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Effect of Regional vs General Anesthesia on Incidence of Postoperative Delirium in Older Patients Undergoing Hip Fracture Surgery
The RAGA Randomized Trial

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IMPORTANCE In adults undergoing hip fracture surgery, regional anesthesia may reduce postoperative delirium, but there is uncertainty about its effectiveness.

OBJECTIVE To investigate, in older adults undergoing surgical repair for hip fracture, the effects of regional anesthesia on the incidence of postoperative delirium compared with general anesthesia.

DESIGN, SETTING, AND PARTICIPANTS A randomized, allocation-concealed, open-label, multicenter clinical trial of 950 patients, aged 65 years and older, with or without preexisting dementia, and a fragility hip fracture requiring surgical repair from 9 university teaching hospitals in Southeastern China. Participants were enrolled between October 2014 and September 2018; 30-day follow-up ended November 2018.

INTERVENTIONS Patients were randomized to receive either regional anesthesia (spinal, epidural, or both techniques combined with no sedation; n = 476) or general anesthesia (intravenous, inhalational, or combined anesthetic agents; n = 474).

MAIN OUTCOMES AND MEASURES Primary outcome was incidence of delirium during the first 7 postoperative days. Secondary outcomes analyzed in this article include delirium severity, duration, and subtype; postoperative pain score; length of hospitalization; 30-day all-cause mortality; and complications.

RESULTS Among 950 randomized patients (mean age, 76.5 years; 247 [26.8%] male), 941 were evaluable for the primary outcome (6 canceled surgery and 3 withdrew consent). Postoperative delirium occurred in 29 (6.2%) in the regional anesthesia group vs 24 (5.1%) in the general anesthesia group (unadjusted risk difference [RD], 1.1%; 95% CI, −1.7% to 3.8%; P = .48; unadjusted relative risk [RR], 1.2 [95% CI, 0.7 to 2.0]; P = .57]). Mean severity score of delirium was 23.0 vs 24.1, respectively (unadjusted difference, −1.1; 95% CI, −4.6 to 3.1). A single delirium episode occurred in 16 (3.4%) vs 10 (2.1%) (unadjusted RD, 1.1%; 95% CI, −1.7% to 3.9%; RR, 1.6 [95% CI, 0.7 to 3.5]). Hypoactive subtype in 11 (37.9%) vs 5 (20.8%) (RD, 11.5; 95% CI, −11.0% to 35.7%; RR, 2.2 [95% CI, 0.8 to 6.3]). Median worst pain score was 0 (IQR, 0 to 20) vs 0 (IQR, 0 to 10) (difference 0; 95% CI, 0 to 0). Median length of hospitalization was 7 days (IQR, 5 to 10) vs 7 days (IQR, 6 to 10) (difference 0; 95% CI, 0 to 0). Death occurred in 8 (1.7%) vs 4 (0.9%) (unadjusted RD, −0.8%; 95% CI, −2.2% to 0.7%; RR, 2.0 [95% CI, 0.6 to 6.5]). Adverse events were reported in 106 episodes in the regional anesthesia group and 102 in the general anesthesia group; the most frequently reported adverse events were nausea and vomiting (47 [44.3%] vs 34 [33.3%]) and postoperative hypotension (13 [12.3%] vs 10 [9.8%]).

CONCLUSIONS AND RELEVANCE In patients aged 65 years and older undergoing hip fracture surgery, regional anesthesia without sedation did not significantly reduce the incidence of postoperative delirium compared with general anesthesia.

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Visual Abstract
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In urban China, the age-standardized incidence of hip fracture was 177 per 100 000 women and 99 per 100 000 men in 2016, although total absolute numbers of hip fractures in persons aged 55 years and older increased about 4-fold between 2012 and 2016 due to population ageing.[1] Nearly all patients with hip fractures undergo surgical treatment, which requires regional neuraxial block or general anesthesia using systemic anesthetic agents.

Postoperative delirium is an acute neuropsychiatric syndrome associated with increased morbidity, mortality, and health care cost. Delirium occurs frequently in older people after hip fracture surgery[2] and is associated with preventable hospital morbidity[3] and mortality.

Predisposing factors include age, cognitive impairment, frailty, and complex comorbidities while emergency surgery, pain, and psychotropic medications are important precipitating factors.[4] Anesthetic drugs have been linked with the development of postoperative delirium,[5] although the pathophysiology remains unclear.

General anesthesia was associated with an increased risk for postoperative delirium in a large population-based cohort study of older adults.[6] Systematic reviews and meta-analyses[7,8] of randomized clinical trials found no evidence that the use of regional or general anesthesia influences the incidence of postoperative delirium. However, the certainty of the evidence was rated as very low using the Grading of Recommendations, Assessment, Development, and Evaluations (GRADE) framework.[9] Limitations of previous randomized trials include the lack of standardized diagnosis of postoperative delirium, excluding patients with existing dementia and delirium, inconsistent reporting of sedation used in regional anesthesia groups, out-of-date anesthetic practice, small sample size, and poor reporting, which prevented adequate assessment of the risk of biases such as randomization and blinding of assessors.[10,11]

In the RAGA (Regional Anesthesia vs General Anesthesia) multicenter, randomized clinical trial, it was hypothesized that in older patients undergoing surgical repair for hip fracture, regional anesthesia compared with general anesthesia would reduce the incidence of postoperative delirium.

Key Points

Question In older adults undergoing surgical repair for hip fracture, does regional anesthesia reduce the incidence of postoperative delirium compared with general anesthesia?

Findings In this randomized clinical trial that included 950 older adults, the incidence of postoperative delirium in regional anesthesia without sedation was 6.2% vs 5.1% with use of general anesthesia, a difference that was not statistically significant.

Meaning Regional anesthesia compared with general anesthesia did not significantly reduce the incidence and severity of postoperative delirium in older adults undergoing fragility hip fracture repair.

Methods

Trial Design

We conducted this pragmatic, randomized, allocation-concealed, open-label, parallel-group, multicenter trial at 9 university teaching hospitals in southeastern China. The trial protocol and statistical analysis plan were designed by the trial investigators and are available online (Supplement 1 and Supplement 2). The trial was sponsored by the Second Affiliated Hospital and Yuying Children's Hospital of Wenzhou Medical University; it was approved by the research ethics committee of both institutions (No. 2014-02) and by the institutional review board at each participating center. Written consent was obtained from patients, their next of kin, or a legal representative. Trial oversight was provided by the independent trial steering committee and data monitoring and ethics committee whose members reviewed accruing outcome and safety data 3 times throughout the trial.

Trial Participants

Patients aged 65 years and older with a fragility hip fracture (femoral neck, femoral head, intertrochanteric, or subtrochanteric fracture), American Society of Anesthesiologists (ASA) physical status I to IV (I [healthy], II [mild systemic disease], III [severe systemic disease], IV [severe systemic disease that is a constant threat to life]), and scheduled for surgical repair were eligible for the trial. Patients were excluded if they had multiple trauma or fractures, contraindications for regional or general anesthesia, malignant hyperthermia, or were enrolled in another randomized clinical trial.

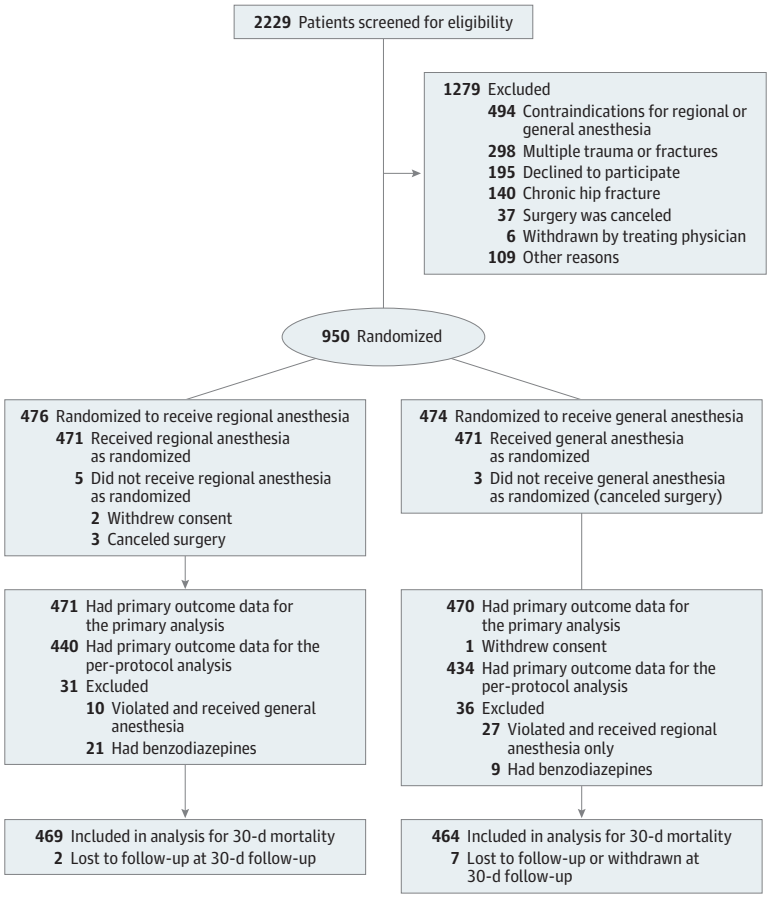
Randomization and Blinding

After giving consent, eligible patients were randomized using a web-based secure electronic central randomization system. Randomization was stratified by center, patient age (65-80 years, >80 years), presence or absence of preoperative delirium, and presence or absence of preexisting dementia to ensure equal balance between treatment groups. Delirium was diagnosed using the Confusion Assessment Method (CAM). A positive or negative result with CAM depends on 4 criteria: (1) acute onset and fluctuating course; (2) inattention; (3) disorganized thinking; and (4) altered levels of consciousness. The CAM is considered to be positive for the presence of delirium if both features 1 and 2 are present, with at least one of features 3 or 4.[12] Cognitive function was measured by the 30-point Mini-Mental State Examination (score range, 0-10 [severe impairment], 11-20, [moderate impairment], 21-25 [mild impairment], 26-30 [normal cognition]).[13] We used this scoring and adjusted for the patient's educational level to define preoperative cognitive dysfunction as a proxy for dementia (<24 for education less than postsecondary education, <23 for below secondary education; <20 for less than primary education, or <18 for illiteracy).[14,15] Participants were randomized using minimization to regional or general anesthesia in a 1:1 allocation (**Figure**). Trained outcome assessors and data collectors were blinded to group allocation throughout the study.

Anesthetic Techniques

Regional anesthesia included spinal, epidural, or combined spinal epidural techniques was provided with no sedation.

Figure. Patient Recruitment, Randomization, and Follow-up in the RAGA Trial



The type, dose, and use of nerve block were at the discretion of the consultant anesthesiologist.

General anesthesia was induced using intravenous induction agents and maintained using intravenous or inhalational anesthetic agents. Airway management and the choice of modes of ventilation were selected according to the preference of the consultant anesthesiologist who was in charge of the patient's care.

For both groups, the study protocol highly recommended application of single injection or continuous infusion of local anesthetics for peripheral nerve block techniques, such as iliac fascia 3-in-1 block, femoral nerve block, or posterior lumbar plexus block. Any medications known to impair cognitive function, including benzodiazepines or ketamine, were prohibited. Postoperative analgesia was prescribed as per local practice.

Outcome Measures

The primary outcome was the incidence of delirium during the first 7 postoperative days, using the CAM assessed daily by blinded assessors during face-to-face assessment combined with proximate look-back medical and nursing notes data extraction method in the preceding 24 hours.[16] Secondary outcomes were episodes, severity, and subtypes of delirium; the worst pain score over the first postoperative 7 days; length of hospitalization; 30-day all-cause mortality; predefined criteria for adverse events; 6-month and 1-year follow-up for delirium incidence, type, and severity; cognitive function, quality of life, and mortality; and hospitalization cost. The severity and subtypes of delirium were based on the Delirium Rating Scale-Revised-98 for severity (score range, 0 [no delirium] to 39 [highest severity of delirium]) and for hyperactive, hypoactive, or mixed subtypes of delirium.[17] The assessors for delirium assessment were fully trained by consultant psychiatrist trial collaborators. A visual analog scale (0 [no pain] to 100 [worst pain]) was used for pain measurement. The predefined criteria for adverse events were nausea, vomiting or hypoxia (oxygen saturation <88% or intermittent supplemental oxygen), or with the events for duration more than 5 minutes, hypotension (systolic blood pressure <90 mm Hg), hypertension (systolic blood pressure ≥140 mm Hg and diastolic blood pressure ≥90 mm Hg), bradycardia (heart rate <60 beats per minute), tachycardia (heart rate >100 beats per minute). All adverse events were categorized to severity, outcome, and association with anesthetic techniques. Analyses of economic and follow-up data beyond 30 postoperative days are not reported in this article.

Table 1. Demographic and Clinical Characteristics at Baseline

Characteristic	Anesthesia, No. (%)[a]	
	Regional (n = 471)	General (n = 471)
Age, median (IQR), y	77 (72-82)	77 (71-82)
Women	343 (72.8)	352 (74.7)
Men	128 (27.2)	119 (25.3)
Body mass index, median (IQR)[b]	21.5 (19.1-23.6)	21.6 (19.5-23.8)
Level of education		
<Elementary school	286 (60.7)	282 (59.9)
Elementary school	124 (26.3)	119 (25.3)
≥Secondary school	61 (13.0)	70 (14.9)
Type of fracture		
Femoral neck	278 (59.0)	264 (56.1)
Intertrochanteric	183 (38.9)	200 (42.5)
Subtrochanteric	8 (1.7)	6 (1.3)
Femoral head	2 (0.4)	1 (0.2)
ASA physical classification status		
I, Healthy	22 (4.7)	17 (3.6)
II, Mild systemic disease	350 (74.3)	363 (77.1)
III, Severe systemic disease	98 (20.8)	90 (19.1)
IV, Severe, life-threatening disease	1 (0.2)	1 (0.2)
MMSE, median (IQR)[c]	20 (15-24)	20(15-25)
Preexisting dementia	182 (38.6)	190 (40.3)
Preoperative delirium	5 (1.1)	3 (0.6)
Comorbid disease by system		
Cardiovascular	280 (59.4)	300 (63.7)
Gastrointestinal	173 (36.8)	145 (30.9)
Urinary tract	112 (23.8)	117 (24.8)
Central nervous system	65 (13.8)	57 (12.1)
Respiratory	37 (7.9)	43 (9.1)
Hematological	18 (3.8)	19 (4.0)

Abbreviations: ASA, American Society of Anesthesiologists; MMSE, Mini Mental State Examination.

[a] Values are reported as No. (%) unless otherwise indicated.

[b] Calculated as weight in kilograms divided by height in meters squared.

[c] The maximum MMSE score is 30 points (<24 [<less than postsecondary education], <23 [<secondary education], <20 [<primary education], or <18 [<elementary education]).

Post hoc outcomes included subsyndromal delirium (presence of any CAM features with absence of full syndromal delirium) and delirium symptoms (subsyndromal delirium plus syndromal delirium).[18]

Sample Size Calculation

Observational studies in China reported that incidence of postoperative day 3 delirium occurred between 11.1% and 23.3%.[19,20] Allowing for 10% missing primary outcome data due to death or missed assessments, the total sample size required 980 participants to provide 80% power to detect a relative risk of 0.7 for the primary outcome among patients receiving regional vs general anesthesia at an α value of 0.05 (2-sided).[21] After a formal review requested by the data monitoring and ethics committee, the sample size was revised to reflect a lower attrition rate than anticipated (see eAppendix in Supplement 3). The final planned sample size, inflated by the actual attrition rate of 6.6%, was 950 (475 patients in each group).

Statistical Analysis

The statistical analysis plan is available in Supplement 2, and has been previously published.[22] Patients were analyzed according to their randomization group in the full analysis set (all patients randomly assigned to receive either anesthetic technique were included). Categorical data were presented as frequencies and percentages and analyzed using 2-tailed χ^2 tests or the Fisher exact test. Relative risks (RR) with 95% CIs were calculated using the log-binomial model for the categorical variables. Continuous variables were presented as means and SDs if normally distributed and medians and IQRs if not. Groups were compared with the *t* test if normally distributed and the Mann-Whitney test if not. We conducted post hoc analyses for using linear and logistic mixed-effects techniques to assess anesthesia treatment group on the incidence of postoperative delirium and 4 prespecified secondary outcomes (episodes, severity, subtypes of delirium, and 30-day mortality), as well as the post hoc outcomes of subsyndromal delirium and delirium symptoms. The fixed effects of these models were anesthesia treatment group, age, preoperative delirium, and preexisting dementia. Possible differences between centers was taken into consideration and each center was treated as a random effect in a post hoc analysis. Absolute risk difference (RD) and mean or median differences are reported with 95% CIs. Because of the potential for type I error due to multiple comparisons, findings for analyses of secondary outcomes should be interpreted as exploratory.

We performed a per-protocol analysis and prespecified subgroups analyses that matched the stratified variables (centers, age, preexisting dementia, and preoperative delirium). Any differential effects were assessed by adding the variable for the interaction of the subgroup with the treatment group to the models. No imputation techniques were applied for missing data. All statistical tests were 2-sided and a *P* value less than .05 was considered to be statistically significant. Statistical analyses were performed using R (R software 3.5.3).

Results

Participants

The flow of patients through the trial is detailed in the Figure. Recruitment took place between October 2014 and September 2018 from 9 centers in university teaching hospitals in southeast China (eTable 1 in Supplement 3). Thirty-day follow-up for the last participant ended in November 2018.

Among the 2229 participants screened for eligibility, 950 consented and were randomly assigned to receive regional anesthesia (n = 476) or general anesthesia (n = 474). In each group, 471 patients underwent surgery. Primary outcome data were available for 471 participants in the regional anesthesia group and 470 participants in the general anesthesia group (Figure). The details of the anesthetic techniques used are shown in the eFigure (Supplement 3), the number of protocol violations are shown in the Figure, and the details of the

Table 2. Intraoperative Characteristics of Patients Undergoing Hip Fracture Surgery and Regional vs General Anesthesia

Characteristic	Anesthesia		Risk difference (95% CI)			
	Regional (n = 471)	General (n = 471)	Unadjusted[a]	Adjusted for center	Adjusted for age, preoperative delirium, preexisting dementia, and center	Unadjusted relative risk (95% CI)
Surgery approaches, No. (%)						
Closed reduction and internal fixation[b]	203 (43.1)	209 (44.4)				1 [Reference]
Open reduction and internal fixation	268 (56.9)	262 (55.6)	-1.3 (-4.1 to 7.2)	0	0	1.0 (0.9 to 1.1)
Duration of anesthesia, median (IQR), h[c]	2.0 (1.6-2.5)	2.0 (1.7-2.5)	0 (-0.1 to 0.1)			
Technical level of surgeons, No. (%)						
Senior	432 (91.7)	420 (89.2)				1 [Reference]
Junior	39 (8.3)	51 (10.8)	-2.5 (-6.2 to 1.1)	3.4 (-8.1 to 0.8)	-3.3 (-8.4 to 1.1)	1.2 (0.9 to 1.5)
Technical level of anesthesiologists, No. (%)						
Senior	197 (41.8)	223 (47.3)				1 [Reference]
Junior	274 (58.2)	248 (52.7)	5.5 (-0.1 to 12.4)	5.9 (0 to 11.3)	6.2 (-0.4 to 12.6)	0.9 (0.8 to 1.0)
Intraoperative hypotension, No. (%)[d]	149 (31.6)	369 (78.3)	-46.7 (-52.4 to -41.6)	-47.4 (-53.2 to -0.0)	-47.6 (-53.6 to -0.1)	2.6 (2.3 to 3.1)
Medicated, No. (%)[e]	124 (83.2)	305 (82.7)	0.6 (-6.1 to 6.0)	0	0 (0 to 0)	1.0 (0.7 to 1.4)
Blood transfusion, No. (%)	69 (14.6)	70 (14.9)	-0.2 (4.3 to 5.2)	-0.1 (5.3 to 4.1)	0.1 (4.9 to 5.2)	1.0 (0.8 to 1.2)

[a] Data are presented as risk differences for categorical outcomes using logistic mixed model, relative risks for categorical outcomes using log-binomial model, and mean (using linear mixed model) or median differences (using Mann-Whitney test) for continuous outcomes.

[b] Indicates the manipulation of the bone fragments of a fracture without open incisions and internal fixation is applied usually using K-wires to stabilize the fracture.

[c] Defined as the interval from administration of anesthetic to discharge from postanesthesia care unit.

[d] Defined as either systolic blood pressure lower than 90 mm Hg, an intraoperative decrease in systolic blood pressure of 30% or greater, or a decrease in blood pressure that the anesthesiologist decides requires treatment.

[e] Indicates participants experiencing intraoperative hypotension who required vasoactive drugs or fluids.

drug uses and dosage are shown in eTable 2 (Supplement 3) for regional anesthesia and in eTable 3 (Supplement 3) for general anesthesia.

Overall baseline and clinical characteristics of patients (**Table 1**) and the majority of intraoperative characteristics (**Table 2**) were well balanced between groups. However, there was a 2.5-fold increase in number of patients who experienced intraoperative hypotension in the general anesthesia group (369 [78.3%]) compared with the regional anesthesia group (149 [31.6%]), with an unadjusted risk difference (RD) of 46.7% (95% CI, 41.6% to 52.4%; $P < .001$), and after adjusting for age, preoperative delirium, preexisting dementia and random center effects, the difference remained significant (RD, 47.6% [95% CI, 10% to 53.6%]; $P < .001$).

Primary Outcome

The number of participants experiencing incidence of delirium on 1 or more occasions during the first postoperative 7 days was 29 (6.2%) in the regional anesthesia group compared with 24 (5.1%) in the general anesthesia group (unadjusted RD, 1.1% [95% CI, -1.7% to 3.8%]; $P = .48$; unadjusted relative risk [RR], 1.2 [95% CI, 0.7 to 2.0]; $P = .57$). In a post hoc analysis adjusting for center, the RD was 1.0% (95% CI, -2.3% to 4.4%; $P = .51$; **Table 3**). Per-protocol analysis produced a similar result for primary outcome (unadjusted RD, 1.1% [95% CI, -2.0% to 4.3%]; unadjusted RR, 1.2 [95% CI, 0.7 to 2.1]; eTable 4 in Supplement 3). Subgroup analyses showed no significant interaction between the treatment groups and patient subgroups (eTable 5 in Supplement 3).

Secondary Outcomes

The incidence of multiple episodes of postoperative delirium was similar, occurring in 13 (2.8%) participants in the regional anesthesia group and 14 (3.0%) in the general anesthesia group (unadjusted RD, 1.1%; 95% CI, -1.7% to 3.9%; RR, 1.6; 95% CI, 0.7 to 3.5). Comparisons between the regional anesthesia group and the general anesthesia group were similar for incidence of hyperactive delirium (55.2% vs 66.7%; unadjusted RR, 1.0 [95% CI, 0.5 to 2.0]), for hypoactive delirium (37.9% vs 20.8%; unadjusted RR, 2.2 [95% CI, 0.8 to 6.3]), and for mixed motor agitation (6.9% vs 12.5%; unadjusted RR, 0.7 [95% CI, 0.1 to 4.0]) (unadjusted RD, 11.5%; 95% CI, -11.0% to 35.7%) (Table 3). There were no significant differences between the regional anesthesia and general anesthesia groups for the worst severity of delirium score (mean [SD], 23.0 [7.76] vs 24.1 [7.26]; unadjusted risk difference, -1.1 [95% CI, -4.6 to 3.1]), the worst pain score (0 [IQR, 0 to 20] vs 0 [IQR, 0 to 10]; median difference, 0 [95% CI, 0 to 0]), and length of hospitalization (7 days [IQR, 5 to 10] vs 7 days [IQR, 6 to 10]; median difference, 0 [95% CI, 0 to 0]). The summary distribution of pain scores in the first 3 days after surgery is presented in eTable 6 in Supplement 3. All-cause 30-day mortality was 8 (1.7%) in the regional anesthesia group compared with 4 (0.9%) in the general anesthesia group, showing no significant difference (unadjusted RD, -0.8% [95% CI, -2.2% to 0.7%]; unadjusted RR, 2.0 [95% CI, 0.6 to 6.5]; Table 3). Per-protocol analysis yielded similar results (eTable 4 in Supplement 3). After adjustment for either center or age, preoperative delirium, preexisting dementia, and

Table 3. Primary and Secondary Outcomes

	Anesthesia, No./total No. (%)[a]		Risk difference (95% CI)			
	Regional (n = 471)	General[b] (n = 471)	Unadjusted	Adjusted for center	Adjusted for age, preoperative delirium, preexisting dementia, and center	Unadjusted relative risk (95% CI)
Primary outcome						
Postoperative delirium	29/471 (6.2)	24/470 (5.1)	1.1 (-1.7 to 3.8)	1.0 (-2.3 to 4.4)	0	1.2 (0.7 to 2.0)
P value			.48	.51	.64	.57
Secondary outcomes						
No. of postoperative delirium episodes[c]						
1	16/471 (3.4)	10/470 (2.1)	1.1 (-1.7 to 3.9)	1.0 (-1.9 to 3.9)	0	1.6 (0.7 to 3.5)
2	5/471 (1.1)	10/470 (2.1)				0.5 (0.2 to 1.5)
≥3	8/471 (1.7)	4/470 (0.9)				2.0 (0.6 to 6.6)
Delirium Rating Scale-Revised-98, mean (SD), score[d]	23.0 (7.76)	24.1 (7.26)	-1.1 (-4.6 to 3.1)	-1.1 (-4.8 to 2.1)	-1.2 (-5.3 to 3.1)	
Subtypes						
Hyperactive	16/29 (55.2)	16/24 (66.7)	11.5 (-11.0 to 35.7)	0.0 (-0.0 to 34.2)	0.0 (-0.6 to 24.0)	1.0 (0.5 to 2.0)
Hypoactive	11/29 (37.9)	5/24 (20.8)				2.2 (0.8 to 6.3)
Mixed motor agitation	2/29 (6.9)	3/24 (12.5)				0.7 (0.1 to 4.0)
30-Day mortality, No./total No.(%)	8/469 (1.7)	4/464 (0.9)	-0.8 (-2.2 to 0.7)	0	0	2.0 (0.6 to 6.5)
Worst pain score VAS, median (IQR)[e]	0 (0 to 20)	0 (0 to 10)	0			
Days of hospitalization, median (IQR)	7 (5 to 10)	7 (6 to 10)	0			
Post hoc outcome						
Subsyndromal delirium[f]	13/442 (2.9)	17/447 (3.8)	-0.9 (-3.1 to 1.5)	0	0	0.8 (0.4 to 1.6)
Delirium symptoms, No./total No.(%)[g]	42/471 (8.9)	41/470 (8.7)	0.2 (-3.9 to 4.0)	-0.1 (-4.5 to 3.6)	0	1.0 (0.7 to 1.5)

Abbreviations: CAM, Confusion Assessment Method; VAS, visual analog scale.

[a] Values are reported as No./total No. (%) unless otherwise indicated.

[b] There is 1 missing data point in the general anesthesia group. Data are presented as risk differences for categorical outcomes using logistic mixed model, relative risks for categorical outcomes using log-binomial model, and as mean (using linear mixed model) or median differences (using the Mann-Whitney test) for continuous outcomes.

[c] Postoperative delirium episodes were defined as discrete CAM-positive calendar days; if there were discrete CAM-positive calendar days on day 2 and 4 postoperatively, this counted as 2 postoperative delirium episodes. If the CAM-positive calendar days were consecutive (eg, days 1, 2, and 3), this was defined as 3 episodes.

[d] Severity of postoperative delirium was reported using the highest value of the Delirium Rating Scale-Revised-98 during the first 7 days for each patient, and subtypes correspond to the severity scores. Delirium Rating Scale-Revised-98 score range, 0 to 39 with higher scores reflecting a worse condition. A score greater than15 supports a diagnosis of delirium.

[e] VAS score range, 0 to 100, and the measurement of VAS was taken from the highest value (worst pain score) over 7 days.

[f] Subsyndromal delirium was defined as the presence of any CAM features in the absence of full syndromal delirium.

[g] Delirium symptoms: subsyndromal plus syndromal delirium.

center, there continued to be no significant differences between groups in number of episodes, subtypes, severity of delirium, and 30-day mortality.

Post Hoc Outcomes

The incidence of subsyndromal delirium occurred in 13 participants (2.9%) in the regional anesthesia group compared with 17 participants (3.8%) in the general anesthesia group, with no significant difference between groups (unadjusted RD, -0.9% [95% CI, -3.1% to 1.5%]; unadjusted RR, 0.8 [95% CI, 0.4 to 1.6]), and there was no significant difference the incidence of delirium symptoms in the regional anesthesia group (42 [8.9%]) vs in the general anesthesia group (41 [8.7%]) (unadjusted RD, 0.2% [95% CI, -3.9% to 4.0%]; unadjusted RR, 1.0 [95% CI, 0.7 to 1.5; Table 3).

Adverse Events

The overall rate of reported adverse events was 17.6% in the regional anesthesia group compared with 16.8% in the general anesthesia group. **Table 4** shows the similar distributions and patterns of episodes of serious adverse events and affected organ systems. Three patients experienced acute myocardial infarction, acute left heart failure, and acute gastric perforation in the regional anesthesia group, and 2 patients had lung infection and stroke in the general anesthesia group. The severity and outcome of adverse events and their association with the anesthetic techniques are presented in eTable 7 in Supplement 3.

Discussion

In this multicenter randomized clinical trial, regional anesthesia without sedation compared with general anesthesia did not significantly reduce the incidence of postoperative delirium during the first 7 days postsurgery in patients older than 65 years with fragility hip fracture. The severity, frequency of episode or subtypes of 7-day postoperative delirium, worst pain score, length of hospitalization, or 30-day all-cause mortality were not significantly different.

This trial has a number of strengths in comparison with previous studies.[8,10,23] First, to our knowledge, this trial is the largest study involving regional anesthetic without sedation for hip fracture surgery with postoperative delirium as an outcome, and it had a low risk of selection bias through strict allocation concealment. The patients were enrolled from 9 surgical centers for hip surgery in large university teaching hospitals in southeastern China and treat a population that represents a typical hip fracture population in Asia.

Second, the trial applied well-validated assessment tools for diagnosis of delirium and for diagnosis of severity and subtypes of delirium.[24] The outcome assessors were specifically trained by local psychiatrists to accurately apply these assessment tools prior to the trial and remained blinded to participants' group allocations during the trial.

Third, the trial had broad inclusion criteria, including preoperative dementia and delirium to enhance generalizability, a pragmatic approach to reflecting the current real-world anesthetic practice while precluding the use of sedation within regional anesthesia and other medications known to cause cognitive impairment.

The mean age of this trial's participants (77 years) was substantially younger compared with cohorts from other countries (mean age, 84 years).[25,26] Recently, a multicenter, randomized clinical trial (the REGAIN trial)[27] reported, as a secondary outcome, an incidence of delirium of 20% at 60 postoperative days, which was similar between spinal anesthesia and general anesthesia groups. However, almost all patients in the regional anesthesia group received sedation, 23% of whom received ketamine and 44% received midazolam, which have strong associations with delirium.[28] Only 30% of REGAIN trial participants, compared with 80% of this trial's patients, were ASA physical status of II or less, which is associated with a lower risk postoperative delirium compared with higher ASA status (RR, 0.56 [95% CI, 0.51 to 0.59]; $P < .001$).[29] Also of note, frailty, which is a major risk factor for delirium, is reported to be lower in China than other low- to middle-income countries and the USA. In addition, the trial population mainly came from rural China, which reports lower frailty prevalence than in urban areas.[30] These reasons may explain the lower comparative incidence of delirium in this trial.

In Chinese culture, postoperative care, including nursing, nutrition, breathing exercises, and physiotherapy, is often provided by close family members. In a randomized clinical trial of older adults undergoing major noncardiac surgery in China,[31] postoperative delirium occurred in 2.6% of participants who received the Tailored, Family-Involved Hospital Elder Life Program intervention compared with 19.4% in the usual care control group. The intervention prevented 16.7% of patients from developing postoperative delirium. Decline in physical and cognitive functions during hospitalization was significantly lower in patients in the intervention group; the effect was sustained 30 days after discharge and the length of hospitalization was significantly reduced (12 vs 16 days; $P < .001$).

This trial's 30-day mortality was lower than cohorts from other countries,[32] which is consistent with the low incidence of delirium in this trial. It is not uncommon that the event rates in randomized clinical trials are much lower than reported in the literature.[26,33] Furthermore, the lack of a national standard in hip fracture management in China prevents examining whether there was any effect of evidence-based perioperative care on the risk of delirium beyond the avoidance of drugs known to impair cognitive function.[23] In the UK, it is notable that the national clinical guidelines and best practice tariffs on time to surgery, nutrition, and geriatric assessment and rehabilitation may have contributed to the recent improvements in patient outcomes.[34]

Guideline committees have cautiously recommended that regional anesthesia should be administered unless contraindicated.[35-37] However, the evidence underpinning these recommendations has been very weak due to the lack

Table 4. Adverse Events[a]

	Anesthesia, No. (%)	
	Regional (n = 471)	General (n = 471)
No. of adverse events episodes	106	102
Digestive system		
Nausea and vomiting	47 (44.3)	34 (33.3)
Abdominal pain	2 (1.9)	1 (1.0)
Diarrhea	0	1 (1.0)
Acute gastric perforation	1 (0.9)	0
Cardiovascular system		
Postoperative hypotension	13 (12.3)	10 (9.8)
Hypertension	4 (3.8)	13 (12.8)
Arrhythmia	3 (2.8)	4 (3.9)
Chest pain	3 (2.8)	2 (2.0)
Acute		
Myocardial infarction	1 (0.9)	0
Left heart failure	1 (0.9)	0
Respiratory system		
Hypoxemia	11 (10.4)	13 (12.8)
Lung infection	0	1 (1.0)
Central nervous system		
Headache and dizziness	2 (1.9)	4 (3.92)
Stroke	0	1 (1.0)
Other		
Shivering	11 (10.3)	11 (10.8)
Skin allergy	4 (3.8)	1 (1.0)
Numbness in the back	1 (0.9)	0
Pharyngodynia	0	1 (1.0)
Mild burns of skin	0	1 (1.0)
Cerebrospinal fluid leak[b]	0	1 (1.0)
Hematoma in neck	1 (0.9)	0
Hyperglycemia[c]	0 (0)	1 (1.0)
Urinary retention	0	1 (1.0)
Anemia[d]	1 (0.9)	0

[a] Adverse event data were obtained by site trial staff from medical records.

[b] Cerebrospinal fluid leak was as result of epidural puncture in general anesthesia combined with epidural.

[c] The elevated blood glucose is clinically significant compared with the baseline value, which is judged by the investigator.

[d] Indicated by a hemoglobin level lower than 81 g/L.

of sufficiently powered randomized clinical trials.[34] The results of this trial suggest such recommendations were premature. The International Fragility Fracture Network Delphi consensus and the management of hip fractures 2020 guideline by the Association of Anaesthetists of Great Britain and Ireland consider the careful delivery of anesthesia may be of greater importance than the type of anesthesia delivered and recommend that "anesthesia should be administered according to agreed standards at each hospital, using age-appropriate doses, with the aims of facilitating early patient remobilization, reenablement and rehabilitation".[23,38,39]

Limitations

This trial has several limitations. First, the incidence of postoperative delirium diagnosed using the Confusion Assessment Method varies between 22% and 50% in Western populations[23,40] and a much lower 3-day postoperative delirium incidence reported in the Chinese population of 11.1% to 23.3%.[19,20] The sample size for this trial was calculated based on a conservative estimate of 26% from the data relevant to the Chinese population.[22] However, the observed incidence of postoperative delirium of 5.1% to 6.2% was much lower than expected, and it was considered unlikely that the trial could achieve the anticipated 30% relative reduction with statistical significance. Historically, the definitions of delirium and the exact time points at which the participants were evaluated have varied widely or were unclear, and incidence has previously been reported to range from 0.9% to 54%.[10] The lower than expected incidence of postoperative delirium likely reflects predisposing factors from age, ASA physical status, culture, and health care system rather than underestimation, although missed diagnoses cannot be ruled out. Second, the majority of participants were recruited from a single hospital, and although recruiting center was included in a post hoc analytic model as a random effect, the influence of the outcomes from 1 hospital may still persist.

Conclusions

In patients aged 65 and older undergoing hip fracture surgery, regional anesthesia without sedation did not significantly reduce the incidence of postoperative delirium compared with general anesthesia.

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