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BMJ Open

Effect of regional versus general anaesthesia on postoperative delirium in elderly patients undergoing surgery for hip fracture: a systematic review

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ABSTRACT

Objective Older patients with hip fractures who are undergoing surgery are at high risk of significant mortality and morbidity including postoperative delirium. It is unclear whether different types of anaesthesia may reduce the incidence of postoperative delirium. This systematic review will investigate the impact of anaesthetic technique on postoperative delirium. Other outcomes included mortality, length of stay, complications and functional outcomes.

Design Systematic review of randomised controlled trials and non-randomised controlled studies.

Data sources Bibliographic databases were searched from inception to June 2018. Web of Science and ZETOC databases were searched for conference proceedings. Reference lists of relevant articles were checked, and clinical trial registers were searched to identify ongoing trials.

Eligibility criteria Studies were eligible if general and regional anaesthesia were compared in patients (aged 60 and over) undergoing hip fracture surgery, reporting primary outcome of postoperative delirium and secondary outcomes of mortality, length of hospital stay, adverse events, functional outcomes, discharge location and quality of life. Exclusion criteria were anaesthetic technique or drug not considered current standard practice; patients undergoing hip fracture surgery alongside other surgery and uncontrolled studies.

Results One hundred and four studies were included. There was no evidence to suggest that anaesthesia type influences postoperative delirium or mortality. Some studies suggested a small reduction in length of hospital stay with regional anaesthesia. There was some evidence to suggest that respiratory complications and intraoperative hypotension were more common with general anaesthesia. Heterogeneity precluded meta-analysis. All findings were described narratively and data were presented where possible in forest plots for illustrative purposes.

Conclusions While there was no evidence to suggest that anaesthesia types influence postoperative delirium, the evidence base is lacking. There is a need to ascertain the impact of type of anaesthesia on outcomes with an adequately powered, methodologically rigorous study.

PROSPERO registration number CRD42015020166.

Strengths and limitations of this study

- This systematic review provides an update to evidence that examines whether the type of anaesthesia affects the development of postoperative delirium in patients with hip fractures.
- The review included randomised and non-randomised studies that included one or more types of regional versus one or more types of general anaesthesia provided they are in current use as described in the UK.
- Other outcomes were mortality, length of hospital stay, adverse events, functional outcomes, discharge location and quality of life.

INTRODUCTION

There are an estimated 70 000–75 000 hip fractures in the UK each year with an annual cost of £2 billion.[1] This is projected to rise and reach 100 000 patients a year and costing £3.6–5.6 billion by 2033.[2]

Patients undergoing hip fracture surgery are often frail with intercurrent illness[3] and are at risk of mortality and significant morbidity. In 2014, the National Hip Fracture Database reported 30-day mortality as 7.5%.[4] Following surgery, adverse outcomes can include delirium, myocardial infarction, pneumonia and cerebrovascular accident.[5]

Delirium is a common neuropsychiatric syndrome defined in the Diagnostic and Statistical Manual of Mental Disorders, 5th edition (DSM-V) as the disturbance of attention, awareness and cognition which develops over a short period of time, represents a change from baseline and tends to fluctuate during the course of the day.[6 7] Postoperative delirium has been reported to affect between 32% and 53.3% of patients and is associated with prolonged hospital stay, discharge to care homes, difficulty in regaining function in activities of daily living and increased risk of development of cognitive dysfunction and

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dementia in the future.[8–13] The aetiology of delirium is multifactorial, with both modifiable and non-modifiable risk factors.[14 15] There is no known treatment for delirium; however, a careful approach in the perioperative period may reduce its incidence and severity.[6 9 15–18] Guideline committees have cautiously recommended that regional anaesthesia should be given unless contraindicated.[1 9 19] Despite this, the type of anaesthesia administered in patients with hip fractures remains varied.[4]

Ninety-eight per cent of patients with hip fracture are offered surgery and will require anaesthesia.[5] Anaesthesia can be broadly classified into general (GA) or regional anaesthesia (RA). RA uses neuraxial blocks that avoid the use of GA drugs and opiates which have been linked to postoperative delirium.[3] Excessive depth of anaesthesia and perioperative hypotension have been reported in GA patients and are both associated with an increased risk of mortality.[20] However, the risk of perioperative hypotension and sedation is not completely eradicated with RA.[21 22]

Findings from previous systematic reviews looking at the effects of type of anaesthesia on postoperative outcomes in patients with hip fracture are broadly suggestive of improved outcomes[3 5 23 24] and reduced incidence of postoperative delirium in patients having RA.[3 5 22 25 26] However, some studies included in these reviews reported use of outdated anaesthetic drugs that are no longer relevant to current clinical practice.[5 24] Further limitations were the inclusion of only randomised controlled trials,[3 5 23 24] lack of focus on delirium as a primary outcome,[3 5 22 24 26] a limited search strategy[22] and restrictive selection criteria (eg, exclusion of studies with patients with cognitive impairment).[23 25 26] Inadequate exploration of heterogeneity relating to delirium assessment and rating scales and assessment time points was also common. This systematic review aims to provide an up-to-date, comprehensive and methodologically robust analysis to examine the effect of RA versus GA on postoperative delirium and other outcomes in older patients undergoing surgery for hip fracture.

METHODS

The protocol for this systematic review has been published and is registered with PROSPERO (CRD42015020166).[27] A summary of the methods is outlined below. Reporting of the systematic review was in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines.[28]

Search strategy and selection criteria

Bibliographic databases (Embase, MEDLINE, CINAHL and the Cochrane Library (CENTRAL)) were searched from inception to June 2018 using a combination of index terms and keywords relating to the population, intervention and comparator (see online supplementary appendix A for sample search strategy). There was no restriction by search date, study design or language. Web of Science and ZETOC databases were searched for conference proceedings. Reference lists of relevant articles were checked, and clinical trial registers (www.clinicaltrials.gov, www.isrctn.com and http://www.who.int/ictrp/en/) were searched to identify ongoing trials (online supplementary appendix B). Endnote V.7 (Thomson Reuters) was used to store records and facilitate screening.

Study selection

Studies were eligible for inclusion if they met the following predefined criteria:

1. Population—patients aged ≥60 years (or with a majority ≥60) undergoing surgery for fragility hip fracture.
2. Intervention and comparator—one or more types of regional versus one or more types of general anaesthesia provided they are in current use as described in the UK.[19]
3. Outcomes—primary outcome: postoperative delirium (any criteria as defined by study authors); secondary outcomes: mortality, length of hospital stay, adverse events, functional outcomes, discharge location and quality of life.
4. Randomised or non-randomised controlled studies (prospective or retrospective).

Exclusion criteria for the primary outcome of 'postoperative delirium' were anaesthetic technique or drug not considered current standard practice (eg, outdated anaesthetic agents—halothane, enflurane, xenon); patients undergoing hip fracture surgery alongside other surgery (eg, multiple trauma injuries); uncontrolled studies. Two reviewers (RC, VP) independently screened titles and abstracts. Any disagreements were resolved with the support of JY. Reasons for exclusion were recorded at the full text stage.

Data extraction and quality assessment

A piloted, standardised data extraction form was used to record information on study design, patient characteristics, type of surgery, anaesthesia type and outcomes. The Cochrane Collaboration risk of bias tool[29] was used to assess the methodological quality of randomised controlled trials and the Newcastle–Ottawa scale[30] for non-randomised studies. Full translations could not be obtained for three included studies[31–33]; extracted data are therefore based mainly on numerical data and the English abstract. Data was extracted by RC and VP, with data checking by JY (for RC) and JD (for VP).

Data analysis and synthesis

Findings were grouped according to outcome. Where there was sufficient data, results were presented in forest plots (delirium, mortality and length of hospital stay). Results for studies not included in the forest plot were reported narratively. Effect estimates were not pooled as clinical and methodological heterogeneity was considered to be too great. Forest plots were thus used for illustrative purposes only and potential sources of heterogeneity

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(such as study design or timing of assessment) have been highlighted. Where studies did not report sufficient data for inclusion into a forest plot (eg, results reported narratively only, or a p value only stated) results or conclusions from the study were nonetheless described in order to report the totality of the available evidence. Occurrence of delirium and mortality were reported as relative risks or ORs; length of stay (days) was reported as a mean difference. Adverse events were tabulated, where possible, according to the postoperative morbidity survey (POMS) criteria.[34] Findings for other outcomes (functional outcomes, quality of life and discharge location) were reported narratively as heterogeneity and/or a paucity of data precluded representation in forest plots. Formal sensitivity analysis according to study quality, and assessment of publication bias using funnel plots were not possible.

Patient and public involvement

This systematic review is part of a programme of research looking at impact of anaesthesia on postoperative delirium. The research programme has received input from patient partner and Clinical Research Ambassador Group at Heart of England National Health Service Foundation Trust.

RESULTS

Of 4859 citations screened, 104 studies met the eligibility criteria (figure 1). There were 7 randomised controlled trials (RCTs), 34 prospective and 63 retrospective controlled studies.

Twenty-two studies reported delirium (5 RCTs,[35–39] 9 prospective[18 40–47] and 8 retrospective studies[48–55]); 58 studies reported mortality (2 RCTs,[35 38] 12 prospective[42 45]

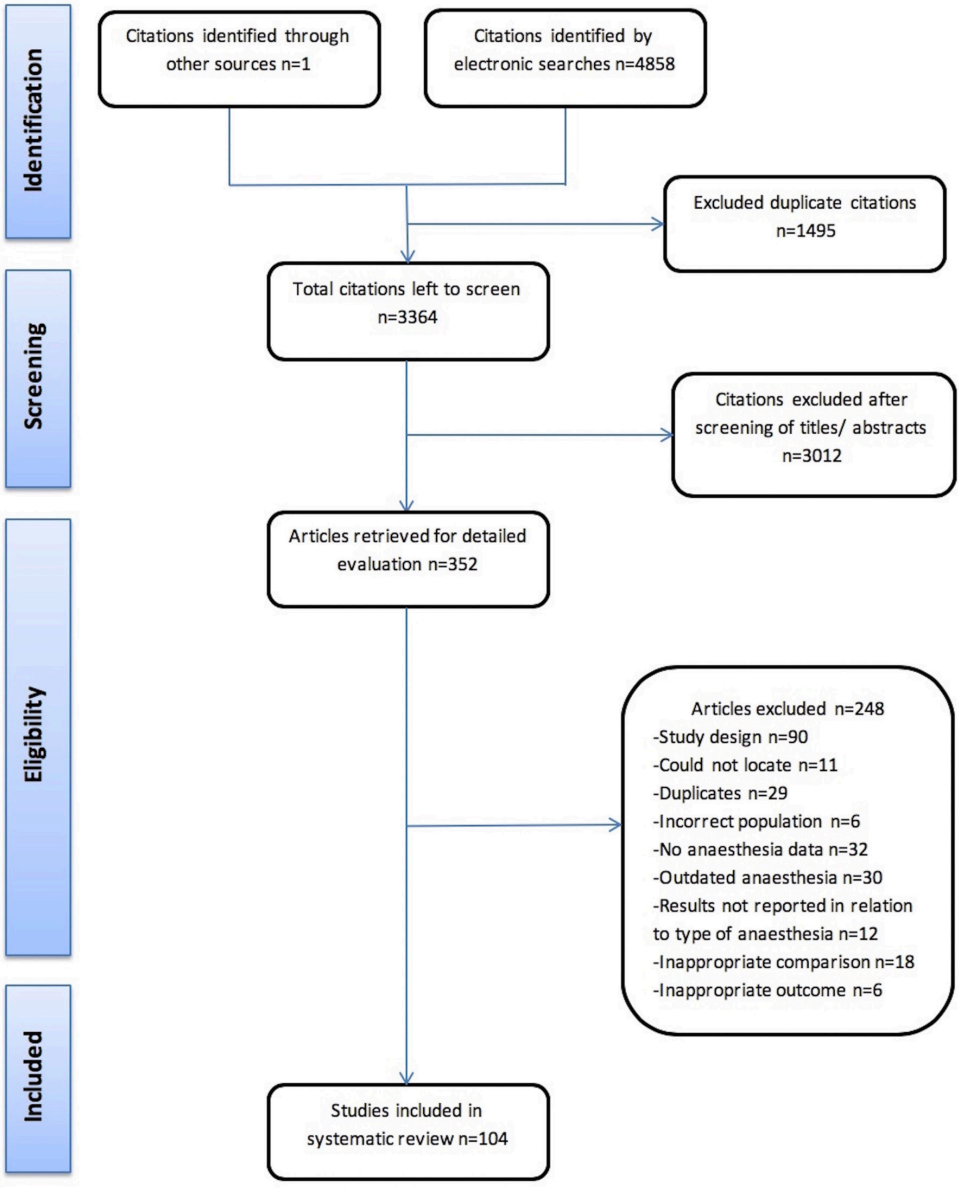

Figure 1 Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram. The PRISMA diagram details our search and selection process applied during the review.

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[56–65] and 44 retrospective studies[4 20 21 31 32 48 51 52 54 66–100]); 25 studies reported length of hospital stay (2 RCTs,[36 38] 6 prospective[42 45 58 101–103] and 17 retrospective studies[21 51 57 68 70 71 75 78 80–83 95 98 99 104 105]); 27 studies reported adverse events (4 RCTs,[35 36 39 106] 7 prospective[42 43 45 58 101 107 108] and 16 retrospective studies[20 21 48 51 52 68 69 71 75 79–81 95 96 109 110]); 11 studies reported functional outcome (3 RCTs,[35 36 111] 4 prospective[42 45 103 112] and 4 retrospective studies[62 73 105 113]); 5 studies reported discharge location (2 prospective[43 114] and 3 retrospective studies[21 48 99]).

Thirteen potentially relevant ongoing trials were identified, with three (ISRCTN15165914, NCT03318133 and NCT02213380) planning to measure delirium postoperatively (online supplementary appendix B). No interim data were available.

Study, population and intervention characteristics

Given the large number of studies identified, only the 22 studies reporting the primary outcome of postoperative delirium have been described in detail (table 1).

Primary outcome

Postoperative delirium

Fifteen studies (four RCTs,[36–39] six prospective studies[18 41–45] and five retrospective studies[22 48 51 52 54]) reporting unadjusted results are represented in the forest plot (figure 2). Of these 15 studies, only one study found a statistically significant benefit in favour of general anaesthesia[52] and overall there was no evidence of a benefit of one type of anaesthesia over another. Seven studies were not included in forest plot due to insufficient data with five studies[40 46 47 50 53] reported only as abstract, one RCT[35] did not report delirium as dichotomous outcome and one retrospective study[55] only included patients who developed delirium post surgery. Only two studies compared delirium according to anaesthetic types. One retrospective study that only included patients with delirium found GA to be a significant risk factor for immediate delirium (within 24 hours of surgery) compared with RA, but GA was not associated with delayed delirium (after 24 hours post surgery).[55] A further study reported as abstract also found that delirium was more common with GA, but this did not remain statistically significant on multivariable analysis. The assessment tool for delirium was not stated.[47]

Overall, there was substantial heterogeneity across the 22 studies regarding assessment tools, assessment time-points and anaesthetic protocol. Many assessment tools were poorly defined. Only 7 out of 22 studies used either DSM-IV criteria[18 40 49 53 54] or Abbreviated Mental Test.[35 50] Delirium or cognitive impairment was frequently not a primary outcome, but listed as one of several complications.

None of the RCTs that were quality assessed reported all relevant details (table 2A). Details were lacking on the delirium assessment tools used[38] and method of randomisation.[35 36 38 39] Blinding of outcome assessment was either not undertaken[38] or unclear.[36] There appeared to be no loss to follow-up in three RCTs,[36 38 39] but this was unclear for the other RCT.[35] The RCT by Kamitani *et al* was not quality assessed as a full translation was not available.[37]

The observational studies were generally considered to be at low risk of bias in terms of patient eligibility; however, most had no details on blinding of outcome assessors and the level of completeness of data (table 2B). There was variation in reporting and adjustment of potential confounding factors such as the American Society of Anesthesiologists Physical Status Classification System (ASA) score, age, gender, comorbidities, surgery type, time to surgery and physical function. There were no details on characteristics of patients who completed follow-up compared with those lost to follow-up. There was also a general lack of detail on the type of assessment tool used and/or where the cut-off for a 'positive' diagnosis of delirium was.

Secondary outcomes

Mortality

Two RCTs reported mortality (table 3). One found a small and statistically significant survival benefit at 120 days and 1 year for GA, but no such benefit was evident at 30 or 90 days of follow-up.[38] Ten observational studies reported adjusted results or results based on a matched analysis (table 3). Two of these[20 68] found a statistically significant benefit in favour of RA for in-hospital mortality. The remaining eight studies found no significant differences. There was a lack of consistency across studies in terms of number and type of variables included in models.

Of the remaining 46 studies (results not shown) reporting unadjusted mortality results only, six[56 60 67 73 74 76] found statistically significant results in favour of RA. The remainder found no statistically significant differences or benefit comparing RA with GA.

Overall, there is a paucity of good-quality evidence evaluating mortality, with only one good-quality RCT[38] suggesting benefit from GA at later but not earlier time-points.

Length of hospital stay

Twenty-five[21 36 38 42 45 51 57 58 68 70 71 75 78 80–83 95 98 99 101–105] studies reported length of hospital stay; nine could be included in a forest plot (figure 3). There was no difference in length of hospital stay based on one RCT.[38] Three retrospective studies[21 68 81] compared patients with propensity score matching and showed a slight benefit towards a shorter length of stay with RA; while this was statistically significant in two studies,[21 68] the absolute reduction was small (up to around a third of a day). Results from the studies reporting unadjusted results were inconsistent, with three finding no difference[71 75 80] and two finding a benefit from RA.[82 101]

Data were not available from the remaining 16 studies due to lack of data (three studies[57 70 98] were abstracts only, six studies[36 42 78 99 104 105] did not provide raw data, two studies[45 95] did not link data with types of anaesthesia and five studies[51 58 83 102 103] only provided median length of stay). The RCT[36] and the five prospective studies[42 45 58 102 103]

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Table 1 Table of characteristics of studies that measured postoperative delirium

Author Year Country	ASA	Comparison and number of patients	Population	Age, mean age and M/F split	Outcomes measured
Randomised controlled trials					
Bigler *et al* 1985[35] Denmark	General: ASA 1: 2 ASA 2: 14 ASA 3: 4 Spinal: ASA 1: 2 ASA 2: 15 ASA 3: 3	General (n=20) vs spinal (n=20)	Patients having acute surgery for hip fracture	Patients above 60 years of age Mean age General: 77.6 years (SEM 2.3) Spinal: 80.1 years (SEM 1.6) M/F: 7/33	▶ Postoperative mental function ▶ Morbidity
Casati *et al* 2003[36] Italy	General: ASA 2: 7 ASA 3: 8 Spinal: ASA 2: 6 ASA 3: 9	General (n=15) vs spinal (n=15)	Patients undergoing hip fracture repair	Patients over 65 years of age Mean age General: 84 years (range 67–88) Spinal: 84 years (range 71–94) M/F: 2/28	▶ Hypotension ▶ Cognitive dysfunction
Kamitani *et al* 2003[37] Japan	ASA not reported. Comparable 'physical status' between GA and RA groups	General (n=21) vs spinal (n=19)	Patients with femoral neck fracture	Patients aged 70 and over Mean age General: 81.4 (SD 6.2) Spinal: 83. (SD 6.0) M/F: 4/36	▶ Postoperative delirium
Neuman *et al* 2016[39] USA Feasibility study/Letter	No details	General (n=6) vs spinal (n=6)	Femoral neck or pertrochanteric hip fracture surgery	Patients aged 18 and over Median age (GA): 62.5 (57–88) Median age (RA): 80.5 (62–92) M/F: 9/3	Primary: ▶ Postoperative delirium Secondary: ▶ Mortality
Parker and Griffiths[38] 2015 UK	General: ASA grade 1 or 2: 98 Spinal: ASA grade 1 or 2: 94.9	General (n=164) vs spinal (n=158)	Patients with acute hip fracture	Patients over 49 years of age Mean age General: 83.0 years (range 59–99) Spinal: 82.9 years (range 52–105) M/F: 87/235	Primary: ▶ Mortality Secondary: ▶ Surgical outcomes ▶ General complications ▶ Hospital stay
Prospective studies					
Atay *et al* 2012[40] Turkey	Unable to obtain full translation	General (n=30) vs spinal (n=40)	Patients with hip fractures	Patients aged 60 years and over Mean age: 76.0±8.2 years M/F: 109/131	▶ Postoperative delirium ▶ Postoperative cognitive function
Bitsch *et al* 2006[41] Denmark	ASA 1: 2 ASA 2: 33 ASA 3: 51 ASA 4: 10	General (n=13) vs regional (n=83)	Patients with hip fracture	No age restriction Mean age No significant decline: 81.6 years (range 75–86) Significant decline: 84.5 years (range 81–89) M/F: 28/68	▶ Risk factors for preoperative, intraoperative and postoperative cognitive dysfunction

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Table 1 Continued

Author Year Country	ASA	Comparison and number of patients	Population	Age, mean age and M/F split	Outcomes measured
Bjorkelund *et al* 2010[18] Sweden	Intervention group (new care plan): ASA 1: 17 ASA 2: 59 ASA 3: 48 ASA 4: 7 Control group (existing care plan): ASA 1: 10 ASA 2: 77 ASA 3: 42 ASA 4: 3	General (n=89) vs spinal (n=174)	Patients with hip fractures	Patients aged 65 years and over Mean age Intervention: 81.1 years (SD 7.5) Control: 82.0 years (SD 7.6) M/F: 78/185	▶ Incidence of delirium
Gilbert *et al* 2000[42] USA	General: ASA 1–2: 105 ASA 3–4: 194 Spinal: ASA 1–2: 109 ASA 3–4: 309	General (n=311) vs spinal (n=430)	Patients with an acute hip fracture	Age 65 years and older Age General: 65–79 years n=120 80+ years n=191 Spinal: 65–79 years n=184 80+ years n=246 M/F: 156/585	▶ Complications (in-hospital and surgical) ▶ Functioning (daily, social, mental)
Ilango *et al* 2015[43] Australia	Not reported	General (n=167) vs spinal (n=151)	Patients with hip fracture	Age not specified within inclusion criteria Mean age General: 81.3 years (SD 10.5) Spinal: 82.1 years (SD 9.0) M/F: 89/229	Primary: ▶ Incidence of postoperative delirium Secondary: ▶ Other postoperative complications ▶ Postdischarge mortality
Juliebø *et al* 2009[44] Norway	ASA 1 or 2: 182	General (n=20) vs spinal (n=337)	Patients with hip fracture	Patients aged 65 years and over Age Delirium: 85 years (range 82–89) No delirium: 82 years (range 77–87) M/F: 88/276	▶ Delirium
Koval *et al* 1999[45] USA	General: ASA 1 or 2: 236 ASA 3 or 4: 120 Spinal: ASA 1 or 2: 131 ASA 3 or 4: 137	General (n=362) vs spinal (n=280)	Patients who sustained a hip fracture	Patients 65 years of age and older Mean age General: 78.5 years Spinal: 81.0 years M/F: 129/513	▶ Inpatient medical complication rate ▶ Hospital mortality rate ▶ 1-year mortality rate
Mohamed 2017[46] UK Abstract	No details	Total n=85 Numbers in GA, GA+block, spinal and spinal+block groups not stated	Patients with hip fracture	No details	▶ Delirium
Ojeda 2018[47] Spain Abstract	No details	Total n=303 Numbers in GA and RA groups not stated	Patients with hip fracture	Patients aged 70 years and over. Mean age: 84 (SD 6) M/F: 39%/61%	▶ Delirium ▶ In-hospital complications ▶ Mortality
Retrospective studies					

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Table 1 Continued

Author Year Country	ASA	Comparison and number of patients	Population	Age, mean age and M/F split	Outcomes measured
Bellelli *et al* 2013[53] Italy Abstract	Not reported	General vs spinal vs peripheral nerve block 392 included patients, but no breakdown of who received what anaesthesia	Patients undergoing hip fracture surgery	Patients aged 65 years and older Mean age: 83 years (SD 6) M/F: not reported	▶ Postoperative delirium
Choi *et al* 2017[55] Republic of Korea	For those who developed delirium: ASA 2: 10 ASA 3: 97 ASA 4: 3	Total n=356 For those who developed delirium: General (n=81) vs spinal (n=29)	Patients with femoral neck fracture	Patients aged 70 years and over M/F: 66/290	▶ Immediate and delayed delirium
Kim *et al* 2013[54] Korea	ASA 1: 6 ASA 2: 311 ASA 3: 189	General (n=246) vs spinal (n=249) vs epidural (n=11)	Patients undergoing hip fracture surgery	Patients aged 60 years and over Age 60–69 years n=83 70–79 years n=227 >80 years n=196 M/F: 140/366	▶ 30-day postoperative complications ▶ Cardiac complications ▶ Pulmonary complications ▶ Delirium ▶ Death
Konttinen and Rosenberg 2006[48] Finland	ASA 3: 8 ASA 4: 6	General (n=3) vs spinal (n=11, single shot: 5, continuous: 6) (14 procedures in 12 patients)	Patients undergoing major emergency surgery	Patients aged 100 years and over Median age: 101 years M/F: 2/10	▶ Intraoperative variables ▶ Complications ▶ Postoperative discharge location ▶ Pain management ▶ Haemodynamics ▶ Mental status ▶ Mobilisation ▶ Mortality
Luger *et al* 2014[49] Austria	Mean ASA: Group 1 (postoperative delirium): 2.9±0.6 Group 2 (unspecified cognitive dysfunction): 88.4±5.2 Control: 2.8±0.6	General (n=116) vs regional (n=213)	Patients scheduled for acute hip fracture surgery	Patients aged 80 years of age and older Age Delirium: 87.9 years (SD 4.5, range 81–97) No delirium: 88.8 years (SD 5.3, range 81–100) M/F: 19/51	▶ Cognitive decline ▶ Time to surgery ▶ Length of hospital stay ▶ Pre-nursing and post-nursing home stay ▶ Comorbidities ▶ Perioperative complications
Michael *et al* 2014[50] UK Abstract	Not reported	General vs spinal (704 patients included in analysis, but unclear how many received which anaesthesia)	Patients with hip fracture	Patients aged 60–100 years Age 60–70 years n=50 70–80 years n=169 80–90 years n=338 90–100 years n=147 M/F: 178/526	Preoperative and postoperative cognitive function
O'Hara *et al* 2000[52] USA	General: ASA 1 or 2: 1698 ASA 3: 3666 ASA 4 or 5: 618 Regional: ASA 1 or 2: 560 ASA 3: 2097 ASA 4 or 5: 438	General (n=6206) vs regional (n=3219, spinal n=3078 and epidural n=141)	Patients with hip fracture	Patients 60 years of age or older Age General: 60–69 years n=910 70–79 years n=1918 80–89 years n=2602 90+ years n=776 Regional: 60–69 years n=325 70–79 years n=881 80–89 years n=1452 90+ years n=561 M/F: 2010/7415	Primary: ▶ 30-day mortality Secondary: ▶ 7-day mortality Other: ▶ 7-day morbidity

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Table 1 Continued

Author Year Country	ASA	Comparison and number of patients	Population	Age, mean age and M/F split	Outcomes measured
Shih *et al* 2010[51] Taiwan	General: ASA 2: 47 ASA 3: 115 ASA 4: 1 Spinal: ASA 2: 45 ASA 3: 120 ASA 4: 2	General (n=167) v Spinal (n=168)	Patients undergoing hip fracture repair	Patients aged 80 and over Mean age General: 83.96 years (SD 3.71) Spinal: 84.93 years (SD 4.04) M/F: 189/146	▲ Postoperative morbidity ▲ Postoperative mortality ▲ Pre and intraoperative variables

ASA, American Society of Anesthesiologists Physical Status Classification System; GA, general anaesthesia; RA, regional anaesthesia.

did not show any significant differences. Results from the 10 retrospective studies were also inconsistent: three studies[57 70 83] reported no difference, four studies[51 78 99 104] found a statistically significant benefit for and one study[95] reported a statistically significant benefit for GA. Fukuda *et al* reported a statistically significant effect in favour of spinal anaesthesia, but this effect was lost after propensity score matching.[105] One large study (Nishi, n=16 687) reported in abstract form only reported a slightly shorter length of stay with RA; it was unclear if this was statistically significant.[98]

Most studies reported mean length of stay, but some also reported the median, which may be more appropriate. Of 12 studies[21 36 45 51 57 70 71 83 95 99 102 103] reporting the median, nine studies[21 36 45 57 70 71 83 102 103] found no statistically significant differences. Three studies found a statistically significant difference in medians, two of which favoured RA[51 99] and one favoured GA.[95]

Adverse events

Twenty-seven studies reported adverse events (table 4). There were many gaps in reporting of POMS adverse events, and it is uncertain whether this reflects non-occurrence or non-reporting of such events. Most commonly reported adverse events were pulmonary (10 studies)[20 21 35 45 48 49 62 69 89 91] and cardiovascular events (9 studies).[21 35 39 48 58 68 69 81 95] For pulmonary events, six studies found no statistically significant differences.[35 45 49 69 89 91] Four studies found a statistically significant difference in favour of RA (fewer cases of ventilatory support,[68] respiratory failure[20 68] and 'overall pulmonary' adverse events[20 51]). There were no differences in occurrences of pneumonia[35 48 52 95] or hypoxia.[75 101] The most commonly reported cardiovascular adverse events were myocardial infarction[39 48 68 95] and thromboembolic events.[35 58 69 81 95] No differences were found for myocardial infarction.[39 48 52 68 75 95] Three studies[69 81 95] reported higher incidence of thromboembolic events in GA group.

Nine studies summarised overall adverse events with the majority finding no differences between the types of anaesthesia. Where there was a significant difference, this was in favour in RA (eg, fewer incidences of 'all complications',[51 69] intensive treatment unit (ITU) admissions,[68] stroke[68] or requirement for blood transfusion). Three studies[106 108 109] found higher incidences of hypotension in the GA group.

The results are thus suggestive of a lower incidence of postoperative respiratory, cardiac and overall complications in the RA group. However, reporting of adverse events, including methods of ascertainment, was inconsistent and limited.

Functional outcomes

Eleven studies reported functional outcomes using a variety of outcome measures. Two RCTs reported a significantly quicker time to ambulation in the RA group (3.3 days RA vs 5.5 days GA)[35] and a statistically significant earlier discharge time from PACU (post-anaesthesia care

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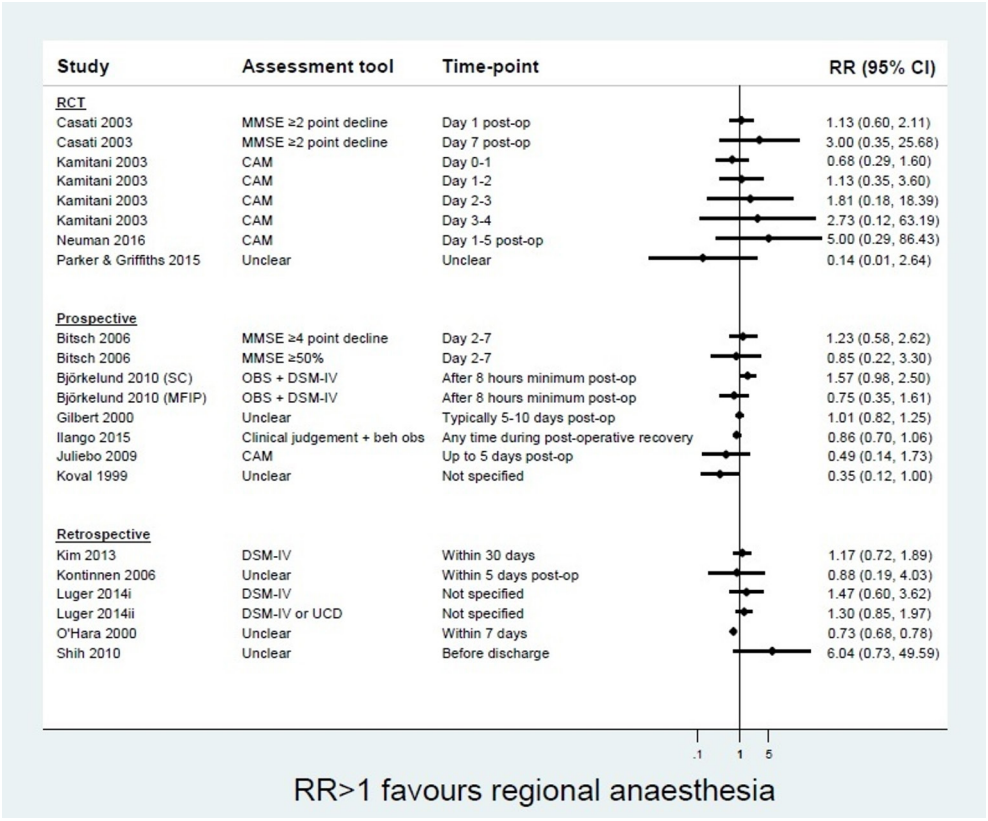

Figure 2 Forest plot of studies reporting the unadjusted relative risk of postoperative delirium with GA compared with spinal anaesthesia. Some studies are represented more than once to show results for different definitions of delirium or for different assessment time-points. CAM, confusion assessment method; DSM-IV, Diagnostic and Statistical Manual of Mental Disorders, 4th edition; MFIP, Multi-factorial Intervention Program; MMSE, Mini–Mental State Examination; RR, relative risk; SC, standard care; UCD, unspecified cognitive dysfunction.

unit) in the RA group (RA 15 (5–30) min vs GA 55 (15–80) min, p=0.0005).[36] However, one RCT found that patients given RA were slower to be discharged from PACU (mean time to discharge GA 35.04 min (SD 3.39) vs RA 41.26 min (SD 8.37), p=0.001).[111] No significant differences were found in the non-randomised studies regarding time to ambulation,[103 112 113] walking speed,[62] time to rise from chair,[42] mean Barthel's score[73] or ambulation at 3, 6 and 12 months post surgery.[45 105] Overall results may suggest a small benefit from RA for immediate post-anaesthetic mobilisation. However, the evidence is limited by small sample size, unknown method of outcome assessment and blinding of assessors.

Discharge location

Five non-randomised studies described discharge locations of patients following hip fracture.[21 43 48 99 114] One study with only 14 patients reported that more patients returned home in the RA group.[45] A large retrospective study reported lower odds of returning to home residence and higher chance of admitting to healthcare facility in GA group compared with RA (16 695 patients, return home adjusted OR 0.91 (95% CI 0.84 to 0.97); healthcare facility admission OR 1.10 (95% CI 1.03 to 1.19).[99] A cohort study of 4815 patients found operation under GA significantly increased risks of rehabilitation admission instead of home (adjusted OR 1.74, 95% CI 1.34 to 2.25, p<0.001).[114] However, two larger studies[21 109] found no difference in discharge location between GA or RA groups.

Quality of life

There were no studies that evaluated the effect of type of anaesthesia on quality of life in patients after hip fracture surgery.

DISCUSSION

For the primary outcome of postoperative delirium, this systematic review did not find any difference between types of anaesthesia. Furthermore, no survival benefit could be demonstrated with either type of anaesthesia up to 1 year postoperatively. A small number of studies suggested that fewer adverse events might be associated with RA. Similarly, some studies were suggestive of a small reduction in hospital stay with RA. Data were limited for functional outcomes and discharge data. Two small RCTs suggested a benefit from RA for immediate post-anaesthetic mobilisation. There were no studies that reported on quality of life after different types of anaesthesia.

This is the most comprehensive and methodologically robust systematic review to date. It includes both RCTs

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Table 2A Quality assessment of randomised controlled trial studies reporting delirium

Study	Randomisation	Concealment of allocation	Similarity at baseline	Blinding of outcome assessor	Incomplete outcome data (for outcome of delirium)	Validity of assessment tool	Assessment tool specific for delirium	Selective reporting
Risk of bias described as LOW, UNCLEAR or HIGH								
Neuman *et al* 2016[39] n=12 (Letter)	UNCLEAR No details	UNCLEAR	Groups similar for age, gender and comorbidities	LOW Blinded research coordinators assessed outcomes	LOW Results reported for all patients	CAM good validity for identifying delirium	Yes	UNCLEAR Insufficient information to permit judgement
Parker and Griffiths 2015[38] n=322	UNCLEAR Randomisation undertaken by opening sealed opaque numbered envelopes prepared by a person independent to the trial	LOW	Groups similar for all baseline characteristics measured, except for proportion of male patients (35% in GA group, 19% in RA group)	HIGH No blinding of outcome assessors	LOW Appears postoperative delirium measured in all patients allocated to respective treatments	Unclear—no details	UNCLEAR	UNCLEAR Insufficient information to permit judgement
Casati *et al* 2003[36] n=30	UNCLEAR *"Using a sealed envelope technique, patients were randomly allocated…"*	LOW	Groups similar for all baseline characteristics measured	UNCLEAR Clinical criteria for patient's discharge applied by staff blinded to anaesthetic technique—but no details for applying MMSE	LOW MMSE for all 30 patients at 1 and 7 days	MMSE good validity for cognitive function	No	UNCLEAR Insufficient information to permit judgement
Bigler *et al* 1985[35] n=40	UNCLEAR No details (other than "*patients randomly allocated*")	UNCLEAR No details	Groups similar for all baseline characteristics measured except for vasopressors being administered more frequently in spinal group	LOW Surgeon undertaking AMT unaware of anaesthesia given	UNCLEAR No details on proportion that AMT was undertaken in at 7 days and 3 months	AMT good validity for cognitive dysfunction	No	UNCLEAR Insufficient information to permit judgement

Quality assessment was not performed for Kamitani *et al*[37] as a full translation was not available. Blinding of patients and surgeons/anaesthetists not possible.
AMT, Abbreviated Mental Test; CAM, confusion assessment method; GA, general anaesthesia; MMSE, Mini–Mental State Examination; RA, regional anaesthesia.

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Table 2B Quality assessment of observational studies reporting delirium

Study	Eligibility criteria	Confounders Low risk	Blinding of outcome assessors	Validity of assessment tool used	Tool specific for delirium	Loss to follow-up/missing data
Risk of bias described as LOW, UNCLEAR or HIGH						
Belleli *et al* 2013[53] (Abstract)	LOW	HIGH for unadjusted data LOW for adjusted data	UNCLEAR	LOW	Yes	UNCLEAR
Retrospective	Patients aged >65 years admitted to one orthogeriatric unit between 2007 and 2011	Baseline characteristics not presented for anaesthesia groups, but multivariable analysis for confounders (age, gender, Charlson Comorbidity Index, ASA score, prefracture disability in Activities of Daily Living (Katz's ADL Index) and prefracture dementia)	No details	DSM-IV-TR criteria		Patients with incomplete data in medical records were excluded from this study. Proportion not stated
Bitsch *et al* 2006[41]	UNCLEAR	HIGH	UNCLEAR	LOW—good validity for cognitive function	No	HIGH
Prospective	Consecutive patients but large number excluded and unclear if similar characteristics to included	No baseline characteristics for groups according to type of anaesthetic; no adjusted analyses	No details	MMSE		12/96 (12.5%) and 35/96 (36%) patients not available for testing on days 4 and 7, respectively. Nursing home patients considered stable and those achieving independent ambulation discharged earlier
Bjorkelund *et al* 2010[18]	LOW	HIGH	UNCLEAR	LOW	No for Organic Brain Syndrome Scale Yes for DSM-IV criteria	LOW
Prospective	Consecutive patients included	No baseline characteristics for groups according to type of anaesthetic; no adjusted analyses.	No details	Organic Brain Syndrome Scale and DSM-IV criteria		Appears to be no loss to follow-up from included patients for delirium assessment
Choi *et al* 2017[55]	LOW	HIGH for unadjusted data LOW for adjusted data	LOW	LOW	Yes	LOW
Retrospective	Consecutive patients included	Variables adjusted for were age, previous dementia, parkinsonism, ASA grade and ICU care	Assessment made by independent psychiatrist	CAM, CAM-ICU		Appears to include all eligible consecutive patients
Gilbert *et al* 2000[42]	LOW	HIGH for unadjusted data LOW for adjusted data	UNCLEAR	LOW (MMSE) HIGH ('mental confusion')	Unclear ('mental confusion') No (MMSE)	UNCLEAR
Prospective	Patients given general and spinal were drawn from the same population	Appear to be some baseline imbalances between general and regional groups, but multivariable analyses for all outcomes. Variables were age, sex, race, comorbidities, pre-fracture physical function, ASA score, fracture type, surgical procedure and physiological status	No details	Mental confusion not further defined; MMSE		No details—only how many included in final analysis
Ilango *et al* 2015[43]	LOW	HIGH	UNCLEAR	HIGH	UNCLEAR	UNCLEAR
Prospective	All patients with hip fracture admitted over a year	Similar baseline characteristics (age, gender, preoperative cognitive function), but no adjusted analyses	No details	Subjective method ('clinical judgement') and several scales; cut-off unclear		19/337 (6%) incomplete data. No details on characteristics

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Table 2B Continued

Study	Eligibility criteria	Confounders Low risk	Blinding of outcome assessors	Validity of assessment tool used	Tool specific for delirium	Loss to follow-up/missing data
Juliebø *et al* 2009[44]	LOW	HIGH	LOW	LOW	Yes	HIGH
Prospective	All eligible patients with hip fracture September 2005 to December 2006	Univariate analysis only for type of anaesthetic and outcome. No details on similarity of groups for this variable. Adjusted analyses not with type of anaesthetic as a variable	Staff performing assessments were not involved in the care of enrolled patients	CAM		No statistically significant differences between patients enrolled and not enrolled for age/sex. No details on the 79 who refused to take part Preoperative delirium an exclusion criterion; 127/364 (35%) included not assessed preoperatively and excluded. No details on their characteristics
Kim *et al* 2013[54]	LOW	HIGH	UNCLEAR	LOW	Yes	LOW
Retrospective	Consecutive sample of patients with hip fracture	No adjusted analyses including type of anaesthesia. No details on similarity of baseline characteristics for groups	No details	DSM-IV criteria		Appears to be no missing data
Konttinen and Rosenberg 2006[48]	LOW	HIGH	UNCLEAR	UNCLEAR	UNCLEAR	UNCLEAR
Retrospective	All patients over 100years old undergoing emergency Surgery in one hospital	No adjusted analyses	No details	Not clearly defined		No details on missing data/exclusions
Koval *et al* 1999[45]	LOW	HIGH	UNCLEAR	UNCLEAR	UNCLEAR	UNCLEAR
Prospective	Patients with hip fracture admitted to one hospital between 1987 and 95. Patient excluded if certain characteristics meant type of anaesthetic was predetermined	Some imbalances in baseline characteristics. Adjustment for covariates described but results presented appear to be unadjusted	No details	Not clearly defined		4.4% of patients lost to follow-up. No further details
Luger *et al* 2014[49]	LOW	HIGH	UNCLEAR	LOW (DSM-IV) HIGH (unspecified)	Yes (DSM-IV) Unclear (unspecified)	HIGH
Retrospective	Patients scheduled for acute hip fracture surgery at Innsbruck Medical University between 2005 and 2007	No details on baseline characteristics between groups. No adjusted analyses	No details	'Unspecified cognitive dysfunction behaviour' and DSM-IV		82/411 (20%) excluded due to incomplete records. Unclear if excluded had different characteristics to those included
Michael *et al* 2014[50] (Abstract)	LOW	HIGH	UNCLEAR	LOW	Yes	UNCLEAR
Retrospective	Consecutive patients	No details on baseline characteristics between groups. No adjusted analyses	No details	AMT		34/738 (5%) excluded retrospectively. No reasons for exclusions
Mohamed *et al* 2016[46] (Abstract)	UNCLEAR	HIGH	UNCLEAR	UNCLEAR	UNCLEAR	LOW
Prospective	Patients from six hospitals; no further details	No details on baseline characteristics between groups. No adjusted analyses	No details	No details		Data from enrolled patients analysed

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Table 2B Continued

Study	Eligibility criteria	Confounders Low risk	Blinding of outcome assessors	Validity of assessment tool used	Tool specific for delirium	Loss to follow-up/missing data
O'Hara *et al* 2000[52]	LOW	HIGH for unadjusted data LOW for adjusted data	UNCLEAR	UNCLEAR	UNCLEAR	UNCLEAR
Retrospective	Consecutive patients from 20 hospitals	Appear to be some baseline imbalances between groups, but multivariable analyses. Variables were gender, history of cardiovascular disease, history of stroke, abnormal preoperative chest radiograph, type of surgical repair, age, hospital and ASA score	No details	Not clearly defined		9425/9598 <2% missing
Ojeda 2018[47] (Abstract)	UNCLEAR	HIGH for unadjusted data LOW for adjusted data	UNCLEAR	UNCLEAR	UNCLEAR	UNCLEAR
Prospective	Patients over 70 years admitted with a hip fracture; no further details	Unclear if any baseline imbalances. Variables in multivariable analysis were time to surgery, ASA status and comorbidities	No details	No details		No details
Shih *et al* 2010[51]	LOW	HIGH	UNCLEAR	UNCLEAR	UNCLEAR	LOW
Retrospective	Octogenarian patients undergoing hip fracture repair in one centre between 2002 and 2006	Some baseline imbalances between groups; no adjusted analyses for delirium (only for 'morbidity') generally	No details	Not clearly defined		Appears to be no missing data from those patients included

Quality assessment was not performed for Atay *et al*[31] as a full translation was not available.
AMT, Abbreviated Mental Test; ASA, American Society of Anesthesiologists Physical Status Classification System; CAM, confusion assessment method; DSM-IV, Diagnostic and Statistical Manual of Mental Disorders, fourth edition; DSM-IV-TR, DSM-IV Text Revision; ICU, intensive care unit; MMSE, Mini–Mental State Examination.

Table 3 Mortality results

Study	Time-point	Deaths/no deaths GA	Deaths/no deaths RA	Unadjusted OR or RR (95% CI)	Adjusted/matched OR or RR (95% CI)	Note
RCTs						
Bigler *et al* 1985[35]	In-hospital	1/19	1/19	RR 1.00 (0.07 to 14.6)		No statistically significant difference in in-hospital mortality
Parker and Griffiths 2015[38]	30 days	8/156	5/153	RR 1.54 (0.52 to 4.58)		No statistically significant difference in mortality at 30 or 90 days Statistically significant difference in mortality at 120 days and 1 year in favour of GA
Parker and Griffiths 2015[38]	90 days	12/152	12/146	RR 0.96 (0.45 to 2.07)		
Parker and Griffiths 2015[38]	120 days	12/152	15/143	RR 0.77 (0.61 to 0.91)		
Parker and Griffiths 2015[38]	1 year	19/145	32/126	RR 0.57 (0.34 to 0.96)		
Prospective cohort						
Withey *et al* 1995[59]	1 year	Total only reported: 303	Total only reported: 161	Not reported	OR 1.28 (0.76 to 2.14)	No statistically significant difference in mortality (adjusted data)
Zhao *et al* 2015[60]	Unknown	65/166	22/238	Not reported	OR 0.687 (0.248 to 1.906)	No statistically significant difference in mortality (adjusted data)
Retrospective cohort						
Chu *et al* 2015[68]	In-hospital	1363/50 681	1107/50 937	Not reported	OR 1.24 (1.15 to 1.35)	Statistically significant difference in mortality (adjusted data) in favour of RA
Neuman *et al* 2012[20]	In-hospital	325/12 579	110/5144	Not reported	OR 0.710 (0.541 to 0.932)	Statistically significant difference in in-hospital mortality in favour of RA (OR <1 indicates benefit from RA)
Patorno *et al* 2014[77]	In-hospital	1477/66 345	144/6939	RR 0.94 (0.79 to 1.11)	RR 0.93 (0.78 to 1.11)	No statistically significant difference in mortality (adjusted or unadjusted)
O'Hara *et al* 2000[52]	7 days	82/6124	53/3076	OR 0.80 (0.56 to 1.13)	OR 0.90 (0.59 to 1.39)	No statistically significant difference in mortality (adjusted or unadjusted)
Basques *et al* 2015[95]	30 days	450/6803	166/2423	0.97 (0.81 to 1.17)	OR 0.98 (0.82 to 1.20)	No statistically significant difference in mortality (adjusted or unadjusted)
O'Hara *et al* 2000[52]	30 days	272/5934	174/2955	OR 0.80 (0.66 to 0.97)	OR 1.08 (0.84 to 1.38)	No statistically significant difference in mortality (adjusted or unadjusted)
Qiu *et al* 2018[99]	In-hospital	226/9629	111/6597	Not reported	HR 1.38 (1.10 to 1.73)	No statistically significant difference in mortality
Seitz *et al* 2014[81]	30 days	1044/7774	1450/10 705	RR 0.99 (0.92 to 1.07) (calculated based on raw data reported)	RR 1.04 (0.94 to 1.15) (calculated based on raw data reported)	No statistically significant difference in 30-day mortality (matched or unmatched)

Continued

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Table 3 Continued

Study	Time-point	Deaths/no deaths GA	Deaths/no deaths RA	Unadjusted OR or RR (95% CI)	Adjusted/matched OR or RR (95% CI)	Note
Whiting *et al* 2015[96]	30 days	Total only stated: 5840	Total only stated: 1924	Not reported	Spinal and regional nerve blocks OR 1.18 (0.91 to 1.53) Spinal only OR 1.20 (0.92 to 1.56) Regional only OR 1.22 (0.54 to 2.76)	No statistically significant difference in 30-day mortality (adjusted data)

GA, general anaesthesia; RA, regional anaesthesia; RCT, randomised controlled trial; RR, relative risk.

and non-randomised controlled studies, focusing on delirium as a primary outcome as well as synthesising findings for a range of other important outcomes including adverse events. Results for RCTs, non-randomised studies, adjusted and unadjusted results were presented and considered separately. It was anticipated that non-randomised studies, which are more prone to bias, may overestimate effect sizes compared with RCTs. No such trends were observed, however, as studies of any design mostly showed no difference in effect.

A sensitive search strategy means it is unlikely that many studies would have been missed. Careful consideration of heterogeneity has meant that no meta-analyses were undertaken, but results were presented in forest plots where possible to show the overall direction of effect and heterogeneity between studies.

Delirium can be diagnosed using the criteria from the DSM-V or WHO's ICD-10 classification of diseases.[7 115] However, in clinical practice, the criteria can be difficult to apply[116] and tools such as the confusion assessment method, Delirium Rating Scale revised-98, Neelon and Champagne Confusion Scale[117] or 4 'A's' Test have been advocated as validated screening tools.[6 116 118] No consensus exists in the literature as to which tool should be the gold standard.[6 119 120] The accurate assessment of delirium can be affected by the presence of pain and residual drugs in the immediate period following surgery; therefore, timing of assessment is also important.[121] No significant differences were found for the incidence of postoperative delirium, based on 4 RCTs and 14 non-randomised studies, but there were significant differences in the assessment tools and the assessment time-points. Most of the RCTs were small and most likely underpowered. In the largest RCT,[38] delirium was not a primary outcome and the assessment tool used or the timing of assessments was not reported. The pathophysiology of delirium remains poorly understood, but there are a combination of pre-existing and precipitating factors that can predispose the patient to postoperative delirium.[11 122 123] Pre-existing patient risk factors including age >70 years, pre-existing cognitive impairment, history of postoperative delirium, visual impairment, cerebrovascular disease and renal impairment[124 125] are associated with higher risk of delirium. Precipitating factors can include acute injury such as a hip fracture, malnutrition, electrolyte imbalance and the use of urinary catheter and physical restraints.[125] Specific perioperative risk factors include intraoperative blood loss, postoperative transfusions and severe acute pain.[126 127] The studies that adjusted for confounders and reported delirium[40 42 52 53] found no association between type of anaesthesia and postoperative delirium. Confounders adjusted for included demographics, ASA classification, comorbidities, nutritional status, fracture type, preoperative blood transfusion and readmission.[42 52 53] However, with multifactorial risk factors for delirium, it is difficult to encompass all variables. Other important characteristics such as anaemia, time to surgery, blood loss, intraoperative hypotension and sedation can also influence outcome but were less frequently included as variables. Given the lack of consistency across studies in

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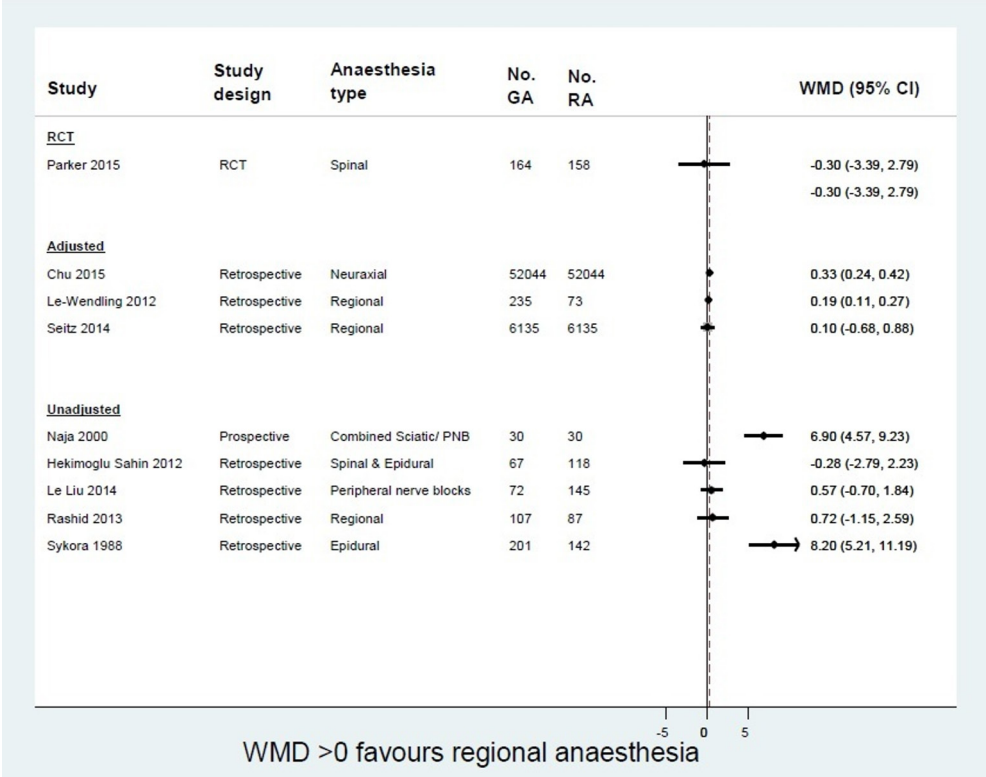

Figure 3 Forest plot of studies reporting length of hospital stay. Weighted mean difference in number of days between GA and RA (GA minus RA). WMD >0 means longer stay for GA and favours RA. WMD <0 means longer stay for RA and favours GA. GA, general anaesthesia; RA, regional anaesthesia; RCT, randomised controlled trial; WMD, weighted mean difference.

terms of number and type of variables included in models and the reporting of these, it is not possible to gauge the overall impact that adjusting for confounders may have on the direction of effect.

There were limitations in the primary data included in this systematic review. There were a limited number of RCTs (3% of total number of patients included for the primary outcome) and many of the non-randomised studies did not make any attempts to adjust for potential confounding factors. When confounding variables were considered, this was often done for mortality only. There was significant heterogeneity across studies in study design, population age, comparators, assessment time-points and definition of outcomes (particularly delirium) that precluded quantitative pooling.

Detailed reporting of anaesthetic techniques was suboptimal especially for GA techniques. RA techniques employed were more commonly reported, but the specific drugs used were not described. Opioids are known to cause delirium[3 128] and acute pain is a well-recognised precipitating factor of delirium, but both were poorly reported. While most studies planned to collect adverse events data, it was unclear whether adverse events were predetermined. Small sample sizes (n<30) and rare occurrences of adverse events mean that many studies were likely underpowered.[35 36 48 101] The style of data reporting in included studies could also lead to over-reporting of complications; for example, a patient could develop pneumonia, which led to respiratory failure and the need for inotropic and ventilatory support and ITU admission. Thus, five adverse events would be attributable to a single patient, but this may not be evident from the data. Incidence of intraoperative hypotension was not captured by POM categories, as inotropic support use was not reported. Hypotension can lead to hypoperfusion and organ damage. A recent analysis of data from an audit of outcomes in patients with hip fracture demonstrated increased risk of death associated with intraoperative hypotension. In our review, three studies[106 108 109] examined hypotension, all of which found higher incidences of hypotension in the GA group. Four studies[52 69 106 109] also found significantly higher volumes of fluids and blood products transfused in the GA group.

Subgroup analysis was not feasible and no individual studies reported findings for different subgroups. It is possible that there are some patients who may, in some circumstances, benefit from RA compared with GA that have not been captured by the evidence presented in this systematic review. Subgroup analysis of specific at-risk patients, for example the frail and the very elderly, may suggest a benefit for either regional or general anaesthesia in certain population groups.

Older patients are at high risk of adverse outcomes postoperatively due to age-related physiological decline, multiple comorbidities and polypharmacy.[129] Principles of care for older patients in the perioperative setting should employ an anaesthetic technique that leads to rapid recovery, dosing of drugs specific to individual pharmacokinetic variation and appropriate pain management strategies.[130] Most recently,

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Table 4 Summary findings table of studies reporting adverse events

POMS categories	Study	Adverse event description	GA	RA	Summary statistic*/p value
Pulmonary	Basques *et al* 2015[95]	Ventilatory support	58/7253 (0.8%)	13/2589 (0.5%)	NR
		Pneumonia	261/7253 (3.6%)	108/2589 (4.2%)	NR
	Bigler *et al* 1985[35]	Pneumonia	2/20	1/20	NR
	Chu *et al* 2015[68]	Respiratory failure	868/52 043 (1.61%)	328/52 044 (0.63%)	OR 2.71 (95% CI 2.38 to 3.01), p<0.001 Favours RA
		Ventilatory support	4008/52 043 (7.70%)	338/52 044 (1.44%)	OR 6.08 (95% CI 5.59 to 6.61), p<0.001 Favours RA
	Konttinen and Rosenberg 2006[48]	Pneumonia	0/3	2/11	NR
	Liu *et al* 2014[75]	Overall pulmonary	18/172 (25%)	27/145 (25.5%)	p=0.934 NS
		Hypoxia	19/72 (26.4%)	23/145 (15.9%)	p=0.065 NS
	Le-Wendling *et al* 2012[21]	Overall pulmonary	17/235 (6%)	1/73 (1%)	OR 2.2 (95% CI 0.7 to 7.2) p=0.0841 Favours RA
	Naja *et al* 2000[101]	Hypoxia	2/30 (6%)	0/30 (0%)	NR
	Neuman *et al* 2012[20]	Overall pulmonary	1030/12 904 (8.1%)	359/5254 (6.8%)	p=0.005 Favours RA
		Respiratory failure	1040/12 904 (5%)	178/5254 (3.4%)	p<0.0001 Favours RA
	O'Hara *et al* 2000[52]	Pneumonia	174/6206 (2.8%)	84/3219 (2.6%)	OR 1.21 (95% CI 0.87 to 1.68) NS
	Shih *et al* 2010[51]	Overall pulmonary	11/167 (6.6%)	3/168 (1.8%)	p<0.03 Favours RA
Cardiovascular	Basques *et al* 2015[95]	Myocardial infarction	137/7253 (1.9%)	49/2859 (1.9%)	NR
		Thromboembolic	138/7253 (1.9%)	25/2589 (1.0%)	NR
	Bigler *et al* 1985[35]	Cardiovascular decompensation	1/20	1/20	NR
		Pulmonary embolism	1/20	1/20	NR
	Chu *et al* 2015[68]	Myocardial infarction	188/52 043 (0.36%)	169/52 044 (0.32%)	OR 1.11 (95% CI 0.9 to 1.37), p=0.31 NS
	Fields *et al* 2015[69]	Thromboembolism	1.64%	0.72%	p=0.004 Favours RA
	Konttinen and Rosenberg 2006[48]	Myocardial infarction	0/3	1/11	NR
	Neuman *et al* 2016[39]	Myocardial infarction	1/6	0/6	NR
	Le-Wendling *et al* 2012[21]	All cardiovascular complications	NR	NR	OR 1.7 (95% CI 0.4 to 6.3) NS
	Seitz *et al* 2014[81]	Deep vein thrombosis	47/8818 (0.5%)	41/12 155 (0.3%)	p=0.03 NS when matched
		Pulmonary embolism	100/8818 (1.1%)	93/12 155 (0.8%)	p=0.006 NS when matched
	Sutcliffe and Parker 1994[58]	Deep vein thrombosis	16/950 (1.7%)	14/383 (3.7%)	p<0.05 NS
		Pulmonary embolism	NR	NR	NS
Infectious	Bigler *et al* 1985[35]	Wound infection	1/20	0/20	NR
	Fields *et al* 2015[69]	Urinary tract infection	5.76%	8.87%	p<0.0001 Favours GA
	Rashid *et al* 2013[80]	Urinary tract infection	NR	NR	NS
	Basques *et al* 2015[95]	Wound infection	94/7253 (1.3%)	39/2589 (1.5%)	NS
Renal	Basques *et al* 2015[95]	Acute renal failure	29/7253 (0.4%)	10/2589 (0.4%)	NS
	Bigler *et al* 1985[35]	Urinary retention	4/20	5/20	NS
	Chu *et al* 2015[68]	Acute renal failure	78/52 043 (0.15%)	56/52 044 (0.11%)	p=0.06 NS
	Naja *et al* 2000[101]	Acute renal failure	2/30 (6%)	0/30 (0%)	NS

Continued

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Table 4 Continued

POMS categories	Study	Adverse event description	GA	RA	Summary statistic*/p value
Overall complications	Gilbert *et al* 2000[42]	Serious medical complications	55/311 (17.7%)	79/430 (18.4%)	OR 0.92 (95% CI 0.61 to 1.4) NS
	Gilbert *et al* 2000[42] Whiting *et al* 2015[96]	Fewer medical complications	109/311 (35.1%)	151/430 (35.1%)	OR 1.28 (95% CI 0.90 to 1.82) NS
		Surgical complications	15/311 (4.8%)	19/430 (4.4%)	OR 1.08 (95% CI 0.65 to 1.21) NS
		Major complications	NR	NR	OR 1.43 (95% CI 1.16 to 1.77) NS
	Whiting *et al* 2015[96] Fields *et al* 2015[69]	Minor complications	NR	NR	OR 1.02 (95% CI 0.82 to 1.26) NS
		All complications	NR	NR	OR 1.24 (95% CI 1.05 to 1.48) NS
		All complications	2357/4813 (48.97%)	830/1815 (45.75%)	OR 1.29 (95% CI 1.13 to 1.47), p=0.0002 Favours RA
	Hekimoglu Sahin *et al* 2012[71]	All complications	NR	NR	NS
	Ilango *et al* 2015[43]	All complications	NR	NR	NS
	Koval *et al* 1999[45]	All complications	41/362 (11.3%)	32/280 (11.4%)	NS
	Liu *et al* 2014[75]	All complications	17/72 (23.6%)	50/145 (34.5%)	p=0.165 NS
	Le-Wendling *et al* 2012[21]	All complications	NR	NR	OR 1.7 (95% CI 0.7 to 4.1) NS
	Rashid *et al* 2013[80]	All complications	22%	19%	Log regression model p=0.002 Favours RA
	Shih *et al* 2010[51]	All complications	21/167 (12.6%)	9/168 (5.4%)	p<0.02 Favours RA
	Chu *et al* 2015[68]	ITU admissions	5743/52 043 (11.03%)	3205/52 044 (6.16%)	OR 1.95 (95% CI 1.87 to 2.05), p<0.001 Favours RA
Specific complications	Chu *et al* 2015[68]	ITU stay >3 days	1206/52 043 (2.32%)	411/52 044 (0.79%)	p<0.001 Favours RA
	Baumgarten *et al* 2012[107]	Pressure ulcers	10/328 (3.0%)	18/313 (5.8%)	OR 1.3 (95% CI 1.0 to 1.6) Favours GA
	Casati *et al* 2003[36]	Hypotension requiring crystalloid infusion	12/15 (80%)	7/15 (46%)	p=0.05 NS
	Maia *et al* 2014[108]	Intraoperative hypotension	25/50	80/173	p=0.014 Favours RA
	Minville *et al* 2008[109]	Intraoperative hypotension	35/42 (83%)	74/109 (68%)	NS
	Gadsden 2016[110]	Intraoperative hypotension	569/745	1144/1528	Favours RA p<0.0001
	Messina *et al* 2013[106]	Haemodynamic changes first 10 min	Mean arterial blood pressure, heart rate, systemic vascular resistance index changes. More disturbance in GA		Favours RA
	Basques *et al* 2015[95]	Blood transfusion	2843/7253 (39.2%)	851/2589 (32.9%)	Matched OR 1.34 (95% CI 1.22 to 1.49), p<0.001 Favours RA
	Fields *et al* 2015[69]	Blood transfusion	45.49%	39.34%	p<0.0001 Favours RA
	Minville *et al* 2008[109]	Blood transfusion	23%	4%	p<0.05 Favours RA
	Shih *et al* 2010[51]	Blood loss	Median 250 (0–1600) mL	Median 200 (0–1200) mL	p=0.01 Favours RA
	Chu *et al* 2015[68]	Stroke	840/52 043 (1.61%)	717/52 044 (1.38%)	OR 1.18 (95% CI 1.07 to 1.31), p=0.001 Favours RA
	Liu *et al* 2014[75]	Stroke	5/72 (5.9%)	4/145 (2.8%)	p=0.145 NS

*OR, GA vs RA.
GA, general anaesthesia; ITU, intensive treatment unit; NR, not reported; NS, not significant; POMS, postoperative morbidity survey; RA, regional anaesthesia.

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the European Society of Anaesthesiology consensus guideline on postoperative delirium also did not find substantial evidence to recommend a specific type of anaesthetic technique but advocates intraoperative monitoring to avoid swings in blood pressure and excessive depth of anaesthesia.[131] Given the lack of standardised assessment tools of delirium and the paucity of suitably powered, methodologically sound studies, uncertainty remains regarding any potential benefits of certain types of anaesthesia. However, even a modest reduction in adverse events and length of hospital stay could benefit many patients and result in cost savings for healthcare providers. Future research examining postoperative delirium should include robust assessment and diagnosis of delirium. There is also an urgent need for high-quality research comparing anaesthetic techniques that focus on patient-related outcomes such as quality of life and functional outcomes.

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