DEPARTMENT OF ANESTHESIOLOGY

JOURNAL CLUB
Via Zoom

Thursday, 30 September, 2021
1630-1800 HOURS

PRESENTING ARTICLES:
Dr. Tracy Cupido & Dr. Sergiy Shatenko

SUGGESTED GUIDELINES FOR CRITICAL APPRAISAL OF PAPERS
ANESTHESIOLOGY JOURNAL CLUB
QUEEN'S UNIVERSITY

Two presenters will be assigned to choose and present summaries of their papers. Ideally the two papers will represent similar topics but contrasting research methodologies. The focus remains on critical appraisal of the research and manuscript, more than on the actual contents of the article. Each presenter will then lead an open discussion about the article, based around the guidelines below. The object is to open up the appraisal to wide discussion involving all participants.

GENERAL

1. Title of paper: Does it seem like an important problem? Does it reflect the purpose/results?
2. Authors, institution and country of origin

INTRODUCTION

1. What is the problem being addressed?
2. What is the current state of knowledge of the problem studied?
3. What is the hypothesis being tested?
4. How does testing the hypothesis help solve the stated problem?

METHODOLOGY

1. Study design:
    a) Clinical trial vs. systematic review/meta-analysis
    b) Prospective vs. retrospective
    c) Observational vs. Experimental
    d) Randomized or not
    e) Blinded or not

2. Population studied:
    a) Human, animal, other
    b) Justification
    c) Control groups: experimental vs. historical
    d) Is the sample size/power calculated, and how?
    e) Is the population similar to your own practice?
    f) Single vs. multi-centre

3. Is the study ethically sound?
    a) Clinical equipoise
    b) Does treatment meet standard of care (esp controls)?
    c) Appropriate consent and institutional ethics approval

4. Exclusions: what groups are excluded and why?

5. Experimental protocol
    a) Is it designed to test the hypothesis?

b) Is it detailed enough to be reproducible?
c) Is the methodology validated?
d) Are the drugs/equipment used detailed?
e) How does the randomization take place?

6. What are the primary endpoints?
7. Is power sufficient to justify secondary endpoints?
8. Is the protocol clinically relevant?
9. Data collection and analysis
10. Statistical analysis: Is it appropriate? Are results

RESULTS

1. Are the groups comparable?
2. Were any subjects/data eliminated?
3. Analyzed by intent to treat?
4. Are adequate details of results provided? - data, graphs, tables

DISCUSSION

1. What is the main conclusion of the study?
2. Do the results support this conclusion?
3. Do the results address the stated purpose/hypothesis of the study?
4. How do the authors explain the results obtained?
5. Are there any alternative interpretations to the data?
6. Are the results clinically as well statistically relevant?
7. How do the results compare with those of previous studies?
8. What do the results add to the existing literature?
9. What are the limitations of the methods or analysis used?
10. What are the unanswered questions for future work?

APPLICABILITY OF THE PAPER

1. Have you learned something important from reading this paper?
2. Will the results of this study alter your clinical practice?

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Published online 2020 August 8. **Research Article**

Effect of General Versus Spinal Anesthesia on Postoperative Delirium and Early Cognitive Dysfunction in Elderly Patients

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Abstract

Background: Postoperative cognitive dysfunction (POCD) and delirium are common in the elderly patients, given the controversial results of previous studies about the impact of anesthesia type on the occurrence of these complications.
Objectives: This study was planned to compare the effects of general and spinal anesthesia on the prevalence of POCD and delirium.
Methods: A single-blind non-randomized clinical trial. Setting was in two academic hospitals. Ninety-four patients over 50 years old scheduled for hip fracture fixation. Patients were divided into two groups to receive either general (GA) or spinal (SA) anesthesia. Both Mini-Mental State examination (MMSE) and Wechsler tests were used before the operation and 3 times postoperatively to assess the cognitive function and detect early POCD. The DSM-IV criteria were also used for the diagnosis of delirium. The incidence of delirium and POCD and their precipitating factors were compared between the two groups.
Results: Ninety-four patients with a mean age of 67.12 years were studied. The overall prevalence of POCD and delirium was 17.02%; however, it was significantly higher in the GA group rather than the SA group, 29.7%, and 4.25%, respectively ($P < 0.001$). There was a significant relationship between age ($P = 0.048$), ASA class ($P = 0.034$), and educational level with the incidence of POCD, meaning that the probability of developing cognitive impairment decreases with patients' higher level of education and lower ASA-physical status. Also, the rate of POCD in men was significantly higher than in women ($P = 0.026$).
Conclusions: The finding of this study showed that, if there is no specific contraindication, neuraxial anesthesia may be preferred over general anesthesia in elderly patients.

Keywords: General Anesthesia, Spinal Anesthesia, POCD, Delirium

1. Background

Postoperative cognitive disorders and delirium are common in the old hospitalized patients, especially after major surgeries, leading to higher mortality and morbidity rates. The prevalence of femoral and pelvic fractures in the elderly is high; according to a health survey result, 320,000 admissions due to hip fractures occur annually in the United States (1-3). All surgeries cause some stress in the elderly, and it will be sufficient to disturb the physiological and psychological balance in these patients. Postoperative delirium is one of the most common complications among hospitalized elderly patients, especially in those undergoing orthopedic surgery (3-6). The prevalence of delirium in patients undergoing pelvic surgery has been reported to be up to 53.3% (3). In the study of Holly et al. (7), delirium levels in people over 65y reached 62%. This complication often occurs 2 - 5 days after surgery in patients with hip fracture (8).

Delirium progression in the hospital is associated with increased mortality, length of stay, dependence on others, hospital-acquired complications, medical costs, and sometimes permanent cognitive impairment. Delirium is also a predictor of treatment failure or delay in functional recovery in patients with hip fractures (3, 7). There are various theories regarding the pathophysiology of delirium, including metabolic encephalopathy, drug poisoning (especially anticholinergics), hypoglycemia, stress, surgery and increased corticosteroids induced by it, hypotension, preoperative hypoxia, type of anesthesia, sleep deprivation, pain, electrolyte imbalance, old age, as well as hearing and visual disorders (9-13). The mortality rate of these patients is between 10% to 65%, which is equal to the risk of acute myocardial infarction and sepsis (7-9).

Therefore, due to the high prevalence of this compli-

cation in patients undergoing hip surgery, high morbidity and mortality rate, hospital-acquired complications due to prolonged hospital stay, economic burden, and also given that there are conflicting results regarding the impact of general or regional anesthesia on delirium and early cognitive disorders in previous studies (14, 15).

2. Objectives

This study aimed to compare the effect of general and spinal anesthesia on the incidence of postoperative delirium and POCD in elderly candidates for surgery due to hip fracture.

3. Methods

The present study was a single-blinded non-randomized clinical trial (RCT). After approving the study protocol by the Ethics Committee (code of ethics: IR.IUMS-FMD.REC1396.9511174001) and by the Iranian Clinical Trial Registration Center (no.: IRCT20121107011398N13), a total number of 108 patients including men and women over the age of 50 years, with the diagnosis of proximal femoral bone fracture who were scheduled for open fixation surgery, were enrolled in the study. Exclusion criteria were: Preoperative cognitive impairment, significant auditory impairment, alcoholism, and drug abuse, American society of anesthesiologists physical status (ASA-PS) > III, acid-base and electrolyte abnormalities, patient's dissatisfaction, a history of similar surgery in the past month, history of a recent cerebrovascular accident as well as taking psychotropic drugs and benzodiazepines in the week before or inadvertently after surgery.

Mini-Mental State examination (MMSE) and Wechsler tests were used to evaluate postoperative delirium and POCD, both of which were used once before surgery to assess the baseline cognitive status of patients, and three times after surgery i.e., in three successive days. The MMSE test can measure patients' orientation to time and place, as well as the patient's attention, memory, and computing power (16). Wechsler's test is a set of intelligence tests used to assess the patient's verbal and nonverbal cognition and the capacity and ability of the patient's overall intelligence and cognitive ability (17).

The primary outcome of this study was POCD, and the secondary outcome was postoperative delirium. Delirium was diagnosed using DSM-IV criteria, and POCD diagnosis was performed using patient-acquired scores from MMSE and Wechsler tests. A decrease of up to 2 points in these tests was considered as mild cognitive impairment, and a decrease of more than 2 points in the postoperative phase as compared to preoperative values was considered as severe cognitive impairment (delirium equivalent).

After obtaining informed consent, the patients were divided into two groups: general (GA) or spinal (SA) anesthesia. The type of anesthesia was selected by an anesthesiologist who was unaware of the study protocol. In the GA group after routine monitoring (ECG, NIBP, SPO2, ET-Co2, BT), for premedication, fentanyl 2 μg/kg and for induction of anesthesia, lidocaine 1 mg/kg, propofol 1.5 mg/kg, and cisatracurium 0.2 mg/kg body weight was used. The patients were then intubated, and for maintenance of anesthesia, propofol 50 - 150 μg/kg/min was infused. Cisatracurium 0.05 mg/kg every 30 min and fentanyl 50 μg every hour was repeated. At the end of the surgery, the neuromuscular block was reversed with 40 μg/kg of neostigmine and 20 μg/kg of atropine, and the patients were extubated according to the clinical criteria.

In the spinal anesthesia group, 12.5 - 15 mg hypertonic bupivacaine plus 25 μg fentanyl in the sitting position were used for spinal anesthesia. In some patients (6 cases), the epidural catheter had been fixed in the L2-L3 before doing spinal anesthesia. Benzodiazepine was not used in any of the study group members during the operation and postoperative phase. In order to control the postoperative pain, 1gr of paracetamol was infused at the end of the operation, and 3 g was perfused with a patient-controlled analgesia pump.

Patients' level of education, drug history, and preoperative laboratory tests, including the plasma hematocrit, plasma glucose, and serum electrolytes, were recorded. The type of surgery, duration of operation and anesthesia, mean intraoperative blood pressure, the blood loss during operation, amount of fluid administered, and in case of transfusion, the type and amount of the blood products used were recorded as well.

3.1. Sample Size Determination and Data Analysis Method

A reduction of POCD incidence from 40% to 15% was considered clinically significant. Power analysis was performed using an online calculator available from the University of British Columbia (Vancouver, BC, Canada) considering α = 0.05 with a power (β) of 80 percent. The sample size was determined to be a minimum of 47 patients in each group. Data were analyzed using SPSS-V22 software. Qualitative variables were reported by relative frequency, percentage, and quantitative variables using mean and standard deviation. Independent *t*-test, chi-square, Fisher exact test, and Mann-Whitney test were used to examine the significance of the variables. The level of significance was set at 0.05.

4. Results

A total of 108 patients were enrolled in the study, of which 14 were excluded because of different reasons, and the final data from 94 patients were analyzed (Figure 1).

Patients were similar in the two study groups in terms of demographic data (Table 1). There was no significant difference in terms of the ASA-PS (P = 0.324), and also educational backgrounds between the study groups. The mean duration of operation in the GA and SA groups were 3.43 ± 0.53 hours and 3.27 ± 0.43 hours, respectively, and it was longer in the GA group (P = 0.031). The amount of bleeding was comparable between the groups, 414.9 ± 265 ml in the GA group versus 416.4 ± 259 in RA (P = 0.978). Ten patients in each group were transferred to the ICU after surgery.

Table 1. Comparison of Demographic Data of Study Subjects in Two Groups

Variables	Study Groups		Total	P Value
	GA	SA		
Sex				0.063
Male	27	18	45	
Female	20	29	49	
ASA class				0.324
1	16	23	39	
2	28	21	49	
3	3	3	6	
Education level				NS[a]
Illiterate	4	0	4	
Elementary	2	10	12	
High school	30	22	52	
Diploma	7	12	19	
Bachelor's	4	3	7	0.131
Age, y	68.06	64.48	67.12	

Abbreviations: GA, general anesthesia; SA, spinal anesthesia.
[a] Non-significant.

The results of MMSE tests showed that the mean scores of the two groups were similar preoperatively (P = 0.765). However, a significant difference in the mean scores was observed in the postoperative phase at 24 and 48 hours, that is, the scores were significantly lower in GA group than those in SA group. On the third day (72 hours after surgery), these variables did not show a significant difference between the two groups (Figure 2). The comparison of the Wechsler test in (Figure 3) shows that the mean value of this score on the first postoperative day was significantly lower in the GA group than in the spinal group (P value = 0.029), whereas in the preoperative stage, second and third postoperative day, there were no significant differences between the study groups.

The overall prevalence of cognitive disorders in the two groups was 17.02% (n = 16). The drops of MMSE test scores were at least 1 point and a maximum of 17 points, with a mean of 4.19 points on the first day and 2.94 points on the second day after surgery. Given that MMSE and Wechsler scores were more than 2 points in the first 48 hours, the severity of perioperative neurocognitive disorders (PND) in most patients (14 out of 16) can be classified as major. The incidence of delirium and POCD was significantly different between GA and SA groups, 14 patients (29.7%), and only 2 patients (4.25%), respectively (P = 0.001).

Based on the results, there was a significant relationship between age and incidence of POCD. The mean age of patients with PND was 67.9 years and the mean age of non-PND patients was 62.2 years (P = 0.048). There was no significant relationship between intraoperative hemorrhage, fluid intake, and operation time with the delirium and POCD (Table 2).

The results also showed that there was a significant relationship between gender, educational level, and ASA class of patients with cognitive impairment occurring postoperatively (Table 3). Increased educational attainment decreased the probability of delirium and POCD (P = 0.034). The results also showed that the rate of cognitive disorders in men was significantly higher than in women (P = 0.026).

5. Discussion

Cognitive disorders after surgery and anesthesia have been known for about 100 years but named as POCD since the late 1990s, and many studies are still ongoing. Definitions and nomenclatures are constantly changing, and in the latest issue of Miller (18), perioperative cognitive disorders were named as perioperative neurocognitive disorders (PND), and were divided into two types of mild and severe form, including delirium and dementia (18).

This study showed that the incidence of POCD was 17.02%, which was significantly higher in the GA group. These findings are consistent with the results of other studies that have shown that general anesthesia causes more cognitive disorders than regional anesthesia. There are some other studies declaring that the type of anesthesia has no effect on such disorders. In general, the idea of the effect of anesthesia on the incidence of delirium and cognitive dysfunction remains controversial.

Anwer et al. (19). and colleagues reported that general anesthesia is associated with an increased risk of early cognitive impairment in elderly patients. However, in young

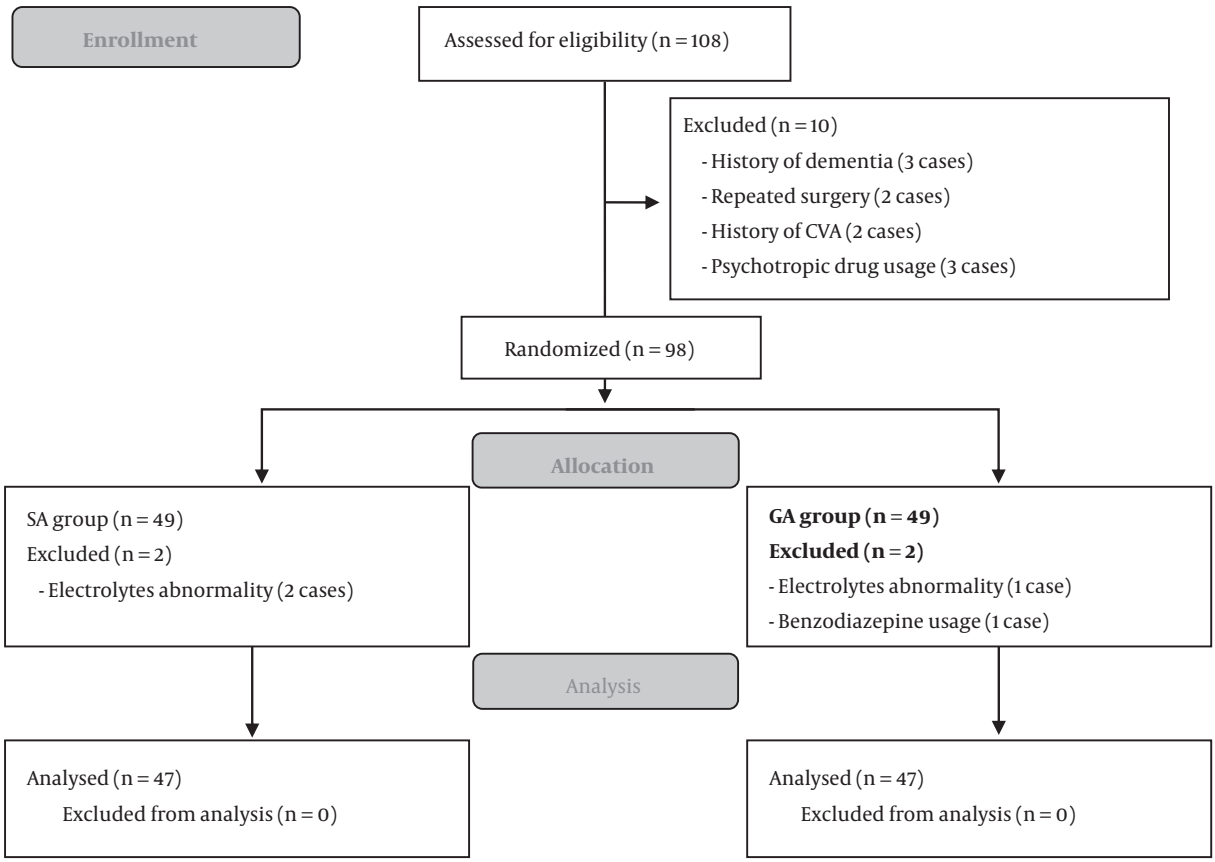


Figure 1. CONSORT flow diagram

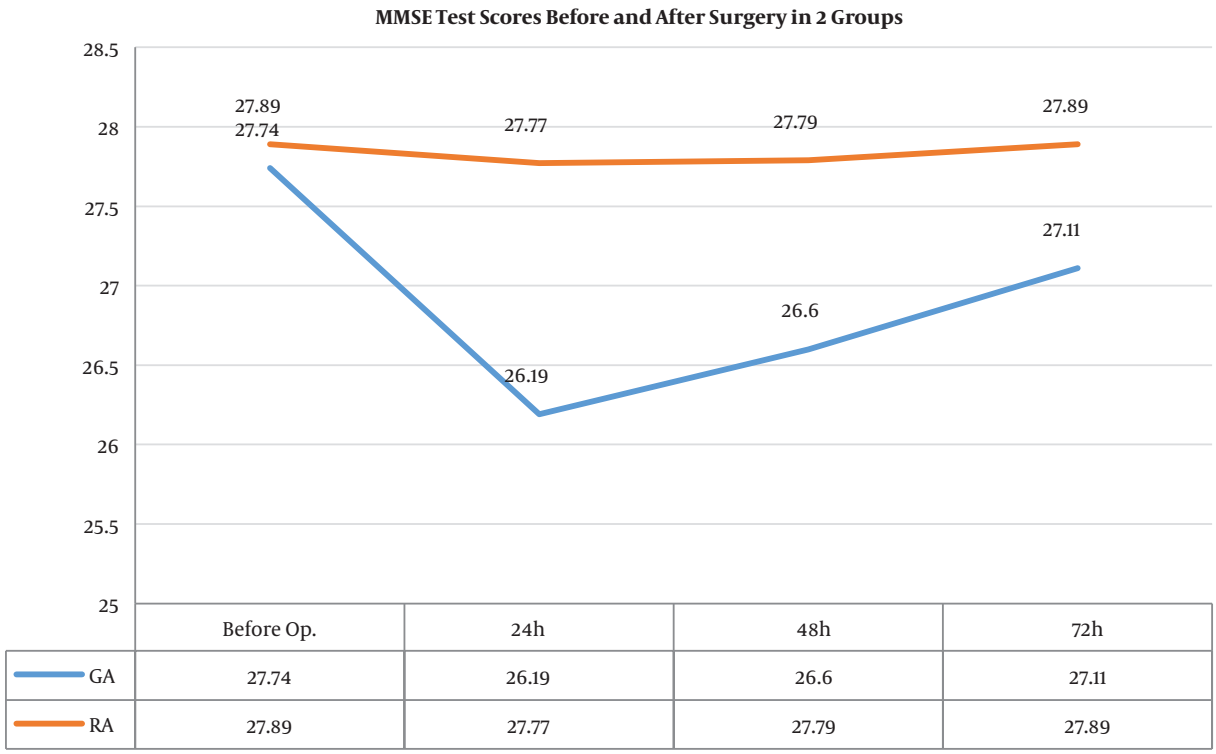
Table 2. Determining the Relationship Between Quantitative Variables and the Incidence of Delirium in the Studied Patients[a]

	POCD	Numbers	Values	P Value
Age, y	No	78	62.25 ± 10.608	0.048
	Yes	16	67.91 ± 7.646	
Bleeding, cc	No	78	402.18 ± 232.412	0.272
	Yes	16	481.25 ± 374.110	
Fluid intake, L	No	78	3.02 ± 0.42	0.960
	Yes	16	3.03 ± 0.28	
Operation time, h	No	78	3.351 ± 0.4840	0.955
	Yes	16	3.344 ± 0.5072	

Abbreviation: POCD, postoperative cognitive disorders.
[a]Values are expressed as mean ± SD.

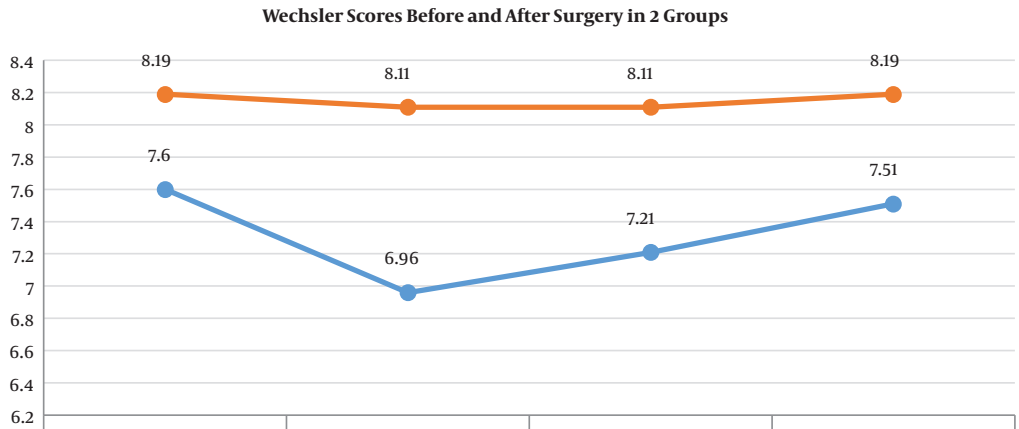
patients, there was no relationship between the type of anesthesia and the incidence of POCD. Also, in a review study by Ritchie et al. (20), similar results were reported, but due to the many confounding factors, this relationship regarding late cognitive impairments and dementia cannot be proven.

In a similar study published by Zhang et al. (21), the authors concluded that spinal anesthesia had better results, in terms of verbal communication, and MMSE score, and a reduced prevalence of POCD in elderly patients undergo-



	Before Op.	24h	48h	72h
GA	27.74	26.19	26.6	27.11
RA	27.89	27.77	27.79	27.89

Figure 2. Comparison of MMSE test score means before and after surgery in 2 group



	Before Op.	24h	48h	72h
GA	7.6	6.96	7.21	7.51
RA	8.19	8.11	8.11	8.19

Figure 3. Comparison of Wechsler test score means before and after surgery in 2 group

ing orthopedic surgery. In a systematic review by Mason et al. (22), they reported that general anesthesia did not increase the incidence of delirium compared to regional, but did minimally increase the chance of cognitive impairment (odd's Ratio = 1.34). They have also concluded that regional anesthesia might be preferred in patients at high

Table 3. Determining the Relationship Between Qualitative Variables and the Incidence of Delirium in the Studied Patients

Variables	POCD Number		P Value
	No	Yes	
Gender			0.026
Male	34	11	
Female	44	5	
ICU-admission			0.346
No	60	14	
Yes	18	2	
Education			0.018
Illiterate	1	3	
Elementary	12	0	
High school	42	9	
Diploma	16	3	
Bachelor	6	1	
ASAclass			0.034
1	36	3	
2	36	13	
3	6	0	

Abbreviations: ASA class, American Society of Anesthesiologists physical status; ICU, Intensive Care Unit; POCD, postoperative cognitive disorders.

risk for cognitive impairment (22).

Contrary to the above studies and this study, Silbert et al. (23). concluded that although the prevalence of POCD in patients undergoing general anesthesia was higher than the regional group at day 7 and 3 months postoperatively, but based on statistical analysis, the type of anesthesia does not affect the prevalence of postoperative cognitive disorders; instead, other risk factors such as the type of operation are important. However, the type of surgery selected in this study (lithotripsy) and the duration of follow-up, perhaps justifies the difference between this study with others. In addition, in a study by Tzimas et al. (24) on 70 elderly patients who were candidates for hip fractures, the prevalence of delirium was reported to be 12% in the general anesthesia group and 27% in the spinal group. Finally, they concluded that the choice of anesthesia did not significantly affect the prevalence of POCD in orthopedic elderly patients.

In a study by Olin et al. (25) in elderly patients with major abdominal surgeries, the prevalence of delirium after general anesthesia was reported in approximately 50% of patients, which was higher than the present study. Of course, this difference may be related to the type of surgery and the age of the patients participating in the two studies. The minimum age of participants in that study was 65 years (25).

The prevalence of delirium and cognitive disorders in this study (17.02%) was lower than from several previous studies, such as the studies of Morimoto et al. (26), Biedler et al. (27), and Juliebo et al. (28) with the reported incidence of 25%, 25.8%, and 36.4%, respectively. The following can be pointed out in explaining the causes of this variability: differences in diagnostic tools, the time of evaluation of cognitive functions, the types of surgeries, elective or emergency, major or minor, and the type of anesthesia performed (general or spinal), as well as ecological differences.

Another result of the present study, as we expected, was that the rate of POCD increased with age. There are some other studies with similar results; increasing age is one of the major risk factors for delirium (1, 13). Also, based on the analysis of the present study, there was a significant relationship between gender, educational level, and ASA class of patients with delirium incidence, such that with an increasing educational level, the probability of delirium and POCD decreased. The results of this study also showed that the rate of POCD in men was significantly higher than in women. There was no significant relationship between delirium and intraoperative bleeding, fluid intake, and duration of operation. However, the duration of operation in the GA group was slightly longer than in the RA group, which was not considered clinically significant.

5.1. Limitations of the Study

As predicted and other studies have also emphasized this, we faced serious limitations in this study, the most important of these were: lack of randomization due to ethical considerations, lack of blindness of the patients, the difficulty of engaging and communicating with patients due to their old age, and the problem of learning impact on repeated tests, as well as the short duration of follow-up.

5.2. Conclusions

The results of this study are consistent with many other studies that have shown a relatively higher incidence of POCD in patients undergoing general anesthesia compared to spinal anesthesia. However, given the fact that these abnormalities are limited to 48 hours postoperatively, and patients' cognitive abilities return to their preoperative status over time, it can be concluded that general anesthesia is associated with early POCD to a greater extent than spinal anesthesia. However, due to the limitations of the study, such as non-randomization and impossibility of blinding, the results of the study cannot be generalized to all patient groups.

Finally, given the results of this study and other beneficial effects that have been proven in previous studies for spinal anesthesia (such as reduced bleeding, and lower thromboembolism risk), this anesthesia technique may be considered as a preferred method to general anesthesia in patients at a high risk of postoperative cognitive impairment.

Acknowledgments

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Footnotes

Authors' Contribution: All authors contributed to the paper, including study concept and design: GM and ER. Data collection: ER and SS. Analysis and interpretation of data: DS and SS. Drafting of manuscript: GM and ZB. Critical revision of the manuscript for important intellectual content editing: GM, DS, and ZB. Statistical analysis: GM and ER. Study supervision: GM and SS. All authors met the criteria for authorship stated in the Uniform Requirements for Manuscripts Submitted to Biomedical Journals. All contributors have read the manuscript and approved it.

Clinical Trial Registration Code: The clinical trial registration code was IRCT20121107011398N13.

Conflict of Interests: All authors declare that they have no financial, personal, or potential conflict of interest.

Ethical Approval: The ethical approval code was IR. IUMS-FMD.REC1396.9511174001.

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Informed Consent: Informed consent was obtained.

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ANESTHESIOLOGY

Delirium in Older Patients after Combined Epidural–General Anesthesia or General Anesthesia for Major Surgery: A Randomized Trial

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ABSTRACT

Background: Delirium is a common and serious postoperative complication, especially in the elderly. Epidural anesthesia may reduce delirium by improving analgesia, reducing opioid consumption, and blunting stress response to surgery. This trial therefore tested the hypothesis that combined epidural–general anesthesia reduces the incidence of postoperative delirium in elderly patients recovering from major noncardiac surgery.

Methods: Patients aged 60 to 90 yr scheduled for major noncardiac thoracic or abdominal surgeries expected to last 2 h or more were enrolled. Participants were randomized 1:1 to either combined epidural–general anesthesia with postoperative epidural analgesia or general anesthesia with postoperative intravenous analgesia. The primary outcome was the incidence of delirium, which was assessed with the Confusion Assessment Method for the Intensive Care Unit twice daily during the initial 7 postoperative days.

Results: Between November 2011 and May 2015, 1,802 patients were randomized to combined epidural–general anesthesia (n = 901) or general anesthesia alone (n = 901). Among these, 1,720 patients (mean age, 70 yr; 35% women) completed the study and were included in the intention-to-treat analysis. Delirium was significantly less common in the combined epidural–general anesthesia group (15 [1.8%] of 857 patients) than in the general anesthesia group (43 [5.0%] of 863 patients; relative risk, 0.351; 95% CI, 0.197 to 0.627; $P < 0.001$; number needed to treat 31). Intraoperative hypotension (systolic blood pressure less than 80 mmHg) was more common in patients assigned to epidural anesthesia (421 [49%] *vs.* 288 [33%]; relative risk, 1.47, 95% CI, 1.31 to 1.65; $P < 0.001$), and more epidural patients were given vasopressors (495 [58%] *vs.* 387 [45%]; relative risk, 1.29; 95% CI, 1.17 to 1.41; $P < 0.001$).

Conclusions: Older patients randomized to combined epidural-general anesthesia for major thoracic and abdominal surgeries had one third as much delirium but 50% more hypotension. Clinicians should consider combining epidural and general anesthesia in patients at risk of postoperative delirium, and avoiding the combination in patients at risk of hypotension.

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EDITOR'S PERSPECTIVE

What We Already Know about This Topic

- Postoperative delirium is common after major surgery in older patients and is associated with major short-term and long-term complications
- Putative causes for delirium include severe pain and high-dose opioids
- Epidural analgesia can provide high-quality analgesia postoperatively

What This Article Tells Us That Is New

- In a randomized trial comparing epidural–general anesthesia *versus* general anesthesia alone in older patients having major surgery, delirium was less common with epidural–general anesthesia
- Intraoperative hypotension was more common in the epidural–general anesthesia group

Delirium is an acute syndrome of brain dysfunction characterized by fluctuating disturbances of concentration, consciousness, and cognitive function.[1]

This article is featured in "This Month in Anesthesiology," page A1. This article is accompanied by an editorial on p. 197 and a companion article on p. 233. This article has a related Infographic on p. A19. Supplemental Digital Content is available for this article. Direct URL citations appear in the printed text and are available in both the HTML and PDF versions of this article. Links to the digital files are provided in the HTML text of this article on the Journal's Web site (www.anesthesiology.org). This article has an audio podcast. This article has a visual abstract available in the online version. Part of the work presented in this article has been presented as an abstract at Euroanaesthesia 2019 in Vienna, Austria, June 1 to 3, 2019. The work was also presented in the OUTCOMES RESEARCH Consortium session at Anesthesiology 2019, Orlando, Florida, October 22, 2019. Y.-W.L. and Huai-Jin Li contributed equally to this article.

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Postoperative delirium is common in older patients, with an incidence that varies widely depending on patient population and type of surgery. For example, the incidence of delirium is reportedly 6 to 46% after cardiac surgery,[2] 5 to 39% after vascular surgery,[3] 8 to 54% after gastrointestinal surgery,[4] and 5 to 14% after total joint arthroplasty.[5] Delirium is associated with worse perioperative outcomes including prolonged hospitalization, complications, high medical expenses, and lower odds of home discharge.[3,6,7] Delirium is also associated with worse long-term outcomes including increased hospital readmission and shortened overall survival, as well as lowered cognition, functional status, and quality of life.[3,6,7] There is currently no convincing evidence that any prophylactic measure or anesthetic approach prevents postoperative delirium.[8–12]

The causes and potential mechanisms leading to delirium after major surgery are multifactorial but may include severe pain, high-dose opioids, and surgery-related stress and inflammation.[13,14] Epidural anesthesia and analgesia is widely used and is recommended for patients having major thoracic and abdominal operations.[15] Advantages of epidural analgesia include excellent pain control, low opioid consumption, and blunted stress and inflammatory response[16–18]—all of which might help prevent delirium. Nonetheless, two systematic reviews reported that regional anesthesia does not reduce delirium in patients recovering from hip fracture surgery compared with general anesthesia.[10,19] Interpretation of these results is complicated, however, because patients given regional anesthesia were also given sedatives, which are themselves thought to promote delirium.[13] Recent observational analyses suggest that neuraxial anesthesia (spinal or epidural blocks) may reduce delirium.[20–22]

Major surgery is usually performed with general anesthesia. Combining epidural and general anesthesia might reduce delirium after major surgery. Indeed, when compared with general anesthesia alone, combined epidural–general anesthesia decreases the requirement of general anesthetics,[23] improves postoperative analgesia, reduces opioid consumption,[15,18] and relieves the stress response to surgery and inflammation.[17,24] We therefore tested the primary hypothesis that in older patients having major thoracic and abdominal surgery, delirium during the initial 7 postoperative days is less common in patients given combined epidural–general anesthesia with postoperative epidural analgesia than in those given general anesthesia followed by intravenous opioids.

Materials and Methods

This multicenter, randomized trial was conducted in five tertiary care hospitals in Beijing, China. The rationale and design of the study were reported previously.[25] The study protocol was approved by the Peking University Institutional Review Board (approval No. 00001052-11048; principal investigator: D.-X.W.) on July 28, 2011, and by the ethics committees of the five participating centers; changes to the trial methods and outcomes are reported in Supplemental Digital Content 1 (http://links.lww.com/ALN/C624). All participants provided written informed consent. The Peking University Clinical Research Institute was responsible for the study monitoring, data quality assessment and management, and data analysis. The study was registered with the Chinese Clinical Trial Registry (www.chictr.org.cn; identifier: ChiCTR-TRC-09000543) and ClinicalTrials.gov (identifier: NCT01661907). Long-term results will be reported in a companion article.

We enrolled patients aged 60 to 90 yr old who were scheduled for major noncardiac thoracic or abdominal surgery expected to last at least 2 h who agreed to use patient-controlled analgesia after surgery. We included patients having thoracoscopic or laparoscopic surgery when the expected incision length was at least 5 cm. We excluded patients who had severe neurologic conditions, acute myocardial infarction or stroke within 3 months, any contraindication for epidural anesthesia, severe heart dysfunction, severe liver dysfunction (Child–Pugh grade C), or renal failure.

Protocol

Patients were centrally randomized using computer-generated codes with a block size of four, stratified by trial site and type of surgery (thoracic or abdominal). Participants were randomized in a 1:1 ratio to either general anesthesia with postoperative intravenous analgesia or combined epidural–general anesthesia with postoperative epidural analgesia. Allocation was concealed until shortly before anesthesia induction or epidural puncture with a 24-h interactive web system (IWRS, Brightech Clinical Information Management System, CIMS Global, USA).

Premedication was not permitted in either group, including anticholinergic drugs, sedatives, or dexmedetomidine. In patients assigned to general anesthesia alone, anesthesia was induced with midazolam (0.02 to 0.03 mg/kg), propofol, and sufentanil. Muscle relaxation was achieved using rocuronium. Anesthesia was maintained with a propofol infusion and/or the volatile anesthetic sevoflurane and/or the inhaled gas nitrous oxide. Postoperative analgesia was provided with a patient-controlled intravenous analgesia with morphine (0.5 mg/ml). The patient-controlled pump was programed to deliver 2-ml boluses with a lockout interval of 6 to 10 min and a background infusion at 1 ml/h.

In patients assigned to combined epidural and general anesthesia, the epidural catheter was inserted before induction of general anesthesia at an intervertebral space selected by the responsible anesthesiologist. Successful epidural block was confirmed by injection of 3 to 4 ml of 2% lidocaine and subsequently maintained with 0.375 to 0.5% ropivacaine during surgery. General anesthesia was induced and maintained as in the general anesthesia alone group, including administration of midazolam (0.02 to 0.03 mg/kg). Postoperative pain was treated with patient-controlled epidural analgesia using a solution of 0.12% ropivacaine and 0.5 μg/ml sufentanil. The pump was programed to deliver

2-ml boluses with a lockout interval of 20 min and a background infusion of 4 ml/h. For patients with failed epidural blocks (including failed catheterization, inadequate analgesia, blocked catheters, and accidental catheter dislodgement), general anesthesia was provided with postoperative patient-controlled intravenous analgesia.

Routine management for intraoperative hypotension included reducing anesthetic depth, fluid infusion, and administration of vasopressors such as ephedrine, phenylephrine, epinephrine, and/or norepinephrine. When indicated, clinicians were permitted to decrease or cease administration of epidural ropivacaine. Supplemental postoperative analgesia was provided at the discretion of attending surgeons or intensive care unit (ICU) physicians and could include opioids, nonsteroidal anti-inflammatory drugs, and other analgesics. Morphine equivalent doses were estimated for comparison of opioid consumption.[12,26,27] Adverse events were managed per routine.

Measurements

Patients and anesthesiologists were aware of study group allocation. However, research staff who did not perform outcome assessments hid patient-controlled analgesia apparatus from investigators who performed assessments who otherwise had no knowledge of randomization and were not permitted to communicate with either patients or care providers about group assignment or treatment.

Baseline data included the Charlson Comorbidity Index.[28] We also evaluated activities of daily living with the Barthel Index, which ranges from 0 to 100, with higher scores indicating better activities.[29] Cognitive function was evaluated with the Mini-Mental State Examination with scores ranging from 0 to 30, with higher scores indicating better function.[30] Anxiety and depression were evaluated with the Hospital Anxiety and Depression Scale, with scores ranging from 0 to 21 for either anxiety or depression, with higher score indicating more severe symptoms. Scores greater than 7 were considered thresholds for both anxiety and depression.[31]

Routine intraoperative monitoring included electrocardiogram, noninvasive blood pressure, pulse oxygen saturation, end-tidal carbon dioxide, volatile anesthetic concentration, and urine output. Intraarterial pressure and central venous pressure were monitored when necessary. For patients admitted to the ICU after surgery, the electrocardiogram, intraarterial pressure, and pulse oxygen saturation were monitored continuously. For patients sent back to the general wards after surgery, electrocardiogram, noninvasive blood pressure, and pulse oxygen saturation were monitored continually through the first postoperative morning and then once or twice daily until hospital discharge. Clinicians instituted more frequent monitoring or transfer to an intensive care unit as indicated.

Our primary outcome was delirium, which was assessed dichotomously with the Confusion Assessment Method for the ICU.[32] The Chinese version of the Confusion Assessment Method for the ICU has been validated in spontaneously ventilating patients with acceptable sensitivity and specificity,[33] and we have considerable experience with the technique.[34,35] Delirium was assessed twice daily (between 8 and 10 AM and between 6 and 8 PM) during the first 7 postoperative days or until hospital discharge or death if earlier. Immediately before assessing delirium, sedation or agitation was assessed using the Richmond Agitation Sedation Scale, with scores ranging from −5 (unarousable) to +4 (combative), where 0 indicates alert and calm.[36] For deeply sedated or unarousable patients (Richmond Agitation Sedation Scale score of −4 or −5), delirium was not assessed, and the patient was recorded as comatose.

Patients with delirium were classified into three subtypes: hyperactive (Richmond Agitation Sedation Scale score consistently positive, from +1 to +4), hypoactive (Richmond Agitation Sedation Scale score consistently neutral or negative, from −3 to 0), and mixed.[37] Investigators who performed follow-up and delirium assessment (G.-J.S., Q.M., Huai-Jin Li, Y. Zhao, H.K., D.H., C.-M.D., Y. Zhang, S.-T.H., P.-F.L., Y.L., and H.-Y.Z.) were trained to use the Confusion Assessment Method for the ICU by a psychiatrist (X.-Y.S.). The training program included lectures introducing delirium and the Confusion Assessment Method for the ICU, as well as simulation with actors. Initial training continued until delirium diagnoses reached 100% agreement between investigators and the psychiatrist and was repeated two to three times a year throughout data acquisition.

Secondary outcomes included ICU admission after surgery, time to onset of delirium, time to oral fluid/food intake, postoperative duration of hospitalization, and 30-day all-cause mortality. For patients admitted to the ICU after surgery, the worst Acute Physiology and Chronic Health Evaluation II (APACHE II) score within 24 h, the percentage with endotracheal intubation, the duration of mechanical ventilation (for those with endotracheal tubes), and the length of ICU stay were recorded. An additional secondary outcome was major complications other than delirium, defined as new-onset medical conditions that were deemed harmful and required therapeutic intervention (*i.e.*, grade II or higher on the Clavien–Dindo classification).[38]

Other prespecified outcomes included pain severity both at rest and with movement, which were assessed with the Numeric Rating Scale (an 11-point scale, where 0 denotes no pain and 10 the worst pain) twice daily at the time of delirium assessment during the first 3 postoperative days. After the first 7 days, evaluations were performed weekly until 30 days after surgery. Discharged patients were contacted by phone.

We recorded anesthetic-related adverse event for 3 postoperative days and thereafter recorded complications until 30 days after surgery. Among anticipated hemodynamic abnormalities, we defined intraoperative hypotension as systolic blood pressure less than 80 mmHg, intraoperative

hypertension as systolic blood pressure greater than 180 mmHg, postoperative hypotension as systolic blood pressure less than 90 mmHg, and postoperative hypertension as systolic blood pressure greater than 160 mmHg.

Statistical Analysis

Patients were primarily analyzed within the groups to which they were assigned, whether or not the designated treatment was received, excluding those with repeated randomizations, cancelled surgeries, or consent withdrawal before anesthesia (modified intention-to-treat population). For the primary outcome, analysis was also performed in the per-protocol population, based on the treatment received.

Our primary outcome, the incidence of postoperative delirium within 7 days, was compared by a chi-square test. A similar analysis was used for the per-protocol analysis. For patients with missing data because of early hospital discharge or death, the last delirium assessment results were considered as the final results. Exploratory analyses were performed to assess differences of the primary outcome in predefined subgroups. Treatment-by-covariate interactions were assessed separately for each subgroup factor using logistic regression.

Continuous variables were analyzed with independent-sample *t* tests for normally distributed data or Mann–Whitney U tests. Differences (and 95% CI) between medians were calculated with Hodges–Lehmann estimators. Categorical variables were analyzed with chi-square tests with continuity correction or Fisher exact tests. Time-to-event results were analyzed with Kaplan–Meier survival analyses with log-rank tests; patients who died within 30 days were censored at the time of death. Missing data were not replaced.

For each hypothesis, a two-sided $P < 0.05$ was considered statistically significant. For the treatment-by-covariate interaction in predefined subgroup analyses, a $P < 0.10$ was considered statistically significant. Statistical analyses were performed with SAS 9.3 software (SAS, USA) and SPSS 25.0 software (IBM SPSS, USA).

An independent data quality committee from the Peking University Clinical Research Institute monitored compliance and completeness of the data, and the Peking University Institutional Review Board reviewed the results and determined whether the trial should be suspended because of high incidence of violations or clear evidence of harm. There were no interim analyses for efficacy or futility.

Sample size was based on a cohort of patients at our facility in whom the incidence of postoperative delirium was 13.1% in older patients given general anesthesia for major abdominal surgery. We estimated that a sample size of 1,664 participants (832 per group), would provide 80% power for detecting a one-third reduction in the primary outcome, with a two-sided significance level of 0.05. We therefore planned to enroll 1,800 patients with the expectation that 7.5% would drop out.

Results

Between November 21, 2011, and May 25, 2015, a total of 3,049 patients were screened for inclusion. Of these, 2,199 were eligible, and 1,802 were enrolled and randomly assigned to either combined epidural–general anesthesia (n = 901) or general anesthesia alone (n = 901). Among the enrolled patients, 8 were excluded because of repeated randomizations, 49 were excluded because surgery was cancelled, and 25 withdrew consent before anesthesia. A total of 1,720 patients were therefore included in the modified intention-to-treat population, with 857 given combined epidural–general anesthesia and 863 given general anesthesia alone. There was a total of 118 protocol deviations, leaving 1,602 patients included in the per-protocol analysis (776 in the epidural–general anesthesia group and 826 in the general anesthesia group; fig. 1).

Demographic and baseline variables were well balanced between the two groups except that preoperative hypertension was less common, and creatinine concentrations were lower in patients assigned to combined epidural–general anesthesia (Table 1). Patients with combined epidural–general anesthesia were given epidural lidocaine (median, 60 mg [interquartile range, 40 to 80]) and ropivacaine (median, 85 mg [interquartile range, 60 to 125]). As expected, patients in the epidural–general anesthesia group consumed less volatile anesthesia, opioids, cisatracurium, and nonsteroidal anti-inflammatory drugs; additionally, they received more artificial colloids and had lower mean arterial pressures, higher heart rates, and greater urine output. Patients assigned to epidural–general anesthesia were given more epidural sufentanil but less intravenous morphine during the first 7 postoperative days. Total perioperative morphine equivalent consumption was significantly less in the combined epidural–general anesthesia patients (mean difference, −32 mg; 95% CI, −41 to −23]; Table 2 and Table S1 in Supplemental Digital Content 2, http://links.lww.com/ALN/C625).

The incidence of postoperative delirium within 7 days was significantly lower in patients assigned to epidural–general anesthesia (15 [1.8%] of 857 patients) than in the general anesthesia group (43 [5.0%] of 863 patients; relative risk, 0.351; 95% CI, 0.197 to 0.627; $P < 0.001$; number needed to treat, 31; fig. 2). The per-protocol analysis showed a similar difference (11 [1.4%] of 776 patients *vs.* 39 [4.7%] of 826 patients; relative risk, 0.300, 95% CI, 0.155 to 0.582; $P < 0.001$). All three subtypes of delirium were significantly less common in the epidural–general anesthesia patients (Table 3). In subgroup analyses, we found a significant interaction for the primary outcome between treatment group and study center (center 1 *vs.* others; $P = 0.067$); there were no significant interactions between treatment group and other predefined factors. The effect of combined epidural–general anesthesia on delirium was roughly similar across all subgroups (fig. 3).

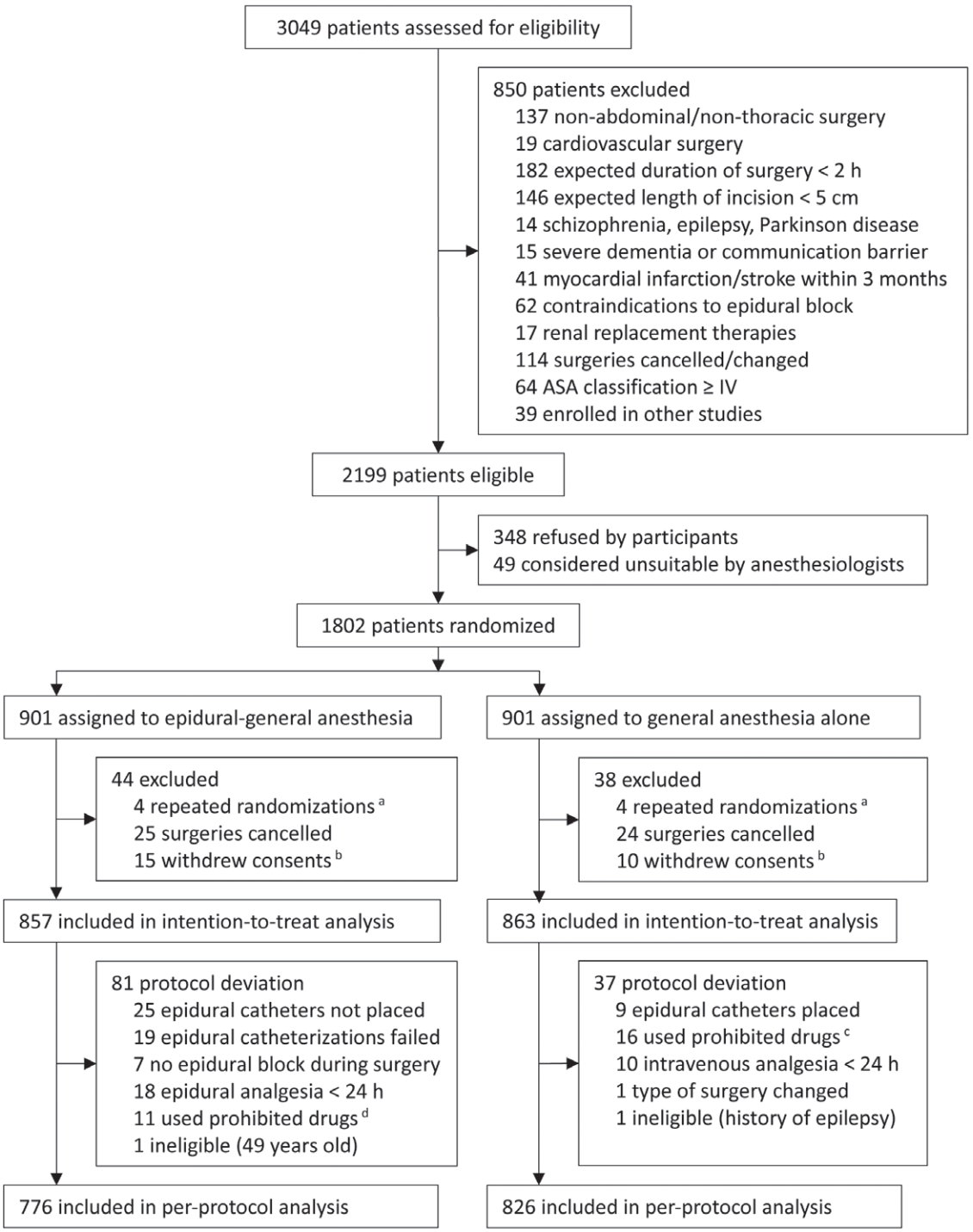


Fig. 1. Trial profile. [a]Acquired a second random number because of rescheduled surgery. [b]Consents withdrawn before anesthesia. [c]Fifteen patients received dexmedetomidine, and one patient received scopolamine. [d]Received dexmedetomidine. ASA, American Society of Anesthesiologists.

Among 339 (20%) patients admitted to the ICU after surgery, those assigned to combined epidural–general anesthesia were 33% less likely to remain intubated, and ICU duration was about 5% shorter. Among all patients, moderate-to-severe pain (Numeric Rating Scale pain score of 4 or higher) at rest was significantly less common in the

Table 1. Demographic and Baseline Variables

	Combined Epidural–General Anesthesia (n = 857)	General Anesthesia (n = 863)	Absolute Standardized Difference
Age, yr	69 ± 6	70 ± 6	0.071
Male sex, n (%)	542 (63)	581 (67)	0.085
Body mass index, kg/m^2	23.6 ± 3.3	23.7 ± 3.4	0.033
Education, yr	9 ± 5	10 ± 4	0.021
Preoperative comorbidities, n (%)			
Stroke	37 (4)	48 (6)	0.061
Transient ischemic attack	10 (1)	13 (2)	0.032
Hypertension	334 (39)	377 (44)	0.097
Coronary heart disease	89 (10)	77 (9)	0.048
Arrhythmia	28 (3)	35 (4)	0.044
Chronic bronchitis	19 (2)	13 (2)	0.048
COPD	16 (2)	16 (2)	0.001
Asthma	14 (2)	13 (2)	0.010
Diabetes	153 (18)	161 (19)	0.021
Thyroid disease*	23 (3)	22 (3)	0.008
Liver dysfunction†	8 (1)	7 (1)	0.013
Renal dysfunction‡	4 (< 1)	4 (< 1)	< 0.001
Previous cancer§	18 (2)	18 (2)	0.001
Charlson Comorbidity Index‖	2 (2, 3)	2 (2, 3)	0.062
Chronic smoking, n (%)#	210 (25)	206 (24)	0.015
Alcoholism, n (%)**	61 (7)	60 (7)	0.006
Opioid therapy within 1 month, n (%)††	3 (< 1)	2 (< 1)	0.024
History of anesthesia, n (%)	394 (46)	405 (47)	0.019
New York Heart Association class, n (%)			0.004
I	648 (76)	651 (75)	
II	209 (24)	212 (25)	
ASA class, n (%)			0.070
I	63 (7)	60 (7)	
II	739 (86)	733 (85)	
III	55 (6)	70 (8)	
Preoperative laboratory tests			
Hematocrit, %	38 ± 5	38 ± 5	0.030
Albumin, g/l	40 ± 4	40 ± 4	0.025
Glucose, mmol/l	5.8 ± 1.5	5.8 ± 1.7	0.003
Sodium, mmol/l	141 ± 3	141 ± 3	0.005
Potassium, mmol/l	4.0 ± 0.4	4.0 ± 0.4	0.018
Creatinine, μmol/l	87 ± 22	90 ± 22	0.132
Delirium before surgery day, n (%)	0 (0)	0 (0)	
Mini-Mental State Examination score‡‡	29 (27, 30) [14]	29 (27, 30) [13]	0.023
Mini-Mental State Examination score of less than 24, n (%)‡‡	37 (4)	36 (4)	0.008
Barthel Index score§§	100 (100, 100) [12]	100 (100, 100) [9]	0.059
Hospital Anxiety and Depression Scale score–Depression‖‖	0 (1, 2.5) [16]	0 (0, 2) [11]	0.051
Hospital Anxiety and Depression Scale score–Depression greater than 7, n (%)‖‖	35 (4) [16]	33 (4) [11]	0.014
Hospital Anxiety and Depression Scale score–Anxiety‖‖	0 (0, 2) [16]	0 (0, 2) [11]	0.001
Hospital Anxiety and Depression Scale score–Anxiety greater than 7, n (%)‖‖	5 (1) [16]	8 (1) [11]	0.045
Hypnotics at preoperative night, n (%)##	38 (4)	33 (4)	0.030
Pathologically diagnosed cancer, n (%)	785 (92)	796 (92)	0.023
Study centers, n (%)			0.007
Center 1	781 (91)	788 (91)	
Center 2	18 (2)	15 (2)	
Center 3	19 (2)	18 (2)	
Center 5	1 (< 1)	3 (< 1)	
Center 6	38 (4)	39 (5)	

The data are presented as mean ± SD, n (%), or median (interquartile range). The numbers in square brackets indicate patients with missing data. An absolute standardized difference of 0.095 or greater is considered imbalanced between the two groups.

*Included hyperthyroidism, hypothyroidism, nodular goiter, Hashimoto's thyroiditis, and thyroid adenoma. †Serum alanine and/or aspartate transaminase higher than five times the upper normal limit. ‡Creatinine concentration higher than 177 μmol/l. §Confirmed by pathologic examination. ‖According to the Charlson Comorbidity Index without age.[26] #Smoking half a pack (10 cigarettes)/day for at least 1 yr, either former or current smoker. **Two drinks or more daily or weekly consumption of the equivalent of 150 ml of alcohol. ††Including oral oxycodone, pethidine, and codeine. ‡‡Scores range from 0 to 30, with higher scores indicating better function. §§Scores range from 0 to 100, with higher scores indicating better function. ‖‖Scores range from 0 to 21 for either depression or anxiety, with higher scores indicating more severe symptoms. A score greater than 7 was adopted as borderline abnormal. ##Including diazepam, estazolam, and zopiclone.

ASA, American Society of Anesthesiologists; COPD, chronic obstructive pulmonary disease.

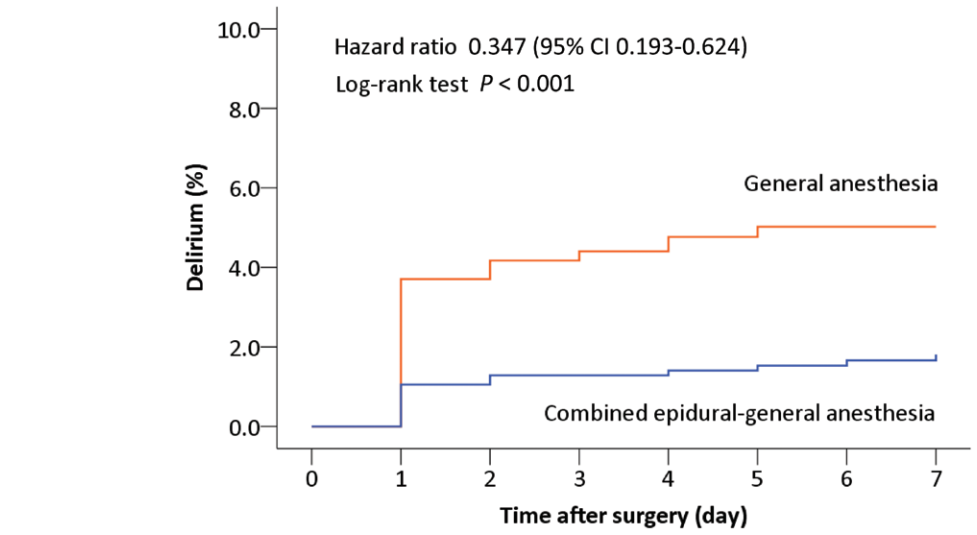
Table 2. Intra- and Postoperative Variables

	Combined Epidural–General Anesthesia (n = 857)	General Anesthesia (n = 863)	*P* Value
Duration of anesthesia, min	305 ± 121	306 ± 122	0.800
Intraoperative medications			
Midazolam, mg	1.5 (1.0, 2.0)	1.5 (1.2, 2.0)	0.172
Propofol, mg	780 (214, 1160)	830 (300, 1275)	0.058
Use of nitrous oxide, n (%)	535 (62)	603 (70)	0.001
Nitrous oxide, MAC × h	0.6 (0.0, 2.2)	1.0 (0.0, 2.5)	0.012
Use of sevoflurane, n (%)	443 (52)	492 (57)	0.027
Sevoflurane, MAC × h	0.9 (0.0, 1.8)	1.1 (0.0, 1.9)	0.015
Remifentanil, μg	180 (0, 800)	1,240 (640, 1912)	< 0.001
Sufentanil, μg	20 (15, 30)	35 (25, 45)	< 0.001
Rocuronium, mg	50 (50, 70)	50 (50, 60)	0.283
Use of cisatracurium, n (%)	513 (60)	586 (68)	0.001
Cisatracurium, mg	6 (0, 16)	10 (0, 20)	< 0.001
Use of atracurium, n (%)	33 (4)	30 (3)	0.769
Use of NSAIDs, n (%)*	152 (18)	219 (25)	< 0.001
Use of 5-HT3 receptor antagonists, n (%)†	750 (88)	778 (90)	0.083
Use of atropine, n (%)	638 (74)	646 (75)	0.845
Use of glucocorticoids, n (%)‡	774 (90)	779 (90)	0.973
Dexamethasone	708 (83)	711 (82)	0.902
Others	96 (11)	92 (11)	0.719
Intraoperative fluid, ml	2,600 (1,950, 3,600)	2,600 (1,800, 3,500)	0.809
Crystalloid, ml	1,950 (1,600, 2,600)	1,850 (1,600, 2,550)	0.494
Use of artificial colloid, n (%)	719 (84)	667 (77)	0.001
Intraoperative blood transfusion, n (%)	123 (14)	141 (16)	0.253
Packed red blood cells	89 (10)	93 (11)	0.792
Fresh frozen plasma	47 (5)	51 (6)	0.704
Estimated blood loss, ml	100 (50, 300)	110 (50, 300)	0.450
Intraoperative urine output, ml§	500 (300, 700) [117]	400 (200, 700) [132]	0.012
Mean arterial pressure, mmHg‖	79 ± 7	83 ± 7	< 0.001
Heart rate, beats/min‖	69 ± 10	67 ± 10	0.003
Duration of surgery, min	249 ± 116	250 ± 117	0.941
Location of surgery, n (%)			0.516
Intrathoracic	207 (24)	197 (23)	
Intraabdominal	650 (76)	666 (77)	
Type of surgery, n (%)			0.492
Open abdominal/thoracic	591 (69)	577 (67)	
Laparo-/thoracoscopic	266 (31)	286 (33)	
Postoperative medications within 7 days			
Opioids in patient-controlled analgesia			
Sufentanil, μg	124 (118, 125)	0 (0, 0)	< 0.001
Morphine, mg	0 (0, 0)	43 (38, 50)	< 0.001
Supplemental analgesics, n (%)			
Opioids#	96 (11)	95 (11)	0.980
NSAIDs**	279 (33)	266 (31)	0.440
Sedatives, n (%)			
Benzodiazepines††	60 (7)	59 (7)	0.893
Propofol	73 (9)	110 (13)	0.004
Dexmedetomidine	8 (1)	10 (1)	0.646
5-HT3 receptor antagonists, n (%)†	573 (67)	587 (68)	0.609
Anticholinergics, n (%)‡‡	12 (1)	10 (1)	0.656
Glucocorticoids, n (%)§§	34 (4)	43 (5)	0.309
Total morphine equivalent, mg‖‖	194 ± 80	226 ± 110	< 0.001

The data are presented as mean ± SD, n (%), or median (interquartile range); numbers in square brackets indicate patients with missing data.

*Including flurbiprofen axetil and parecoxib. †Including ondansetron, tropisetron, and palonosetron. ‡Mainly for the prevention of postoperative nausea and vomiting. §Data were missing in patients who underwent bladder or prostate surgery. ‖Average value from the start of epidural block (for patients with combined epidural–general anesthesia) or anesthetic induction (for patients with general anesthesia) to the end of surgery. #Including morphine, pethidine, oxycodone, fentanyl, and codeine. **Including flurbiprofen axetil, parecoxib, aspirin-DL-lysine, and indomethacin. ††Including diazepam, estazolam, and midazolam. ‡‡Including anisodamine and atropine. §§Including dexamethasone (5 to 10 mg), hydrocortisone (50 mg), methylprednisolone (40 mg), and prednisone (10 mg, *per os*). ‖‖Including intraoperative and postoperative opioids: morphine (*per os*) 30 mg = morphine (iv) 10 mg = fentanyl (iv) 100 μg = remifentanil (iv) 100 μg = sufentanil (iv) 10 μg = sufentanil (epidural) 10 μg = tramadol (iv) 100 mg = tramadol (*per os*) 200 mg = pethidine (iv) 100 mg = oxycodone (*per os*) 15 mg = dezocine (iv) 10 mg.[12,26,27]

5-HT3, 5-hydroxytryptamine-3; MAC, minimum alveolar concentration; NSAID, nonsteroid anti-inflammatory drug.



Number of cases								
Combined epidural-general	857	857	845	838	823	792	724	653
General anesthesia	863	863	830	825	795	745	669	607

Fig. 2. Probability of postoperative delirium by day 7 after surgery.

epidural–general anesthesia group on the first postoperative morning (relative risk, 0.72; 95% CI, 0.55 to 0.95; $P = 0.019$); moderate-to-severe pain during movement was also significantly less common on the first postoperative morning (relative risk, 0.82; 95% CI, 0.73 to 0.93; $P = 0.001$) and afternoon (relative risk, 0.83; 95% CI, 0.74 to 0.95; $P = 0.005$), and the second postoperative morning (relative risk, 0.86; 95% CI, 0.74 to 0.99; $P = 0.040$). Other secondary outcomes including nondelirium complications within 30 days did not differ between the two groups (Table 3 and Table S2 in Supplemental Digital Content 2, http://links.lww.com/ALN/C625).

Patients randomized to epidural–general anesthesia had more intraoperative hypotension (421 [49%] *vs.* 288 [33%]; relative risk, 1.47; 95% CI, 1.31 to 1.65; $P < 0.001$), spent more time with mean arterial pressure of less than 65 mmHg (17 min [interquartile range 3 to 42] *vs.* 8 min [0 to 25]), and were more likely to require vasopressors (495 [58%] *vs.* 387 [45%]; relative risk, 1.29; 95% CI, 1.17 to 1.41; $P < 0.001$); in contrast, they had less hypertension (183 [21%] *vs.* 302 [35%]; relative risk, 0.61; 95% CI, 0.52 to 0.71; $P < 0.001$). Over the initial 3 postoperative days, patients assigned to epidural–general anesthesia were less likely to experience hypertension (64 [7%] *vs.* 161 [19%]; relative risk, 0.40; 95% CI, 0.30 to 0.53; $P < 0.001$) or postoperative nausea and vomiting (80 [9%] *vs.* 116 [13%]; relative risk, 0.69; 95% CI, 0.53 to 0.91; $P = 0.007$). One patient in the epidural–general anesthesia group died from pulmonary embolism on the first day after surgery, a complication that was considered unrelated to study group assignment (Table 4).

Discussion

There was less delirium during the first 7 postoperative days in older patients randomized to combined epidural–general anesthesia for major thoracic and abdominal surgeries compared with general anesthesia alone. The reduction was consistent across all three motoric subtypes of delirium and similar for all predefined subgroups. The treatment effect was substantial and highly statistically significant, with the incidence being only about a third in patients assigned to combined epidural–general anesthesia. Because the incidence of delirium in the general anesthesia alone group was only 5%, the number needed to treat was 31 (the reciprocal of the absolute risk reduction). We note, however, that the same relative treatment effect would correspond to a number needed to treat of 15 at a baseline delirium risk of 10% and 10 at a baseline risk of 15%—both of which are well within reported ranges.[2,4,5]

Two systematic reviews reported that the incidence of delirium was similar after neuraxial and general anesthesia for hip fracture surgery.[10,19] However, more recent observational analyses observed less delirium in patients who had neuraxial rather than general anesthesia for hip or knee arthroplasties.[20–22] One small trial randomized 70 older patients to general anesthesia and intravenous analgesia or combined epidural–general anesthesia with epidural analgesia; that is, a protocol similar to ours. Despite better analgesia and improved mental status in the combined anesthesia patients, the frequency of postoperative delirium was similar in each group (24% *vs.* 26%, respectively). Because

Table 3. Efficacy Outcomes

	Combined Epidural–General Anesthesia (n = 857)	General Anesthesia Alone (n = 863)	Relative Risk, Hazard Ratio, or Estimated Difference (95% CI)*	*P* Value
Primary endpoint				
Delirium within 7 days, n (%)	15 (1.8)	43 (5.0)	Relative risk = 0.351 (0.197, 0.627)	< 0.001
Delirium within 7 days, n (%; per-protocol analysis)	11 (1.4; n = 776)	39 (4.7; n = 826)	Relative risk = 0.300 (0.155, 0.582)	< 0.001
Secondary endpoints				
ICU admission after surgery, n (%)	158 (18)	181 (21)	Relative risk = 0.88 (0.73, 1.06)	0.186
APACHE II score at ICU admission†	9.3 ± 3.6	9.2 ± 3.6	Mean difference = 0.1 (-0.7, 0.8)	0.598
With endotracheal intubation, n (%)	73 (9)	109 (13)	Relative risk = 0.67 (0.51, 0.89)	0.006
Duration of mechanical ventilation in ICU, h‡	6 (4, 8)	8 (6, 10)	Hazard ratio = 1.30 (0.96, 1.76)	0.086
Length of ICU stay, h	19 (18, 20)	21 (19, 22)	Hazard ratio = 1.30 (1.05, 1.62)	0.017
Nondelirium complications within 30 days, n (%)§	186 (22)	210 (24)	Relative risk = 0.89 (0.75, 1.06)	0.195
Time to fluid intake, days	4 (4, 4)	4 (4, 4)	Hazard ratio = 1.01 (0.92, 1.12)	0.768
Time to food intake, days	5 (5, 5)	5 (5, 5)	Hazard ratio = 1.00 (0.91, 1.10)	0.949
Length of stay in hospital after surgery, days	9 (9, 9)	9 (9, 9)	Hazard ratio = 1.01 (0.92, 1.12)	0.778
All-cause 30-day mortality, n (%)	6 (< 1)	2 (< 1)	Relative risk = 3.02 (0.61, 14.93)	0.177
Prespecified analyses				
Moderate to severe pain (at rest), n (%)‖				
Day 1, AM	77 (9%) [3]	108 (13%) [2]	Relative risk = 0.72 (0.55, 0.95)	0.019
Day 1, PM	77 (9%) [3]	76 (9%) [2]	Relative risk = 1.02 (0.76, 1.38)	0.885
Day 2, AM	51 (6%) [3]	60 (7%) [1]	Relative risk = 0.86 (0.60, 1.23)	0.405
Day 2, PM	1 (< 1%) [6]	0 (0%) [3]		0.497
Day 3, AM	0 (0%) [7]	0 (0%) [3]		
Day 3, PM	0 (0%) [13]	0 (0%) [11]		
Moderate to severe pain (with movement), n (%)‖				
Day 1, AM	314 (37) [3]	384 (44) [2]	Relative risk = 0.82 (0.73, 0.93)	0.001
Day 1, PM	281 (33) [3]	340 (39) [1]	Relative risk = 0.83 (0.74, 0.95)	0.005
Day 2, AM	230 (27) [3]	271 (31) [1]	Relative risk = 0.86 (0.74, 0.99)	0.040
Day 2, PM	190 (22) [7]	202 (23) [3]	Relative risk = 0.95 (0.80, 1.13)	0.577
Day 3, AM	172 (20) [7]	165 (19) [3]	Relative risk = 1.06 (0.87, 1.28)	0.586
Day 3, PM	154 (18) [13]	135 (16) [11]	Relative risk = 1.15 (0.93, 1.42)	0.188
Exploratory analyses				
Motoric subtype of delirium, n (%)				0.003
None	842 (98)	820 (95)		
Hypoactive	11 (1)	30 (3)		
Hyperactive	3 (< 1)	9 (1)		
Mixed	1 (< 1)	4 (< 1)		

The data are presented as mean ± SD, n (%), or median (95% CI). The numbers in square brackets indicate patients with missing data.

*Calculated as the combined epidural–general anesthesia group *versus* or minus the general anesthesia group. †Result of patients who were admitted to ICU after surgery. ‡Result of patients who were admitted to ICU with endotracheal intubation. §Nondelirium complications were generally defined as new-onset medical conditions other than delirium that were harmful to patients' recovery and that required therapeutic intervention within 30 days after surgery. ‖Defined as Numeric Rating Scale (an 11-point scale where 0 = no pain and 10 = the worst pain) of pain > 3. Data are missing in some patients because of sedation, hospital discharge, or death.

APACHE, Acute Physiology and Chronic Health Evaluation; ICU, intensive care unit.

the number of events was small, only 16, CIs around the true treatment effect were large.[39] Our results based on more than 25 times as many enrolled patients and 4 times as many outcomes are presumably more reliable. We did not observe any statistically significant or clinically important subgroup differences, suggesting that the effects of combining epidural and general anesthesia on delirium apply broadly.

Various mechanisms may contribute to delirium sparing in patients given combined epidural–general anesthesia. First, epidural blocks reduced the consumption of general anesthetics during surgery; specifically, sevoflurane exposure was reduced by 18%, which is consistent with previous reports.[23] Previous work shows that deep general anesthesia is associated with more delirium[40] and that deep propofol sedation during spinal anesthesia promotes delirium.[41] Reduced general anesthetic consumption in the combined epidural–general anesthesia group may therefore have contributed to less delirium in the combined anesthesia patients.

Epidural blocks improved postoperative analgesia; specifically, moderate-to-severe pain was reduced by 28% at rest and by 18% with movement, benefits that are consistent with previous studies.[18] Severe pain is an important risk factor of postoperative delirium.[13] Better analgesia with epidural blocks might therefore have helped to reduce delirium.

Opioids are strongly associated with delirium.[42,43] Because analgesia was better, patients randomized to

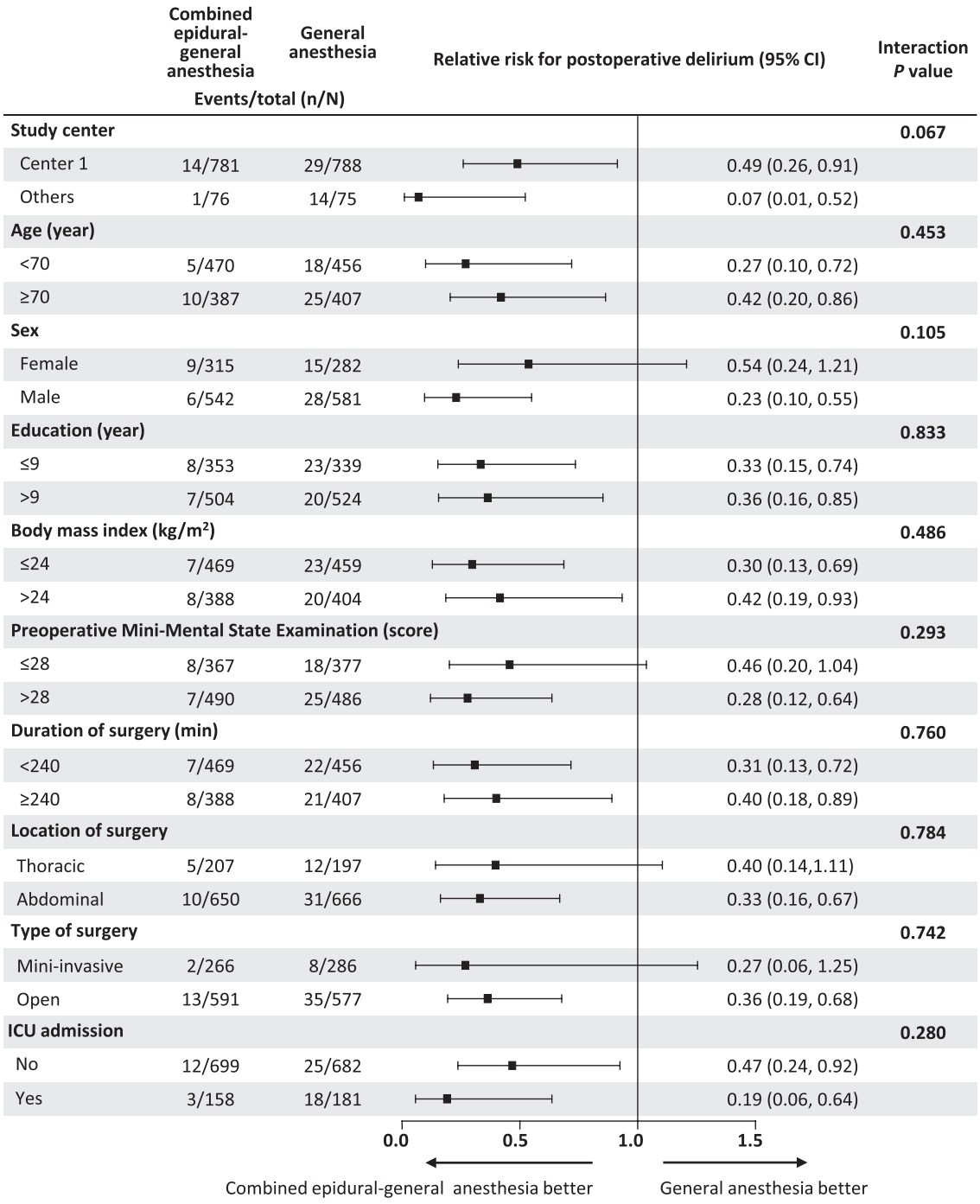


Fig. 3. Forest plot in predefined subgroups. Forest plot assessing the effect of combined epidural–general anesthesia *versus* general anesthesia alone in predefined subgroups. Logistic models were applied for assessment of treatment-by-covariate interactions. Treatment-by-covariate interactions were assessed separately for each subgroup factor, including study center, age, sex, education level, body mass index, preoperative mini-mental status evaluation, duration of surgery, location of surgery, and type of surgery. ICU, intensive care unit.

combined epidural–general anesthesia were given only 28% as much intraoperative opioid and postoperatively were given a short-acting opioid rather than morphine. Reduced opioid consumption and use of sufentanil rather than morphine may therefore have reduced delirium in patients given combined anesthesia.[44]

An additional factor is that epidural analgesia blunts the stress and inflammatory responses to surgical tissue

Table 4. Adverse Events

	Combined Epidural–General Anesthesia (n = 857)	General Anesthesia (n = 863)	Relative Risk or Estimated Median Difference (95% CI)*	*P* Value
Intraoperative period				
Accidental dural puncture, n (%)	2 (0)			
Failure of epidural catheterization, n (%)	17 (2)			
Epidural catheter obstruction, n (%)	2 (0)			
Hypotension (SBP < 80 mmHg), n (%)	421 (49)	288 (33)	1.47 (1.31, 1.65)	< 0.001
MAP < 65 mmHg, min	17 (3, 42)	8 (0, 25)	Median D = 5 (3, 6)	< 0.001
Use of vasopressors, n (%)†	495 (58)	387 (45)	1.29 (1.17, 1.41)	< 0.001
Hypertension (SBP > 180 mmHg), n (%)	183 (21)	302 (35)	0.61 (0.52, 0.71)	< 0.001
Bradycardia (HR < 40 beats/min), n (%)	62 (7)	54 (6)	1.16 (0.81, 1.65)	0.419
Tachycardia (HR > 100 beats/min), n (%)	319 (37)	340 (39)	0.95 (0.84, 1.06)	0.354
Anaphylactic shock, n (%)‡	1 (0)	1 (0)	1.01 (0.06, 16.1)	> 0.999
Postoperative period within 3 days				
Epidural catheter obstruction, n (%)	8 (1)			
Inadequate epidural analgesia, n (%)	4 (0)			
Epidural catheter dislodgement, n (%)	11 (1)			
Leg weakness and numbness, n (%)§	3 (0)			
Hypotension (SBP < 90 mmHg), n (%)	43 (5)	28 (3)	1.55 (0.97, 2.47)	0.065
Hypertension (SBP > 160 mmHg), n (%)	64 (7)	161 (19)	0.40 (0.30, 0.53)	< 0.001
Bradycardia (HR < 50 beats/min), n (%)	21 (2)	15 (2)	1.41 (0.73, 2.72)	0.302
Tachycardia (HR > 100 beats/min), n (%)	59 (7)	77 (9)	0.77 (0.56, 1.07)	0.117
Postoperative nausea and vomiting, n (%)	80 (9)	116 (13)	0.69 (0.53, 0.91)	0.007
Transient deafness, n (%)‖	1 (0)	2 (0)	0.50 (0.05, 5.54)	> 0.999
Death, n (%)#	1 (0)	0 (0)		0.498

The data are presented as n (%) or median (interquartile range).

*Calculated as the combined epidural–general anesthesia group *versus* or minus the general anesthesia group. †Including *e*phedrine, phenylephrine, epinephrine, and norepinephrine. ‡Anaphylaxis accompanied with hypotension that required adrenaline and/or noradrenaline therapy. §Lower limb muscle strength of grade 4 or less. Symptoms recovered after cessation of epidural analgesia. ‖Diagnosed by otolaryngologists. #Died from pulmonary embolism on the first day after surgery, which was considered unrelated to study intervention.

HR, heart rate; MAP, mean arterial pressure; SBP, systolic blood pressure.

injury.[17,24] Because inflammation is thought to promote delirium, blunted stress responses may have reduced the incidence of postoperative delirium in patients assigned to combined anesthesia.[14] Finally, intubation and concomitant sedation promotes delirium.[45] Because epidural blocks decreased the proportion of patients who were admitted to the ICU with endotracheal intubation, delirium might have been reduced as well.[45]

The incidence of delirium in our general anesthesia alone group was lower than that reported in many previous studies including ours,[8,12,34,35,41] but within previously reported ranges.[3,5,46] Our lower incidence presumably reflects relatively low baseline risk. For example, we enrolled patients as young as 60 yr, whereas many delirium trials restrict enrolment to patients exceeding 65 or even 70 yr. Consequently, when compared with other studies, our patients were younger, had fewer comorbidities, had and better baseline Mini-Mental State Examination scores[34,35,41]—all of which presumably reduced the incidence of delirium.[13] We also took precautions to reduce delirium. For example, we did not allow premedication with sedatives and/or anticholinergics and used an ultra-short-acting opioid intraoperatively. Postoperative nursing care has also improved in recent years and now routinely includes early mobilization and efforts to minimize night-time disruptions.[13] Finally, about a third of our patients had minimally invasive surgeries, which presumably reduce surgical stress and consequent inflammation, both of which are thought to contribute to delirium.[14]

Epidural blocks are considered to be safe in patients without specific contraindications.[16] Our results are consistent because the incidence of severe adverse events was low, and none was attributed to epidural anesthesia and analgesia. However, epidural anesthesia significantly increased the incidence of intraoperative hypotension and the need for vasopressor treatment, which is a well known consequence of combining general and epidural anesthesia.[18] In recent years intraoperative hypotension has been linked to delirium,[4] myocardial injury,[47] acute kidney injury,[47] and even perioperative mortality,[48] although there remains limited randomized evidence of harm.[49] The benefit of combined epidural–general anesthesia thus needs to be balanced against potential risks of hypotension in individual patients.

For pragmatic reasons, participants and care providers were not masked from group assignment. However, investigators who performed postoperative follow-ups and outcome assessment did not participate in perioperative care and had no knowledge of treatment assignments, although blinding was surely imperfect. We only enrolled patients scheduled for major thoracic and abdominal surgeries, and patients with severe comorbidities were excluded.

Our results can presumably be generalized to other major noncardiac operations; the benefits of combined epidural–general anesthesia may differ for minor operations or cardiac surgery, which has a higher baseline delirium incidence. For various reasons, we excluded 82 (5%) patients from our intention-to-treat analysis and 200 (11%) patients from our per-protocol analysis. Most exclusions were for technical reasons that seem unlikely to have resulted from bias. As might therefore be expected, results were similar with intention-to-treat and treatment-received analyses.

With 1,720 patients completing the trial, ours is far larger than others comparing combined epidural–general anesthesia with general anesthesia alone. However, the baseline incidence of delirium was low in the reference group and even lower in the combined epidural–general group. Consequently, the total number of delirium cases was only 58. Thus, from the perspective of outcome events, the trial is relatively small. Furthermore, a factor-of-three reduction in a complex and multifactorial outcome such as delirium seems unlikely. It is therefore plausible—and perhaps likely—that the true effect of combined epidural–general anesthesia on delirium is less than we observed. Pain evaluations were suboptimal because we assessed pain intensity just twice daily, starting the first postoperative morning; furthermore, some data were missing in some cases. The use of patient-controlled analgesia with background continuous morphine infusion in the general anesthesia group may threaten the external validity of our results. In a companion paper, we report results for an outcome at 5 yr, thus giving us two primary outcomes. We did not correct for multiplicity, but our results are robust ($P < 0.001$) and statistical compensation for multiple outcomes would not change our conclusions.

In summary, delirium is a common and serious postoperative complication with few if any established preventive measures. Older patients randomized to combined epidural–general anesthesia with epidural analgesia for major noncardiac surgeries had one third as much delirium compared with those assigned to general anesthesia alone with opioid analgesia. Patients given combined epidural–general anesthesia also required less opioid and experienced less nausea and vomiting—but had more hypotension. Clinicians deciding whether to use combined epidural–general anesthesia for prevention of delirium should consider baseline delirium risk (which strongly influences the number-needed-to-treat) and individual patient risk of hypotension.

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Competing Interests

The authors declare no competing interests.

Reproducible Science

Full protocol available at: dxwang65@bjmu.edu.cn. Raw data available at: dxwang65@bjmu.edu.cn.

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