ANESTHESIOLOGY

Comparative Effectiveness Research on Spinal *versus* General Anesthesia for Surgery in Older Adults

Mark D. Neuman, M.D., M.Sc., Frederick Sieber, M.D., Derek Dillane, M.D.

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ABSTRACT

Comparative effectiveness research aims to understand the benefits and harms of different treatments to assist patients and clinicians in making better decisions. Within anesthesia practice, comparing outcomes of spinal versus general anesthesia in older adults represents an important focus of comparative effectiveness research. The authors review methodologic issues involved in studying this topic and summarize available evidence from randomized studies in patients undergoing hip fracture surgery, elective knee and hip arthroplasty, and vascular surgery. Across contexts, randomized trials show that spinal and general anesthesia are likely to be equivalent in terms of safety and acceptability for most patients without contraindications. Choices between spinal and general anesthesia represent "preference-sensitive" care in which decisions should be guided by patients' preferences and values, informed by best available evidence.

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Comparative effectiveness research aims to understand the benefits and harms of different clinical treatments; the ultimate goal of comparative effectiveness research is to assist patients, clinicians, and policymakers to make better decisions that can improve health and health care at both the individual and population levels.[1,2] Within anesthesia practice, understanding the relative benefits and harms of spinal *versus* general anesthesia as the primary anesthetic approach for common surgical procedures, particularly among older adults, represents an important, long-standing focus of comparative effectiveness research. For patients without contraindications,[3] spinal anesthesia and general anesthesia represent potential options for surgeries that occur frequently in U.S. adults aged 65 and older, such as knee and hip arthroplasty,[4,5] and for procedures that are associated with high rates of adverse postoperative outcomes, including hip fracture repair[6] and lower extremity vascular surgery.[7] In the context of an aging population[8] and projected increases in demand for surgical services in the older population,[9] understanding the comparative effectiveness of common anesthesia options represents an important step toward designing better systems of care for older surgical patients[10–12] and increasing the extent of shared decision-making between anesthesiologists, patients, and families.[13]

During the past decade, multiple studies have compared the effectiveness of spinal anesthesia *versus* general anesthesia for hip fracture surgery, elective knee and hip replacement, and lower extremity vascular surgery.[14–18] These studies have used various methodologies, including randomized, nonrandomized, and quasi-experimental designs, and have at times produced divergent findings both within and across specific surgical populations. As a result, patients, clinicians, and policymakers may face challenges in interpreting available evidence regarding the anticipated outcomes of spinal *versus* general anesthesia in older adults and in integrating new evidence as it becomes available.

The goal of this review article is to provide clinicians, policymakers, and other stakeholders with information that can aid interpretation of available research on the comparative effectiveness of spinal *versus* general anesthesia in older adults. First, we review methodologic considerations for observational, nonrandomized studies and randomized controlled trials comparing outcomes with spinal *versus* general anesthesia in older populations. We use directed acyclic graphs, a graphical approach to modeling study assumptions and potential sources of bias that are widely used in epidemiology,[19] to illustrate threats to inference in nonrandomized *versus* randomized studies in this context. Next, we provide an overview of available evidence from randomized trials and selected nonrandomized studies on the effect of spinal *versus* general anesthesia on outcomes after

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Mark D. Neuman, M.D., MSc.; Department of Anesthesiology and Critical Care, Perelman School of Medicine, University of Pennsylvania Perelman School of Medicine, Philadelphia, Pennsylvania; Center for Perioperative Outcomes Research and Transformation, University of Pennsylvania Perelman School of Medicine, Philadelphia, Pennsylvania.

Frederick Sieber, M.D.; Department of Anesthesiology and Critical Care Medicine, Johns Hopkins Medical Institutions, Baltimore, Maryland.

Derek Dillane, M.D.; Department of Anesthesiology and Pain Medicine, University of Alberta Hospital, Edmonton, AB, Canada.

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hip fracture surgery, elective knee and hip arthroplasty, and lower extremity vascular repair across a range of outcomes relevant to older adults and their families. Additionally, we review available evidence on two therapies that are commonly coadministered with spinal anesthesia—intraoperative sedation and peripheral nerve block use—that have been hypothesized to modify the effect of spinal *versus* general anesthesia on outcomes.[20,21] Articles included in our review were identified by informal literature searches by each author and did not follow a prespecified search strategy. We conclude by summarizing implications of current evidence for practice and highlighting potential opportunities for future research.

Types of Studies Comparing the Effectiveness of Spinal Anesthesia *versus* General Anesthesia

Overview

An extensive empirical literature exists comparing outcomes of spinal anesthesia *versus* general anesthesia in older adults, using a range of methods and approaches. Randomized studies have included smaller one- or two-center efficacy trials[22,23] and large multicenter studies.[24,25] Nonrandomized studies have included studies of single-[26] and multicenter[27,28] clinical registries as well as retrospective analyses of administrative health databases,[29] and have used a wide range of statistical and study design approaches to severity adjustment and control for potential confounding.[30,31]

Although the number and diversity of studies in this area highlight the broad relevance of this topic, it may create challenges for clinicians in reconciling potentially conflicting findings from studies using drastically different approaches to causal inference. The present review focuses on available randomized evidence comparing outcomes with spinal *versus* general anesthesia; however, to provide context for this discussion, we here briefly review (1) major considerations related to nonrandomized (observational) *versus* randomized (interventional) comparisons of outcomes with spinal *versus* general anesthesia; and (2) interpretation of explanatory trials, which compare treatments under "best case scenario" conditions *versus* pragmatic trials, which compare treatments as typically applied in practice.[32]

Observational Studies

Observational studies compare outcomes of patients identified in clinical registries or administrative databases as having been treated with spinal *versus* general anesthesia. Advantages of such studies may include access to large samples of patients for analysis, improving study power and incorporation of data across many practice sites, allowing for comparisons of "real-world" care. Observational studies may also allow for measurement of rare outcomes or endpoints assessed across long periods of time that may be difficult to capture in randomized trials.

In the context of comparisons between spinal and general anesthesia, however, such studies typically cannot measure the causal effect of these treatments on outcomes due to biases common to nonrandomized comparisons.[33,34] Most importantly, such studies are frequently unable to fully account for confounding due to differences in baseline health between patients selected to receive spinal *versus* general anesthesia. Most administrative and clinical databases lack information on multiple important factors that may influence treatment choices. These factors may include preoperative neurocognitive disorders, including cognitive impairment and delirium; use of anticoagulant or antiplatelet medications; hypotension; underlying diseases causing coagulation disorders. Conventional statistical methods for risk adjustment, such as multivariable regression and propensity score matching, are unable to exclude potentially important residual confounding due to unmeasured patient factors. Instrumental variable analysis[17,30] may account for some of these factors even if they are not directly captured in the study database, often by using variation in spinal anesthesia use across hospitals or clinicians to measure outcome differences by anesthesia type. However, such analyses may still be confounded by differences in provider training or hospital quality across facilities that use more *versus* less spinal anesthesia. Additional potential biases may arise in observational studies due to measurement error in variables that indicate comorbidities and other markers of baseline health status; the type of anesthesia received; and study outcomes. Notably, in trial settings, between 8 and 20% of patients assigned to spinal anesthesia may ultimately receive general anesthesia,[22,24,35] due to changes in clinical status, inability to place a neuraxial block, or other factors. To the extent that observational databases may not distinguish between patients who received general anesthesia as a rescue technique *versus* their primary anesthetic, comparisons using these sources may encode bias arising from measurement error related to anesthesia type. Similarly, to the extent that measurement error in outcome variables or key risk-adjustment variables may be influenced by factors that influence treatment, such mismeasurement may lead to additional biases in observational studies.

Importantly, the large sample sizes often used in retrospective observational research do not mitigate these biases. On the contrary, examples from the empirical literature[36] and simulation studies[37] have shown that the likelihood of obtaining spurious findings of statistically significant and clinically meaningful differences due to inadequate control for confounding and misclassification bias increases as study sample sizes increase. Figure 1 presents a case study using directed acyclic graphs[19] to demonstrate common threats to inference in observational studies of spinal *versus* general anesthesia.

Randomized Studies

Randomized studies address key sources of bias in observational studies *via* random assignment of patients to either

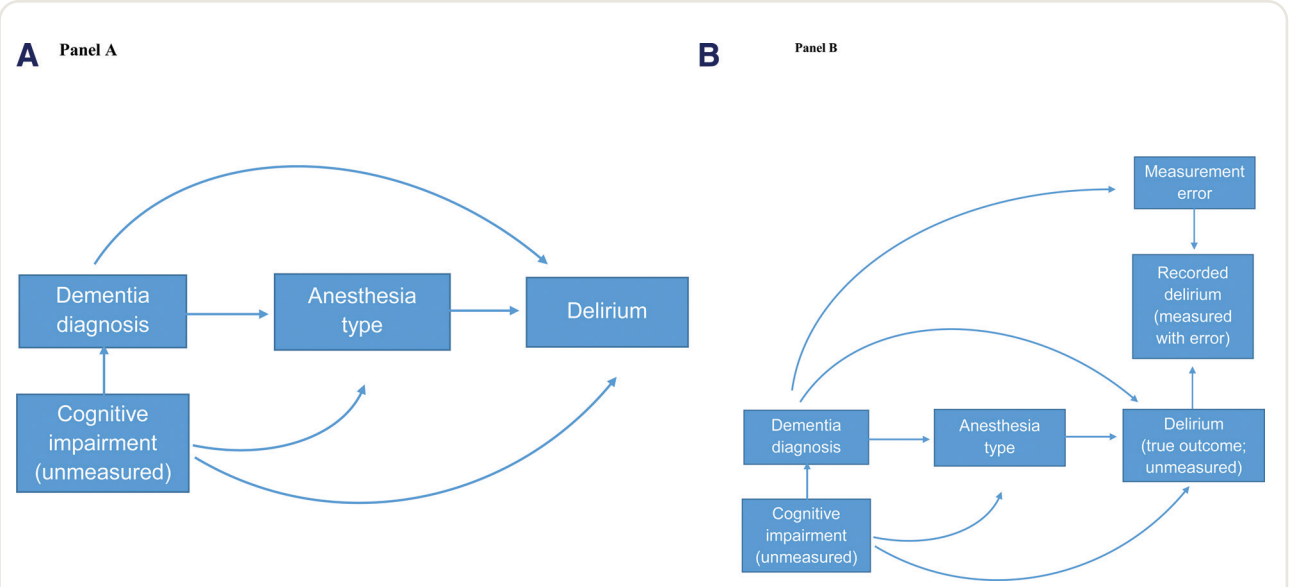

Fig. 1. Case study: an observational study to estimate the effect of spinal *versus* general anesthesia on postoperative delirium. A 2019 retrospective study by Ravi *et al.*[93] of patients undergoing hip fracture surgery in Ontario, Canada, compared the incidence of delirium among 26,853 patients receiving general anesthesia *versus* 41,278 patients receiving spinal or other anesthesia type. 2,943 (11%) of patients in the general anesthesia group developed delirium *versus* 4,207 (10.2%) of patients receiving spinal or other anesthesia. After adjustment for dementia and other factors using logistic regression, anesthesia type was reported as being associated with delirium (odds ratio: 1.07, 95% CI, 1.01 to 1.13, $P = 0.02$). (*A*) A simplified directed acyclic graph illustrating the potential impact of various factors on potential inferences from Ravi's study. The principal relationship under study is whether anesthesia type causes delirium. Two confounders of the anesthesia type to delirium relationship are shown: dementia diagnosis and degree of cognitive impairment, each independently influences (cause) the receipt of spinal *versus* general anesthesia and also the development of delirium (*i.e.,* each is a confounder). Dementia diagnosis is recorded in the study dataset, whereas cognitive impairment severity is not. By adjusting for dementia diagnosis, Ravi's study accounts for confounding due to dementia; however, bias due to differences in cognitive impairment for patients receiving spinal *versus* general anesthesia is not accounted for, leading to bias in the estimated effect of anesthesia type on dementia. (*B*) A more detailed directed acyclic graph for the same study that now illustrates potential mismeasurement of delirium status in the Ravi study. This graph represents the true outcome status (whether the patient does or does not truly have delirium), the outcome as recorded (which may or may not represent the true outcome—*i.e.,* is measured with error), and the (unknown) measurement error function, which influences the value of the recorded outcome. Here, the measured value of the delirium outcome reflects underlying measurement error in addition to the confounding relationship shown in *A*. Misdiagnosis of delirium may be more common in persons with underlying cognitive dysfunction. Measurement error for delirium is thus caused by cognitive dysfunction, which also influences the receipt of spinal *versus* general anesthesia (*i.e.,* measurement error for the outcome is differential with regard to treatment). This leads to further bias in the effect estimate for spinal anesthesia on delirium. Because cognitive dysfunction is not measured in Ravi's study, statistical risk adjustment alone cannot overcome this bias.

spinal or general anesthesia, which addresses confounding due to factors captured in the study database as well as those not recorded; moreover, incorporation of blinding allows trials to mitigate potential biases due to differential mismeasurement of outcomes in treated *versus* control groups. Finally, unlike most observational studies, randomized trials allow investigators to identify instances where conversion to general anesthesia from spinal anesthesia is required, and to conduct specific analyses to assess the potential impact of such "crossover" events on the study findings.[39] Figure 2 presents a case study using directed acyclic graphs[19] to illustrate approaches to causal inference regarding outcomes with spinal anesthesia in randomized trials. Commonly cited disadvantages of randomized studies include cost, administrative and regulatory complexity, and time required for completion. Where narrow inclusion and exclusion criteria are used, or enrollment is restricted to highly specialized centers, trial samples may fail to accurately represent the target population of interest. Single-center trials may provide insufficient sample sizes for testing of study hypotheses, particularly in subgroups of patients such as those with specific medical conditions or the oldest old. Nonetheless, multiple large multicenter studies comparing outcomes with spinal *versus* general anesthesia in older adults have been recently completed[24,25] or are in progress,[40] highlighting the feasibility of establishing large, randomized samples to compare a range of short- and long-term outcomes of relevance to diverse stakeholders. Finally, use of pragmatic designs that approximate "real-world" conditions *via* broad inclusion or exclusion criteria and flexible treatment designs and enroll subjects from diverse hospitals may increase the direct applicability of randomized trial findings to clinical practice.[41]

From the standpoint of evidence synthesis, current guidance recommends use of information from

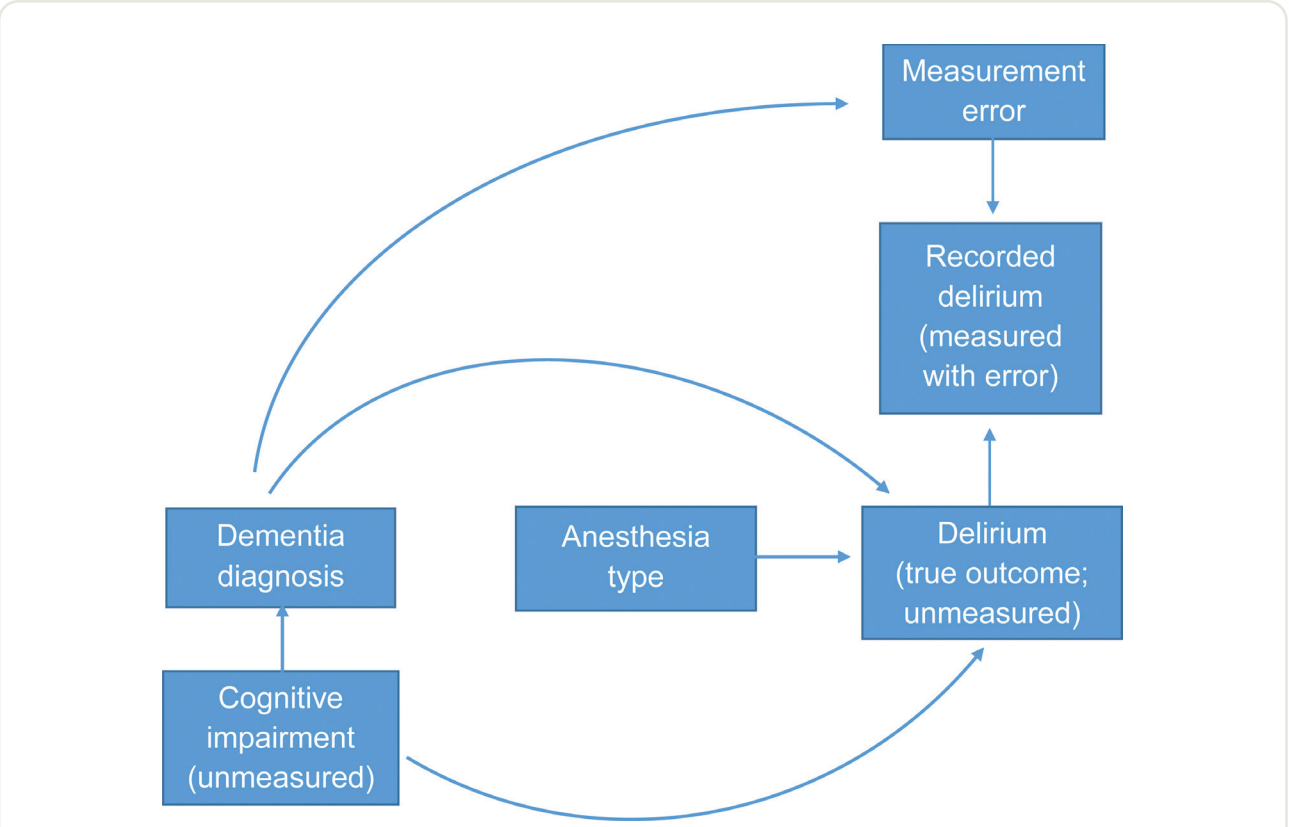

Fig. 2. Case study: a randomized trial to estimate the effect of spinal *versus* general anesthesia on postoperative delirium. Illustration of a randomized study (such as Li *et al.*[25]) comparing delirium with spinal *versus* general anesthesia. Due to randomization of treatment assignment, receipt of anesthesia is thus separated from both dementia status (measured in the study database) and cognitive impairment (not measured in the database); this removes the potential for confounding of the effect of anesthesia type on delirium. Moreover, mismeasurement of delirium status may still occur in a randomized study, and it may be caused by cognitive impairment. However, because cognitive impairment no longer impacts treatment assignment (due to randomization), and treatment assignment does not otherwise impact outcome measurement (given blinded outcome assessment), bias due to differential measurement error of the outcome based on treatment assignment does not occur.

nonrandomized studies to frame recommendations for practice only when sufficient randomized data are not available.[42] Although evidence that synthesis methods such as meta-analysis at times combine information from both randomized and nonrandomized studies, advanced statistical methods may be required to account for potential biases introduced by inclusion of nonrandomized studies.[43,44] In practice, meta-analyses that combine randomized and nonrandomized data frequently fail to incorporate assessments of risk of confounding bias due to inclusion of nonrandomized studies.[45]

Randomized Studies Comparing Outcomes of Spinal Anesthesia *versus* General Anesthesia

The majority of randomized trial evidence comparing spinal *versus* general anesthesia in older adults comes from studies focusing on the context of hip fracture surgery.[46] Table 1 describes three recently completed and in-progress multicenter trials comparing spinal *versus* general anesthesia for hip fracture surgery. Fewer randomized trials have compared outcomes with spinal *versus* general anesthesia for elective joint replacement[16] and lower extremity vascular surgery.[18]

Delirium and Other Cognitive Outcomes

Postoperative delirium is a common complication among older surgical patients[48,49] and affects approximately 30 to 50% of those undergoing surgery for hip fracture.[50] Spinal anesthesia has been hypothesized to limit onset of delirium compared with general anesthesia by minimizing exposure to medications with cognitive effects. Randomized trials examining delirium published through 2011 are reviewed in Guay *et al.*,[51] Kunutsor *et al.*.[15] and Bhushan *et al.* [52] and present results updated through 2022. In pooled analysis of nine studies conducted between 2003 and 2022 enrolling 2,963 patients, Kunutsor *et al.*[15] found no significant difference in the risk of delirium with spinal *versus* general anesthesia

Table 1. Recently Completed and In-progress Multicenter Trials Comparing Spinal Anesthesia *versus* General Anesthesia in Older Adults

Name	REGAIN (Regional *vs.* General Anesthesia for Promoting Independence after Hip Fracture)[100]	RAGA (Regional Anesthesia *vs.* General Anesthesia)[47]	iHOPE (Improve Hip Fracture Outcome in the Elderly Patient)[39]
Funder(s)	Patient Centered Outcomes Research Institute (Washington, D.C.)	Recruitment Program of Global Experts, China; Zhejiang Province (China); National Institutes of Health Research (UK)	Federal Ministry of Education and Research (Germany)
Registry identifier	ClinicalTrials.gov Identifier: NCT02507505	ClinicalTrials.gov Identifier: NCT02213380	German clinical trials registry identifier: DRKS00013644
Enrollment status	Closed	Closed	Ongoing
Enrollment dates	February 2016 to February 2021	October 2014 to September 2018	April 2018 to present
Accrual (planned/ actual)	1,600/1,600	950/950	1,032/N/A (recruitment ongoing)
Number of sites	46	9	17
Countries	United States, Canada	China	Germany
Major eligibility criteria	Included: Patients aged 50 yr and older with a femoral neck, femoral head, intertrochanteric, or subtrochanteric fracture and planned surgical repair. Excluded: patients who were unable to ambulate without human assistance before fracture, those with contraindications for regional anesthesia, periprosthetic fracture; concurrent procedure not amenable to spinal; malignant hyperthermia.	Included: Patients aged 65 yr and older with a femoral neck, femoral head, intertrochanteric, or subtrochanteric fracture and planned surgical repair. Excluded: patients with multiple trauma or fractures, contraindications for regional or general anesthesia, malignant hyperthermia, enrollment in another trial.	Included: Patients aged 65 yr and older with a femoral neck, femoral head, intertrochanteric, or subtrochanteric fracture and planned surgical repair. Excluded: contraindications for regional anesthesia, concurrent procedure not amenable to spinal; periprosthetic fracture; malignant hyperthermia.
Primary outcome	Death or new inability to ambulate without human assistance at 60 days after randomization	Delirium within 7 days after surgery	Time to death or new major cardiac or pulmonary complication within first 30 days after surgery
Secondary outcomes	Delirium (postoperative days 1–3); postoperative medical and surgical complications; length of stay; discharge destination; satisfaction with care; in-hospital and postdischarge pain and opioid use; 60-, 180-, and 365-day recovery of ambulation, location of residence, survival, cognitive function and overall health and disability.	Delirium severity, duration, and subtype; postoperative pain score; length of hospitalization; 30-day all-cause mortality; and complications.	In-hospital adverse events, delirium, satisfaction, length of hospital stay; discharge destination. 30-, 180-, and 365-day mortality, independence in walking, chronic pain, ability to return home, cognitive function and overall health and disability
Neuraxial anesthesia regimen	Single-shot spinal anesthesia with sedation as needed for comfort, titrated to maintain arousability to tactile stimulus or voice	Regional anesthesia included spinal, epidural, or combined spinal and epidural techniques was provided with no sedation.	Single-shot spinal anesthesia with sedation as needed for comfort, titrated to maintain arousability to tactile stimulus or voice
General anesthesia regimen	General anesthesia using inhalational agent for maintenance; airway management *via* endotracheal tube or supraglottic airway	General anesthesia using inhalational agent for maintenance; airway management *via* endotracheal tube or supraglottic airway	General anesthesia using inhalational agent for maintenance; airway management *via* endotracheal tube or supraglottic airway
Peripheral nerve block use	Permitted in either arm at provider discretion	Highly recommended for both arms per protocol	Permitted in either arm at provider discretion

(relative risk, 1.07; 95% CI, 0.90 to 1.29). Notably, 74% of patients included in this analysis came from one of two studies: Neuman *et al.* [24] and Li *et al.*[25] Neuman *et al.*[24] reported an incidence of delirium during postoperative days 1 to 3 of 20.5% with spinal anesthesia *versus* 19.7% with general anesthesia (relative risk, 1.04; 95% CI, 0.84 to 1.30) in a pragmatic study using standard-care treatment protocols for spinal anesthesia. Li *et al.*[25] reported similar results (regional anesthesia: 6.2%; general anesthesia: 5.1%; relative risk 1.2; 95% CI, 0.7 to 2.0) in a different trial that required avoidance of any intraoperative sedation and permitted use of either spinal or epidural anesthesia.[25] Notably, 94% of patients randomly assigned to regional anesthesia received either spinal or combined spinal epidural anesthesia. Interpretation of the Li study is complicated by an overall rate of delirium substantially lower than expected at the time of planning (expected rate in general anesthesia arm: 26%); nonetheless, the overall findings align with other available evidence arguing against a difference in delirium with spinal *versus* general anesthesia on average.[16] In two randomized trials published in 1990 enrolling 146 and 64 persons older than age 60 undergoing elective joint replacement, Nielson *et al.*[53] and Jones *et al.*[54] each found similar cognitive and psychosocial outcomes with either spinal or general anesthesia at 3 months.

Other In-hospital Medical Complications

Two studies of hip fracture patients[55,56] and one trial of patients undergoing elective hip replacement[57] conducted between 1981 and 1989 found lower rates of deep venous thrombosis among patients treated with spinal anesthesia; notably, patients in these studies did not receive pharmacologic deep venous thrombosis prophylaxis, limiting applicability to current practice. Subsequent trials enrolling patients receiving deep venous thrombosis prophylaxis did not observe differences in deep venous thrombosis by anesthesia type.[51] Other major complications, including postoperative myocardial infarction, pneumonia, and stroke, have not been found in past trials to differ by anesthesia type[14]; however, due to relatively low event rates for these specific outcomes, available samples are not fully able to exclude potential differences. An ongoing multicenter trial in Europe plans to evaluate differences in a composite outcome of cardiac or pulmonary complications and is anticipated to complete enrollment in 2024.[40]

Among patients undergoing lower extremity vascular reconstruction, one 1986 single-center randomized trial of 101 patients found lower rates of postoperative chest infection with spinal *versus* general anesthesia.[58] A subsequent meta-analysis including 696 patients enrolled in this study and three other trials conducted between 1993 and 2007 concluded that spinal anesthesia may be associated with a lower risk of postoperative pneumonia after lower extremity vascular surgery using data from two trials enrolling 201 patients in total (odds ratio, 0.37; 95% CI, 0.15 to 0.89). Available data were insufficient to draw conclusions about other outcomes, including mortality or myocardial infarction.[18]

Hospital Length of Stay and Location of Discharge

Summarizing four studies conducted between 2003 and 2022, Kunutsor *et al.*[15] estimated the mean difference in length of stay for patients assigned to spinal *versus* general anesthesia to be 0.14 days (95% CI, –0.71 to 0.43 days). Parker and Griffiths[22] found no difference in the rate of discharge to the preadmission residence by anesthesia type (relative risk, 0.99; 95% CI, 0.92 to 1.06). In a study of 1,600 patients undergoing spinal *versus* general anesthesia for hip fracture surgery, Neuman *et al.*[24] found the same median length of stay with spinal *versus* general anesthesia for patients in the United States (median length of stay, 3 days) or Canada (median length of stay, 6 days), as well as similar rates of discharge to home *versus* institutional care (*e.g.*, nursing home, inpatient rehabilitation, or another acute care hospital) by anesthesia type.

In two randomized trials enrolling 120 patients each, Harsten *et al.* found that general anesthesia was associated with shorter time to meet ward discharge criteria compared with spinal anesthesia for both elective total hip replacement[59] and total knee replacement.[60] In contrast, Chu *et al.*[61] found a shorter time to hospital discharge among 60 elective knee arthroplasty patients randomly assigned to combined spinal-epidural anesthesia *versus* general anesthesia.

Mortality

Assessing the relationship between anesthesia type and mortality has been a major focus of past work; in the context of hip fracture, 16 separate randomized trials evaluating survival at various time points from hospitalization through 1 yr. In one 1978 trial, McLaren *et al.*[62] found a mortality rate of 34.6% at 28 days among patients randomly assigned to general anesthesia (9 of 26 patients) *versus* 3.4% among patients randomly assigned to spinal anesthesia (1 of 29, $P < 0.01$). Subsequent comparisons failed to confirm this dramatic finding; in a meta-analysis of 11 studies (including McLaren's) published between 1978 and 2012 that included 2,152 participants, Guay *et al.*[51] failed to observe a difference in mortality with spinal *versus* general anesthesia at 1 month (relative risk, 0.78, 95% CI, 0.57 to 1.06). Kunutsor *et al.*[15] failed to observe a difference in 30-day mortality in a meta-analysis of four trials of hip fracture patients between 2012 and 2022 (relative risk, 1.07; 95% CI, 0.52 to 2.23). A 2013 meta-analysis of randomized trials enrolling patients receiving spinal *versus* general anesthesia for lower extremity vascular surgery found no difference in postoperative mortality by anesthesia type.[18]

Although multiple past studies have examined 30-day mortality with spinal *versus* general anesthesia, fewer have examined later time points, despite their potential relevance of such outcomes older adults and families.[63] Neuman *et al.*[24] found similar mortality at 60 days by anesthesia type: among patients randomly assigned to spinal anesthesia 3.9% died by day 60 *versus* 4.1% patients assigned to general anesthesia (relative risk, 0.97; 95% CI, 0.59 to 1.57).

Functional Recovery

Recovery of functional independence represents an outcome of major importance to patients and families[64] but has been minimally examined in past work. Neuman *et al.*[24] found no difference in a composite outcome of dying or becoming newly unable to walk approximately 10 feet without human assistance at 60 days by anesthesia type (relative risk, 1.03; 95% CI, 0.84 to 1.27). Similar proportions of patients surviving to day 60 in each group demonstrated either new inability to walk without human assistance or new need for assistive devices (spinal anesthesia: 60.0%; general anesthesia: 57.2%). Overall functional status, as measured by the World Health Organization Disability Assessment Schedule, did not differ at day 60 across groups.

Pain

Casati *et al.* [23], and Haghighi *et al.* [65] found similar postanesthesia care unit pain with spinal anesthesia *versus* general anesthesia for hip fracture surgery; however, it is unclear

if these findings reflect persistent block effects *versus* later impacts on postoperative pain. A small trial conducted at one center in Italy found similar pain scores at 12 h after spinal *versus* general anesthesia for hip fracture surgery.[23] In contrast, a trial in 387 patients conducted at two hospitals in Iran found lower pain scores with spinal *versus* general anesthesia on postoperative day 2.[66]

The Li *et al.*[25] trial reported no difference in the worst postoperative pain score greater than 7 days postoperatively by group. Of note, the authors report a value of zero for the median maximum pain score in each group, substantially lower than typical reports of pain experiences after hip fracture. Most recently, Neuman *et al.*[67] observed no differences in pain beyond the first 24 h after surgery or up to 365 days after discharge. However, spinal anesthesia was associated with higher rates of prescription analgesic use at 60 days.

Satisfaction

Few past studies have examined patient satisfaction with spinal *versus* general anesthesia. One French study of 40 patients assessed satisfaction using a single questionnaire item rating experience from poor to excellent on a 5-point scale. Although no differences were observed, the number of patients enrolled likely limited the authors' ability to draw inferences on this outcome. More recently, Neuman *et al.*[68] assessed satisfaction using the Bauer anesthesia satisfaction questionnaire, a 15-item tool assessing anesthesia-related discomfort and satisfaction with aspects of anesthesia care, as well as the United Kingdom National Health Service's 2013 "Friends and Family Test."[69,70] In terms of anesthesia-related discomfort, patients randomly assigned to general anesthesia more often reported severe sore throat, whereas severe shivering occurred more often in patients assigned to spinal anesthesia. Dissatisfaction with an aspect of anesthesia care and unwillingness to recommend the same care to a friend or family member were similar across groups.

Impact of Coadministered Therapies on Outcomes of Spinal Anesthesia

Intravenous Sedation

Intravenous sedation is commonly coadministered to older adults undergoing spinal anesthesia. Commonly administered agents for sedation during spinal anesthesia include propofol, ketamine, benzodiazepines, opioids, and dexmedetomidine. Spinal anesthesia itself causes sedation and enhances the effects of sedative drugs.[71] During spinal anesthesia, a positive correlation exists between the level of sensory block and the degree of sedation, as determined by sedation score.[72] In addition, patients given spinal anesthesia are more sensitive to sedative medications,[73] and providers may frequently administer hypnotics concurrently with spinal anesthesia that yield electroencephalogram (EEG) patterns consistent with general anesthetic-level hypnosis. In one single-center cohort of older patients undergoing hip fracture repair given spinal anesthesia with propofol sedation, sedation levels consistent with general anesthesia occurred during 32% of total operative time on average.[74] Separate investigations report similar findings in other surgical settings.[75,76]

Randomized trials have examined the effect of sedation during spinal anesthesia on postoperative delirium. Sieber *et al.*[77] randomly assigned hip fracture patients given spinal anesthesia to light or deep sedation. Intention-to-treat analysis showed no difference between light- and heavy-sedation groups in incident postoperative delirium, total days of postoperative delirium, or total days of postoperative delirium or subsyndromal delirium symptoms. Secondary analyses of this study found that sedation levels were associated with lower postoperative delirium incidence in a subgroup of patients with low levels of comorbidity. Nonetheless, any conclusions concerning sedation-level interactions with preoperative comorbidity and their effects on postoperative delirium require further study because the study sample size was small and prone to chance findings[77] as may commonly occur with trial subgroup analyses.[78] Long-term follow-up found that intraoperative level of sedation was not associated with differences in mortality or return to prefracture ambulation at up to 1 yr after surgery.[79]

Administration of spinal anesthesia without intraoperative sedation is uncommon in Western countries,[21] likely due to the desire of many patients to receive some degree of sedation or anxiolysis during surgery.[80] Notably, the Li *et al.*[25] trial incorporated a protocol for neuraxial anesthesia in which no sedation was permitted to be administered during surgery.[47] No difference was found between this regimen and general anesthesia in postoperative delirium incidence or severity or other outcomes. As noted earlier, this study reported an unusually low postoperative delirium incidence (5.6% overall), potentially due to enrollment of a population that was substantially healthier than those enrolled in past hip fracture studies.

The impact of specific sedative agents on outcomes with spinal anesthesia represents an area of ongoing inquiry. Shin *et al.*[81] compared propofol *versus* dexmedetomidine sedation in a randomized trial enrolling 748 patients undergoing spinal anesthesia for lower limb surgery. This trial found that dexmedetomidine sedation compared with propofol sedation led to decreased postoperative delirium. These findings replicated a previous retrospective cohort reported by the same group.[82] Another randomized controlled trial in total knee replacement patients given spinal anesthesia found significantly lower rates of postoperative delirium with dexmedetomidine *versus* propofol.[83] Of note, available trials comparing dexmedetomidine sedation compared to propofol have focused on samples of relatively healthy older adults; additional research is needed to characterize outcomes of these regimens in populations at high risk for delirium, such as persons with dementia, and to assess the cardiovascular effects of propofol *versus* dexmedetomidine.[84]

Peripheral Nerve Blockade

Lower extremity orthopedic procedures represent a common context for delivery of spinal anesthesia in older adults; in this setting, peripheral nerve blockade may be coadministered with spinal anesthesia where indicated to treat pain after surgery. Concurrent use of peripheral nerve blockade with spinal anesthesia has been theorized to potentially modify the effect of spinal anesthesia on outcomes.[20] Although few past studies have directly examined this theory among older surgical patients, findings from mixed samples of surgical patients suggest potential advantages to combining these techniques. In a prospective, randomized study of 57 patients undergoing foot and ankle surgery with spinal anesthesia with or without ankle block, patients who received an ankle block reported both a lower mean postoperative pain score and a longer onset to pain after surgery.[85]

In the context of hip fracture surgery, preoperative femoral nerve block or fascia iliaca compartment block may also aid positioning for the performance of spinal anesthesia. Femoral nerve blockade, performed before spinal anesthesia, in patients undergoing hip fracture surgery can be performed as a single shot block immediately preoperatively or as a continuous catheter technique several hours or even days in advance of surgery. A meta-analysis of 10 randomized trials enrolling a total of 584 patients showed significantly less pain during spinal placement for patients who received a femoral nerve block within 30 min of positioning compared with intravenous analgesia.[86]

Integrating Findings from Randomized and Nonrandomized Studies

Due to their inability to exclude potentially important confounding due to variables not measured in the study database (fig. 1), nonrandomized studies using propensity score methods or regression covariate adjustment should not be viewed as a substitute for randomized trials when comparing outcomes of spinal *versus* general anesthesia in older adults. Although advanced inferential methods, such as instrumental variable analysis, can overcome some limitations of basic retrospective study designs, similar caution is warranted because these methods rely on unverifiable assumptions. Because clinical practice guideline recommendations based on nonrandomized, observational studies are more prone to reversal or revision over time than those drawn from randomized trials, we recommend that practitioners refrain from drawing clinical inferences or initiating changes in practice solely based on such evidence.[87]

At the same time, findings from observational, nonrandomized studies may provide important complementary evidence to randomized trial findings about spinal *versus* general anesthesia under certain conditions.[88–90] Specifically, in settings where nonrandomized data analyses successfully replicate trial findings,[91] methods such as target trial emulation[92] may be used to evaluate endpoints not considered in the original trial[93] or extend trial inferences to populations of patients who may be underrepresented in trials due to eligibility criteria, treatment at nonparticipating hospitals, or other barriers to enrollment.

Where observational study results fail to replicate trial findings, efforts should be made to identify and ameliorate reasons for divergent findings based on hypothesized sources of bias. For example, divergent findings regarding the association of anesthesia type with delirium after hip fracture surgery in nonrandomized[38] *versus* randomized[24,25] studies could be due to residual confounding from unmeasured differences in cognition among patients receiving spinal *versus* general anesthesia. Similarly, divergent findings regarding length of stay with spinal *versus* general anesthesia for hip fracture studies from observational retrospective studies using instrumental variable analysis[94] *versus* a subsequent large trial[24] could be due to differences in the severity of baseline comorbidities or hospital quality. Given the cost and logistical complexity involved in conducting randomized trials comparing spinal *versus* general anesthesia, using observational analyses to extend the findings of completed trials can help in obtaining the maximum amount of insight from randomized trials. As such, future efforts should focus on developing observational data sources that address potentially important reasons for divergence between available retrospective studies and randomized trials.

Implications for Practice and Areas for Further Investigation

Data from randomized trials reviewed here indicate that choices between spinal and general anesthesia for older adults are likely to represent "preference-sensitive" care in most cases.[95,96] In other words, choosing between spinal and general anesthesia should be balanced based on patients' preferences and values (*e.g.*, avoiding endotracheal intubation; avoiding neuraxial injection), guided by best available evidence from comparative effectiveness studies. In the context of hip fracture care and elective knee and hip replacement, evidence from those randomized trials that we reviewed does not provide strong evidence of superior effectiveness of either technique for improving end outcomes on average; in the context of lower extremity vascular surgery, trial data from small samples and quasi-experimental studies offer preliminary evidence to suggest some reductions in complications with spinal anesthesia; however, these results require confirmation in subsequent trials.

For patients undergoing hip fracture surgery, data from identified randomized trials can support informed conversations for patients represented within study populations; these findings argue for similar outcomes with spinal *versus* general anesthesia across a range of endpoints, including delirium, length of stay, mortality, functional recovery, and medical complications. Depth of sedation does not appear to impact outcomes, but use of dexmedetomidine

versus propofol may reduce postoperative delirium based on identified evidence, with further confirmation required in additional trials. Identified evidence does not suggest that avoiding sedation altogether during spinal anesthesia reduces delirium. Use of peripheral nerve blocks in addition to spinal anesthesia reduces pain after surgery and, when placed before surgery, can decrease pain with positioning for spinal anesthesia. In the context of surgery for hip fracture, future research could include subanalyses of individual randomized studies focusing on patients with specific comorbidities, such as dementia, or at higher or lower risk of adverse outcomes based on multidimensional risk scores,[97] individual patient data meta-analyses using data from multiple completed randomized trials; or studies that use observational data analyses to extend trial results *via* benchmarking[91] and target trial emulation methods[92] as described earlier.

In the context of elective knee and hip replacement and lower extremity vascular surgery, the limited number of randomized trials we found highlights a need for additional prospective randomized research, particularly given increasing trends toward performance of these procedures in an outpatient context.[98] As recommended by efforts to standardize endpoints in perioperative trials, such investigations should consider patient-centered outcomes, such as mortality and short- and long-term recovery, in addition to traditional endpoints such as in-hospital complications.[99] Identified randomized studies of spinal *versus* general anesthesia for elective joint replacement do not suggest major differences in outcomes with either technique.[16] In the context of lower extremity vascular surgery, limited trial data and rigorous nonrandomized studies provide preliminary evidence that postoperative pulmonary complications are reduced with spinal anesthesia, although further confirmation of these findings is needed in prospective trials. Some nonrandomized studies have suggested potential outcome benefits to spinal anesthesia relative to general anesthesia in each of the contexts we consider here; in considering such studies, practitioners should exercise caution in ascribing these findings to actual treatment effects without carefully considering alternative explanations based on known biases in nonrandomized studies.

In the context of an aging population, incorporation of evidence from rigorous randomized studies provides a growing opportunity for anesthesiologists and other perioperative practitioners to add value to patient care by increasing engagement of older adults and families in decisions about their care. The available base of randomized data comparing outcomes of spinal *versus* general anesthesia in older adults has increased markedly over time. Yet opportunities still remain to better characterize outcomes according to anesthesia technique among certain subgroups of patients undergoing hip fracture surgery, such as patients with dementia and those at highest risk of adverse outcomes, and among individuals undergoing procedures that have been understudied in trials to date, such as elective joint arthroplasty and lower extremity vascular surgery. We encourage pursuit of such work, which holds promise to not only improve the clinical outcomes of the treatments that anesthesiologists provide, but also to make choices about anesthesia care more informed and patient-centered through time.

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Correspondence

Address correspondence to Dr. Neuman: Department of Anesthesiology and Critical Care, University of Pennsylvania Perelman School of Medicine, 308 Blockley Hall, 423 Guardian Drive, Philadelphia, Pennsylvania 19106. neumanm@pennmedicine.upenn.edu.

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