Neuraxial and Combined Neuraxial/General Anesthesia Compared to General Anesthesia for Major Truncal and Lower Limb Surgery: A Systematic Review and Meta-analysis

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Neuraxial anesthesia may improve perioperative outcomes when compared to general anesthesia; however, this is controversial. We performed a systematic review and meta-analysis using randomized controlled trials and population-based observational studies identified in MEDLINE, PubMed, and EMBASE from 2010 to May 31, 2016. Studies were included for adult patients undergoing major surgery of the trunk and lower extremity that reported: 30-day mortality (primary outcome), cardiopulmonary morbidity, surgical site infection, thromboembolic events, blood transfusion, and resource use. Perioperative outcomes were compared with general anesthesia for the following subgroups: combined neuraxial-general anesthesia and neuraxial anesthesia alone. Odds ratios (ORs) and 99% confidence intervals (CIs) were calculated to identify the impact of anesthetic technique on outcomes. Twenty-seven observational studies and 11 randomized control trials were identified. This analysis comprises 1,082,965 records from observational studies or databases and 1134 patients from randomized controlled trials. There was no difference in 30-day mortality identified when combined neuraxial-general anesthesia was compared with general anesthesia (OR 0.88; 99% CI, 0.77–1.01), or when neuraxial anesthesia was compared with general anesthesia (OR 0.98; 99% CI, 0.92–1.04). When combined neuraxial-general anesthesia was compared with general anesthesia, combined neuraxial-general anesthesia was associated with a reduced odds of pulmonary complication (OR 0.84; 99% CI, 0.79–0.88), surgical site infection (OR 0.93; 99% CI, 0.88–0.98), blood transfusion (OR 0.90; 99% CI, 0.87–0.93), thromboembolic events (OR 0.84; 99% CI, 0.73–0.98), length of stay (mean difference −0.16 days; 99% CI, −0.17 to −0.15), and intensive care unit admission (OR 0.77; 99% CI, 0.73–0.81). For the combined neuraxial-general anesthesia subgroup, there were increased odds of myocardial infarction (OR 1.18; 99% CI, 1.01–1.37). There was no difference identified in the odds of pneumonia (OR 0.94; 99% CI, 0.87–1.02) or cardiac complications (OR 1.04; 99% CI, 1.00–1.09) for the combined neuraxial-general anesthesia subgroup. When neuraxial anesthesia was compared to general anesthesia, there was a decreased odds of any pulmonary complication (OR 0.38; 99% CI, 0.36–0.40), surgical site infection (OR 0.76; 99% CI, 0.71–0.82), blood transfusion (OR 0.85; 99% CI, 0.82–0.88), thromboembolic events (OR 0.79; 99% CI, 0.68–0.91), length of stay (mean difference −0.29 days; 99% CI, −0.29 to −0.28), and intensive care unit admission (OR 0.50; 99% CI, 0.48–0.53). There was no difference in the odds of cardiac complications (OR 0.99; 99% CI, 0.94–1.03), myocardial infarction (OR 0.91; 99% CI, 0.81–1.02), or pneumonia (OR 0.92; 99% CI, 0.84–1.01). Randomized control trials revealed no difference in requirement for blood transfusion (RR 1.05; 99% CI, 0.65–1.71) and a decreased length of stay (mean difference −0.15 days; 99% CI, −0.27 to −0.04). Neuraxial anesthesia when combined with general anesthesia or when used alone was not associated with decreased 30-day mortality. Neuraxial anesthesia may improve pulmonary outcomes and reduce resource use when compared with general anesthesia. However, because observational studies were included in this analysis, there is a risk of residual confounding and therefore these results should be interpreted with caution. (Anesth Analg 2017;125:1931–45)

Neuraxial anesthesia has advantages compared to general anesthesia including reduced requirements for sedatives, opioid analgesics, and airway instrumentation. However, conflicting data exist regarding the differing perioperative morbidity and mortality outcomes between the anesthetic techniques,[1,2] and therefore

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many anesthesiologists may be reluctant to routinely recommend neuraxial anesthesia to their patients undergoing major surgery.

Health care practice has evolved significantly over the past 2 decades with the development of evidence-based therapies providing prophylaxis against surgical site infection and thromboembolic events. Furthermore, perioperative care has evolved with the introduction of new surgical techniques, expansion of interventions to an ageing population, introduction of anesthetic agents with predictable pharmacokinetics and rapid recovery times, improved antiemetic and multimodal analgesic therapies, and changes in anesthetic techniques. Therefore, there is an ongoing need to evaluate perioperative outcomes using studies that reflect recent and current practice.

Several contemporary randomized control trials (RCTs) have investigated perioperative outcomes associated with neuraxial anesthesia compared with general anesthesia.[3–13] RCTs are the gold standard of evidence-based medicine; however, their content forms only a portion of the available knowledge. Recently, large, observational population-based studies have provided unique insights into the impact of neuraxial anesthesia on a surgical population.[14–39] In contrast to RCTs, these studies do not have strict inclusion and exclusion criteria, thus their findings reflect routine clinical practice.

In this systematic review and meta-analysis of both RCTs and large-scale population studies, our goal was to evaluate the role of neuraxial anesthesia as a health care intervention in the context of contemporary perioperative care. Specifically our objectives were the following: (1) to summarize findings of contemporary RCTs and large-scale population-based studies, where neuraxial anesthesia was used for major truncal and lower extremity surgery in adults; (2) to quantify the effect size of neuraxial anesthesia when used alone or when combined with general anesthesia, if it exists, compared to general anesthesia with regard to predefined outcomes (30-day mortality, cardiopulmonary morbidity, surgical site infection, thromboembolic events, blood transfusion, and resource use [critical care services, length of hospital stay]); and (3) evaluate the quality of the evidence using the GRADE (Grading of Recommendations Assessment, Development and Evaluation) system.[40] The main question to be answered was: is the use of neuraxial anesthesia alone or when combined with general anesthesia associated with superior perioperative outcomes when compared to general anesthesia for major surgery of the trunk and lower extremity.

METHODS

This systematic review was conducted in adherence to the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analysis) guidelines.[41] Our health care question was defined a priori using the PICO (Population, Intervention, Comparator and Outcomes) format.

Eligibility Criteria

Inclusion criteria were RCTs with no lower limit in sample size and large (n > 500) observational, cohort, case-control, and cross-sectional studies. English language studies were included that involved adult (over 18-years-old), nonpregnant patients, published between January 1, 2010 and May 31, 2016, undergoing major truncal or lower extremity surgery, where combined neuraxial-general anesthesia and/or neuraxial anesthesia was compared to general anesthesia. Studies were included if they reported one or more of the following outcomes: 30-day mortality (primary outcome), cardiopulmonary morbidity (including pneumonia, myocardial infarction), surgical site infection, thromboembolic events, blood transfusion, and resource use (critical care services, length of hospital stay). For this review, neuraxial anesthesia, defined as spinal or epidural anesthesia, were differentiated from regional techniques (eg, peripheral nerve blockade). Previously published meta-analyses and strictly descriptive articles were excluded. Studies were excluded if they did not contain the population of interest; that is, did not compare combined neuraxial-general anesthesia or neuraxial anesthesia with general anesthesia; or did not report the outcomes of interest. Reasons for exclusion of full-text articles are outlined in Appendix 2 and Appendix 3.

Data Sources and Search Strategy

Two authors systematically searched bibliographic databases including the US National Library of Medicine database, MEDLINE, and the Excerpta Medica database, Ovid EMBASE, and retrieved relevant studies fulfilling the inclusion criteria, with the final search being conducted on May 31, 2016. The references of relevant publications were manually reviewed for additional material. Our core search consisted of MeSH terms related to anesthesia type ("anesthesia, epidural," "anesthesia, spinal," "anesthesia, general") combined with specific MeSH terms relating to outcomes ("treatment outcome," "treatment failure," "mortality," "outcome," "postoperative complications," "complication," "morbidity"). Articles with the relevant MeSH terms within the title or abstract of the article were identified, with both "anaesthesia" and "anesthesia" being included in the search. A summary of the search strategy is available in Appendix 1.

The search yielded 1393 results. Bibliographies of identified relevant studies and previously published systematic reviews were reviewed to identify any additional studies that may have been missed in the primary literature search.

Study Selection

Titles and abstracts were assessed for eligibility by 2 investigators (YU and LS) working independently and in duplicate. Studies that fulfilled the eligibility criteria were selected and the full-text articles obtained and reviewed. Authors (CC, LS, MB) conducted a full-text review of all included articles. Any discrepancy in study selection between the reviewers was resolved by consensus agreement between all authors.

Data Extraction

Data were manually extracted in duplicate from the full-text versions of eligible studies by authors LS and CC. Data extracted included the total number of events and controls for each outcome for neuraxial anesthesia alone, general anesthesia alone, and, where, applicable combined neuraxial and general anesthesia. Data presented in tabular format were used as the primary source for data extraction. Due to potential for overlap of patient records from the source databases and observational studies, publications were excluded from analysis on an outcome basis if there was an overlap in data collection time and surgical type for the same database. In cases of overlap, studies with larger sample sizes were included preferentially in the analysis if potential overlap in records was identified. Exclusion of studies on an outcome basis due to potential overlap of patient records is outlined in Appendix 4.

Risk of Bias

We utilized the GRADE system to summarize the quality of the evidence.[40] The risk of bias was assessed according to limitations in study design inherent to study type.[42] Study limitations in RCTs include allocation concealment, blinding, follow-up, selective reporting, and premature trial cessation for early benefit. Observational trials are limited by lack of randomization, failure to develop and apply appropriate eligibility criteria, flawed measurement of exposure or outcome, failure to adjust for prognostic imbalance, and incomplete follow-up. According to GRADE, RCTs and observational studies are considered high- and low-quality evidence, respectively. Each study was evaluated for limitations in study design and risk of bias was established across studies for each outcome.

Heterogeneity

Criteria for evaluating heterogeneity include similarity of point estimates, extent of overlap of confidence intervals (CIs), and the I^2 statistic.[43] We predefined a potential source of heterogeneity as whether neuraxial anesthesia was used alone or in combination with general anesthesia. Therefore, we created subgroup comparisons of combined neuraxial-general anesthesia and neuraxial anesthesia, comparing both subgroups with general anesthesia. According to GRADE,[43] the level of evidence was downgraded for outcomes where large heterogeneity in results remained, after exploration of reasons that could explain inconsistency.

Indirectness

Direct evidence comes from studies that directly compare the interventions of interest in the target population.[44] To ensure there was a high level of directness regarding the impact of neuraxial anesthesia, subgroup analysis was performed in 2 steps to answer the health care question: (1) Was the use of neuraxial anesthesia associated with no increase in adverse outcomes compared with the use of general anesthesia? (2) Was the addition of neuraxial anesthesia to general anesthesia beneficial compared to the sole use of general anesthesia? Due to the low number of randomized controlled trials available in this context, this separation was only feasible for observational trials.

Imprecision

The optimal information size (OIS), meaning the number of patients required for an adequately powered individual trial was calculated for each outcome and downgrading was performed if OIS was not met by outcome.[45]

Publication Bias

Publication bias was assessed by utilizing the funnel plot and assessing whether the outcomes of effect were symmetrical around the best estimate of effect or pooled odds ratios (ORs).[46]

Evaluating the Quality of Evidence

The GRADE approach was used to upgrade the quality of evidence, for example, where there were large pooled effects and dose-response relations, and when all plausible confounders would decrease the estimate of effect.[47]

Statistical Analysis

Data were entered into the Cochrane Review Manager software RevMan, version 5.3, The Cochrane Collaboration, Oxford, United Kingdom, 2015, by 1 author (CC) and checked by another (LS). In addition to dichotomous data, RevMan facilitates the pooling of continuous data such as length of hospital stay, when reported as mean and standard deviation. For studies that reported length of stay in median and interquartile ranges, the method utilized by Hozo et al[48] was used to estimate mean and standard deviation as required for analysis in RevMan. Outcomes were expressed as ORs or mean differences. To account for multiple comparisons, the level of statistical significance was set at $P < .01$ and effect sizes presented with 99% CIs.

RESULTS

After screening the 1393 identified results, 51 full-text articles, comprising 32 observational studies and 19 RCTs, were assessed for eligibility. In total, 27 observational studies and 11 RCTs met the inclusion criteria, summarized in the PRISMA flow diagram (Figure 1).

Study Characteristics

A qualitative summary of observational studies and RCTs included in the meta-analysis are outlined in Tables 1 and 2, respectively. This review included studies that included a total of 1,084,099 patients, 1,082,965 from observational studies, and 1134 from RCTs. These included observational studies investigating hip fracture surgery (7 studies, 229,472 pat ients),[14,17,21,22,25,28,29] total hip arthroplasty (3 studies, 41,842 patients),[15,18,31] total hip or knee arthroplasty (4 studies, 415,341 patients),[19,20,31,38] and total knee arthroplasty alone (3 studies, 46,294 patients).[23,24,26] The remainder of observational studies investigated lower extremity amputation,[27] elective surgical procedures (single study investigating procedures on vasculature, bladder, bowel, lung, gastrointestinal),[30] high-risk patients having noncardiac surgery,[49] multiple surgical types in patients with chronic obstructive pulmonary disease,[33] open lung resection,[32] open colectomies,[34] percutaneous nephrolithotomy,[35] lower extremity vascular surgeries,[36,39] and endovascular aortic aneurysm repair.[37] The RCTs investigated percutaneous nephrolithotomy,[7,9,12] total knee arthroplasty,[3] total hip arthroplasty,[13] hip fracture surgery,[5] abdominal hysterectomy,[4] laparoscopic colonic resection,[11] emergency laparotomy,[10] gynecological surgery,[8] and urogenital surgery.[50] In total, 13 studies investigated truncal surgery (125,838 patients),[4,6–12,32,34,35,37,50] 22 studies investigated lower limb surgery (923,347 patie

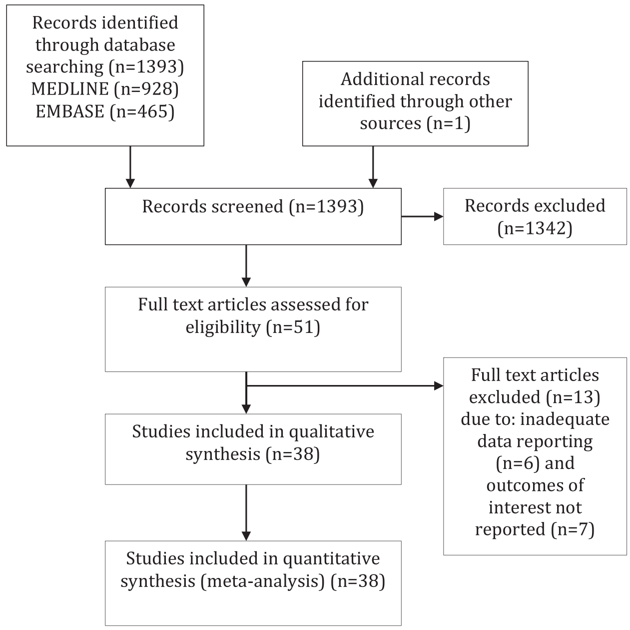


Figure 1. PRISMA 2009 flow diagram. PRISMA indicates Preferred Reporting Items for Systematic Reviews and Meta-Analysis.

nts),[3,5,13–24,26–29,31,36,38,39] and 3 studies investigated both truncal and lower limb surgery (34,914 patients).[30,33,49] When categorized by anesthetic type, 14 studies investigated spinal anesthetic alone,[3–5,8,11,13–15,17,23,25,27,35,49] 5 studies investigated epidural anesthetic alone,[6,9,10,39,50] and 19 studies investigated both spinal or neuraxial anesthesia, or did not specify which type of neuraxial anesthesia was used.[7,16,18–21,24,26,28–34,36–38,51] The following number of participants (N [percentage]) were included in operative types: total knee or hip arthroplasty (503,597 [46.5]), hip fracture surgery (229,794 [21.2]), mixed types of hip surgery (182,307 [16.8]), truncal surgery (125,838 [11.6]), mixed surgical types (34,914 [3.2]), and nonorthopedic lower extremity surgery (7649 [0.70]). A summary of the databases used for the included studies is outlined in Appendix 4.

Risk of Bias Analysis

Due to the intervention being neuraxial anesthesia, none of the RCTs masked participants or personnel; however, we did not exclude or downgrade the quality of evidence on these grounds. Serious risk of bias in specific outcome analysis was identified in 9 studies as follows. One study was excluded because of a significantly different baseline risk in cardiac complications.[49] Three studies were excluded because of in-hospital mortality instead of 30-day mortality were reported.[16,22,28] Five studies reporting LOS were excluded because of significant variation in LOS thought to be related to the procedure itself (lower extremity amputation,[27] transurethral procedure,[52] inappropriate outcome measurement,[16] method of reporting LOS,[53] and large number of included surgical procedure types [21]).[30]

Heterogeneity

The outcomes of myocardial infarction (in the combined neuraxial and general anesthesia group), thromboembolic events (in the combined neuraxial and general anesthesia group), and the outcome LOS (in the RCT group) were downgraded by 1 level because of variation in point estimates of treatment effect.

Indirectness

Three studies were excluded for indirectness or noncompliance with the health care question. One study was excluded because the intervention was linked to surgical type,[54] one used a surrogate marker of LOS (duration of postanesthesia care unit stay),[55] and the third administered epidural opioid only at wound closure.[56]

Imprecision

The outcomes of myocardial infarction (combined neuraxial and general anesthesia versus general anesthesia), thromboembolic events (neuraxial versus general anesthesia), and blood transfusion (RCTs) were downgraded for imprecision.

Publication Bias

The outcome cardiac composite (neuraxial versus general anesthesia) was downgraded for suspected publication bias.

Rating Up the Quality of Evidence

In our analysis of population-based studies, a large effect size was established for the outcomes of intensive care unit (ICU) admission (neuraxial versus general anesthesia) and pulmonary composite complications (neuraxial versus general anesthesia), and therefore level of evidence was upgraded by one level.

Overall, the level of evidence from available studies, regarding the health care question ranged from moderate to very low by outcomes. A summary of findings with GRADE analysis is outlined in Table 3.

Results From Meta-analysis by Outcome

30-Day Mortality

Six observational studies[20,29,30,32,49,53] compared combined neuraxial-general anesthesia with general anesthesia with a total of 396,869 patients. There was no difference in the odds of 30-day mortality (OR 0.88; 99% CI, 0.77–1.01). Thirteen observational studies[17,18,20,21,23,25,27,29,36,37,39,49,51] compared neuraxial with general anesthesia with a total of 491,611 patients. There was no difference in the odds of 30-day mortality (OR 0.98; 99% CI, 0.92–1.04) (Figure 2). The quality of the evidence for 30-day mortality by GRADE analysis was determined as low. Subgroup analysis was performed for 30-day mortality: studies investigating hip fracture surgery comparing neuraxial with general anesthesia included 4 studies with a total of 90,037 patients.[17,21,25,29] This subgroup analysis resulted in no difference in odds of 30-day mortality (OR 1.00; 99% CI, 0.93–1.07). Further subgroup analysis of studies investigating hip and/or knee arthroplasty that compared neuraxial with general anesthesia included 5 studies with a total of 389,355 patie nts.[18,20,23,31,51] This subgroup analysis resulted in no difference in odds of 30-day mortality (OR 0.72; 99% CI, 0.51–1.01).

Myocardial Infarction

Four observational studies[20,30,32,34] compared combined neuraxial-general anesthesia with general anesthesia with a

Table 1. Summary of Population-Based Studies Included in Meta-analysis

Author, Year	Anesthesia Type	Database	Surgical Type	N	Outcomes	Main Results
Basques, 2015[15]	GA, SA	ACS-NSQIP	Primary total hip arthroplasty	20,936 GA 60.9% SA 39.1%	Operating room times Length of stay 30-day adverse events Readmission in the first 30 postoperative days	GA associated with increased operative and postoperative room time ($P < .001$), prolonged postoperative ventilator use ($P = .018$), unplanned intubation ($P = .024$), stroke ($P = .046$), cardiac arrest ($P = .032$), blood transfusion ($P < .001$), and any adverse event ($P < .001$) when compared to SA.
Basques, 2015[14]	GA, SA	ACS-NSQIP	Hip fracture surgery in patients >70 years of age	9842 GA 73.7% SA 26.3%	Operating room times Length of stay Any adverse event Thromboembolic event Blood transfusion Urinary tract infection	No clear advantage of one type of anesthetic over the other in patients aged 70 y or older. GA associated with slightly increased operating theater time and postoperative time ($P < .001$), decreased length of stay ($P < .001$), increased risk of any adverse event ($P < .001$), thromboembolic events ($P = .003$), blood transfusion ($P < .001$). GA associated with decreased risk of UTI ($P < .001$) when compared to SA.
Chu, 2015[16]	GA, NA	Taiwan in-patient claims database	Hip surgery in patients >65 years of age	182,307 GA 29.3% NA 70.7%	Mortality Stroke Transient ischemic stroke Myocardial infarction Respiratory failure Renal failure	GA patients had greater percentage and increased odds of adverse outcomes when compared to NA group-Mortality ($P < .001$), stroke ($P = .001$), respiratory failure ($P < 001$), ICU admission ($P < .001$). GA patients had increased length of stay ($P < .001$) and increased costs ($P < .001$) when compared to NA patients.
Fields, 2015[17]	GA, SA	ACS-NSQIP	Hip fracture surgery	6133 GA 72.6% SA 27.4%	30-day morbidity and mortality	SA group had lower frequency of blood transfusions ($P < .0001$), deep vein thrombosis ($P = .004$), urinary tract infection ($P < .0001$), and overall complications ($P = .001$). GA was significantly associated with increased risk for complication after hip fracture surgery. Risk factors for complications were identified as age, female sex, BMI, hypertension, transfusion, emergency procedure, operation time, and ASA score.
Helwani, 2015[18]	GA, NA	ACS-NSQIP	Total hip arthroplasty	12,929 GA 60.5% RA 39.5%	Postoperative morbidity and mortality	NA group had lower odds for development of deep surgical site infections ($P < .01$) when compared with GA group. NA decreased length of stay ($P < .001$), decreased odds of prolonged hospitalization ($P < .001$). No significant difference on mortality.
Memtsoudis, 2013[19]	GA, Combined GA + NA, NA	Premier Inc	Primary total hip or knee arthroplasty in patients with sleep apnea	30,024 NA 11% Combined 15% GA 74%	Postoperative complications	Patients with diagnosis of sleep apnea who underwent procedures under NA had significantly lower complications than patients who received combined GA + NA or GA alone ($P = .0177$).
Memtsoudis, 2013[20]	GA, Combined GA + NA, NA	Premier Inc	Primary hip or knee arthroplasty	382,236 NA 11% Combined 14.2% GA 74.8%	Postoperative complications 30-day mortality Length of stay Patient cost	NA group had significantly lower 30-day mortality ($P < .001$). Prolonged length of stay, increased cost, and postoperative complications were decreased in the NA group.
Neuman, 2012[22]	GA, RA	New York State Inpatient Database	Hip fracture surgery	18,158 RA 29% GA 71%	Inpatient mortality Cardiovascular complications Pulmonary complications	Unadjusted rates of mortality and cardiovascular complications did not differ by anesthesia type. RA group experienced fewer pulmonary complications ($P < .005$)

(*Continued*)

Table 1. Continued

Author, Year	Anesthesia Type	Database	Surgical Type	N	Outcomes	Main Results
Pugely, 2013[23]	GA, SA	ACS-NSQIP	Primary total knee arthroplasty	14,052 SA 42.9% GA 57.1%	Mortality 30-day complication rates	SA group had a reduced frequency of superficial wound infections (P = .0003), blood transfusions (P = .0086), and overall complications (P = .0032) when compared to GA group. Length of surgery and length of stay were shorter in SA group.
Stundner, 2012[24]	GA, Combined GA + NA, NA	Premier Inc	Bilateral total knee arthroplasty	15,687 NA 6.8% GA 80.1% Combined 13.1%	Mortality Complication rates	NA group required blood transfusions significantly less frequency (P < .0001). No significant difference in 30-day mortality and complication rates.
Liu, 2013[26]	GA, NA	ACS-NSQIP	Total Knee arthroplasty	16,555 GA 55.4% NA 44.6%	Infection related 30-day postoperative complications	No significant difference in mortality between the 2 groups. NA subjects had lower incidences of pneumonia (P = .035) and composite systemic infection (P = .006) when compared with GA group.
Khan, 2013[27]	GA, RA	Singapore General Hospital operating theater database	Major lower extremity amputation	1365	30-day mortality Length of stay	30-day mortality was significantly increased in GA group when compared to RA group.
Patorno, 2014[28]	GA, Combined GA + NA, NA	Premier Inc	Hip fracture surgery	73,284 GA 84% Combined 6.5% NA 9.5%	In hospital all-cause mortality	Mortality risk did not differ significantly between groups.
White, 2014[29]	GA, SA	National Hip Fracture Database	Hip fracture surgery	59,191	5-day and 30-day mortality	No significant difference in mortality between GA and SA groups.
Nash, 2015[30]	Combined GA + NA, GA	ICES database	Elective procedures (major procedures involving aorta/ peripheral vasculature, bladder, bowel, lung, other gastrointestinal)	GA 21,701 Combined 8042	Major medical complications (acute kidney injury, stroke, myocardial infarction, and all-cause mortality)	Combined GA + NA was not associated with a reduced risk of major medical complications.
Chen, 2015[31]	GA, NA	National Health Insurance Research Database	Total hip arthroplasty	7977 GA 37.5% NA 62.5%	Postoperative mortality Length of stay Hospital treatment costs	NA was associated with lower treatment costs and a shorter length of stay. No significant difference in short-term postoperative mortality. NA found to be associated with a better survival than was shown for GA, becoming statistically significant at 5 y after surgery.
Ozbek, 2015[32]	Combined GA + NA, GA	Premier Inc	Open lung resections	19,843 GA 79% Combined 21%	Acute myocardial infarction Pulmonary complications Blood transfusion Mechanical ventilation Deep vein thrombosis/ Pulmonary embolism	Combined GA + NA had a lower incidence of myocardial infarction (P = .018), pulmonary complications (P = .006), blood transfusion (P < .0001), and mechanical ventilation (P < .0001). Combined GA + NA was associated with higher odds of deep vein thrombosis and pulmonary embolism.

(*Continued*)

Table 1. Continued

Author, Year	Anesthesia Type	Database	Surgical Type	N	Outcomes	Main Results
Hausman, 2015[33]	GA, RA	ACS-NSQIP	All surgical types in patients with chronic obstructive pulmonary disease	5288 RA 2644 GA 2644	Morbidity and mortality	GA patients had higher incidence of postoperative pneumonia (P = .0384), prolonged ventilator dependence (P = .0008), unplanned postoperative intubation (P = .0487). RA patients had lower incidences of all-cause morbidity (P = .0038). No significant difference in mortality between RA and GA groups.
Poeran, 2015[34]	GA, Combined GA + NA	Premier Inc	Open colectomies	98,290 GA 93.9% Combined 6.1%	Thromboembolism Acute myocardial infarction Postoperative infection Postoperative ileus Cerebrovascular events Blood transfusion ICU admission Mechanical ventilation	Combined GA + NA associated with significantly decreased risk for thromboembolism and cerebrovascular events. Combined GA + NA associated with an increased risk of acute myocardial infarction, UTI, blood transfusion, and ICU admission. No significant differences in other outcomes.
Seitz, 2014[25]	GA, SA	ICES database	Hip fracture surgery in older adults with dementia	6135 matched pairs	30-day mortality ICU admission Postoperative medical complications Length of stay	No significant difference in postoperative 30-day mortality, postoperative medical complications, or length of stay. GA was associated with higher rates of ICU admissions.
Neuman, 2014[21]	GA, NA	SPARCS	Hip fracture surgery	56,729 RA 28% GA 72%	30-day mortality Length of stay	NA was associated with a shorter length of stay (P < .001). No significant difference in mortality by anesthesia type.
Cicek, 2013[35]	GA, SA	Single hospital database	PCNL	1004 GA 564 SA 440	Length of stay Blood transfusion	SA associated with significantly shorter duration of hospitalization (P < .01). GA group had significantly higher rates of blood transfusion (P < .01)
Ghanami, 2013[36]	RA, GA	ACS-NSQIP	Lower extremity vascular bypass procedures	5462	Morbidity Length of stay Mortality	No significant differences by anesthesia type in incidence of morbidity, mortality, or length of stay.
Edwards, 2011[37]	GA, NA	ACS-NSQIP	Endovascular aortic aneurysm repair	6009	Morbidity Length of stay 30-day mortality	GA associated with increased pulmonary morbidity when compared to SA (P = .02). GA associated with increased length of stay when compared with SA (P = .001). No significant association between anesthesia type and mortality.
Chang, 2010[38]	GA, NA	Longitudinal Health Insurance Database	Total hip or knee replacements	3081	Surgical site infection	Odds of surgical site infection were 2.21 times higher in those who had GA when compared with NA.
Leslie, 2013[49]	GA, NA, Combined GA + NA	POISE trial	Noncardiac surgery in patients with high risk of cardiovascular complications	NA 3909 GA 4016	Cardiovascular death Nonfatal myocardial infarction Nonfatal cardiac arrest	NA associated with increased risk of composite cardiovascular death (P = .03), but were not at increased risk of stroke, death, or clinically significantly hypotension. Thoracic epidural with GA was associated with a worse primary outcome than GA alone (P < .001).
Wiis, 2014[39]	EA, GA	Danish Vascular Registry	Lower extremity in situ bypass graft surgery	822	30-day mortality	No significant difference in mortality between groups.

Abbreviations: ACS-NSQIP, American College of Surgeons National Quality Improvement Program; EA, epidural anesthesia; GA, general anesthesia; ICES, Institute for Clinical Evaluative Sciences; ICU, intensive care unit; NA, neuraxial anesthesia (spinal + epidural); PCNL, percutaneous nephrolithotomy; POISE, Perioperative ischemic evaluation; PNB, peripheral nerve block; RA, regional anesthesia (epidural, spinal or peripheral nerve blockade); SA, spinal anesthesia; SPARCS, Statewide Planning and Research Cooperative System; UTI, urinary tract infection.

Table 2. Summary of Randomized-Controlled Trials Included in the Meta-analysis

Author, Year	Anesthesia Type	Surgical Type	N	Outcome Measured	Relevant Outcomes
Harsten, 2015[13]	GA, SA	Total hip arthroplasty	120	Length of stay Mortality	GA resulted in decreased length of stay (26 h vs 30 h, $P = .004$)
Nouralizadeh, 2013[12]	GA, SA	Percutaneous nephrolithotomy	100	Length of stay Complications according to the Clavien grading system (grading for surgical complications)	Mean length of stay in the GA group and SA group was 3.04 (2–5) d and 2.82 (2–6) d, respectively 8% patients in GA, 10% patients in SA had blood transfusion
Salman, 2013[6]	Combined EA + GA, combined Meperidine +GA	Elective abdominal aortic surgery	80	Postoperative myocardial infarction Length of stay ICU admission	Hospital length of stay combined Meperidine + GA group 6.7 ± 2.2 d, Combined EA + GA group 7.0 ± 2.4 d ($P = .604$). Rate of myocardial infarction 5% in each group ($P = 1$)
Tangpaitoon, 2012[9]	GA, EA	Percutaneous nephrolilthotomy	50	Pulmonary complications Length of stay Blood transfusion requirement	No significant difference between treatment groups
Wongyingsinn, 2012[11]	Combined GA + SA, GA	Laparoscopic colonic resection	50	Length of stay Blood transfusion requirement	No significant difference in length of stay. Anemia requiring blood transfusion 4% each group ($P = 1$)
Kjolhede, 2012[4]	GA, SA	Fast-track abdominal hysterectomy	162	Length of stay Postoperative complications	No significant difference in length of stay or postoperative complications
Singh, 2011[7]	GA, CSE	Percutaneous nephrolithotomy	64	Length of stay Blood transfusion requirement	Length of stay CSE 4.0 ± 0.9 d, GA 4.56 ± 1.0 ($P = .02$) No significant difference in blood transfusion requirement
Tyagi, 2011[10]	Combined GA+ thoracic epidural, GA	Laparotomy for perforation peritonitis	66	Postoperative major morbidity (respiratory, cardiovascular, renal, hepatic, hematological, gastrointestinal failure) 30-day mortality Length of stay Postoperative ventilation	Length of stay GA 8 ± 2 d, combined GA + thoracic epidural 6 ± 1 d ($P < .001$) No significant difference in 30-day mortality, postoperative major morbidity or postoperative ventilation
Parker, 2015[5]	GA, SA	Hip fracture surgery	322	Length of stay Blood transfusion requirement Postoperative complications 30-day mortality	No significant differences in outcome between the 2 techniques
Orsolya, 2015[50]	GA, combined GA + EA	Robotic urogenital oncosurgery	40	Length of stay	No significant difference in length of stay between the 2 techniques
Surico, 2010[8]	GA, SA	Gynecological surgery	80	Length of stay Morbidity Blood transfusion requirement	Length of stay, SA 1.84 ± 0.51 d, GA 2.55 ± 0.5 ($P < .0001$)

Abbreviations: CSE, combined spinal and epidural anesthesia; EA, epidural anesthesia; GA, general anesthesia; NA, neuraxial anesthesia (spinal + epidural); PACU, postanesthesia care unit; RA, regional anesthesia (epidural, spinal, or peripheral nerve blockade); SA, spinal anesthesia.

total of 471,812 patients. There was an increase in the odds of myocardial infarction (OR 1.18; 99% CI, 1.01–1.37), that is general anesthesia was protective. The quality of this evidence by GRADE analysis was rated as very low. Nine observational studies[14,16,17,20,22,23,25,36,37] compared neuraxial with general anesthesia with a total of 520,052 patients. This analysis resulted in no difference in the odds of myocardial infarction (OR 0.91; 99% CI, 0.81–1.02) (see Supplemental Digital Content 1, Figure 1, http://links.lww.com/AA/B726). The quality of this evidence by GRADE analysis was rated as low.

Cardiac Composite Complications

Four observational studies[19,20,24,32] compared combined neuraxial-general anesthesia with general anesthesia with a total of 361,143 patients. There was no difference in the odds of cardiac composite complication (OR 1.04; 99% CI, 1.00–1.09). The quality of this evidence by GRADE analysis was rated as low. Eleven observational studies[17,18,20,22–25,36,37,39,51] compared neuraxial with general anesthesia with a total of 447,748 patients. There was no significant difference in the odds of cardiac composite complications (OR 0.99; 99% CI, 0.94–1.03) (see Supplemental Digital Content 2, Figure 2, http://links.lww.com/AA/B727). The quality of this evidence by GRADE analysis was rated as very low.

Pulmonary Complications Including Mechanical Ventilation

Three observational studies[20,32,34] compared combined neuraxial-general anesthesia with general anesthesia with a total of 459,433 patients. The odds of pulmonary complications (OR 0.84; 99% CI, 0.79–0.88) was reduced in favor of

Table 3. Summary of Findings

Outcomes	Anticipated Absolute Effects[a] (99% CI): Risk With General Anesthesia	Anticipated Absolute Effects[a] (99% CI): Risk With Neuraxial Anesthesia	Relative Effect (99% CI)	Number of Participants (Studies)	Quality of the Evidence (GRADE)
30-day mortality GA, GA + NA	6 per 1000	6 per 1000 (5–6)	OR 0.88 (0.77–1.01)	396,869 (6 observational studies)	⊕⊕○○ LOW
30-day mortality GA, NA	10 per 1000	10 per 1000 (9–11)	OR 0.98 (0.92–1.04)	491,611 (13 observational studies)	⊕⊕○○ LOW
Myocardial infarction GA, GA + NA	5 per 1000	6 per 1000 (5–7)	OR 1.18 (1.01–1.37)	471,812 (4 observational studies)	⊕○○○ VERY LOW[b,c]
Myocardial infarction GA, NA	5 per 1000	4 per 1000 (4–5)	OR 0.91 (0.81–1.02)	520,052 (9 observational studies)	⊕⊕○○ LOW
Cardiac composite GA, GA + NA	75 per 1000	78 per 1000 (75–81)	OR 1.04 (1.00–1.09)	361,143 (2 observational studies)	⊕⊕○○ LOW
Cardiac composite GA, NA	60 per 1000	60 per 1000 (57 to 62)	OR 0.99 (0.94–1.03)	447,748 (11 observational studies)	⊕○○○ VERY LOW[d]
Pulmonary composite incl. ventilation GA, GA + NA	67 per 1000	57 per 1000 (54–60)	OR 0.84 (0.79–0.88)	459,433 (3 observational studies)	⊕⊕○○ LOW
Pulmonary composite incl. ventilation GA, NA	35 per 1000	14 per 1000 (13–14)	OR 0.38 (0.36–0.40)	498,229 (9 observational studies)	⊕⊕⊕○ MODERATE
Pneumonia GA, GA + NA	28 per 1000	27 per 1000 (25–29)	OR 0.94 (0.87–1.02)	471,812 (4 observational studies)	⊕⊕○○ LOW
Pneumonia GA, NA	13 per 1000	12 per 1000 (11–13)	OR 0.92 (0.84–1.01)	396,106 (8 observational studies)	⊕⊕○○ LOW
Surgical site infection GA, GA + NA	53 per 1000	49 per 1000 (47–52)	OR 0.93 (0.88–0.98)	459,433 (3 observational studies)	⊕⊕○○ LOW
Surgical site infection GA, NA	42 per 1000	32 per 1000 (30–34)	OR 0.76 (0.71–0.82)	380,682 (7 observational studies)	⊕⊕○○ LOW
Blood transfusion GA, GA + NA	177 per 1000	162 per 1000 (158–167)	OR 0.90 (0.87–0.93)	459,433 (3 observational studies)	⊕⊕○○ LOW
Blood transfusion GA, NA	189 per 1000	166 per 1000 (161–171)	OR 0.85 (0.82–0.88)	369,653 (6 observational studies)	⊕⊕○○ LOW
Blood transfusion GA, NA (RCTs)	155 per 1000	163 per 1000 (101–265)	RR 1.05 (0.65–1.71)	585 (5 RCTs)	⊕⊕⊕○ MODERATE
Thromboembolic complications GA, GA + NA	9 per 1000	8 per 1000 (7–9)	OR 0.84 (0.73–0.98)	459,433 (3 observational studies)	⊕⊕○○ LOW
Thromboembolic complications GA, NA	6 per 1000	4 per 1000 (4–5)	OR 0.79 (0.68–0.91)	397,806 (7 observational studies)	⊕○○○ VERY LOW[b,c]
Length of stay GA, GA + NA		The mean LOS was reduced by 3.84 h (4.08 lower to 3.6 lower) with NA + GA compared to GA	–	142,998 (3 observational studies)	⊕⊕○○ LOW
Length of stay GA, NA		The mean was reduced by 6.96 h (6.96 lower to 6.72 lower) with NA compared to GA	–	120,755 (9 observational studies)	⊕⊕○○ LOW
Length of stay GA, NA (RCTs)		The mean LOS was reduced by 3.6 h (6.48 lower to 0.96 lower) with NA compared to GA	–	1131 (11 RCTs)	⊕⊕⊕○ MODERATE[b]
ICU admission GA, GA + NA	137 per 1000	109 per 1000 (104–114)	OR 0.77 (0.73–0.81)	459,433 (3 observational studies)	⊕⊕⊕○ MODERATE
ICU admission GA, NA	48 per 1000	25 per 1000 (24–26)	OR 0.50 (0.48–0.53)	474,156 (4 observational studies)	⊕⊕⊕○ MODERATE

Abbreviations: CI, confidence interval; GRADE, Grades of Recommendation Assessment, Development, and Evaluation; GA, general anesthesia; ICU, intensive care unit; MD, mean difference; NA, neuraxial anesthesia; OR, odds ratio; RCTs, randomized control trials. GRADE Working Group grades of evidence: High quality, We are very confident that the true effect lies close to that of the estimate of the effect; Moderate quality, We are moderately confident in the effect estimate. The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different; Low quality, Our confidence in the effect estimate is limited. The true effect may be substantially different from the estimate of the effect; Very low quality, We have very little confidence in the effect estimate. The true effect is likely to be substantially different from the estimate of effect.

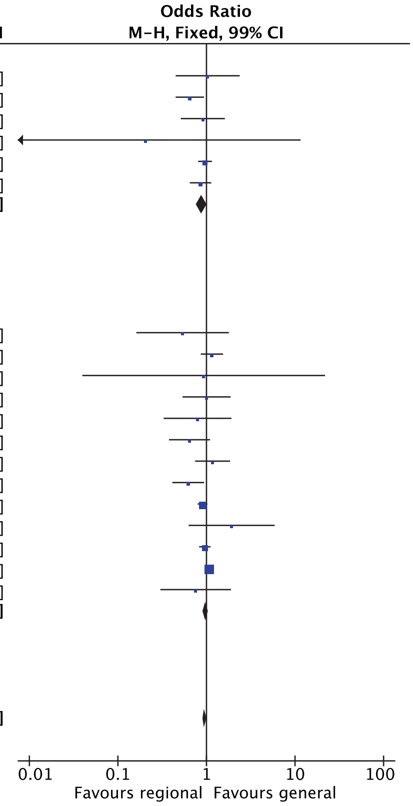
[a]The risk in the intervention group (and its 95% CI) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

[b]Significant test for heterogeneity.

[c]Sample size not met.

[d]Funnel plot asymmetric.

Study or Subgroup	Regional anaesthesia Events	Regional anaesthesia Total	General anaesthesia Events	General anaesthesia Total	Weight	Odds Ratio M-H, Fixed, 99% CI
1.1.1 GA vs GA+NA						
Leslie 2013	13	709	39	2194	0.5%	1.03 [0.45, 2.37]
Memtsoudis Periop 2013	54	49396	493	292804	3.6%	0.65 [0.45, 0.94]
Nash 2015	32	4773	56	7606	1.1%	0.91 [0.51, 1.61]
Wax 2010	2	479	0	19	0.0%	0.20 [0.00, 11.54]
White 2014 (1)	281	4280	1066	15666	10.7%	0.96 [0.80, 1.15]
Özbek 2015	108	4031	464	14912	4.8%	0.86 [0.65, 1.13]
Subtotal (99% CI)		**63668**		**333201**	**20.7%**	**0.88 [0.77, 1.01]**
Total events	490		2118			
Heterogeneity: Chi² = 7.36, df = 5 (P = 0.20); I² = 32%						
Test for overall effect: Z = 2.43 (P = 0.01)						
1.1.2 GA vs NA						
Edwards 2011	5	750	60	4868	0.4%	0.54 [0.16, 1.79]
Fields 2015	121	1815	281	4813	3.6%	1.15 [0.86, 1.54]
Gabriel 2015	1	9150	2	17021	0.0%	0.93 [0.04, 21.81]
Ghanami 2013	20	694	137	4768	0.9%	1.00 [0.54, 1.88]
Helwani 2015	15	5102	20	5396	0.5%	0.79 [0.33, 1.91]
Khan 2013	44	475	65	475	1.5%	0.64 [0.38, 1.10]
Leslie 2013	48	1425	106	3673	1.4%	1.17 [0.74, 1.85]
Memtsoudis Periop 2013	42	40036	493	292804	3.0%	0.62 [0.41, 0.94]
Neuman Anesth 2014	835	15904	920	15904	21.9%	0.90 [0.80, 1.02]
Pugely 2013	13	6030	9	8022	0.2%	1.92 [0.63, 5.88]
Seitz 2014	665	6135	691	6135	15.5%	0.96 [0.83, 1.11]
White 2014 (2)	1713	23665	1066	15666	29.9%	1.07 [0.96, 1.19]
Wiis 2014	13	386	22	499	0.5%	0.76 [0.30, 1.89]
Subtotal (99% CI)		**111567**		**380044**	**79.3%**	**0.98 [0.92, 1.04]**
Total events	3535		3872			
Heterogeneity: Chi² = 27.74, df = 12 (P = 0.006); I² = 57%						
Test for overall effect: Z = 0.91 (P = 0.36)						
Total (99% CI)		**175235**		**713245**	**100.0%**	**0.96 [0.90, 1.02]**
Total events	4025		5990			
Heterogeneity: Chi² = 38.07, df = 18 (P = 0.004); I² = 53%						
Test for overall effect: Z = 1.92 (P = 0.06)						
Test for subgroup differences: Chi² = 3.18, df = 1 (P = 0.07), I² = 68.6%						



Footnotes
(1) GA only vs GA + spinal
(2) GA only vs All spinal

Figure 2. Forest plot of studies reporting 30-day mortality when general anesthesia was compared to combined general and neuraxial anesthesia and neuraxial anesthesia alone. CI indicates confidence interval; GA, general anesthesia; GA + NA, combined general and neuraxial anesthesia; NA, neuraxial anesthesia; OR, odds ratio.

combined general and neuraxial anesthesia. The quality of this evidence by GRADE analysis was rated as low. Nine observational studies[16–18,20,22,23,36,37,39] compared neuraxial with general anesthesia with a total of 498,229 patients. The odds of pulmonary complications (OR 0.38; 99% CI, 0.36–0.40) was reduced in favor of neuraxial anesthesia (Figure 3). The quality of this evidence by GRADE analysis was rated as moderate.

Pneumonia

Four observational studies[20,30,32,34] compared combined neuraxial-general anesthesia with general anesthesia with a total of 471,812 patients. There was no difference in the odds of developing pneumonia (OR 0.94; 99% CI, 0.87–1.02). The quality of this evidence by GRADE analysis was rated as low. Eight observational studies[14,17,20,22,25,33,36,37] compared neuraxial with general anesthesia with a total of 396,106 patients. There was no difference in the odds of developing pneumonia (OR 0.92; 95% CI, 0.84–1.01) (Figure 4). The quality of this evidence by GRADE analysis was rated as low.

Surgical Site Infection

Three observational studies[20,32,34] compared combined neuraxial-general anesthesia with general anesthesia with a total of 459,433 patients. There was a reduced odds of surgical site infection (OR 0.93; 99% CI, 0.88–0.98), in favor of combined general and neuraxial anesthesia. The quality of this evidence by GRADE analysis was rated as low. Seven observational studies[17,18,20,26,36–38] compared neuraxial with general anesthesia with a total of 380,682 patients. There was a reduced odds of surgical site infection (OR 0.76; 99% CI, 0.71–0.82) in favor of neuraxial anesthesia (see Supplemental Digital Content 3, Figure 3, http://links.lww.com/AA/B728). The quality of this evidence by GRADE analysis was rated as low.

Requirement for Blood Transfusion

Three observational studies[20,32,34] compared combined neuraxial-general anesthesia with general anesthesia with a total of 459,433 patients. There was a reduced odds of requiring blood transfusion (OR 0.90; 99% CI, 0.87–0.93), in favor of combined general and neuraxial anesthesia. The quality of this evidence by GRADE analysis was rated as low. Six observational studies[14,17,20,23,35,37] compared neuraxial anesthesia with general anesthesia with a total of 369,653 patients. There was a reduced odds of requiring blood transfusion (OR 0.85; 99% CI, 0.82–0.88), in favor of neuraxial anesthesia (see Supplemental Digital Content 4, Figure 4, http://links.lww.com/AA/B729). The quality of this evidence by GRADE analysis was rated as low. Five RCTs[5,7,9,11,12] compared neuraxial anesthesia with general

Study or Subgroup	Regional anaesthesia Events	Regional anaesthesia Total	General anaesthesia Events	General anaesthesia Total	Weight	Odds Ratio M-H, Fixed, 99% CI
1.4.1 GA vs GA+NA						
Memtsoudis Periop 2013	1024	49396	6925	292804	15.8%	0.87 [0.80, 0.95]
Poeran 2015	835	5989	15160	92301	12.9%	0.82 [0.75, 0.91]
Özbek 2015	1120	4031	4855	14912	12.1%	0.80 [0.72, 0.88]
Subtotal (99% CI)		**59416**		**400017**	**40.8%**	**0.84 [0.79, 0.88]**
Total events	2979		26940			
Heterogeneity: Chi² = 3.33, df = 2 (P = 0.19); I² = 40%						
Test for overall effect: Z = 8.42 (P < 0.00001)						
1.4.2 GA vs NA						
Chu 2015	1077	52044	4876	52044	38.6%	0.20 [0.19, 0.22]
Edwards 2011	8	750	155	4868	0.3%	0.33 [0.13, 0.84]
Fields 2015	101	1815	291	4813	1.2%	0.92 [0.67, 1.24]
Ghanami 2013	23	694	201	4768	0.4%	0.78 [0.44, 1.39]
Helwani 2015	23	5102	47	5396	0.4%	0.52 [0.27, 0.99]
Memtsoudis Periop 2013	628	40036	6925	292804	13.3%	0.66 [0.59, 0.73]
Neuman Comp 2012	359	5254	1040	12904	4.5%	0.84 [0.71, 0.99]
Pugely 2013	30	6030	53	8022	0.4%	0.75 [0.42, 1.36]
Wiis 2014	10	386	23	499	0.2%	0.55 [0.20, 1.48]
Subtotal (99% CI)		**112111**		**386118**	**59.2%**	**0.38 [0.36, 0.40]**
Total events	2259		13611			
Heterogeneity: Chi² = 728.75, df = 8 (P < 0.00001); I² = 99%						
Test for overall effect: Z = 41.21 (P < 0.00001)						
Total (99% CI)		**171527**		**786135**	**100.0%**	**0.57 [0.54, 0.59]**
Total events	5238		40551			
Heterogeneity: Chi² = 1293.49, df = 11 (P < 0.00001); I² = 99%						
Test for overall effect: Z = 36.28 (P < 0.00001)						
Test for subgroup differences: Chi² = 617.13, df = 1 (P < 0.00001), I² = 99.8%						

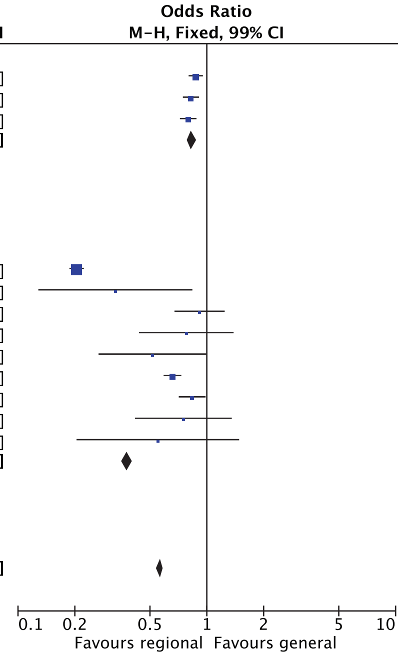


Figure 3. Forest plot of studies reporting pulmonary complications including mechanical ventilation when general anesthesia was compared to combined general and neuraxial anesthesia and neuraxial anesthesia alone. CI indicates confidence interval; GA, general anesthesia; GA + NA, combined general and neuraxial anesthesia; NA, neuraxial anesthesia; OR, odds ratio.

anesthesia with a total of 585 patients. There was no difference in the relative risk of blood transfusion requirement (RR 1.05; 99% CI, 0.65–1.71) (see Supplemental Digital Content 5, Figure 5, http://links.lww.com/AA/B730). The quality of this evidence by GRADE analysis was rated as moderate.

Thromboembolic Events

Three observational studies[20,32,34] compared combined neuraxial-general anesthesia with general anesthesia with a total of 459,433 patients. There was a reduced odds of thromboembolic events (OR 0.84; 99% CI, 0.73–0.98), in favor of combined general and neuraxial anesthesia. The quality of this evidence by GRADE analysis was rated as low. Seven observational studies[14,17,20,23,25,36,37] compared neuraxial with general anesthesia with a total of 397,806 patients. This analysis resulted in a reduction in the odds of thromboembolic events (OR 0.79; 99% CI, 0.68–0.91) (see Supplemental Digital Content 6, Figure 6, http://links.lww.com/AA/B731), in favor of neuraxial anesthesia. The quality of this evidence by GRADE analysis was rated as very low.

Length of Stay

Three observational studies[19,32,34] compared combined neuraxial-general anesthesia with general anesthesia with a total of 142,998 patients. There was a reduced length of stay (mean difference −0.16 days; 99% CI, −0.17 to −0.15), in favor of combined general and neuraxial anesthesia. The quality of this evidence by GRADE analysis was rated as low. Nine observational studies[18,19,21,23,25,31,36,37,39] compared neuraxial with general anesthesia with a total of 120,755 patients. This analysis resulted in a reduced length of stay (mean difference −0.29 days; 99% CI, −0.29 to −0.28), in favor of neuraxial anesthesia. The quality of this evidence by GRADE analysis was rated as low. Eleven RCTs compared neuraxial anesthesia with general anesthesia,[4–13,50] with a total of 1131 patients. This analysis resulted in a reduced length of stay (mean difference −0.15; 99% CI, −0.27 to −0.04) (see Supplemental Digital Content 7, Figure 7, http://links.lww.com/AA/B732), in favor of neuraxial anesthesia. The quality of this evidence by GRADE analysis was rated as moderate.

ICU Admission

Three observational studies[20,32,34] compared combined neuraxial-general anesthesia with general anesthesia with a total of 459,433 patients. There was a reduced odds for ICU admission (OR 0.77; 99% CI, 0.73–0.81), in favor of combined general and neuraxial anesthesia. The quality of this evidence by GRADE analysis was rated as moderate. Four observational studies[16,20,25,51] compared neuraxial versus general anesthesia with a total of 474,156 patients. There was a reduced odds for ICU admission (OR 0.50; 99% CI, 0.48–0.53) (Figure 5), in favor of neuraxial anesthesia. The quality of this evidence by GRADE analysis was rated as moderate.

DISCUSSION

This meta-analysis of studies reflective of contemporary clinical care indicates that, compared to general anesthesia, neuraxial anesthesia when used alone or when combined with general anesthesia is not likely to decrease 30-day mortality, our primary outcome. This analysis indicates that general anesthesia may protect against myocardial infarction compared to neuraxial anesthesia. Although neuraxial anesthesia was not associated with a reduced risk of pneumonia when compared to general anesthesia, neuraxial

Study or Subgroup	Regional anaesthesia Events	Regional anaesthesia Total	General anaesthesia Events	General anaesthesia Total	Weight	Odds Ratio M–H, Fixed, 99% CI
1.5.1 GA vs GA+NA						
Memtsoudis Periop 2013	435	49396	2669	292804	19.3%	0.97 [0.84, 1.10]
Nash 2015	58	4773	67	7606	1.3%	1.38 [0.87, 2.20]
Poeran 2015	401	5989	6690	92301	19.2%	0.92 [0.80, 1.05]
Özbek 2015	510	4031	2054	14912	19.3%	0.91 [0.79, 1.04]
Subtotal (99% CI)		**64189**		**407623**	**59.2%**	**0.94 [0.87, 1.02]**
Total events	1404		11480			
Heterogeneity: Chi² = 5.53, df = 3 (P = 0.14); I² = 46%						
Test for overall effect: Z = 2.06 (P = 0.04)						
1.5.3 GA vs NA						
Basques 2 2015	140	2589	377	7253	4.7%	1.04 [0.80, 1.35]
Edwards 2011	5	750	67	4868	0.4%	0.48 [0.15, 1.59]
Fields 2015	65	1815	171	4813	2.3%	1.01 [0.69, 1.48]
Ghanami 2013	12	694	88	4768	0.6%	0.94 [0.42, 2.08]
Hausman 2015	61	2644	87	2644	2.2%	0.69 [0.45, 1.07]
Memtsoudis Periop 2013	295	40036	2669	292804	16.1%	0.81 [0.69, 0.95]
Neuman Comp 2012	153	5254	359	12904	5.1%	1.05 [0.81, 1.35]
Seitz 2014	413	6135	399	6135	9.4%	1.04 [0.86, 1.25]
Subtotal (99% CI)		**59917**		**336189**	**40.8%**	**0.92 [0.84, 1.01]**
Total events	1144		4217			
Heterogeneity: Chi² = 15.65, df = 7 (P = 0.03); I² = 55%						
Test for overall effect: Z = 2.26 (P = 0.02)						
Total (99% CI)		**124106**		**743812**	**100.0%**	**0.93 [0.88, 0.99]**
Total events	2548		15697			
Heterogeneity: Chi² = 21.27, df = 11 (P = 0.03); I² = 48%						
Test for overall effect: Z = 3.03 (P = 0.002)						
Test for subgroup differences: Chi² = 0.19, df = 1 (P = 0.66), I² = 0%						

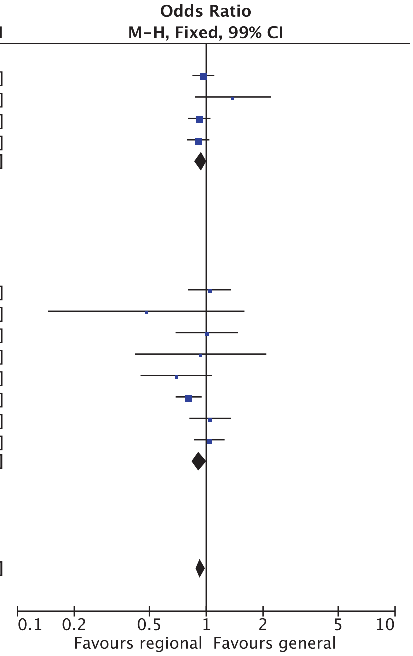
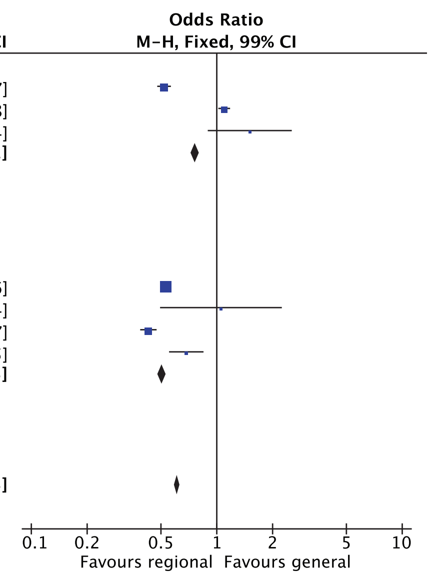


Figure 4. Forest plot of studies reporting pneumonia when general anesthesia was compared to combined general and neuraxial anesthesia and neuraxial anesthesia alone. CI indicates confidence interval; GA, general anesthesia; GA + NA, combined general and neuraxial anesthesia; NA, neuraxial anesthesia; OR, odds ratio.

Study or Subgroup	Regional anaesthesia Events	Regional anaesthesia Total	General anaesthesia Events	General anaesthesia Total	Weight	Odds Ratio M–H, Fixed, 99% CI
1.10.1 GA vs GA+NA						
Memtsoudis 2012	1029	49396	11514	292804	23.0%	0.52 [0.48, 0.57]
Poeran 2015	1976	5989	28601	92301	16.5%	1.10 [1.02, 1.18]
Özbek 2015	4002	4031	14751	14912	0.3%	1.51 [0.89, 2.54]
Subtotal (99% CI)		**59416**		**400017**	**39.9%**	**0.77 [0.73, 0.81]**
Total events	7007		54866			
Heterogeneity: Chi² = 309.63, df = 2 (P < 0.00001); I² = 99%						
Test for overall effect: Z = 12.74 (P < 0.00001)						
1.10.2 GA vs NA						
Chu 2015	3205	52044	5743	52044	38.2%	0.53 [0.50, 0.56]
Gabriel 2015 (1)	19	9373	30	15585	0.2%	1.05 [0.49, 2.24]
Memtsoudis 2012	689	40036	11514	292804	19.3%	0.43 [0.39, 0.47]
Seitz 2014	259	6135	371	6135	2.5%	0.68 [0.55, 0.85]
Subtotal (99% CI)		**107588**		**366568**	**60.1%**	**0.50 [0.48, 0.53]**
Total events	4172		17658			
Heterogeneity: Chi² = 41.46, df = 3 (P < 0.00001); I² = 93%						
Test for overall effect: Z = 35.50 (P < 0.00001)						
Total (99% CI)		**167004**		**766585**	**100.0%**	**0.61 [0.59, 0.63]**
Total events	11179		72524			
Heterogeneity: Chi² = 594.99, df = 6 (P < 0.00001); I² = 99%						
Test for overall effect: Z = 34.96 (P < 0.00001)						
Test for subgroup differences: Chi² = 217.36, df = 1 (P < 0.00001), I² = 99.5%						



Footnotes
(1) Unexpected ICU

Figure 5. Forest plot of studies reporting intensive care unit admission when general anesthesia was compared to combined general and neuraxial anesthesia and neuraxial anesthesia alone. CI indicates confidence interval; GA, general anesthesia; GA + NA, combined general and neuraxial anesthesia; NA, neuraxial anesthesia; OR, odds ratio.

anesthesia alone or when combined with general anesthesia was associated with a reduced risk of pulmonary complications and requirement for mechanical ventilation (60% risk reduction, upper CI 0.40, Figure 3) and requirement for ICU admission (19% risk reduction, upper CI 0.81, Figure 5). Neuraxial anesthesia was also associated with reduced risk of surgical site infection and thromboembolic events, albeit with smaller effect sizes. Neuraxial anesthesia was associated with a reduced length of stay in our analysis of both RCTs and observational studies. Our analysis comparing neuraxial and general anesthesia yielded conflicting results for risk of blood transfusion. The RCTs indicated no difference in the relative risk, whereas the observational studies indicated that neuraxial anesthesia was associated with a reduced risk of blood transfusion. This apparent disconnect between results for the observational and RCTs for this outcome may indeed be consistent with confounding bias present in observational trials. However, the difference could also be accounted for by the poor quality of the included RCTs, which even when pooled did not meet the OIS required to adequately power the result for this outcome. Because observational studies with their inherent risks of bias are included in this analysis, these results need to be interpreted with caution. Furthermore, the reductions in OR for many outcomes were small and the GRADE analysis evaluated the data as being low quality.

The increased risk of myocardial infarction in patients receiving combined neuraxial-general anesthesia compared to general anesthesia deserves comment. A plausible mechanism for this association is the potential for sympathetic blockade and resultant hypotension associated with the combined anesthetic technique; however, due to the observational nature of the dataset, no causal mechanism for this result can be established.

Previous systematic reviews and meta-analyses of RCTs have compared neuraxial with general anesthesia for morbidity and mortality outcomes, and include older studies which are no longer representative of current clinical practice.[1,2,57,58] The purpose of this review was to provide a review and analysis of studies which are likely to be representative of outcomes associated with contemporary anesthetic and surgical techniques.

To the authors' knowledge, this systematic review and meta-analysis is the only analysis which includes both contemporary large-scale observational studies and RCTs. Therefore the results of this review are more reflective of current practice compared to studies published in previous decades. Large-scale population studies provide clinicians with an opportunity to pool the results of an entire population undergoing a procedure or surgery and gain unique insights into the quality of clinical care. Outcomes reported from large-scale observational studies are likely representative of actual current clinical practice, because they do not use rigid filters in the form of inclusion and exclusion criteria before sampling. Moreover, for this review there was insufficient information available from RCTs for many of our predefined outcomes of interest, and as a result, only 0.1% of patient data utilized in this analysis was from RCTs. The RCTs identified during our search were, even when pooled for meta-analysis, inadequately powered to assess our outcomes of interest, with the overall quality of the individual RCTs being low. The large sample sizes used in observational studies allow reporting of infrequently occurring yet important outcomes and thus have the ability to detect a difference between groups.

However, there are clearly limitations to including observational studies in a systematic review and meta-analysis. Due to the lack of randomization, observational studies bear the risk of bias relating to residual confounding of known or unknown factors that could impact on the primary outcome. One purpose of randomization is to increase the likelihood that the experimental and the control group have similar baseline risks for the primary outcome. However, a recent study identified an association between both age and American Society of Anesthesiologists (ASA) status and choice of anesthesia for total knee arthroplasty.[59] Patients who were in older age and higher ASA categories were more likely to receive neuraxial anesthesia compared to general anesthesia. Therefore, for some surgical types, patients receiving neuraxial anesthesia may be at a higher baseline risk compared to those receiving general anesthesia.

Given the high risk of bias inherent in observational studies, meticulous analysis of risk of bias is required to determine the validity of any effect demonstrated by our meta-analysis. We utilized the methodological approach of GRADE because it provides a systematic process of presenting evidence summaries and the quality of the body of evidence. Notably, in GRADE the quality of a body of evidence is evaluated for each individual outcome across studies.[42] In contrast, many systematic reviews rate the quality of evidence across outcomes, rather than separately for each outcome, which limits the usefulness for guideline development.[42] Regardless of the methods used to assess the quality of the evidence, it is likely to be subjective.

Heterogeneity between studies can be measured using the I^2 statistic, which assesses the percentage of variability in treatment estimates; however, sole reliance on a single measure of heterogeneity can be misleading. Heterogeneity can be evaluated based on the similarity of point estimates, extent of overlap of confidence intervals, and statistical tests.[43] For example, in our analysis of pulmonary complications, including mechanical ventilation, the I^2 statistic for the neuraxial versus general anesthesia group was 99% (Figure 3), which if interpreted alone would indicate very high heterogeneity between included studies. However, as shown by Rucker,[60] the heterogeneity statistic I^2 greatly depends on precision, meaning the size of the studies included. Therefore, as precision increases, estimates of I^2 increase toward 100%. We observed this limitation of I^2 in our analysis of large sample size studies. As such, for the outcome of pulmonary complications, the point estimates show largely a consistent effect favoring neuraxial anesthesia and large overlap of confidence intervals, which despite the apparently large heterogeneity when assessed by the I^2 statistic, should not reduce the confidence in the result favoring neuraxial anesthesia, given the consistency of the point estimates.

The best quality of outcome variables is attained when included studies investigate the outcome of interest as their primary outcome. For the included RCTs, the outcome of length of stay was the only outcome that was listed as a primary outcome of interest for a number of individual studies. The remainder of the outcomes of interest investigated was secondary outcomes, and, as such, this has been identified as a limitation within our analysis. For the included observational studies, the majority investigated our outcomes of interest as primary outcomes.

Implications

This review provides a summary of the pool of knowledge obtained from contemporary observational and RCTs that compare neuraxial with general anesthesia. It is relevant to anesthesiologists who care for patients undergoing major truncal or lower extremity surgery. Because this review included nonrandomized trials and the quality of the evidence ranged between very low and moderate, these current results should be interpreted with caution. No causal relationship can be established; however, this analysis adds to the existing body of evidence that suggest that neuraxial anesthesia may improve perioperative outcomes for major surgery. Large multicenter RCTs are required to more definitively investigate the potential impact that neuraxial anesthesia has on perioperative outcomes.

CONCLUSIONS

Compared to general anesthesia, neuraxial anesthesia when used alone or when combined with general anesthesia was not associated with decreased 30-day mortality. General anesthesia may protect against myocardial infarction compared to neuraxial anesthesia. Neuraxial anesthesia when used alone or when combined with general anesthesia may improve important perioperative outcomes when compared with general anesthesia. Neuraxial anesthesia (alone) was associated with a significantly reduced incidence of pulmonary complications including the requirement for mechanical ventilation. Neuraxial anesthesia was associated with superior treatment effects for nonpulmonary outcomes; however, these effects were reduced in magnitude. However, due to the inclusion of observational studies and database records within this analysis, results should be interpreted with caution.

DISCLOSURES

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