 months	25.89±4.02	24.56±3.63	25.11±3.88	0.583

Data analyzed using One-way ANOVA. P<0.05 was considered significant. MOCA – Montreal cognitive assessment, SD – Standard deviation

Figure 2: Intragroup difference in mean Hopkin's verbal learning test scores

Table 2b: Intragroup difference in mean montreal cognitive assessment scores

	Baseline and day 4	*P*	Baseline and 3 months	*P*	Day 4 and 3 months	*P*
Difference in mean in propofol group	0.16	1.00	1.16	0.040*	1.00	0.059
Difference in mean in desflurane group	0.17	1.00	2.00	0.000*	1.83	0.000*
Difference in mean in sevoflurane group	0.42	0.84	1.94	0.000*	1.53	0.000*

Data analyzed using repeated measure ANOVA. *P≤0.05 was considered significant

Most of the previous studies were done in elderly patients undergoing surgery; but, there are very few studies which have been done in relatively younger age group. Two major studies in younger age group patients were done by ISPOCD 2 group[10] and by Dokkedal *et al*.[11] In ISPOCD 2, the authors reported that the incidence of cognitive dysfunction at 7th postoperative day was 19.2% among patients and 4.0% among controls while at 3 months after surgery, 6.2% had POCD. In another large study by Dokkedal *et al*.,[11] the authors tried to find the relationship between surgery and anesthesia and the POCD in 8503 twins in middle-aged and elderly age group and could not find any significant difference in cognitive scores in middle-aged patients over controls. Moreover, they found higher cognitive scores in patients with hip and knee arthroplasty. Hence, whether cognitive functions do get impaired after surgery and exposure to anesthesia in younger patients still remains a question to be answered.

In our study, we performed MOCA test to assess the following domains of cognition - visuospatial/executive functions, naming, attention, language, abstraction, recall (delayed), and orientation. Furthermore, we assessed verbal memory, attention, and fluency in detail with other appropriate neuropsychological tests as these domains are thought to be affected in postoperative periods. In our analysis, we did not find any cognitive decline in both

Table 3a: Intergroup Hopkin's verbal learning test

	Propofol	Desflurane	Sevoflurane	*P*
Total HVLT score, mean±SD				
Baseline	23.11±4.702	20.72±4.725	21.26±5.772	0.345
Day 4	24.33±5.594	22.72±5.529	23.84±6.030	0.689
3 months	26.06±5.286	24.67±5.325	25.26±6.100	0.757
Delayed recall, mean±SD				
Baseline	6.83±2.203	6.39±1.787	6.05±2.718	0.583
Day 4	7.50±2.256	7.00±2.058	7.21±2.637	0.813
3 months	8.56±2.093	7.83±2.007	7.63±2.712	0.448
True positives, mean±SD				
Baseline	10.89±1.079	10.56±1.423	10.62±1.677	0.593
Day 4	10.83±1.295	10.67±1.414	10.74±1.558	0.940
3 months	11.22±1.114	10.78±1.478	11.05±1.129	0.563

Data analyzed using One-way ANOVA. $P \leq 0.05$ was considered significant. HVLT – Hopkin's verbal leaning test; SD – Standard deviation

Table 3b: Intragroup differences in Hopkin's verbal learning test

HVLT	Baseline and day 4	*P*	Baseline and 3 months	*P*	Day 4 and 3 months	*P*
Intragroup difference in propofol group						
Total	1.22	0.275	2.94	0.004*	1.72	0.012*
Delayed recall	0.66	0.055	1.72	0.000*	1.06	0.002*
True positive	0.06	1.000	0.33	0.413	0.39	0.207
Intragroup difference in desflurane group						
Total	2.00	0.25	3.94	0.005*	1.94	0.017*
Delayed recall	0.61	0.035	1.44	0.000*	0.83	0.002*
True positive	0.11	0.994	0.22	0.645	0.11	1.000
Intragroup difference in sevoflurane group						
Total	2.57	0.008*	4.00	0.000*	1.42	0.000*
Delayed recall	1.15	0.003*	1.57	0.000*	0.42	0.049*
True positive	0.31	0.412	0.63	0.072	0.31	0.332

Data analyzed using repeated Measure ANOVA. *$P \leq 0.05$ was considered significant. HVLT – Hopkin's verbal learning test

Table 4a: Intergroup digit span test

Digit span test	Propofol	Desflurane	Sevoflurane	*P*
Digit forward, mean±SD				
Baseline	8.17±2.618	7.56±2.093	7.95±2.656	0.755
Day 4	8.44±2.455	7.56±2.202	8.11±2.706	0.555
3 months	8.72±2.539	7.89±2.166	8.53±2.674	0.574
Digit backward, mean±SD				
Baseline	5.56±2.307	3.83±1.790	4.58±2.631	0.085
Day 4	5.78±2.264	3.89±1.605	4.95±2.483	0.039
3 months	6.06±2.100	4.28±1.638	5.37±2.216	0.034
Digit total, mean±SD				
Baseline	13.72±4.586	11.39±3.256	12.53±5.081	0.289
Day 4	14.22±4.400	11.44±3.258	13.05±5.071	0.164
3 months	14.78±4.333	12.17±3.222	13.89±4.760	0.171

Data analyzed using One-way ANOVA. $P<0.05$ was considered significant. SD – Standard deviation

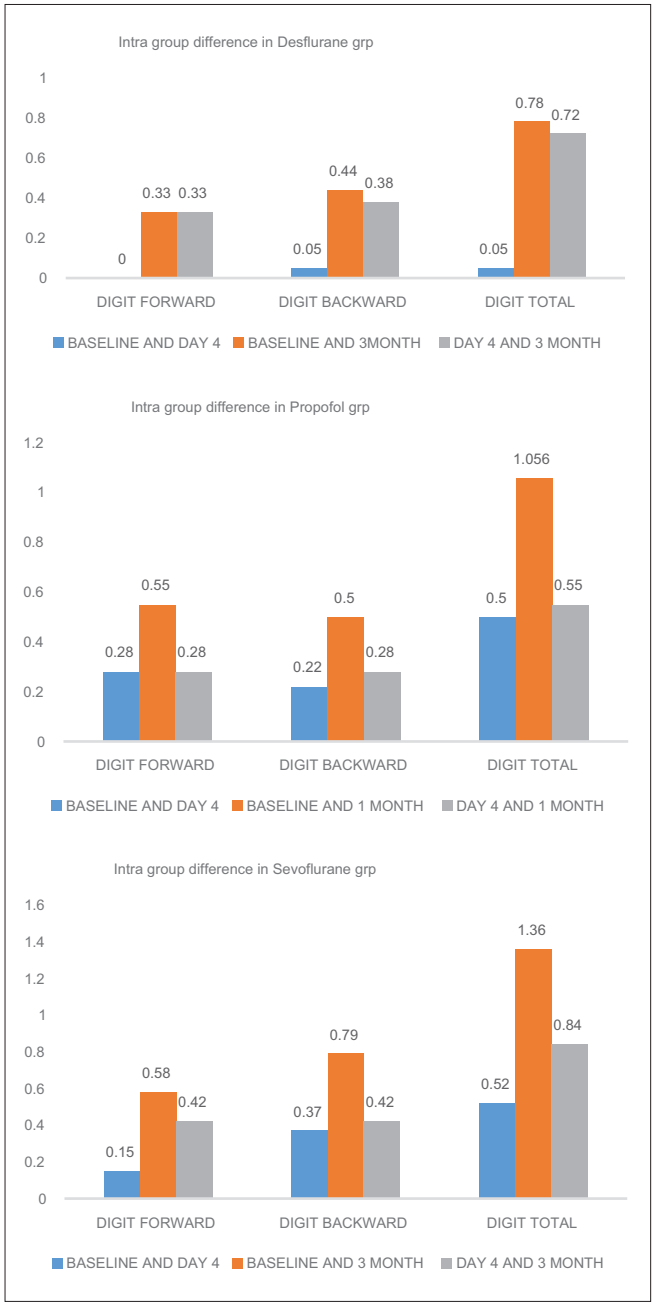


Figure 3: Intragroup difference in mean digit span scores

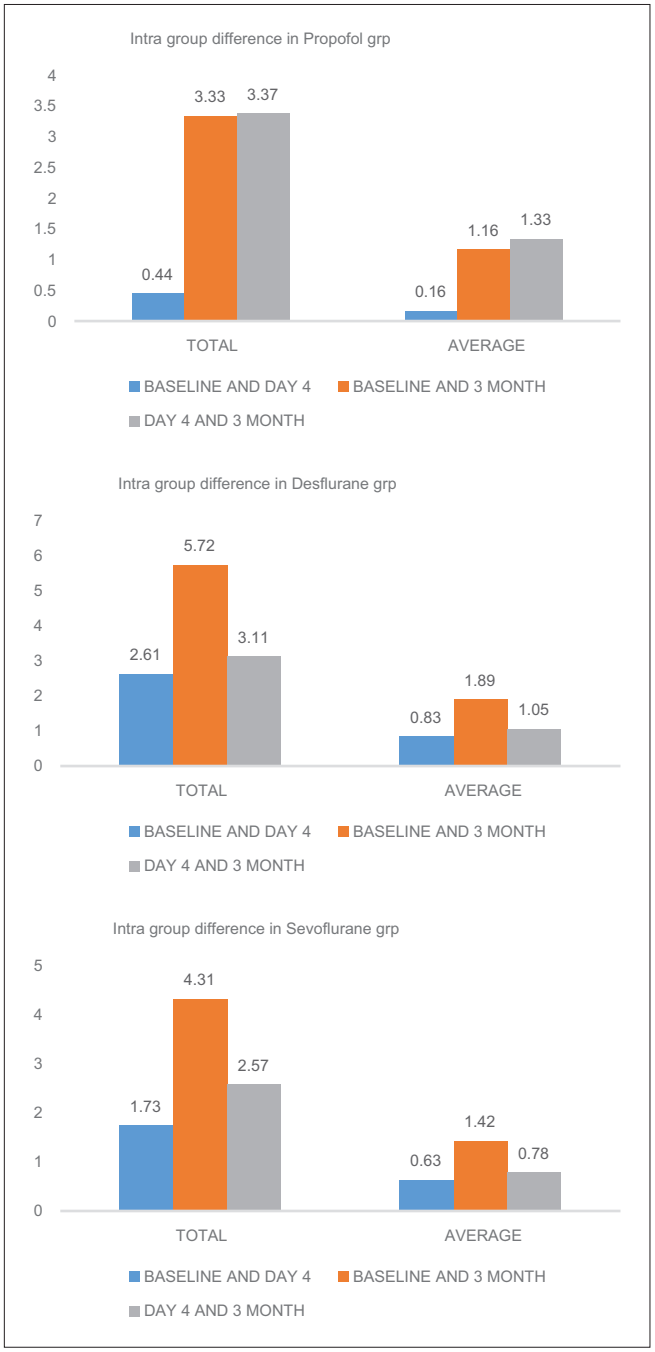


Figure 4: Intergroup mean controlled oral word association test

early and late postoperative period; rather, in our patients, there was slight improvement in cognitive scores in early postoperative period and significant improvement in scores in late postoperative period in all the groups.

Although there are various studies on POCD, it is difficult to compare our results with those studies as majority of the studies were done in elderly patients, and the methodology and group allocations are quite different in all the studies. The results can be explained by the fact that majority of patients with spine disorders present to hospital with pain due to nerve compression. This might have an impact on the cognitive functions before surgery, and successful relief of pain postsurgery might have resulted in improvement of cognitive functions. Studies have shown that preoperative and postoperative pain can affect cognition.[12] Furthermore, the cognitive assessment was done 1 day before surgery, which might falsely have led to lower values due to preoperative anxiety. Patients are usually scared about pain, awareness during surgery, and for unknown life-threatening complications during and after surgery, and the unfamiliar and uncertain environment might have affected their cooperation and concentration to perform these tests. Studies also support the fact that anxiety can affect the cognition.[13]

Table 4b: Intragroup difference in digit span test

Digit span test	Baseline and day 4	*P*	Baseline and 1 month	*P*	Day 4 and 1 month	*P*
Difference in mean in propofol group						
Digit span forward	0.28	0.616	0.55	0.012*	0.28	0.168
Digit span backward	0.22	0.645	0.50	0.010*	0.28	0.168
Digit total	0.50	0.104	1.056	0.000*	0.55	0.041
Difference in mean in desflurane group						
Digit span forward	0	1.000	0.33	0.165	0.33	0.165
Digit span backward	0.05	1.000	0.44	0.048*	0.38	0.044*
Digit total	0.05	1.000	0.78	0.008*	0.72	0.010*
Difference in mean in sevoflurane group						
Digit span forward	0.15	1.000	0.58	0.036*	0.42	0.049*
Digit span backward	0.37	0.207	0.79	0.004*	0.42	0.022*
Digit total	0.52	0.258	1.36	0.000*	0.84	0.006*

Data analyzed using repeated measure ANOVA. *$P \leq 0.05$ was considered significant

Table 5a: Intergroup mean controlled oral word association test

COVAS	Propofol	Desflurane	Sevoflurane	*P*
Total, mean±SD				
Baseline	32.72±10.824	24.61±12.329	29.05±12.747	0.138
Day 4	32.28±12.870	27.22±12.614	30.79±15.017	0.521
3 months	36.06±12.730	30.33±13.092	33.37±15.738	0.474
Average, mean±SD				
Baseline	10.89±3.579	8.22±4.023	9.63±4.072	0.132
Day 4	10.72±4.336	9.06±4.022	10.26±4.942	0.515
3 months	12.06±4.359	10.11±4.324	11.05±5.169	0.460

Data analyzed using one-way ANOVA. *$P \leq 0.05$ was considered significant. SD – Standard deviation; COVAS – Controlled oral word association test

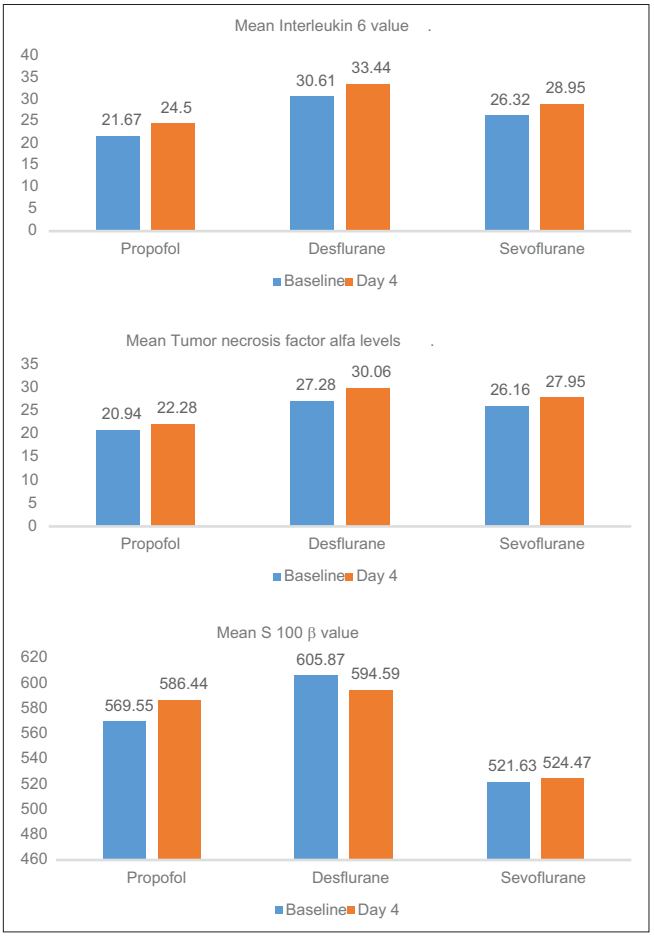


Figure 5: Mean serum biomarker

Moreover, studies have reported higher anxiety scores in younger age group than in elderly groups.[13] Similar to our results, Dokkedal *et al*.[11] also could not find any significant difference in cognitive scores in middle-aged patients over controls, and they also found higher cognitive scores in patients with hip and knee arthroplasty in postoperative period. They concluded by explaining that reduced pain and increased mobility after successful joint replacements and subsequent improvement in level of functioning might have resulted in higher cognitive scores in postoperative period. Hence, they emphasized on the fact that underlying disease could have affected the cognition in postoperative period rather than exposure to anesthesia and surgery. Fischer *et al*.[14] also reported that there was no association between number of general anesthesia and cognitive deficiency in elderly patients aged 75 years or older. Similarly, Monk *et al*.[15] in their study reported that the incidence of cognitive dysfunction was similar between age-matched controls and young and middle-aged patients but was significantly higher in the elderly patients when compared to elderly controls.

Qiao *et al*.[5] used MOCA to compare sevoflurane with propofol for POCD and reported that the scores were significantly poor in sevoflurane group than in the propofol group on the 1st, 3rd, and 7th postoperative days; but, contrary to our study, they assessed cognition in elderly patients in their study, so their results cannot be extrapolated to our study.

Our results were different with respect to results reported by ISPOCD 2 group who have reported incidence of cognitive dysfunction at 7th postoperative day as 19.2%

Table 5b: Intragroup differences in mean controlled oral word association test

COVAS	Baseline and day 4	*P*	Baseline and 3 months	*P*	Day 4 and 3 months	*P*
Difference in mean in Propofol group						
Total	0.44	1.000	3.33	0.006*	3.37	0.000*
Average	0.16	1.000	1.16	0.007*	1.33	0.000*
Difference in mean in desflurane group						
Total	2.61	0.249	5.72	0.006*	3.11	0.001*
Average	0.83	0.288	1.89	0.004*	1.05	0.001*
Difference in mean in sevoflurane group						
Total	1.73	0.204	4.31	0.001*	2.57	0.000*
Average	0.63	0.186	1.42	0.003*	0.78	0.000*

Data analyzed using repeated measure ANOVA. *$P \leq 0.05$ was considered significant. COVAS – Controlled oral word association test

Table 6: Serum biomarkers

Mean S-100β value	Baseline (ng/L)	Day 4 (ng/L)	*P*
Propofol	569.55±416	586.44±443	0.705
Desflurane	605.87±682	594.59±698	0.682
Sevoflurane	521.63±554	524.47±558	0.892
Mean interleukin 6 value	**Baseline (pg/ml)**	**Day 4 (ng/L)**	***P***
Propofol	21.67±41.56	24.50±38.07	0.279
Desflurane	30.61±63.29	33.44±63.83	0.074
Sevoflurane	26.32±38.04	28.95±48.36	0.606
Mean tumor necrosis factor alfa	**Baseline (pg/ml)**	**Day 4 (pg/ml)**	***P***
Propofol	20.94±15.22	22.28±13.16	0.566
Desflurane	27.28±18.06	30.06±18.82	0.329
Sevoflurane	26.16±27.49	27.95±28.47	0.594

Data analyzed using Paired *t*-test. *$P \leq 0.05$ was considered significant

among patients, and after 3 months, the incidence was 6.2% in patients which was not significant.[10] This difference may be due to metacentric nature and inclusion of all types of surgeries. They also acknowledged the fact that due to multicenter assessment, the resources and practice of assessment of the cognitive testing might have varied with center, with some centers reporting higher incidence of POCD. In our study, we included patients who underwent the surgery for spine diseases; so, our study group, type of anesthesia, and surgery were uniform.

Overall, better HVLT scores in our study postoperatively can be explained by confounding factors such as preexisting pain and anxiety which could have affected our preoperative values. The improvement on verbal tasks can also be likely due to practice effects as the tests were repeated in short intervals.[16] Our reported results were similar to findings reported by Ancelin *et al*.[17] in their study done in old individuals undergoing elective orthopedic surgery, in which they found significant recovery in verbal cognitive tasks including immediate and delayed verbal recall in the postoperative periods.

Our results also demonstrated better scores with sevoflurane anesthesia. Goswami *et al*.[6] in their study compared two anesthetic agents – propofol and sevoflurane on cognitive function in the postoperative period and reported that cognitive functions were better in sevoflurane group in the early postoperative period. In another study, Schoen *et al*.[18] mentioned significantly better early memory cognitive functions in sevoflurane compared to propofol in the patients undergoing CABG similar to our study.

Our scores for attention and fluency were found to improve over time in the postoperative period. However, Ancelin *et al*.[17] did not find any difference in attention and fluency scores in patients in postoperative period. This subtle difference might be attributed to the fact that they did their study in elderly population while our study was done in young and middle-aged patients. In spite of methodological differences, our results were similar to few studies which described nonexistence of cognitive decline in younger and middle age group. Mashour *et al*.[19] in their review had pointed out that when patients recover from the insult of surgery, they might revert to their predicted cognitive paths, based on their preoperative trajectories. This could occur when surgery results in decreased pain, decreased inflammation, increased cerebral blood flow, and enhanced ability to function in daily life. Similarly, Seminowicz *et al*.[20] in their study proved that with effective management of chronic low back pain in humans, there is reversal of abnormal brain anatomy and function. They found that with treatment, there was increase in cortical thickness in the left dorsolateral prefrontal cortex, which was found to be thinner before treatment compared with controls. Increased dorsolateral prefrontal cortex thickness correlated with the reduction of both pain and physical disability. Similar findings were also reported by Sato *et al*.[21] in which they reported that there was gain in cerebral white matter fractional anisotropy on diffusion tensor magnetic resonance imaging in postoperative period which correlated with cognitive improvement after surgery for uncomplicated carotid endarterectomy.

Role of inflammatory biomarkers

S-100β is predominantly found in astrocytes, glial, and Schwann cells in the CNS; so, any rise in its value may reflect neuroinflammation and injury which we may

be related to any cognitive decline in the postoperative period.[22] TNF-α is released by monocyte and macrophages which in turn promotes the release of other inflammatory mediators and pro-inflammatory cytokines such as IL-6, thus starting the inflammatory cascade reaction.[23] The role of IL-6 was discovered as a regulator for synapse formation, and local high concentration was found to inhibit synaptic function.[24] Administration of a neutralizing protein for IL-6 considerably improves long-term potentiation (LTP) and memory in rats. The impact of IL-6 on the LTP, and its inhibitory consequences on learning and memory formation describes its role in development of POCD.[25] Hence, we decided to assess levels of S-100β, IL-6, and TNF a as surrogate biomarker of cognitive function. Our study revealed that there was slight increase in the levels of all the biomarkers in early postoperative period which was not statistically significant. We could not find any association with cognitive functions. The slight increase in the concentration of biomarkers in our study might be due to the disease and surgery itself. Various studies have varied in their results with respect to use of inflammatory biomarkers as test for cognitive functions. Qiao *et al*.[5] in their study had reported that there was significant increase in the concentration of S-100β, IL-6, and TNF a in postoperative period in sevoflurane group as compared to propofol group which correlated with their higher incidence of POCD in sevoflurane group. This might be due to the fact that they had done their study in elderly patients who are posted for surgery for colorectal cancer. The age group and the nature of disease itself might have resulted in higher concentration in postoperative period. Similarly, Peng *et al*.[26] in their meta-analysis on the role of peripheral inflammatory marker on POCD stated that high concentrations of S-100β and IL-6 are definitely correlated with the POCD, but also acknowledged that there might be some sources of heterogeneity, including assay methodology, age, gender, and medical comorbidity which could have affected the results. Moreover, most studies in their meta-analysis had reported very large standard deviations suggesting substantial unexplained interindividual variations. Micha *et al*.[27] could not find any correlation between inflammatory biomarkers and POCD. Similarly, Saleem *et al*.[28] did a meta-analysis and their findings did not support the use of elevations in peripheral inflammatory factors in mild cognitive impairment; similarly, we also did not find any correlation of inflammatory biomarkers with cognitive scores.

Limitations

In our study, we did not have age-matched controls who were not exposed to anesthesia and surgery, which could have given a better idea about the degree of change in cognitive functions. Assessments of cognitive functions were done 12–24 h before surgery; so, our baseline values might have been affected by confounding factors such as pain and preoperative anxiety. Baseline cognitive tests should have been done at least a week before surgery which was not possible in our hospital settings as patients are admitted in our hospital only 24–48 h before surgery. Other important consideration was the practice effect on cognitive scores which should be taken seriously. The cognitive tests should be done in calm and quiet room to avoid any disturbance so that patients could concentrate and cooperate during the test, which was not possible in all the cases.

Conclusion

In young and middle-aged persons undergoing surgery for spine disorders, there is no effect of commonly used shorter acting anesthetic agents on the postoperative cognitive functions. Furthermore, there is no association of inflammatory markers with respect to the patient's cognitive status.

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Conflicts of interest

There are no conflicts of interest.

References

1. Rundshagen I. Postoperative cognitive dysfunction. Dtsch Arztebl Int 2014;111:119-25.
2. Bedford PD. Adverse cerebral effects of anaesthesia on old people. Lancet 1955;269:259-63.
3. Moller JT, Cluitmans P, Rasmussen LS, Houx P, Rasmussen H, Canet J. Long-term postoperative cognitive dysfunction in the elderly ISPOCD1 study. ISPOCD investigators. International study of post-operative cognitive dysfunction. Lancet 1998;351:857-61.
4. Chung F, Assmann N. Car accidents after ambulatory surgery in patients without an escort. Anesth Analg 2008;106:817-20.
5. Qiao Y, Feng H, Zhao T, Yan H, Zhang H, Zhao X, *et al.* Postoperative cognitive dysfunction after inhalational anesthesia in elderly patients undergoing major surgery: The influence of anesthetic technique, cerebral injury and systemic inflammation. BMC Anesthesiol 2015;15:154.
6. Goswami U, Babbar S, Tiwari S. Comparative evaluation of the effects of propofol and sevoflurane on cognitive function and memory in patients undergoing laparoscopic cholecystectomy: A randomised prospective study. Indian J Anaesth 2015;59:150-5.
7. Loepke AW, Istaphanous GK, McAuliffe JJ 3rd, Miles L, Hughes EA, McCann JC, *et al.* The effects of neonatal isoflurane exposure in mice on brain cell viability, adult behavior, learning, and memory. Anesth Analg 2009;108:90-104.
8. Cata JP, Abdelmalak B, Farag E. Neurological biomarkers in the perioperative period. Br J Anaesth 2011;107:844-58.
9. Royse CF, Andrews DT, Newman SN, Stygall J, Williams Z, Pang J, *et al.* The influence of propofol or desflurane on postoperative cognitive dysfunction in patients undergoing coronary artery bypass surgery. Anaesthesia 2011;66:455-64.
10. Johnson T, Monk T, Rasmussen LS, Abildstrom H, Houx P, Korttila K, *et al.* Postoperative cognitive dysfunction in middle-aged patients. Anesthesiology 2002;96:1351-7.
11. Dokkedal U, Hansen TG, Rasmussen LS, Mengel-From J,

Christensen K. Cognitive functioning after surgery in middle-aged and elderly Danish twins. Anesthesiology 2016;124:312-21.
12. Wang Y, Sands LP, Vaurio L, Mullen EA, Leung JM. The effects of postoperative pain and its management on postoperative cognitive dysfunction. Am J Geriatr Psychiatry 2007;15:50-9.
13. Robinson OJ, Vytal K, Cornwell BR, Grillon C. The impact of anxiety upon cognition: Perspectives from human threat of shock studies. Front Hum Neurosci 2013;7:203.
14. Fischer P, Wallner H, Jungwirth S, Weissgram S, Krampla W, Bauer P, *et al.* Cumulative exposure to general anesthesias and cognitive dysfunction at age 75 in the Vienna transdanube aging "VITA" study. J Neuropsychiatry Clin Neurosci 2007;19:21-6.
15. Monk TG, Weldon BC, Garvan CW, Dede DE, van der Aa MT, Heilman KM, *et al.* Predictors of cognitive dysfunction after major noncardiac surgery. Anesthesiology 2008;108:18-30.
16. Goldberg TE, Harvey PD, Wesnes KA, Snyder PJ, Schneider LS. Practice effects due to serial cognitive assessment: Implications for preclinical Alzheimer's disease randomized controlled trials. Alzheimers Dement (Amst) 2015;1:103-11.
17. Ancelin ML, de Roquefeuil G, Scali J, Bonnel F, Adam JF, Cheminal JC, *et al.* Long-term post-operative cognitive decline in the elderly: The effects of anesthesia type, apolipoprotein E genotype, and clinical antecedents. J Alzheimers Dis 2010;22 Suppl 3:105-13.
18. Schoen J, Husemann L, Tiemeyer C, Lueloh A, Sedemund-Adib B, Berger KU, *et al.* Cognitive function after sevoflurane vs. propofol-based anaesthesia for on-pump cardiac surgery: A randomized controlled trial. Br J Anaesth 2011;106:840-50.
19. Mashour GA, Woodrum DT, Avidan MS. Neurological complications of surgery and anaesthesia. Br J Anaesth 2015;114:194-203.
20. Seminowicz DA, Wideman TH, Naso L, Hatami-Khoroushahi Z, Fallatah S, Ware MA, *et al.* Effective treatment of chronic low back pain in humans reverses abnormal brain anatomy and function. J Neurosci 2011;31:7540-50.
21. Sato Y, Ito K, Ogasawara K, Sasaki M, Kudo K, Murakami T, *et al.* Postoperative increase in cerebral white matter fractional anisotropy on diffusion tensor magnetic resonance imaging is associated with cognitive improvement after uncomplicated carotid endarterectomy: Tract-based spatial statistics analysis. Neurosurgery 2013;73:592-8.
22. Tomaszewski D. Biomarkers of brain damage and postoperative cognitive disorders in orthopedic patients: An update. Biomed Res Int 2015;2015:402959.
23. Wan Y, Xu J, Ma D, Zeng Y, Cibelli M, Maze M, *et al.* Postoperative impairment of cognitive function in rats: A possible role for cytokine-mediated inflammation in the hippocampus. Anesthesiology 2007;106:436-43.
24. Vallières L, Campbell IL, Gage FH, Sawchenko PE. Reduced hippocampal neurogenesis in adult transgenic mice with chronic astrocytic production of interleukin-6. J Neurosci 2002;22:486-92.
25. Balschun D, Wetzel W, Del Rey A, Pitossi F, Schneider H, Zuschratter W, *et al.* Interleukin-6: A cytokine to forget. FASEB J 2004;18:1788-90.
26. Peng L, Xu L, Ouyang W. Role of peripheral inflammatory markers in postoperative cognitive dysfunction (POCD): A meta-analysis. PLoS One 2013;8:e79624.
27. Micha G, Tzimas P, Zalonis I, Kotsis K, Papdopoulos G, Arnaoutoglou E. Propofol vs. sevoflurane anaesthesia on postoperative cognitive dysfunction in the elderly. A randomized controlled trial. Acta Anaesthesiol Belg 2016;67:129-37.
28. Saleem M, Herrmann N, Swardfager W, Eisen R, Lanctôt KL. Inflammatory markers in mild cognitive impairment: A meta-analysis. J Alzheimers Dis 2015;47:669-79.