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A systematic review and meta-analysis of anesthesia type on hip fracture post-surgery outcomes

Christopher Leibold, DO[a,*], Ryan Falbo, DO[a], Anil Gupta, MD[b], Richard Miller, DO[a], John M. Pederson, BS[c], Manashree Malpe, PhD[c]

Abstract

Objective: To compare technical, clinical, and safety outcomes among hip fracture patients treated with procedures supplemented by general anesthesia (GA) or spinal/regional anesthesia (S/R).

Data sources: We searched for original studies on PubMed, Ovid MEDLINE, Ovid Embase, and Cochrane databases.

Study selection: Studies that reported clinical outcomes in patients that underwent hip fracture surgery, had available data on type of anesthesia administered, and clinical follow-up data were selected for data extraction.

Data extraction: The primary outcomes of interest were odds of mortality, including in-hospital, 30-day, 90-day, and 1-year mortality. Various adverse events (AEs) were also compared.

Data synthesis: Twenty-eight studies met our selection criteria, including 190,394 patients. A total of 107,314 (56.4%) patients were treated with procedures involving GA while 83,080 (43.6%) were treated with procedures involving S/R. There was no difference in 30-day or >1-year mortality rates between the GA and SR groups; however, compared to S/R group, the GA group had a significantly higher odds of in-hospital ($P = .004$) and 90-day mortality ($P = .004$). There was no difference in odds of adverse events between the GA and the S/R group.

Conclusions: Patients administered S/R for hip fracture procedures demonstrate lower risk of in-hospital mortality and 90-day mortality compared to patients administered GA.

Level of evidence: Therapeutic level III.

Keywords: anesthesia, femoral neck fracture, hip fracture

1. Introduction

Hip fractures are a public health concern with an estimated 2.6 million cases worldwide by the year 2025.[1] A majority of these patients are over 65 years of age and present with an array of comorbidities.[2,3] Age and preexisting medical conditions are known to have a negative impact on hip fracture prognosis and treatment.[4] Surgical interventions are used to treat approximately 98% of hip fractures,[5] and it is postulated that in patients with hip fractures, choice of anesthesia influences postsurgical outcomes.[6]

Current literature evaluating the effect of general versus regional anesthesia in hip fracture surgeries have provided conflicting results. One meta-analysis of ten randomized controlled trials (RCTs) of patients undergoing elective total hip replacement showed a reduction in deep vein thrombosis, operative time, and intraoperative blood loss when neuraxial anesthesia was used instead of general anesthesia (GA).[7] A meta-analysis of similar size (15 RCTs) observed a lower prevalence of deep vein thrombosis and reduced 30-day mortality in the regional anesthesia group; however, the GA group had a significantly reduced operation time.[8] Other meta-analyses have reported no differences in 30-day mortality between patients receiving regional anesthesia or GA.[9,10] Conflicting evidence of varying quality has made it difficult to adopt standard anesthetic recommendations for hip surgery[11,12]; some relevant meta-analyses report inconsistency in the definition and reporting of certain outcomes,[13,14] while others fail to adequately specify methodology.[15] Therefore, in this meta-analysis, our objective was to provide a rigorous, updated evaluation of the published literature to identify

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[a] Department of Orthopedic Surgery, Mercy Health St. Vincent Medical Center, [b] Toledo Orthopaedic Surgeons, Toledo, OH, [c] Superior Medical Experts, Minneapolis, MN, USA.

[*] Corresponding author. Address: 2409 Cherry Street, Suite 10, Toledo, OH, 43608. Tel: +740 507 3720; fax: +419 251 6553. E-mail address: cxleibold@mercy.com (C. Leibold).

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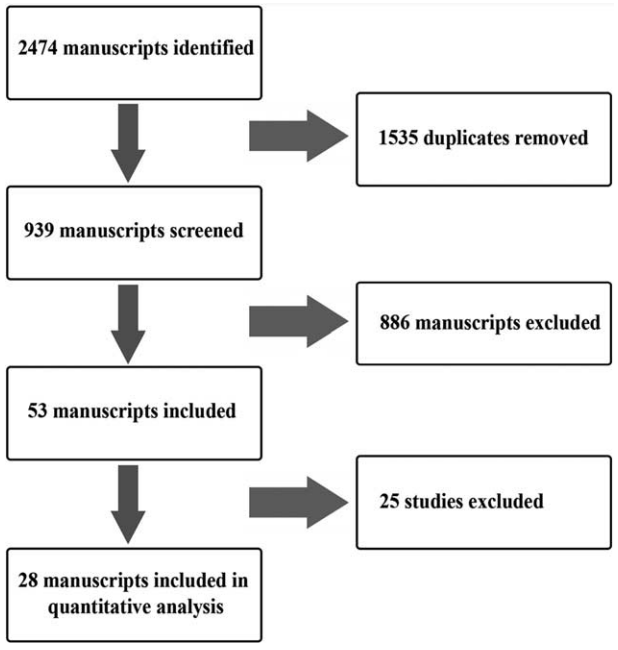

Figure 1. PRISMA flowchart. PRISMA = Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

whether anesthesia administration affects mortality following surgical treatment for hip fracture.

2. Methods

2.1. Literature search and study selection

Eligible studies were identified by conducting a systematic review of PubMed, Ovid MEDLINE, Ovid Embase, and Cochrane databases as per the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines (Fig. 1).[16] The study was registered with PROSPERO, number CRD42020172799. The major search terms used were "hip fractures," "surgery," and "anesthesia." A complete list of search strings can be found in Table, Supplemental Digital Content 1, http://links.lww.com/OTAI/A51. All studies published through May 2020 with information on anesthetic type and outcomes of hip fracture surgery were identified. Only 2-arm comparison studies evaluating outcomes for both spinal/regional (S/R) anesthesia and GA were eligible for inclusion. Background patient characteristics and type of procedure performed were not relevant criteria for study exclusion. Studies were excluded if they were preclinical (animal) studies, case series with <5 patients, opinions/editorials, review articles, published in a foreign language, or if they were not relevant to the search topic.

2.2. Data extraction and outcomes

Two independent reviewers (MM and JMP) extracted data from included manuscripts. All data were entered into a Microsoft Excel sheet, which was imported into R for further analysis using the metafor package.[17] When available, background characteristics were collected, including age, sex, body mass index, and preexisting medical conditions. Patients treated with procedures involving GA were allocated to the GA group, while patients treated with procedures involving S/R anesthesia were allocated to the S/R group.

The primary outcomes of interest were odds of in-hospital, 30-day, 90-day, and >1-year mortality between hip fracture patients operated under S/R anesthesia or GA. Data for adverse events (AEs) was collected based on availability, including: (1) stroke, (2) general cerebrovascular events (unrelated to stroke), (3) myocardial infarction, (4) general cardiovascular events (unrelated to myocardial infarction), (5) general respiratory events, (6) general renal events, (7) wound/surgery site infection, (8) general infections (unrelated to wound infection), (9) sepsis, and (10) deep vein thrombosis.

In certain studies, insufficient information was presented to extract direct measures of variance for continuous parameters. Study authors were contacted when data were missing. If data remained unavailable, the studies were either omitted or statistical methods were used to derive estimated measures of variance. In cases where the median and interquartile range and/or range were presented, the mean and/or variance was estimated using methods described by Wan et al[18] when the assumption of approximately normally distributed data was justified.

2.3. Data analysis

The magnitude of heterogeneity unrelated to sampling error was evaluated by I^2 statistics.[19] Significance of heterogeneity was measured by Cochrane's Q, with $P<.10$ considered significant.[19] A separate random-effects model was fit for each outcome comparison. Effect sizes were computed as mean differences (MDs) for continuous data or as log transformed odds ratios (ORs) for dichotomous data. To aid in interpretation, log transformed effect sizes were converted back to a probability scale. Between-study variance was estimated using a restricted effects maximum likelihood estimator with 95% confidence intervals (CIs) computed using the Q-profile method.[20] After performing univariate meta-analyses under random-effects scenarios, a meta-regression using a generalized linear model framework was considered, regressing mortality against covariates such as background and study characteristics. Forest plots were generated to depict both univariate comparisons of primary and secondary outcomes. Funnel plots were used to visually depict small study bias; asymmetry in funnel plots was assessed by Egger's linear regression after the assumption of linearity was tested.[21] P values $<.05$ were considered significant for effect size comparisons. Statistics were performed in RStudio (Version 1.3.959, RStudio, Boston, MA).

3. Results

3.1. Search results

The search strategy identified a total of 2474 records; after removing duplicates, 939 articles were screened based on title/abstract. Full texts were retrieved and reviewed for 53 articles. Ultimately, 28 studies met all inclusion criteria,[22–49] consisting of 11 prospective studies and 17 retrospective studies (Fig. 1). Among these studies, there was a total population of 190,394 patients with confirmed cases of hip fractures and information about type of anesthesia used. In the patient population, 107,314 (56.4%) belonged to the GA group, while 83,080 (43.6%) were in the S/R group. A summary of individual study and patient characteristics is shown in Table 1.

3.2. Background characteristics and comorbidities

The GA group had a slightly younger age distribution compared to the S/R group (MD: −1.19 [95% CI: −1.30; −1.08],

Table 1

Study characteristics.

Author (Year)	Study type	Center type	Randomized	Sample size	
				GA	S/R
Bigler et al (1985)[21]	Prospective	Single	Yes	20	20
Davis and Laurenson (1981)[24]	Prospective	Single	Yes	68	64
Davis et al (1987)[25]	Prospective	Multi-center	Yes	279	259
Koval et al (1999)[31]	Prospective	Single	No	362	280
McKenzie et al (1984)[35]	Prospective	Single	Yes	75	73
Sutcliffe and Parker (1994)[42]	Prospective	Multi-center	No	950	383
Valentin et al (1986)[44]	Prospective	Single	Yes	297	281
White and Chappell (1980)[45]	Prospective	Single	Yes	20	36
Ilango et al (2016)[30]	Prospective	Single	No	167	151
McLaren et al (1978)[40]	Prospective	Single	Yes	29	26
Parker and Griffiths (2015)[38]	Prospective	Single	Yes	164	158
Brox et al (2016)[23]	Retrospective	Multi-center	No	4257	3059
Desai et al (2018)[26]	Retrospective	Multi-center	No	9629	6597
Fukuda et al (2018)[28]	Retrospective	Multi-center	No	6918	5424
Gremillet and Jakobsson (2018)[29]	Retrospective	Multi-center	No	2190	11,257
Le-wendling et al (2012)[32]	Retrospective	Single	No	235	73
Lončarić-Katušin et al (2017)[34]	Retrospective	Single	No	77	38
O'Hara et al (2000)[37]	Retrospective	Multi-center	No	6206	3219
Rashid et al (2013)[39]	Retrospective	Single	No	107	87
Şahin et al (2012)[41]	Retrospective	Single	No	67	118
Tung et al (2016)[43]	Retrospective	Multi-center	No	6036	11,153
White et al (2014)[46]	Retrospective	Multi-center	No	15,181	18,333
White et al (2016)[47]	Retrospective	Multi-center	No	985	1.506
Basques et al (2015)[20]	Retrospective	Multi-center	Yes	7253	2589
Bilsel et al (2013)[22]	Retrospective	Multi-center	No	32	32
Fields et al (2015)[27]	Retrospective	Multi-center	No	4813	1815
Liu et al (2014)[33]	Retrospective	Single	No	72	145
Neuman et al (2014)[36]	Retrospective	Multi-center	No	40,825	15,904

GA = General anesthesia group; S/R = spinal/regional anesthesia group.

$P < .001$), had a higher composition of patients with diabetes (OR: 1.09 [95% CI: 1.01; 1.17], $P = .028$), and a lower composition of patients with respiratory disease (OR: 0.73 [95% CI: 0.63; 0.84], $P < .001$), each representing possible risk factors that need to be controlled for (Table 2). There was no difference in body mass index, composition of female patients, or patients with hypertension, cardiovascular disease, myocardial infarction, history of stroke, delirium, dementia, or renal disease (Table 2). Study-level and pooled effect sizes for each of these background characteristics are shown in Figures, Supplemental Digital Content 2–13, http://links.lww.com/OTAI/A51, respectively.

Table 2

Comparison of background characteristics and comorbidities between the general anesthesia and spinal/regional anesthesia group.

Variable	OR or mean diff.	95% CI	*P* value
Age (years)	−1.19	−1.30; −1.08	<.001***
Body mass index	0.31	−0.38; 1.01	.379
Female sex	0.99	0.91; 1.07	.749
Hypertension	1.02	0.95; 1.05	.581
Cardiovascular disease	1.09	0.88; 1.35	.411
Myocardial infarction	0.93	0.86; 1.01	.069
Stroke	0.98	0.83; 1.14	.769
Diabetes	1.09	1.01; 1.17	.028*
Respiratory disease	0.73	0.63; 0.84	<.001***
Delirium	1.34	0.69; 2.57	.385
Dementia	0.99	0.95; 1.03	.728
Renal Disease	0.99	0.92; 1.08	.910

CI = confidence interval; OR = odds ratio.

All comparisons are directionally general anesthesia versus spinal/regional anesthesia: values less than 1 have a lower relative odds of the event of interest in the GA group compared to the S/R group and values higher than 1 have a higher relative odds of the event of interest in the GA group compared to the S/R group. For age: negative means that it is lower in the GA group and positive means it is higher in the GA group.

* *P* value is statistically significant.

*** *P* value is highly significant.

3.3. Mortality

Among the included studies, 32.1% (9/28) had sufficient information to compare odds of in-hospital mortality between the GA and S/R group. Under a univariate random-effects model, the GA group had a significantly higher odds of in-hospital mortality compared to the S/R group (OR: 1.38 [95% CI: 1.16; 1.63], Fig. 2A). A total of 67.9% (19/28) of studies had sufficient information to assess 30-day mortality; no difference was observed between the GA and S/R group (OR: 0.98 [95% CI: 0.93; 1.04], Fig. 2B). Based on data extracted from 10.7% (3/28) of studies, the GA group had a significantly higher odds of mortality at 90 days compared to the S/R group (OR 1.13 [95% CI: 1.04; 1.23], Fig. 2C). Finally, 25.0% (7/28) of studies had data to assess 1-year mortality; the analysis did not show any difference in odds of mortality at >1 year between groups (OR: 0.98 [95% CI: 0.75; 1.30], Fig. 2D).

3.4. Adverse events

There was no significant difference in odds of any AE between the GA and S/R group, including stroke, delirium, respiratory events,

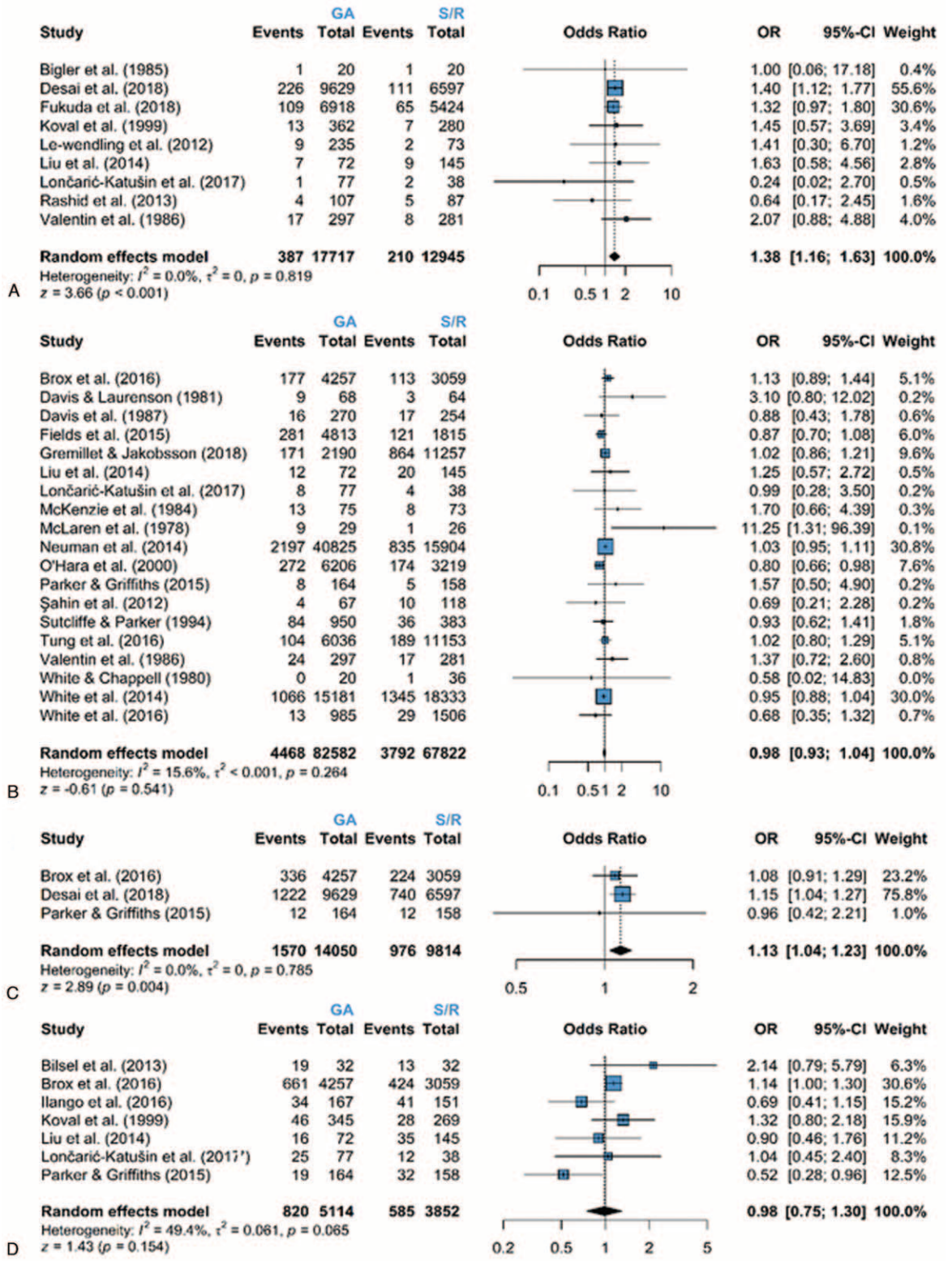

Figure 2. General anesthesia versus spinal/regional anesthesia odds ratios of mortality. (A) In-hospital mortality, $P = .004$; (B) 30-day mortality, $P = .525$; (C) 90-day mortality, $P = .004$; (D) 1-year mortality, $P = .909$. GA = General anesthesia; S/R = Spinal/regional anesthesia.

myocardial infarction, renal events, wound/surgery site infections, general infections, sepsis, and deep vein thrombosis. ORs for each individual AE are summarized in Table 3; study-level and pooled effect sizes for each AE are shown in Figures, Supplemental Digital Content 14–22, http://links.lww.com/OTAI/A51, respectively.

3.5. Meta-regression of 30-day mortality against background and study characteristics

Of the primary clinical outcomes evaluated, only 30-day mortality had sufficient data[50] to perform a reliable meta-regression to evaluate the influence of covariates on 30-day

Table 3

Comparison of certain postoperative adverse events between the general anesthesia and spinal/regional anesthesia group.

Adverse event	No. of studies	Odds ratio	95% - CI	*P* value
Stroke	14.3% (4/28)	0.93	0.64; 1.37	.721
Delirium	17.9% (5/28)	0.75	0.50; 1.13	.170
Respiratory events	46.4% (13/28)	1.03	0.95; 1.12	.474
Myocardial infarction	28.6% (8/28)	1.18	0.98; 1.43	.089
Renal events	21.4% (6/28)	0.82	0.55; 1.22	.328
Wound/surgery site infections	21.4% (6/28)	1.24	0.98; 1.57	.069
General infections	21.4% (6/28)	0.84	0.58; 1.20	.336
Sepsis	7.1% (2/28)	1.06	0.82; 1.36	.652
Deep vein thrombosis	25% (7/28)	1.12	0.64; 1.94	.699

CI = confidence interval.

Note: All comparisons are directionally general anesthesia versus spinal/regional anesthesia: values less than 1 have a lower relative odds of the event of interest in the GA group compared to the S/R group and values higher than 1 have a higher relative odds of the event of interest in the GA group compared to the S/R group; No of studies: number of studies with sufficient information to compare odds of event between general anesthesia and spinal/regional anesthesia.

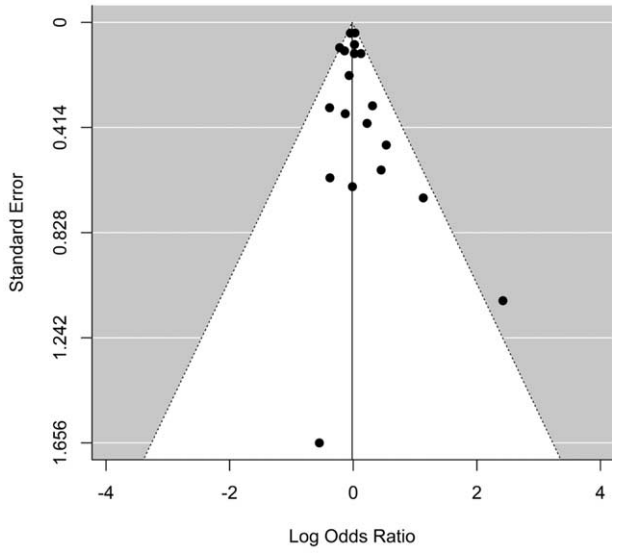

Figure 3. Funnel plots of 30-day mortality from a random-effects model. Small study bias was not detected using Egger's linear regression method ($P = .168$).

mortality rates between the GA and S/R groups. To account for between-study differences in mortality risk factors, we used categorical moderators, study-level standardized MDs (for continuous predictors), and log transformed ORs (for dichotomous predictors) as covariates in a generalized linear model framework. Due to insufficient matched cases between 30-day mortality and most predictors in the between-study *variance–covariance matrix* ($k < 10$), we considered the following covariates: study year, study type (retrospective or prospective), age, and female sex. None of the covariates considered significantly moderated the odds of 30-day mortality between the GA and S/R groups (Table 4).

3.6. Risk of bias

The impact of small study bias on 30-day mortality was depicted visually using funnel plots. Egger's linear regression test showed that there was no detectable bias influenced by small study effects regarding overall mortality rate among the study population within the random-effects model ($P = .168$; Fig. 3). Due to insufficient number of studies to reliably measure funnel plot asymmetry, small study effects are assumed to influence in-hospital, 90-day, and >1-year mortality comparisons.

4. Discussion

Results from this meta-analysis indicated that patients in the S/R anesthesia group had a significantly lower risk of in-hospital mortality and 90-day mortality compared to the GA group. Choice of anesthesia did not significantly affect 30-day mortality, mortality after 1 year, or incidence of AEs between patient groups. While linear regression detected no small study bias for 30-day mortality, other timepoints for mortality may have been affected by small study bias. Collectively, this evidence suggests that use of regional anesthesia in procedures for treatment of hip fractures may reduce early mortality.

Table 4

Meta-regression from regressing background characteristics and comorbidities on 30-day mortality.

Variable	df	Log OR	SE	*Z* value	*P* value
Age	10	0.266	0.307	0.867	.389
Female sex	12	−0.295	0.260	−1.135	.256
Study type	17	–	–	–	–
Prospective[21,24,25,30,31,35,38,40,42,44,45]		–	–	–	–
Retrospective[20,22,23,26–29,32–34,36,37,39,41,43,46,47]		−0.192	0.146	−1.312	.187
Study year	17	0.001	0.005	0.132	.895

df = degrees of freedom; OR = odds ratio; SE = standard error.

There is varied and conflicting evidence in the literature regarding the effect of regional anesthesia on mortality in this population. Several meta-analyses published since 2015 have reported no significant differences in 30-day mortality between patients who receive regional or GA.[10,13,14] The current review did not find a significant difference in 30-day mortality but did identify a reduced risk of in-hospital mortality for those receiving regional anesthesia. Of note, 2 recent meta-analyses by Chen et al[51] and Van Waesberghe et al[9] reported nearly identical outcomes following hip fracture surgery; they found no differences in 30-day mortality between groups, but reported a decrease of in-hospital mortality when neuraxial anesthesia was used instead of GA.[9,51] Mean length of hospital stay for those undergoing this type of procedure is estimated to be 6.2 days.[38] Therefore, it is possible that patients treated with GA may have higher risk of mortality immediately postoperatively, but that this risk is reduced following hospital discharge.

The results of the current review should also be interpreted in light of the risk of bias testing performed. Of all mortality timepoints, only 30-day mortality had sufficient data points to evaluate influence of small study bias; indeed, 30-day mortality had the largest portion of data available for analysis. The risk of bias assessment did not detect bias from small studies for 30-day mortality, whereas some amount of bias is assumed for in-hospital mortality, 90-day mortality, and mortality after 1 year. It is unclear the degree to which these biases may have affected mortality rates; furthermore, it is unclear whether a larger pool of patients may have distilled or diluted "true" effects of anesthesia on mortality following hip fracture surgery.

Other reports indicate that factors such as age, comorbidities, and procedural characteristics may have substantial influence on 30-day mortality. It has been shown that in the first 3 months after hip fractures, the risk of mortality in adults over 50 years of age is 5- to 8-times greater than for those under 50.[52] Likewise, patients with diabetes have been shown to have increased risk of in-hospital mortality after hip fracture surgery.[53,54] Accumulating comorbidities may place patients at additional risk; patients with 3 or more morbidities at admission have been shown to have an increased risk of postoperative mortality, with presence of respiratory disease playing an important role in patient recovery.[55,56] Procedural factors, such as preoperative waiting period of >24 hours, have also been reported to increase postoperative mortality in this population.[57,58] In the present study, the GA group was slightly younger in age compared to the S/R group; however, the GA group had a higher percentage of patients with diabetes and respiratory diseases, so it is unclear what effect these variables ultimately had on mortality in the GA and S/R groups. Unfortunately, procedural factors were out of the scope of this review.

Taken together, there are compelling trends in the literature regarding S/R anesthesia and the possibility of early reduced mortality following surgery for hip fracture. Importantly, these trends are reflected in the current meta-analysis, which thoroughly assesses forms of potential bias with rigorous statistical and quality assessments. However, it must be acknowledged that some conflicting evidence persists.[59] In the absence of clear guidelines, some researchers have advocated for anesthesia selection to be based on the physical condition of individual patients.[60] Other factors to consider when deciding anesthesia mode include postoperative pain management, which may be improved with S/R anesthesia.[61,62] Additional scholarship with patient-level data and thorough bias assessments is needed in order to develop clear, evidence-based guidelines for anesthesia during hip fracture surgery. As evidence accumulates for different types of regional anesthesia, these methods should also be compared to better guide anesthetists and surgeons.

5. Limitations

Our model did not adjust for potential confounding variables such as type of care received, procedural characteristics, pain levels in patients, preoperative waiting times, and pre-injury quality of life. Surgical interventions for hip fracture may range from relatively minor procedures to total hip arthroplasty; it is unclear what effect this may have had on outcomes. Since technical and procedural outcomes were out of scope for this study, additional research should be conducted to evaluate the effect of anesthesia on these outcomes following various types of hip fracture surgery. Furthermore, most outcomes were only evaluated on univariate random-effects models, as data were most often too sparse to perform a complex analysis by meta-regression. Another limitation of our study is the lack of RCTs comparing patient outcomes between the GA and S/R techniques; indeed, most of the evidence from our study was obtained from retrospective cohort analyses. For several outcome comparisons, small-study effects are assumed to influence effect sizes to some unknown degree. Further research on this topic is required for a more robust analysis of anesthesia and its effects on clinical outcomes following hip fracture surgery.

6. Conclusion

In this meta-analysis, patients administered S/R for hip fracture procedures had a lower risk of both in-hospital mortality and 90-day mortality compared to those administered GA. This suggests that use of regional anesthesia may reduce early mortality for the population undergoing surgery for hip fracture, who are likely to be over 50 and have risk-raising comorbidities.

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