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The Effects of Isoflurane and Desflurane on Cognitive Function in Humans

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Abstract

BACKGROUND: The etiology of postoperative cognitive decline (POCD) remains to be determined. Anesthetic isoflurane, but not desflurane, may induce neurotoxicity. However, the functional consequences of these effects have not been assessed. We therefore performed a pilot study to determine the effects of isoflurane and desflurane on cognitive function in humans.

METHODS: The subjects included patients who had lower extremity or abdominal surgery under spinal anesthesia alone (S, n = 15), spinal plus desflurane anesthesia (SD, n = 15), or spinal plus isoflurane anesthesia (SI, n = 15) by randomization. Each of the subjects received cognitive tests immediately before and 1 week after anesthesia and surgery administered by an investigator who was blinded to the anesthesia regimen. POCD was defined using the scores from each of these tests.

RESULTS: We studied 45 subjects, 24 males and 21 females. The mean age of the subjects was 69.0 ± 1.9 years. There was no significant difference in age and other characteristics among the treatment arms. The mean number of cognitive function declines in the S, SD, and SI groups was 1.13, 1.07, and 1.40, respectively. POCD incidence after SI (27%), but not SD (0%), anesthesia was higher than that after S (0%), $P = 0.028$ (3-way comparison).

CONCLUSION: These findings from our pilot study suggest that isoflurane and desflurane may have different effects on postoperative cognitive function, and additional studies with a larger sample size and longer times of follow-up testing are needed.

Postoperative cognitive dysfunction or decline (POCD) is an increasingly recognized phenomenon after major surgery¹ and is associated with impairments in daily functioning² and increased morbidity and mortality.³ Previous studies have identified advanced age as the major risk factor for long-term POCD, but its etiology remains largely unknown.

Several studies have shown that the commonly used inhaled anesthetic isoflurane may induce neurotoxicity associated with cognitive dysfunction or learning/memory impairment, which includes caspase activation, apoptosis, A β oligomerization and accumulation, neuroinflammation, τ protein hyperphosphorylation, mitochondria dysfunction, and impairment of learning and memory.⁴⁻¹¹ Desflurane, another commonly used inhaled anesthetic, has been reported not to have these effects.^{10,12} The underlying mechanisms and functional consequences of the different effects of isoflurane and desflurane remain to be determined.

We hypothesized, based on in vitro and animal studies, that isoflurane, but not desflurane, would induce POCD and we performed a pilot 3-arm randomized trial comparing the effects of different anesthetics on human cognitive function. All patients received spinal anesthesia, and some patients randomly received additional general anesthesia with either isoflurane or desflurane. We examined the effects of these 3 anesthesia regimens on cognitive function, specifically changes in performance on a neurocognitive test administered preoperatively and 1 week postoperatively.

METHODS

The protocol was approved by the research ethics committee in the Capital Medical University in Beijing, P.R. China and the IRB of Partners Human Research Committee, Boston, Massachusetts to perform this prospective randomized clinical study. Eligible subjects were ASA I or II patients between 64 to 73 years of age who had either lower extremity or lower abdominal surgery under spinal anesthesia alone (S), spinal plus desflurane anesthesia (SD), or spinal plus isoflurane anesthesia (SI) in the Beijing Friendship Hospital, Capital Medical University, Beijing, P. R. China. The exclusion criteria included (1) cognitive impairment as evidenced by a Mini Mental State Examination score below 24 (of 30 possible points) from the screening test of overall cognitive status at patients' initial visit; (2) history of alcoholism, drug dependence, psychiatric, or neurological diseases, e.g., Alzheimer disease, stroke, and psychosis; (3) severe visual or auditory disorder; (4) unwillingness to comply with the protocol or procedures; (5) inability to understand the language (Mandarin Chinese) used; and/or (6) terminal status.

After obtaining written patient consent, all of the subjects had spinal anesthesia. Two mL of 1% tetracaine was administered into the spinal space via a spinal needle. The subjects were randomly assigned into the S (n = 15), SD (n = 15), or SI (n = 15) group. No sedative medicines were given to any patient. General anesthesia was then induced with 1.5 to 2.0 mg/kg propofol (AstraZeneca, Beijing, P.R. China) to subjects in the SD and SI groups. Patients were not tracheally intubated; rather, a laryngeal mask airway (a device for maintaining airway patency) was used for subjects who received general anesthesia. Desflurane (Baxter, Deerfield, IL) or isoflurane (Baxter) was administered to subjects in the SD or SI groups from an anesthesia machine through the laryngeal mask airway, respectively. Standard anesthesia care was provided, including routine monitoring of electrocardiogram, arterial blood pressure, and oxygen saturation. All subjects had a Bispectral Index (BIS) monitor to determine the relative depth of general anesthesia. The desflurane or isoflurane concentration was adjusted to maintain a BIS value between 50 to 60, values that indicate a satisfactory depth of general anesthesia. We chose to maintain similar BIS values between the SI and SD groups to exclude the contribution of depth of general anesthesia to POCD incidence. Desflurane or isoflurane was given for 2 hours.

The primary outcomes in our human studies were cognitive function after isoflurane and desflurane anesthesia. This pilot study has a parallel arm trial design. The 11 cognitive tests were performed in all 45 subjects. Each of these subjects received the cognitive tests preoperatively on the day of anesthesia and surgery, and again 7 days later when the patients were still in hospital. All subjects had both pre- and postoperative tests. The cognitive tests took approximately 40 minutes to administer in a quiet environment with only the subject and investigator present. The tests were performed in Chinese (Mandarin). The investigators who performed the cognitive tests were blinded to the assigned groups (e.g., S, SD, or SI groups). The tests included Hopkins Verbal Learning Test-Revised (HVLT-R), Brief Visuospatial Memory Test-Revised (BVM-T-R), Benton Judgment of Line Orientation Test, Digit Span Test, Symbol-Digit Modalities Test, HVLT-R Delayed Recall Test, HVLT-R Recognition Discrimination Index, BVM-T-R Delayed Recall Test, BVM-T-R Recognition Discrimination Index, Trail Making Test, and Verbal Fluency Test. These tests are highly sensitive to different types of cognitive impairments and are widely used in the field of neuropsychology. The "change" score of each of the cognitive tests was obtained by subtracting the raw score of the baseline preoperative test from the raw score of the postoperative cognitive test. Given that subjects in this study had repeat assessments, we chose tests that have alternate versions (version A and version B) to minimize practice effects. POCD was defined when 4 or more of the change scores were negative and the absolute value of each of these change scores was larger than 1 SD of the baseline score of

the same cognitive test from all subjects. We used this 1 SD criteria as described in previous studies.¹³⁻¹⁶

One-way ANOVA was used to compare the difference of BIS value among the S, SD, and SI groups. The POCD incidence among the S, SD, and SI groups was determined by Fisher's exact test. The mean, SD, and 95% confidence intervals (CIs) for BIS in each group were calculated to provide a basis for sample size and power calculations for future study. *P* values <0.05 (*) were considered statistically significant.

RESULTS

Forty-five subjects were included in the studies. Among them, 24 subjects were male, and 21 subjects were female. The mean age of the subjects was 69.0 ± 1.9 years, and the range was between 64 to 73 years old. There were no significant differences in age, height, body weight, education, sex ratio, ASA classification, length of anesthesia, length of surgery, or estimated blood loss in any group (Table 1). The preoperative Mini Mental State Examination score and the postoperative course, including the amount of pain medicines, were comparable among all groups (data not shown).

As expected, the BIS values were lower in the SI and SD groups than in the S group (Fig. 1). The Bonferroni adjusted 95% CI of mean difference between SD and S was (-42.12, -39.60), and between SI and S was (-41.75, -39.45). There was no significant difference [Bonferroni adjusted 95% CI of mean differences (-1.86, 1.34)], however, in BIS values between SD and SI subjects (Fig. 1), indicating that the mean anesthesia depth was similar between the SD and SI subjects. These results suggest that the depth of anesthesia may not have been a factor that could contribute to any difference in cognitive tests between the SD and SI groups.

The change scores for each of the 11 cognitive tests for all 15 subjects from all groups were obtained. Change scores that were negative and had absolute values larger than one SD of the baseline scores of the same test were considered significantly different. The number of subjects with these significant change scores are presented in Table 2, e.g., there were 2, 3, and 4 subjects whose change scores in the HVLt-R were significantly different in the S, SD, and SI groups, respectively. The mean number of subjects with cognitive function decline in the S, SD, and SI groups was 1.13 (Bonferroni corrected CI: 0.52 to 1.74), 1.07 (Bonferroni corrected CI: 0.35 to 1.79), and 1.40 (Bonferroni corrected CI: 0.31 to 2.49), respectively. The 3-way comparison led to a *P* value of 0.770. These results suggest that a larger scale study with more subjects is needed to either support or reject the hypothesis that the SI group may have had more cognitive function decline.

Next, we defined a subject as having POCD when the subject exhibited impairment in 4 or more of 11 cognitive tests.¹⁵⁻¹⁸ Collectively, as can be seen in Table 2, 4 of 15 subjects (27%) developed POCD 7 days after SI anesthesia. In contrast, none of subjects in either the S or the SD group developed POCD. The Fisher's exact test showed that the POCD incidence after SI anesthesia is higher than that after S anesthesia, *P* = 0.028 (3-way comparison). Finally, power analysis based on the findings from these studies showed that we would need 440 patients in each anesthesia arm to have adequate power (>80%) to detect a significant difference among S, SI, and SD on the mean number of patients with cognitive function decline.

DISCUSSION

The results of our pilot 3-arm randomized trial suggest that isoflurane (SI), but not desflurane (SD), may cause impairment of cognitive function and lead to POCD as compared to S.

Isoflurane, but not desflurane, has been reported to cause neurotoxicity and promote Alzheimer disease neuropathogenesis by inducing caspase activation, apoptosis, A β oligomerization, A β accumulation, neuroinflammation, τ protein hyperphosphorylation, and mitochondrial dysfunction.⁴⁻¹¹ Therefore, it is conceivable that isoflurane, but not desflurane, may induce neurotoxicity, leading to POCD. Because of its chemical structure, isoflurane may be less stable than desflurane during metabolism,¹⁹ and it is possible that the difference in metabolism between isoflurane and desflurane may contribute to the varying effects of isoflurane and desflurane on neurotoxicity and cognitive function. Specifically, the metabolism of equal amounts of desflurane and isoflurane generates different amounts of trifluoroacetic acid in blood, and trifluoroacetic acid may induce cytotoxicity.²⁰ Alternatively, it has been reported that sympathomimetic effects may improve cognitive function.²¹ Desflurane has a shorter action time²² and more sympathomimetic effects²³ as compared to isoflurane, which may also contribute to the different effects of isoflurane and desflurane on neurotoxicity and POCD. More studies are necessary to test this hypothesis and to further determine the underlying mechanisms behind the effects of isoflurane and desflurane on neurotoxicity and cognitive function.

A recent study by Sieber et al.²⁴ showed that the use of light propofol sedation (BIS value higher than 80) decreased the prevalence of postoperative delirium by 50% compared with deep sedation (BIS value was approximately 50). Our results showed that BIS values between SD and SI were similar, thus the observed differences in POCD incidence between SD and SI were not due to the difference in the depth of general anesthesia.

Although the diagnostic criteria for human POCD are still being developed,¹⁶ there have been many clinical reports and research findings on POCD.^{3,17,25-34} However, there are also opposing findings. The varying results in regard to POCD incidence could be due to heterogeneity of patients' baseline status (e.g., education, other diseases), type of surgery, as well as the methods used to determine POCD. In the current studies, POCD was defined when 4 or more of the change scores were negative and the absolute value of each of these change scores was larger than 1 SD of the baseline score of the same cognitive test from all of the subjects, which are consistent with other studies.¹³⁻¹⁶ Interestingly, several studies suggests that there is no significant difference in the incidence of POCD between surgery with general anesthesia and surgery without it (with epidural, spinal, or local anesthesia).^{13,33,35-40} These studies, however, did not compare the severity of POCD between surgery with general anesthesia and surgery without it. Future studies should test a hypothesis that anesthesia enhances the severity of surgery-induced POCD or vice versa.

In the present studies, we have demonstrated that a higher incidence of POCD occurs after SI, but not SD, as compared to S alone. The limitations of the study include small sample size and that we only investigated POCD incidence 1 week after anesthesia and surgery. It is therefore unclear whether the changed cognitive function was due to the fact that isoflurane is longer-acting or due to a more direct toxicity of isoflurane. Thus, the current research will serve as a pilot study to establish a system to further determine the potential difference of isoflurane and desflurane on human cognitive function. Future studies may include more subjects and longer follow-up times.

In the current pilot studies, POCD was defined when 4 or more of the change scores were negative and the absolute value of each of these change scores was larger than 1 SD of the baseline score of the same cognitive test from all subjects. A different definition of POCD (e.g., 2 SD changes on only 2 tests) would change the outcomes of the POCD studies. In future larger scale studies, we may compare whether a different definition of POCD will lead to a different conclusion regarding the effects of isoflurane and desflurane on cognitive function in humans. Furthermore, it would be important to determine not only how all of the patients perform on a specific test, but also how specific patients perform on all of the tests. In addition, we will include a control group to calculate Z-scores and use the Z-scores to determine POCD incidence. Moreover, we will perform factor analysis to make sure that each cognitive test is not counting overlapping domains. Finally, we may use the control subjects to adjust for the learning effects.

Delirium is usually detected by using the confusion assessment method (CAM) test.^{41,42} The CAM algorithm consists of 4 clinical criteria: (1) acute onset and fluctuating course, (2) inattention, (3) disorganized thinking, and (4) altered level of consciousness. For delirium to be defined, both the first and the second criteria have to be present, plus either the third or the fourth criterion. Cognitive tests in the current studies did not include the criteria of the CAM test. Thus, changes in postoperative cognitive function detected 1 week after surgery are unlikely to represent postoperative delirium.

In conclusion, we have established a system to compare the effects of isoflurane and desflurane on human cognitive function. The current findings suggest that we will need a larger scale study to test a hypothesis that isoflurane, but not desflurane, may induce cognitive dysfunction or decline in humans after surgery. The current study serves as a pilot study and raises novel concerns regarding the use of isoflurane in individuals who are susceptible to the development of cognitive function decline, including Alzheimer disease patients and older adults. These concerns warrant further study. ■■

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Figure 1.

There is no difference in Bispectral Index (BIS) values between desflurane (SD) and isoflurane anesthesia (SI) anesthesia subjects. The average BIS value from subjects in the SD group was not different from that in the SI group. Moreover, the BIS values from both the SD and SI groups are lower than that of the spinal anesthesia group.

Table 1**Admission Characteristics of Study Population**

Admission characteristics	S (n = 15)	SD (n = 15)	SI (n = 15)
Age (year)	68.7 ± 2.8	68.7 ± 2.1	69.1 ± 3.8
Height (cm)	167.4 ± 8.1	166.1 ± 7.6	167.2 ± 9.6
Body weight (kg)	66.9 ± 6.6	66.1 ± 6.9	66.5 ± 8.5
Education (year)	8.2 ± 2.6	7.9 ± 3.1	8.3 ± 2.8
Sex (M/F)	9/6	7/8	8/7
ASA I	5	6	5
ASA II	10	9	10
Length of anesthesia (min)	170.0 ± 23.2	176.0 ± 24.4	172.7 ± 20.5
Length of surgery (min)	134.3 ± 24.8	139.3 ± 25.3	140.3 ± 22.2
Orthopedic surgery	6	6	7
Abdominal surgery	9	9	8
Estimated blood loss (ml)	178.7 ± 165.9	183.7 ± 177.3	168.7 ± 154.0

The age, height, body weight, education, sex ratio, ASA classification, length of anesthesia, length of surgery and estimated blood loss in the spinal, spinal plus desflurane, and spinal plus isoflurane groups.

ASA indicates American Society of Anesthesiologists; SD, spinal plus desflurane; SI, spinal plus isoflurane; S, spinal.

Table 2

Postoperative Cognitive Decline Incidence and the Number of Subjects Who Declined by 1 SD or More on Each Cognitive Test at 1 Week Relative to Preoperation

Name of the cognitive tests	S (n = 15)	SD (n = 15)	SI (n = 15)
Hopkins Verbal Learning Test-Revised (HVLTR)	2	3	4
Brief Visuospatial Memory Test-Revised (BVMT-R)	2	0	0
Benton Judgment of Line Orientation Test	0	1	0
Digit Span Test	1	0	1
Symbol Digital Modalities Test	0	1	1
HVLT-R Delayed Recall Test	2	3	4
HVLT-R Recognition Discrimination Index	4	4	3
BVMT-R Delayed Recall Test	3	1	2
BVMT-R Recognition Discrimination Index	0	1	0
Trail making test	1	1	2
Verbal fluency test	1	1	5
Mean number of cognitive function decline *	1.13 ± 0.99	1.07 ± 1.16	1.40 ± 1.76 <i>P</i> = 0.770, NS
The POCD incidence (defined by decline in four or more cognitive tests) [†]	0 (0%)	0 (0%)	4 (27%) <i>P</i> = 0.028 *

POCD indicates postoperative cognitive decline; SD, spinal plus desflurane; SI, spinal plus isoflurane; S, spinal; NS, not significant.

* The change score was the difference of one week postoperative raw score minus the baseline raw score. The number of subjects whose change score was more than one standard deviation was recorded in the S, SD and SI groups.

[†]The mean number of cognitive function decline in each of the groups was presented and the calculated POCD incidence.