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Title Page

The effect of regional versus general anaesthesia on post-operative delirium in elderly patients undergoing surgery for hip fracture: a systematic review

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Abstract

Background

Older patients with hip fractures who are undergoing surgery are at high risk of significant mortality and morbidity including post-operative delirium. It is unclear whether different types of anaesthesia may reduce the incidence of post-operative delirium.

Objective

This systematic review will investigate the impact of anaesthetic technique on post-operative 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 October 2016. 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 on-going 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 post-operative 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

Eighty-nine studies were included. There was no evidence to suggest that anaesthesia type influences post-operative 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

Whilst there was no evidence to suggest that anaesthesia types influences post-operative delirium, the evidence base is lacking. There is a need to ascertain the impact of type of anaesthesia on outcomes with an adequately powered, methodological rigorous study.

This review is registered with PROSPERO (CRD42015020166).

Strengths and limitations of this study

- This systematic review provides an update to evidence that examines whether the type of anaesthesia affect the development of post-operative 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 £2billion. [1] This is projected to rise and reach 100 000 patients a year and costing £3.6-5.6billion by 2033. [2]

Patients undergoing hip fracture surgery are often frail with inter-current 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 (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] Post-operative delirium has been reported to affect between 32%-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 dementia in the future. [8–12][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 careful approach in the peri-operative 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 percent 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 post-operative delirium. [3] Excessive depth of anaesthesia and perioperative hypotension has 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 post-operative outcomes in hip fracture patients are broadly suggestive of improved outcomes [3,5,25,26] and reduced incidence of post-operative delirium in patients having RA. [3,5,22–24] However some studies included in these reviews reported use of out-dated anaesthetic drugs that are no longer relevant to current clinical practice. [5,26] Further limitations were the inclusion of only randomised controlled trials, [3,5,25,26] lack of focus on delirium as a primary outcome, [3,5,22,24,26] a limited search strategy [22] and restrictive selection criteria (e.g. exclusion of studies with patients with cognitive impairment). [23–25] 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 post-operative 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 (PRISMA) guidelines. [28]

Search strategy and selection criteria

Bibliographic databases (Embase, MEDLINE, CINAHL and the Cochrane Library (CENTRAL)) were searched from inception to October 2016 using a combination of index terms and key words relating to the population, intervention and comparator and outcomes (see 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 on-going trials. (Appendix B) Endnote 7 (Thomson Reuters) was used to store records and facilitate screening.

Study selection

Studies were eligible for inclusion if they met the following pre-defined 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: post-operative 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 were: anaesthetic technique or drug not considered current standard practice (e.g. outdated anaesthesic agents - halothane, enflurane, xenon); patients undergoing hip fracture surgery alongside other surgery (e.g. multiple trauma injuries); and uncontrolled studies. 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 is therefore based mainly on numerical data and the English abstract.

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). 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 (such as study design or timing of assessment) have been highlighted. Adverse events were tabulated, where possible, according to the post-operative morbidity survey (POMS) criteria. [34] Findings for other outcomes (functional outcomes, quality of life, 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.

Results

Of 4223 citations screened, 89 studies met the eligibility criteria (Figure 1). There were 5 randomised controlled trials (RCTs), 28 prospective and 56 retrospective controlled studies.

Eighteen studies reported delirium (4 RCTs, [35–38] 7 prospective [18,39–44]and 7 retrospective studies [45–51]; 51 studies reported mortality (2 RCTs, [35,38] 10 prospective [41,44,52–59] and 38 retrospective studies [4,20,21,31,32,45,48,49,51,60–88]); 21 studies reported length of hospital stay (2 RCTs, [36,38] 5 prospective, [41,44,54,89,90] and 14 retrospective studies [21,48,53,62,64,65,69,72,74–77,91,92]); 25 studies reported adverse events (3 RCTs [35,36,93] 7 prospective [41,42,44,54,89,94,95] and 15 retrospective studies [20,21,45,48,49,62,63,65,69,73–75,91,96,97]); 8 studies reported functional outcome (2 RCTs, [35,36] 3 prospective [41,44,98] and 3 retrospective studies [58,67,99]) and 3 studies reported discharge location (1 prospective [42] and 2 retrospective studies [21,45]).

Ten potentially relevant ongoing trials were identified, with two (NCT02190903 and NCT02213380) planning to measure delirium post-operatively (Appendix B). No interim data was available.

Study, population and intervention characteristics

Given the large number of studies identified, only the 18 studies reporting the primary outcome of post-operative delirium have been described in detail (Table 1).

Primary Outcome

Post-operative delirium

Fourteen studies are represented in the forest plot (Figure 2), including three of the four RCTs. Based on these 14 studies, there is no evidence of a benefit of one type of anaesthesia over another. Four further studies not represented in the forest plot (one RCT, [35] two retrospective analyses reported as abstracts only, [47,50] and one prospective study [31]), also found no significant differences in delirium based on Abbreviated Mental Test (AMT) or DSM-IV.

None of the RCTs that were quality assessed reported all relevant details (Table 2a). Details were lacking on the assessment tools used [38] and method of randomisation. [35,36,38] Blinding of outcome assessment was either not undertaken [38] or unclear, [36] with only one RCT having a clear statement on blinding. [35] There appeared to be no loss to follow-up in two RCTs [36,38], but this was unclear for the other RCT. [35] The RCT by Kamitani 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 was not well described (Table 2b). There were no details on characteristics of completers compared with those lost to follow up. There was also a lack of detail on the type of assessment tool used and/or where the cut-off for a "positive" diagnosis of delirium was.

Most studies did not adjust for potential confounders, but four studies [31,41,49,50], one of which is also represented in the above plot [49], did present adjusted results (Figure 2). There was some variation in terms of which confounders were adjusted for. None found that type of anaesthesia was predictive of post-operative delirium.

There was substantial heterogeneity across the 18 studies regarding assessment tools, assessment time-points and anaesthetic protocol. Many assessment tools were poorly defined. Only 6 out of 18 studies used either DSM-IV criteria [18,46,50,51] or AMT. [35,47] Delirium or cognitive impairment was frequently not a primary outcome, but listed as one of several complications.

Secondary outcomes

Mortality

Two RCTs and 9 studies reported adjusted mortality (Figure 3, supplementary data). Most studies found no statistically significant differences between types of anaesthesia. One RCT found a small and statistically significant mortality benefit at 120 days and one year for GA; but no such benefit was evident at 30 or 90 days follow-up. [38] Two further studies[41,73] reporting adjusted results did not find statistically significant results favouring either type of anaesthesia. Where studies reported both adjusted and unadjusted results, it is notable that in some cases the direction of effect or statistical significance changes; this emphasises the fact that unadjusted results should be interpreted very cautiously. Furthermore, there was a lack of reporting and consistency in terms of which variables were adjusted for.

Of the remaining 38 studies reporting unadjusted mortality results only, six [52,56,61,67,68,70] found statistically significant results in favour of RA. The remainder found no statistically significant differences and no consistent trend of benefit.

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-one [21,36,38,41,44,48,53,54,62,64,65,69,72,74–77,89–92] studies reported length of hospital stay; nine could be included in a forest plot (Figure 4, supplementary data). There was no difference in length of hospital stay based on one RCT. [38] The adjusted results, based on three retrospective studies, [21,62,75] showed a slight trend towards a shorter length of stay with RA; whilst this was statistically significant in two studies, [21,62] 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, [65,69,74] and two finding a benefit from RA. [76,89]

Of the remaining twelve studies [36,41,44,48,53,54,64,72,77,90,91,100], neither the RCT [36] nor the four prospective studies [41,44,54,90] showed any significant differences. Results from the seven retrospective studies were also inconsistent (three studies [53,64,77] reported no difference, two studies [48,72] found a statistically significant benefit for RA [72] and one [91] a statistically significant benefit for GA.)

Most studies reported mean length of stay, but some also reported the median, which may be more appropriate. Of ten studies [21,36,44,48,53,64,65,77,90,91] reporting the median, eight studies [21,36,44,53,64,65,77,90] found no statistically significant differences. Two studies found a statistically significant difference in medians favouring RA [48] or GA [91] respectively.

Adverse Events

Twenty-five studies reported adverse events (Table 3, supplementary data). 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 (8 studies). [21,35,45,54,62,63,75,91] 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 [62], respiratory failure [20,62] and 'overall pulmonary' adverse events [20,48]). There were no differences in occurrences of pneumonia [35,45,49,91] or hypoxia. [69,89] The most commonly reported cardiovascular adverse events were myocardial infarction [45,62,91] and thromboembolic events. [35,54,63,75,91] No differences were found for myocardial infarction. [45,49,62,69,91] Three studies [63,75,91] 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 (e.g. fewer incidences of 'all complications', [48,63] ITU admissions, [62] stroke [62] or requirement for blood transfusion). Three studies [93,95,97] found higher incidences of hypotension in the GA group.

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

Functional outcomes

Eight studies reported functional outcomes using a variety of outcome measures. A small RCT reported a significantly quicker time to ambulation in the RA group (3.3 days RA vs 5.5 days GA). [35] A further RCT [36] reported a statistically significant earlier discharge time from PACU (post-anaesthesia care unit) in RA group (RA 15 (5-30) min vs. GA 55 (15-80) min, p=0.0005). No differences were found in the non-randomised studies regarding time to ambulation, [98,99] walking speed, [58] time to rise from chair, [41] mean Barthel's score [67] or ambulation at 3, 6 and 12 month post-surgery. [44] 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

Three non-randomised studies described discharge locations of patients following hip fracture. [21,42,45] One study with only 14 patients reported that more patients returned home in RA group [45]. However, two larger studies [21,42] found no difference in discharge location between GA or RA group.

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 post-operative 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 one year post-operatively. 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 was limited for functional outcomes and discharge data. Two small RCTs suggested a benefit from RA for immediate post-anaesthetic mobilization. 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 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. 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 the WHO's ICD-10 classification of diseases. [7,101] However in clinical practice the criteria can be difficult to apply [102] and tools such as the confusion assessment method (CAM), Delirium Rating Scale revised-98 (DRS-R-98), Neelon and Champagne (NEECHAM) confusion scale [103] or 4AT have been advocated as validated screening tools. (4 'A's' Test) [6,102,104] No consensus exists in the literature as to which tool should be the gold standard. [6,105,106] 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. [107] No significant differences were found for the incidence of post-operative delirium, based on four 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 pre-dispose the patient to post-operative delirium. [11,108,109] Pre-existing patient risk factors including age > 70 years, pre-existing cognitive impairment, history of post-operative delirium, visual impairment, cerebrovascular disease and renal impairment [110,111] 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. [111] Specific perioperative risk factors include intraoperative blood loss, post-operative transfusions and severe acute pain. [112,113] The studies that adjusted for confounders and reported delirium [31,41,49,50] found no association between type of anaesthesia and post-operative delirium. Confounders adjusted for were demographics, ASA classification, co-morbidities, nutritional status, fracture type, pre-operative blood transfusion and readmission. [41,49,50] 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, intra-operative hypotension and sedation, can also influence outcome.

There were limitations in the primary data included in this systematic review. There were a limited number of RCTs (3% of total evidence 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 technique. RA techniques employed were more commonly reported, but the specific drugs used were not described. Opioids are known to cause delirium [3,114] and acute pain is a well-recognised precipitating factor of delirium but both were poorly reported. Whilst 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 means that many studies were likely underpowered. [35,36,45,89]. 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 sprint audit of outcomes in hip fracture patients demonstrated increased risk of death associated with intraoperative hypotension. In our review, three studies [93,95,97] examined hypotension all of which found higher incidences of hypotension in the GA group. Four studies [49,63,93,97] 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 sub-groups. It is possible that there are some patients who may, in some circumstances, benefit from RA compared to 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 post-operatively due to age-related physiological decline, multiple co-morbidities and polypharmacy. [115] Principles of care for the older patients in the peri-operative setting should employ an anaesthetic technique that leads to rapid recovery, dosing of drugs specific to individual pharmacokinetic variation and appropriate pain management strategies. [116] 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 health care providers. Future research examining post-operative 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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Data sharing statement: There are no unpublished data from this review.

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
RCTs					
Bigler 1985 DENMARK	General: ASA 1: 2 ASA 2: 14 ASA 3: 4 Spinal: ASA 1: 2 ASA 2: 15 ASA 3: 3	General (n=20) v 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 2003 ITALY	General: ASA 2: 7 ASA 3: 8	General (n=15) v Spinal (n=15)	Patients undergoing hip fracture repair	Patients over 65 years of age Mean age General: 84 years (67-88)	-Hypotension -Cognitive dysfunction

	Spinal: ASA 2: 6 ASA 3: 9			Spinal: 84 years (71-94) M/F: 2/28	
Kamitani 2003 JAPAN	ASA not reported. Comparable 'physical status' between GA and RA groups	General (n=21) v Spinal (n=19)	Patients with femoral neck fracture	Patients aged 70 and over Mean age General: 81.4±6.2 Spinal: 83.6±6.0 M/F: 4/36	-Postoperative delirium
Parker & Griffiths 2015 UK	General: ASA Grade 1 or 2: 98 Spinal: ASA Grade 1 or 2: 94.9	General (n=164) v Spinal (n=158)	Patients with acute hip fracture	Patients over 49 years of age Mean age General: 83.0 years (59-99) Spinal: 82.9 years (52-105) M/F: 87/235	Primary: -Mortality Secondary: -Surgical outcomes -General complications -Hospital stay

PROSPECTIVE STUDIES					
Atay 2012 TURKEY	Unable to obtain full translation.	General (n=30) v Spinal (n=40)	Patients with hip fractures	Patients aged 60 years and over Mean age M/F:	-Postoperative delirium -Postoperative cognitive function
Bitsch 2006 DENMARK	ASA 1=2 ASA 2=33 ASA 3=51 ASA 4=10	General (n=13) v Regional (n=83)	Hip fracture patients	No age restriction Mean age No significant decline: 81.6 years (75-86) Significant decline: 84.5 years (81-89) M/F: 28/68	-Risk factors for pre, intra and post operative cognitive dysfunction
Bjorkelund 2010 SWEDEN	Intervention group (new care plan): ASA 1=17	General (n=89) v Spinal (n=174)	Patients with hip fractures	Patients aged 65 years and over Mean age	-Incidence of Delirium

	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			Intervention: 81.1 years (SD 7.5) Control: 82.0 years (SD 7.6) M/F: 78/185	
Gilbert 2000 USA	General: ASA 1-2: 105 ASA 3-4: 194 Spinal: ASA 1-2: 109	General (n=311) v 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	-Complications (in-hospital and surgical) -Functioning (daily, social, mental)

	ASA 3-4: 309			Spinal: 65-79 years n=184 80+ years n=246 M/F: 156/585	
Ilango 2015 AUSTRALIA	Not reported	General (n=167) v Spinal (n=151)	Hip fracture patients	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 -Post-discharge mortality
Juliebo 2009 NORWAY	ASA 1 or 2 = 182	General (n=20) v Spinal (n=337)	Patients with hip fracture	Patients aged 65 years and over Age	-Delirium

				Delirium: 85 years (82-89) No delirium: 82 years (77-87) M/F: 88/276	
Koval 1999 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) v 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
RETROSPECTIVE STUDIES					
Bellelli 2013 ITALY Abstract	Not reported	General v Spinal v Peripheral nerve block 392 included	Patients undergoing hip fracture surgery	Patients aged 65 years and older Mean age: 83 years (SD 6)	-Postoperative delirium

		patients, but no breakdown of who received what anaesthesia		M/F: Not reported	
Kim 2013 KOREA	ASA 1: 6 ASA 2: 311 ASA 3: 189	General (n=246) v Spinal (n=249) v Epidural (n=11)	Hip fracture surgery patients	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 2006 FINLAND	ASA 3: 8 ASA 4: 6	General (n=3) v 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 -Post-op discharge location -Pain management -Haemodynamics -Mental status -Mobilisation

					-Mortality
Luger 2014 AUSTRIA	Mean ASA: Group 1 (post-op delirium): 2.9 +/- 0.6 Group 2 (unspecified cognitive dysfunction): 88.4 +/- 5.2 Control: 2.8 +/- 0.6	General (n=116) v 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 and post nursing home stay -Comorbidities -Perioperative Complications
Michael 2014 UK Abstract	Not reported	General v Spinal (704 patients included in analysis, but unclear how many received which anaesthesia)	Hip fracture patients	Patients aged 60-100 years Age 60-70 years n=50 70-80 years n=169 80-90 years 338 90-100 years	Pre and post-operative cognitive function

				147 M/F: 178/526	
O'Hara 2000 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) v Regional (n=3219, spinal n=3078 and epidural n=141)	Hip fracture patients	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

Shih 2010 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

Table 2a: Quality assessment of RCT 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								
Parker & Griffiths 2015 N=322	UNCLEAR	LOW	Groups similar for all baseline characteristics measured, except for proportion of male patients (35% in GA group, 19% in RA group).	HIGH	LOW	Unclear-no details	Unclear	UNCLEAR
	Randomisation undertaken by opening sealed opaque numbered envelopes prepared by a person independent to the trial.			No blinding of outcome assessors	Appears post-operative delirium measured in all patients allocated to respective treatments			Insufficient information to permit judgement.
Casati 2003	UNCLEAR	LOW	Groups similar for all baseline characteristics measured.	UNCLEAR	LOW	MMSE good validity for cognitive function	No	UNCLEAR
N=30	*"Using a sealed envelope technique, patients were randomly allocated…"*			Clinical criteria for patient's discharge applied by staff blinded to anaesthetic technique-but no details for applying MMSE.	MMSE for all 30 patients at 1 and 7 days.			Insufficient information to permit judgement.
Bigler1985	UNCLEAR	UNCLEAR	Groups similar for all baseline characteristics measured except for vasopressors being administered more frequently in spinal group.	LOW	UNCLEAR	AMT good validity for cognitive dysfunction	No	UNCLEAR
N=40	No details (other than *"patients randomly allocated"*)	No details		Surgeon undertaking AMT unaware of anaesthesia given	No details on proportion that AMT was undertaken in at 7 days and 3 months.			Insufficient information to permit judgement.

NB Quality assessment was not performed for Kamitani [37] as a full translation was not available. Blinding of patients and surgeons/anaesthetists not possible.

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 2013 (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 multivariate analysis for confounders.	No details	DSM-IV-TR criteria		Patients with incomplete data in medical records were excluded from this study. Proportion not stated.
Bitsch 2006	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 day 4 and 7 respectively. Nursing home patients considered stable and those achieving independent ambulation discharged earlier.
Björkelund 2010	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
Gilbert 2000	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 multivariate analyses for all outcomes.	No details	Mental confusion not further defined; MMSE		No details-only how many included in final analysis
Ilango 2015	LOW	HIGH	UNCLEAR	HIGH	Unclear	UNCLEAR

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
PROSPECTIVE	All hip fracture patients admitted over a year	Similar baseline characteristics (age, gender, pre-op 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.
Juliebo 2009	LOW	HIGH	LOW	LOW	Yes	HIGH
PROSPECTIVE	All eligible hip fracture patients 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. Pre-operative delirium an exclusion criterion; 127/364 (35%) included not assessed pre-operatively and excluded. No details on their characteristics.
Kim 2013	LOW	HIGH	UNCLEAR	LOW	Yes	LOW
RETROSPECTIVE	Consecutive sample of hip fracture patients	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
Kontinnen 2006	LOW	HIGH	UNCLEAR	UNCLEAR	Unclear	UNCLEAR
RETROSPECTIVE	All patients over 100 years old undergoing emergency Surgery in one hospital	No adjusted analyses.	No details	Not clearly defined		No details on missing data/exclusions.
Koval 1999	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 pre-determined.	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

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
Luger 2014	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 2014 (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.
O'Hara 2000	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 multivariate analyses.	No details	Not clearly defined		9425/9598 < 2% missing
Shih 2010	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.

NB Quality assessment was not performed for Atay [31] as a full translation was not available.

Table 3: Summary findings table of studies reporting adverse events. *OR = Odds Ratio GA vs. RA; NR = not reported; NS = not significant

POMS categories	Study	Adverse event description	GA	RA	Summary statistic*/p-value
Pulmonary	Basques 2015	*Ventilatory support*	58/7253 (0.8%)	13/2589 (0.5%)	NR
		Pneumonia	261/7253 (3.6%)	108/2589 (4.2%)	NR
	Bigler 1985	*Pneumonia*	2/20	1/20	NR
	Chu 2015	*Respiratory Failure*	868/52043 (1.61%)	328/52044 (0.63%)	OR 2.71 (95%CI 2.38 to 3.01), p<0.001 Favours RA
		Ventilatory support	4008/52043 (7.70%)	338/52044 (1.44%)	OR 6.08 (95%CI 5.59 to 6.61), p<0.001 Favours RA
	Konttinen 2006	*Pneumonia*	0/3	2/11	NR
	Le Liu 2014	*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 2012	*Overall pulmonary*	17/235 (6%)	1/73 (1%)	OR 2.2 (95%CI 0.7 to 7.2) P=0.0841 Favours RA
	Naja 2000	*Hypoxia*	2/30 (6%)	0/30 (0%)	NR
	Neuman 2012	*Overall pulmonary*	1030/12904 (8.1%)	359/5254 (6.8%)	P=0.005 Favours RA
		Respiratory Failure	1040/12904 (5%)	178/5254 (3.4%)	P<0.0001 Favours RA

	O'Hara 2000	*Pneumonia*	174/6206 (2.8%)	84/3219 (2.6%)	OR 1.21 (95%CI 0.87 to 1.68) NS
	Shih 2010	*Overall pulmonary*	11/167 (6.6%)	3/168 (1.8%)	P<0.03 Favours RA
Cardiovascular	Basques 2015	*Myocardial infarction*	137/7253 (1.9%)	49/2859 (1.9%)	NR
		Thromboembolic	138/7253 (1.9%)	25/2589 (1.0%)	NR
	Bigler 1985	*Cardiovascular decompensation*	1/20	1/20	NR
		Pulmonary embolism	1/20	1/20	NR
	Chu 2015	*Myocardial infarction*	188/52043 (0.36%)	169/52044 (0.32%)	OR 1.11 (95%CI 0.9 o 1.37), p=0.31 NS
	Fields 2015	*Thromboembolism*	1.64%	0.72%	P=0.004 Favours RA
	Konttinen 2006	*Myocardial infarction*	0/3	1/11	NR
	Le Wendling 2012	*All cardiovascular complications*	NR	NR	OR 1.7 (95%CI 0.4 to 6.3) NS
	Seitz 2014	*Deep vein thrombosis*	47/8818 (0.5%)	41/12155 (0.3%)	P=0.03 NS when matched
		Pulmonary Embolism	100/8818 (1.1%)	93/12155 (0.8%)	P=0.006 NS when matched
	Sutcliffe 1994	*Deep vein thrombosis*	16/950 (1.7%)	14/383 (3.7%)	P<0.05 NS
		Pulmonary Embolism	NR	NR	NS
Infectious	Bigler 1985	*Wound infection*	1/20	0/20	NR
	Fields 2015	*Urinary Tract infection*	5.76%	8.87%	P<0.0001 Favours GA

	Rashid 2013	*Urinary Tract infection*	NR	NR	NS
	Basques 2015	*Wound infection*	94/7253 (1.3%)	39/2589 (1.5%)	NS
Renal	Basques 2015	*Acute Renal Failure*	29/7253 (0.4%)	10/2589 (0.4%)	NS
	Bigler 1985	*Urinary retention*	4/20	5/20	NS
	Chu 2015	*Acute Renal Failure*	78/52043 (0.15%)	56/52044 (0.11%)	P=0.06 NS
	Naja 2000	*Acute Renal Failure*	2/30 (6%)	0/30 (0%)	NS
Overall complications	Gilbert 2000	*Serious medical complications*	55/311 (17.7%)	79/430 (18.4%)	OR 0.92 (95%CI 0.61 to 1.4) NS
	Gilbert 2000 Whiting 2015	*Less 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 1.16-1.77) NS
	Whiting 2015 Fields 2015	*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 2012	*All complications*	NR	NR	NS
	Ilango 2015	*All complications*	NR	NR	NS
	Koval 1999	*All complications*	41/362 (11.3%)	32/280 (11.4%)	NS
	Le Liu 2014	*All complications*	17/72 (23.6%)	50/145 (34.5%)	P=0.165 NS

	Le Wendling 2012	*All complications*	NR	NR	OR 1.7 (95%CI 0.7 to 4.1) NS
	Radcliffe 2013	*All complications*	22%	19%	Log regression model p=0.002 Favours RA
	Shih 2010	*All complications*	21/167 (12.6%)	9/168 (5.4%)	P<0.02 Favours RA
	Chu 2015	ITU admissions	5743/52043 (11.03%)	3205/52044 (6.16%)	OR 1.95 (95%CI 1.87 to 2.05), p<0.001 Favours RA
Specific complications	Chu 2015	ITU stay >3 days	1206/52043 (2.32%)	411/52044 (0.79%)	P<0.001 Favours RA
	Baumgarten 2012	Pressure ulcers	10/328 (3.0%)	18/313 (5.8%)	OR 1.3 (1.0-1.6) Favours GA
	Casati 2003	Hypotension requiring crystalloid infusion	12/15 (80%)	7/15 (46%)	P=0.05 NS
	Maia 2014	Intraoperative hypotension	25/50	80/173	P=0.014 Favours RA
	Minville 2008	Intraoperative hypotension	35/42 (83%)	74/109 (68%)	NS
	Messina 2013	Haemodynamic changes first 10min	Mean arterial blood pressure, heart rate, systemic vascular resistance index changes. More disturbance in GA		Favours RA
	Basques 2015	Blood transfusion	2843/7253 (39.2%)	851/2589 (32.9%)	Matched OR 1.34 (1.22 to 1.49), p<0.001 Favours RA
	Fields 2015	Blood transfusion	45.49%	39.34%	P<0.0001

					Favours RA
	Minville 2008	Blood transfusion	23%	4%	P<0.05 Favours RA
	Shih 2010	Blood loss	Median 250 (0-1600) ml	Median 200 (0-1200) ml	P=0.01 Favours RA
	Chu 2015	Stroke	840/52043 (1.61%)	717/52044 (1.38%)	OR 1.18 (95%CI 1.07 to 1.31), p=0.001 Favours RA
	Le Liu 2014	Stroke	5/72 (5.9%)	4/145 (2.8%)	P=0.145 NS

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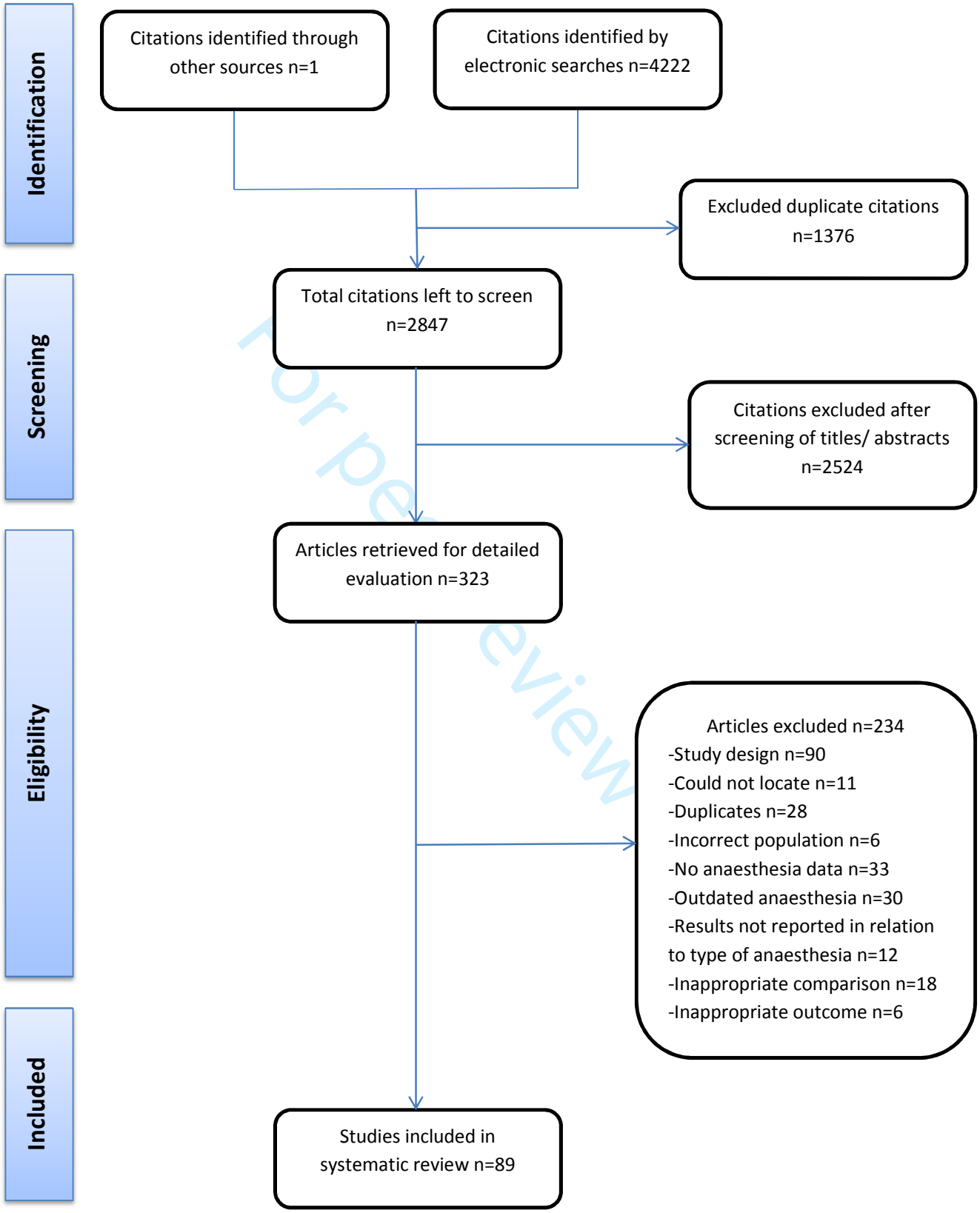


Figure 1: Flowchart showing study selection process

Appendix 1: Example of search strategy

1 exp Hip fracture/
2 hip fracture.mp.
3 (fracture$ adj2 (hip or femur$ or femor$)).tw.
4 or/1-3
5 exp an$esthesia/
6 an$esthesia.mp.
7 (anesthe$ or anaesthe$).tw.
8 an$ethetic.mp.
9 exp anesthetics/
10 exp general an$esthesia/
11 general an$esthesia.mp.
12 Anesthesia/ (43366)
13 exp Anesthesia, General/
14 general an$esthesia.mp.
15 sedation.mp. (28516)
16 exp regional an$esthesia/
17 regional an$esthesia.mp.
18 peripheral an$esthesia.mp.
19 central blockade.mp.
20 central block.mp.
21 exp spinal an$esthesia/
22 spinal an$esthesia.mp.
23 exp epidural an$esthesia/
24 epidural an$esthesia.mp.
25 exp local an$esthesia/
26 local an$esthesia.mp.
27 infiltrative an$esthesia.mp.
28 peripheral nerve block.mp.
29 intravenous regional an$esthesia.mp.
30 systemic local an$esthesia.mp.
31 exp nerve block$/
32 nerve block$.mp.
33 neuroaxial blockade.mp.
34 Anesthesia/ or exp Anesthesia, Intravenous/
35 exp inhalation an$esthesia/
36 inhalation an$esthesia.mp.
37 or/5-36
38 4 and 37

Appendix 2: Table of eligible on-going studies

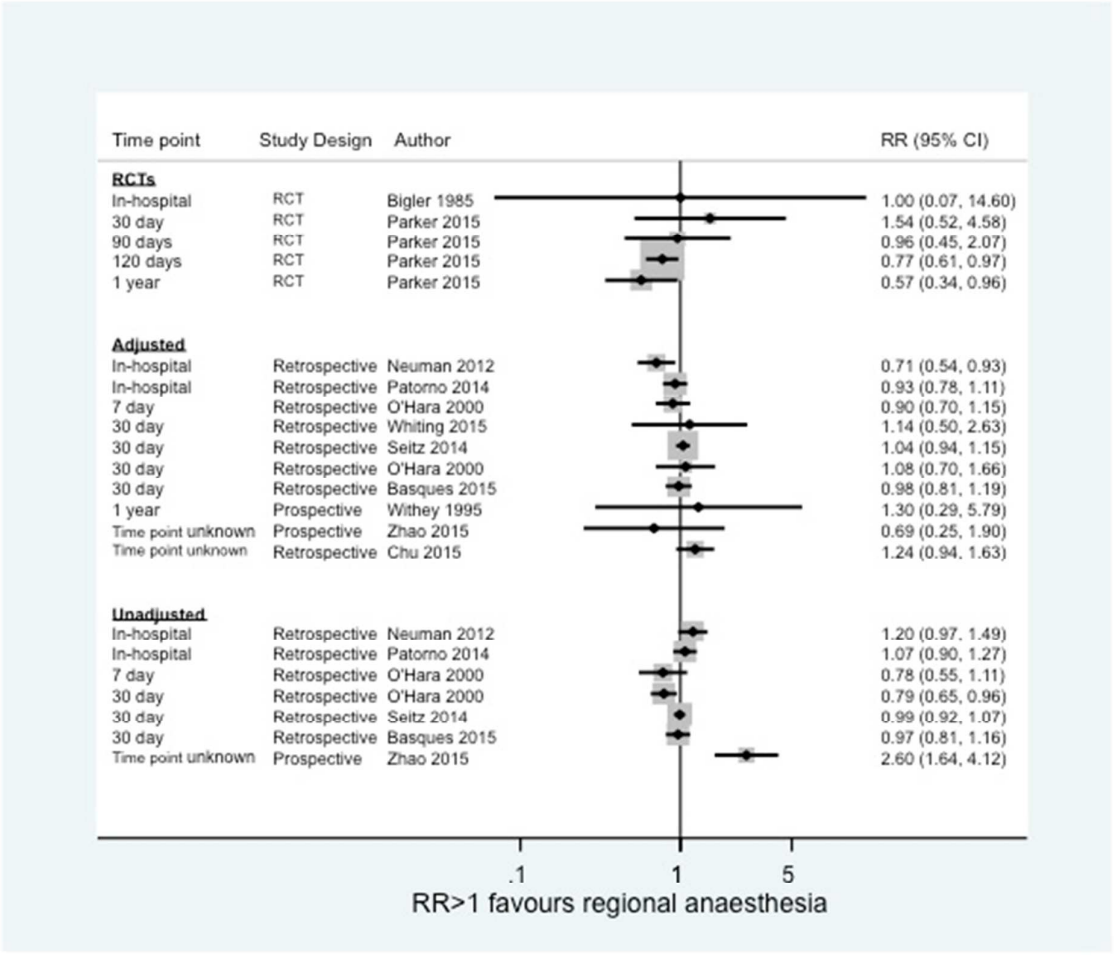
Title	ID	Comparison	Status	Design	Contact	Country
ClinicalTrials.gov						
Variations in Anaesthesia care for hip fracture surgery	NCT02787031	General v Neuraxial	Recruitment completed but no results available	Retrospective observational cohort	Ottawa Hospital Research Institute	Canada
A trial to assess the risk of delirium in older adults undergoing hip fracture surgery with spinal or general anaesthesia	NCT02190903	General v Spinal	Recruitment completed but no results available	Open label randomised trial	Mark D Neuman	USA
Regional versus general anaesthesia for promoting independence after hip fracture	NCT02507505	General v Regional	Recruiting patients	Double blind randomised trial	Mark Powell/ Mark Neuman	USA
Effect of anaesthesia on post-operative delirium in elderly patients undergoing hip fracture surgery	NCT02213380	General v Regional	Recruiting patients	Open label randomised controlled trial	Ting Li/ Sishi Chen	China

The safety of anaesthesia management for traumatic hip surgery in elderly	NCT02692989	General v Regional	Ongoing, but not recruiting patients	Retrospective observational cohort	Subhi M Alghanem	Jordan
Anaesthesia and post-operative mortality after proximal femur fractures	NCT02406300	Peripheral nerve block/ General v Subarachnoid anaesthesia	Enrolling patients by invite only	Double blind randomised controlled trial	Raul Carvalho	Portugal
Effect of anaesthesia in fracture healing	NCT02621255	General v Regional	Recruiting patients	Double blind randomised trial	Ebru Biricik	Turkey
Mortality following surgery for proximal femoral fractures	NCT01807039	General vs. Subarachnoid anaesthesia	Study has been completed	Retrospective observational cohort	Petr Štourač	Czech Republic
Practice survey on femoral neck fractures and the incidence of type of anaesthesia on patient outcome	NCT02198820	General v Regional	**WITHDRAWN	Prospective observational cohort	Eric P Deflandre	Belgium
ICTRP						
Hemodynamic effects of general	IRCT201308316280N4	General v	Completed	Double blind	Mohammad	Iran

and spinal anaesthesia for hip fracture surgery		Spinal		randomised trial	Haghighi	

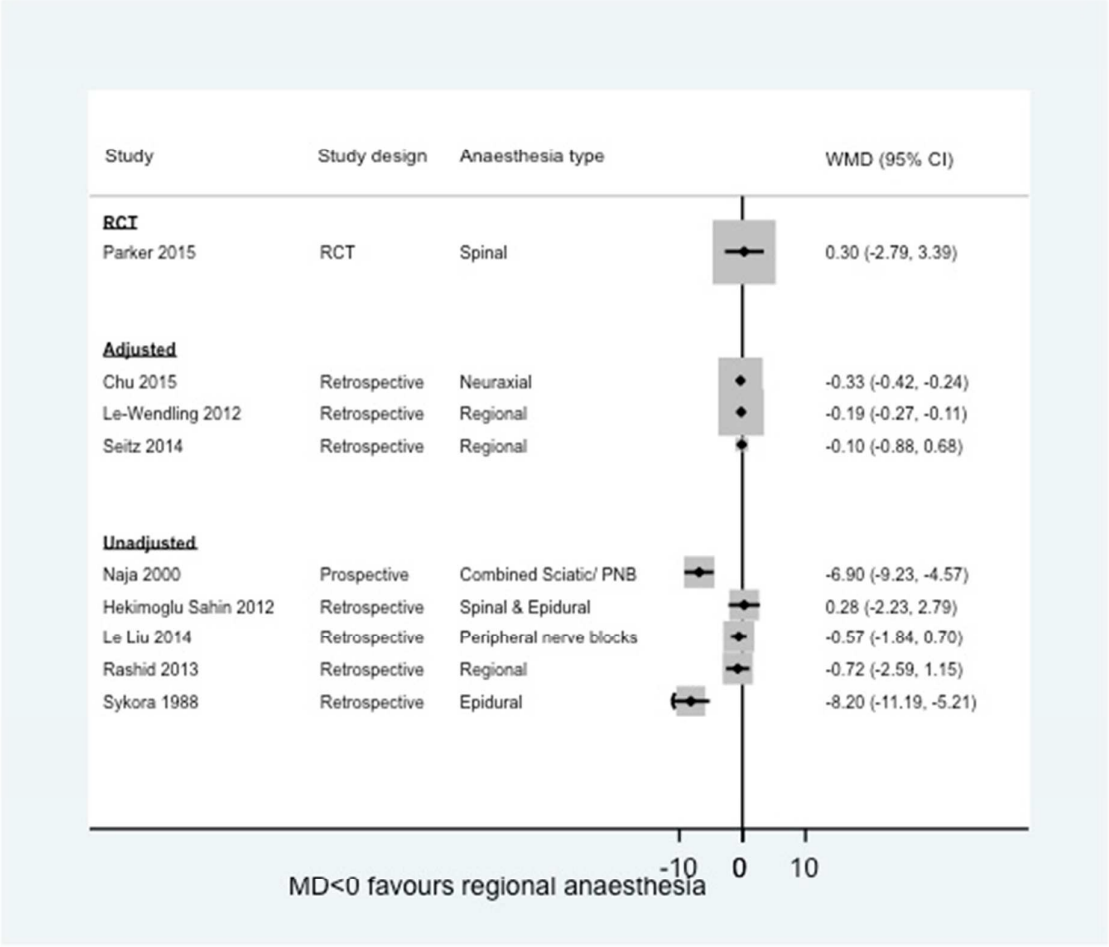
Appendix 3

Figure 3: Forest plot of unadjusted and adjusted studies reporting mortality. RR = relative risk; RA = regional anaesthesia; CI = confidence interval.



Appendix 4

Figure 4: Forest plot of studies reporting length of hospital stay. WMD=weighted mean difference, CI=confidence interval



Appendix 5

Table 3: Summary findings table of studies reporting adverse events. *OR = Odds Ratio GA vs. RA; NR = not reported; NS = not significant

POMS categories	Study	Adverse event description	GA	RA	Summary statistic*/p-value
Pulmonary	Basques 2015	*Ventilatory support*	58/7253 (0.8%)	13/2589 (0.5%)	NR
		Pneumonia	261/7253 (3.6%)	108/2589 (4.2%)	NR
	Bigler 1985	*Pneumonia*	2/20	1/20	NR
	Chu 2015	*Respiratory Failure*	868/52043 (1.61%)	328/52044 (0.63%)	OR 2.71 (95%CI 2.38 to 3.01), p<0.001 Favours RA
		Ventilatory support	4008/52043 (7.70%)	338/52044 (1.44%)	OR 6.08 (95%CI 5.59 to 6.61), p<0.001 Favours RA
	Konttinen 2006	*Pneumonia*	0/3	2/11	NR
	Le Liu 2014	*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 2012	*Overall pulmonary*	17/235 (6%)	1/73 (1%)	OR 2.2 (95%CI 0.7 to 7.2) P=0.0841 Favours RA
	Naja 2000	*Hypoxia*	2/30 (6%)	0/30 (0%)	NR
	Neuman 2012	*Overall pulmonary*	1030/12904 (8.1%)	359/5254 (6.8%)	P=0.005 Favours RA
		Respiratory Failure	1040/129	178/5254	P<0.0001

			04 (5%)	(3.4%)	Favours RA
	O'Hara 2000	*Pneumonia*	174/6206 (2.8%)	84/3219 (2.6%)	OR 1.21 (95%CI 0.87 to 1.68) NS
	Shih 2010	*Overall pulmonary*	11/167 (6.6%)	3/168 (1.8%)	P<0.03 Favours RA
Cardiovascular	Basques 2015	*Myocardial infarction*	137/7253 (1.9%)	49/2859 (1.9%)	NR
		Thromboembolic	138/7253 (1.9%)	25/2589 (1.0%)	NR
	Bigler 1985	*Cardiovascular decompensation*	1/20	1/20	NR
		Pulmonary embolism	1/20	1/20	NR
	Chu 2015	*Myocardial infarction*	188/52043 (0.36%)	169/52044 (0.32%)	OR 1.11 (95%CI 0.9 o 1.37), p=0.31 NS
	Fields 2015	*Thromboembolism*	1.64%	0.72%	P=0.004 Favours RA
	Konttinen 2006	*Myocardial infarction*	0/3	1/11	NR
	Le Wendling 2012	*All cardiovascular complications*	NR	NR	OR 1.7 (95%CI 0.4 to 6.3) NS
	Seitz 2014	*Deep vein thrombosis*	47/8818 (0.5%)	41/12155 (0.3%)	P=0.03 NS when matched
		Pulmonary Embolism	100/8818 (1.1%)	93/12155 (0.8%)	P=0.006 NS when matched
	Sutcliffe 1994	*Deep vein thrombosis*	16/950 (1.7%)	14/383 (3.7%)	P<0.05 NS
		Pulmonary Embolism	NR	NR	NS
Infectious	Bigler 1985	*Wound infection*	1/20	0/20	NR
	Fields 2015	*Urinary Tract*	5.76%	8.87%	P<0.0001

		infection			Favours GA
	Rashid 2013	*Urinary Tract infection*	NR	NR	NS
	Basques 2015	*Wound infection*	94/7253 (1.3%)	39/2589 (1.5%)	NS
Renal	Basques 2015	*Acute Renal Failure*	29/7253 (0.4%)	10/2589 (0.4%)	NS
	Bigler 1985	*Urinary retention*	4/20	5/20	NS
	Chu 2015	*Acute Renal Failure*	78/52043 (0.15%)	56/52044 (0.11%)	P=0.06 NS
	Naja 2000	*Acute Renal Failure*	2/30 (6%)	0/30 (0%)	NS
Overall complications	Gilbert 2000	*Serious medical complications*	55/311 (17.7%)	79/430 (18.4%)	OR 0.92 (95%CI 0.61 to 1.4) NS
	Gilbert 2000 Whiting 2015	*Less 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 1.16-1.77) NS
	Whiting 2015 Fields 2015	*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 2012	*All complications*	NR	NR	NS
	Ilango 2015	*All complications*	NR	NR	NS
	Koval 1999	*All complications*	41/362 (11.3%)	32/280 (11.4%)	NS
	Le Liu 2014	*All complications*	17/72	50/145	P=0.165 NS

			(23.6%)	(34.5%)	
	Le Wendling 2012	*All complications*	NR	NR	OR 1.7 (95%CI 0.7 to 4.1) NS
	Radcliffe 2013	*All complications*	22%	19%	Log regression model p=0.002 Favours RA
	Shih 2010	*All complications*	21/167 (12.6%)	9/168 (5.4%)	P<0.02 Favours RA
	Chu 2015	ITU admissions	5743/52043 (11.03%)	3205/52044 (6.16%)	OR 1.95 (95%CI 1.87 to 2.05), p<0.001 Favours RA
Specific complications	Chu 2015	ITU stay >3 days	1206/52043 (2.32%)	411/52044 (0.79%)	P<0.001 Favours RA
	Baumgarten 2012	Pressure ulcers	10/328 (3.0%)	18/313 (5.8%)	OR 1.3 (1.0-1.6) Favours GA
	Casati 2003	Hypotension requiring crystalloid infusion	12/15 (80%)	7/15 (46%)	P=0.05 NS
	Maia 2014	Intraoperative hypotension	25/50	80/173	P=0.014 Favours RA
	Minville 2008	Intraoperative hypotension	35/42 (83%)	74/109 (68%)	NS
	Messina 2013	Haemodynamic changes first 10min	Mean arterial blood pressure, heart rate, systemic vascular resistance index changes. More disturbance in GA		Favours RA
	Basques 2015	Blood transfusion	2843/7253 (39.2%)	851/2589 (32.9%)	Matched OR 1.34 (1.22 to 1.49), p<0.001 Favours RA

	Fields 2015	Blood transfusion	45.49%	39.34%	P<0.0001 Favours RA
	Minville 2008	Blood transfusion	23%	4%	P<0.05 Favours RA
	Shih 2010	Blood loss	Median 250 (0-1600) ml	Median 200 (0-1200) ml	P=0.01 Favours RA
	Chu 2015	Stroke	840/52043 (1.61%)	717/52044 (1.38%)	OR 1.18 (95%CI 1.07 to 1.31), p=0.001 Favours RA
	Le Liu 2014	Stroke	5/72 (5.9%)	4/145 (2.8%)	P=0.145 NS

Appendix 6

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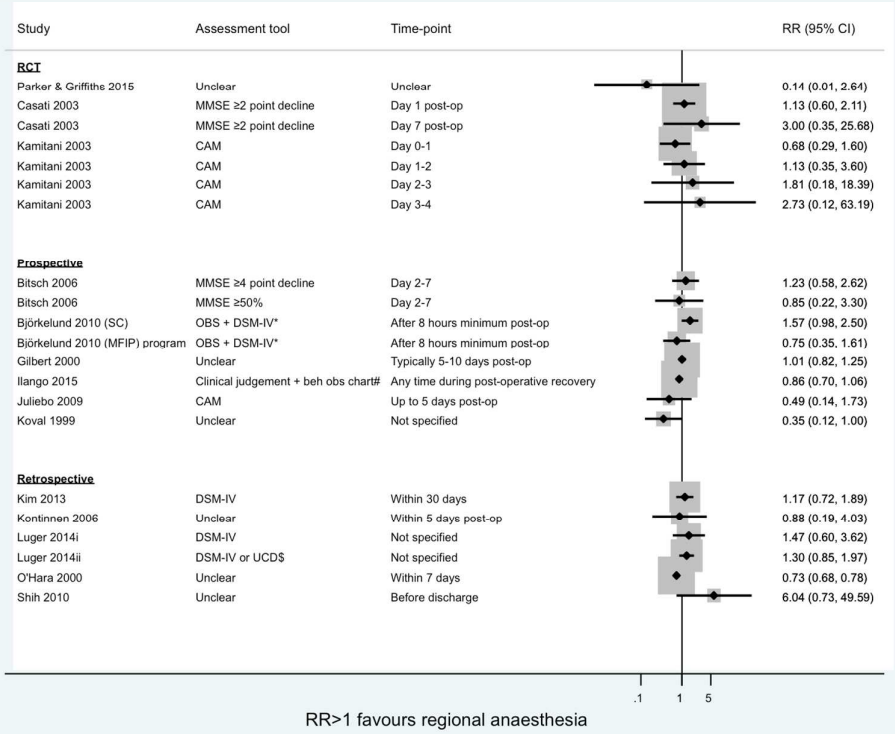

Figure 2: Forest plot of studies reporting the unadjusted relative risk of post-operative delirium with GA compared to spinal anaesthesia. Some studies are represented more than once to show results for different definitions of delirium, or for different assessment time-points. RR= relative risk, CI=confidence interval, MMSE= mini mental state examination, CAM= confusion assessment method, DSM-IV= Diagnostic and statistical manual of mental disorders 5, UCD = unspecified cognitive dysfunction.

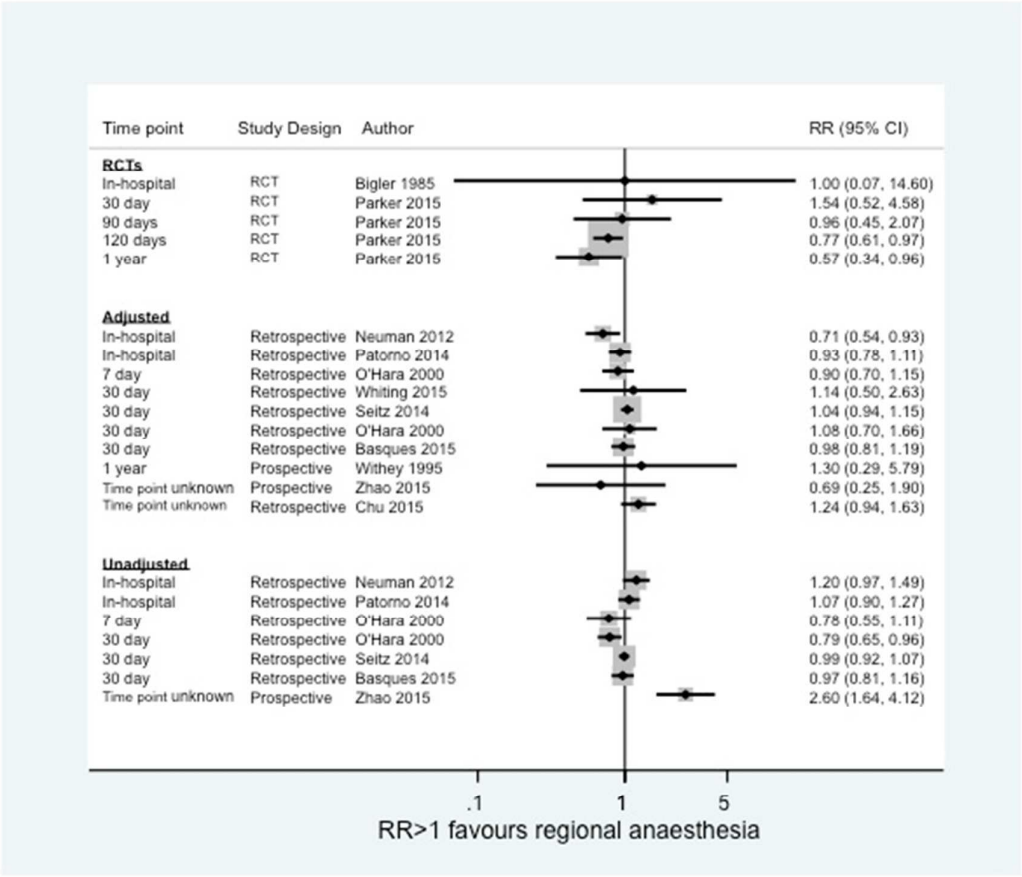

Figure 3: Forest plot of unadjusted and adjusted studies reporting mortality. RR = relative risk; RA = regional anaesthesia; CI = confidence interval.

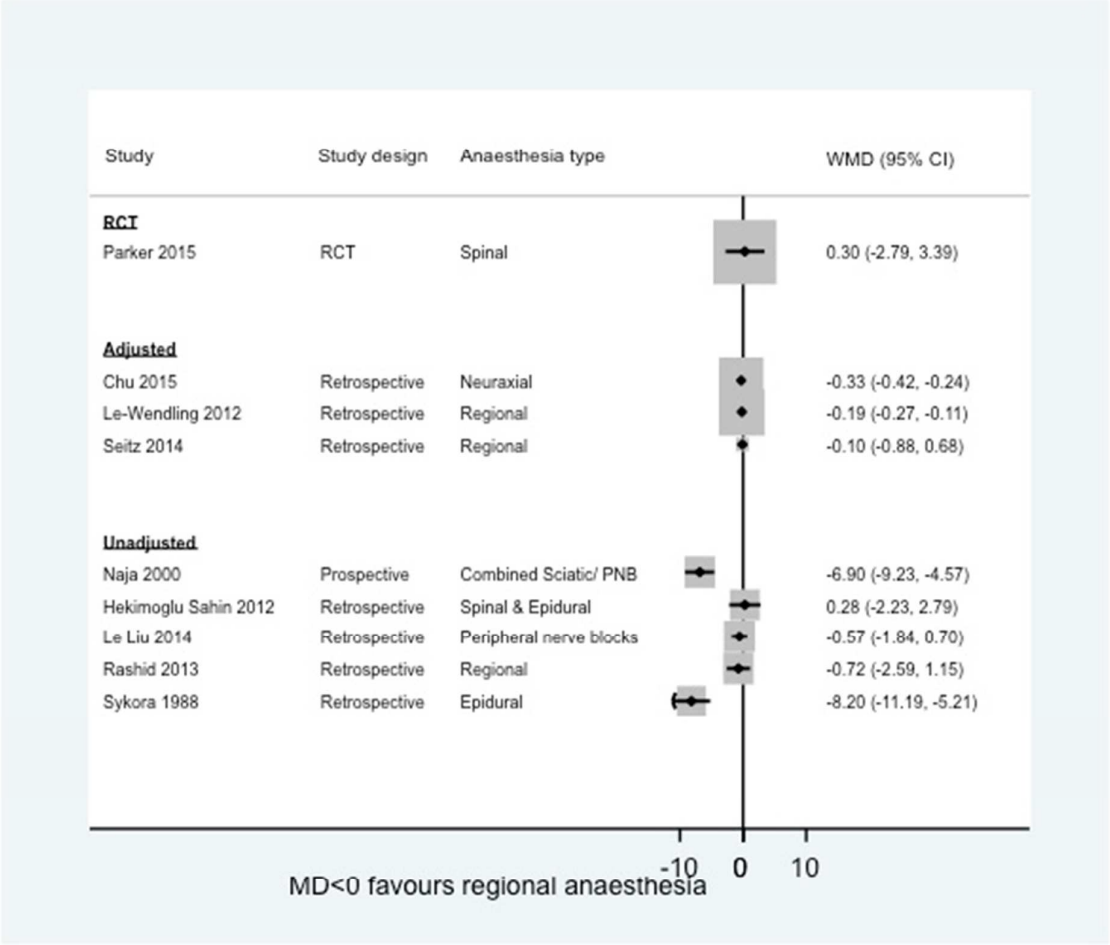

Figure 4: Forest plot of studies reporting length of hospital stay. WMD=weighted mean difference, CI=confidence interval

Appendix A: Example of search strategy

1 exp Hip fracture/
2 hip fracture.mp.
3 (fracture$ adj2 (hip or femur$ or femor$)).tw.
4 or/1-3
5 exp an$esthesia/
6 an$esthesia.mp.
7 (anesthe$ or anaesthe$).tw.
8 an$ethetic.mp.
9 exp anesthetics/
10 exp general an$esthesia/
11 general an$esthesia.mp.
12 Anesthesia/ (43366)
13 exp Anesthesia, General/
14 general an$esthesia.mp.
15 sedation.mp. (28516)
16 exp regional an$esthesia/
17 regional an$esthesia.mp.
18 peripheral an$esthesia.mp.
19 central blockade.mp.
20 central block.mp.
21 exp spinal an$esthesia/
22 spinal an$esthesia.mp.
23 exp epidural an$esthesia/
24 epidural an$esthesia.mp.
25 exp local an$esthesia/
26 local an$esthesia.mp.
27 infiltrative an$esthesia.mp.
28 peripheral nerve block.mp.
29 intravenous regional an$esthesia.mp.
30 systemic local an$esthesia.mp.
31 exp nerve block$/
32 nerve block$.mp.
33 neuroaxial blockade.mp.
34 Anesthesia/ or exp Anesthesia, Intravenous/
35 exp inhalation an$esthesia/
36 inhalation an$esthesia.mp.
37 or/5-36
38 4 and 37

Appendix B: Table of eligible on-going studies

Title	ID	Comparison	Status	Design	Contact	Country
ClinicalTrials.gov						
Variations in Anaesthesia care for hip fracture surgery	NCT02787031	General v Neuraxial	Recruitment completed but no results available	Retrospective observational cohort	Ottawa Hospital Research Institute	Canada
A trial to assess the risk of delirium in older adults undergoing hip fracture surgery with spinal or general anaesthesia	NCT02190903	General v Spinal	Recruitment completed but no results available	Open label randomised trial	Mark D Neuman	USA
Regional versus general anaesthesia for promoting independence after hip fracture	NCT02507505	General v Regional	Recruiting patients	Double blind randomised trial	Mark Powell/ Mark Neuman	USA
Effect of anaesthesia on post-operative delirium in elderly patients undergoing	NCT02213380	General v Regional	Recruiting patients	Open label randomised controlled trial	Ting Li/ Sishi Chen	China

hip fracture surgery						
The safety of anaesthesia management for traumatic hip surgery in elderly	NCT02692989	General v Regional	Ongoing, but not recruiting patients	Retrospective observational cohort	Subhi M Alghanem	Jordan
Anaesthesia and post-operative mortality after proximal femur fractures	NCT02406300	Peripheral nerve block/ General v Subarachnoid anaesthesia	Enrolling patients by invite only	Double blind randomised controlled trial	Raul Carvalho	Portugal
Effect of anaesthesia in fracture healing	NCT02621255	General v Regional	Recruiting patients	Double blind randomised trial	Ebru Biricik	Turkey
Mortality following surgery for proximal femoral fractures	NCT01807039	General vs. Subarachnoid anaesthesia	Study has been completed	Retrospective observational cohort	Petr Štourač	Czech Republic
Practice survey on femoral neck fractures and the incidence of type of anaesthesia on	NCT02198820	General v Regional	**WITHDRAWN	Prospective observational cohort	Eric P Deflandre	Belgium

patient outcome						
ICTRP						
Hemodynamic effects of general and spinal anaesthesia for hip fracture surgery	IRCT201308316280N4	General v Spinal	Completed	Double blind randomised trial	Mohammad Haghighi	Iran

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2-3
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	4-5
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	5
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	5
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	6
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	5
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	5
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	6
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	6
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	6
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	8-12
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	15-25
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	8-12

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	26-29
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	7
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	8-12
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	15-25
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	12-15
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	Figure1,2,3
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	Figure1,2,3
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	26-29
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	NA
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	12-13
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	12-15
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	12-15
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	15

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Title Page

The effect of regional versus general anaesthesia on post-operative delirium in elderly patients undergoing surgery for hip fracture: a systematic review

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Abstract

Background

Older patients with hip fractures who are undergoing surgery are at high risk of significant mortality and morbidity including post-operative delirium. It is unclear whether different types of anaesthesia may reduce the incidence of post-operative delirium.

Objective

This systematic review will investigate the impact of anaesthetic technique on post-operative 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 October 2016. 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 on-going 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 post-operative 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

Eighty-nine studies were included. There was no evidence to suggest that anaesthesia type influences post-operative 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

Whilst there was no evidence to suggest that anaesthesia types influences post-operative delirium, the evidence base is lacking. There is a need to ascertain the impact of type of anaesthesia on outcomes with an adequately powered, methodological rigorous study.

This review is registered with PROSPERO (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 post-operative 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 £2billion. [1] This is projected to rise and reach 100 000 patients a year and costing £3.6-5.6billion by 2033. [2]

Patients undergoing hip fracture surgery are often frail with inter-current 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 (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] Post-operative delirium has been reported to affect between 32%-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 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 peri-operative 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 percent 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 post-operative 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 post-operative outcomes in hip fracture patients are broadly suggestive of improved outcomes [3,5,23,24] and reduced incidence of post-operative delirium in patients having RA. [3,5,22,25,26] However some studies included in these reviews reported use of out-dated 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 (e.g. 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 post-operative 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 (PRISMA) guidelines. [28]

Search strategy and selection criteria

Bibliographic databases (Embase, MEDLINE, CINAHL and the Cochrane Library (CENTRAL)) were searched from inception to October 2016 using a combination of index terms and key words relating to the population, intervention and comparator (see 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 on-going trials. (Appendix B) Endnote 7 (Thomson Reuters) was used to store records and facilitate screening.

Study selection

Studies were eligible for inclusion if they met the following pre-defined 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: post-operative 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 'post-operative delirium' were: anaesthetic technique or drug not considered current standard practice (e.g. outdated anaesthesic agents - halothane, enflurane, xenon); patients undergoing hip fracture surgery alongside other surgery (e.g. multiple trauma injuries); and 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 is 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). 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 (such as study design or timing of assessment) have been highlighted. Where studies did not report sufficient data for inclusion into a Forest plot (e.g. 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 odds ratios; length of stay (days) was reported as a mean difference. Adverse events were tabulated, where possible, according to the post-operative 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 post-operative delirium. The research programme has received input from patient partner and Clinical Research Ambassador Group at Heart of England NHS Foundation Trust.

Results

Of 4223 citations screened, 89 studies met the eligibility criteria (Figure 1). There were 5 randomised controlled trials (RCTs), 28 prospective and 56 retrospective controlled studies.

Eighteen studies reported delirium (4 RCTs, [35–38] 7 prospective [18,39–44]and 7 retrospective studies [45–51]; 52 studies reported mortality (2 RCTs, [35,38] 10 prospective [41,44,52–59] and 40 retrospective studies [4,20,21,31,32,45,48,49,51,60–90]); 21 studies reported length of hospital stay (2 RCTs, [36,38] 5 prospective, [41,44,54,91,92] and 14 retrospective studies [21,48,53,62,64,65,69,72,74–77,89,93]); 25 studies reported adverse events (3 RCTs [35,36,94] 7 prospective [41,42,44,54,91,95,96] and 15 retrospective studies [20,21,45,48,49,62,63,65,69,73–75,89,90,97]); 8 studies reported functional outcome (2 RCTs, [35,36] 3 prospective [41,44,98] and 3 retrospective studies [58,67,99]) and 3 studies reported discharge location (1 prospective [42] and 2 retrospective studies [21,45]).

Ten potentially relevant ongoing trials were identified, with two (NCT02190903 and NCT02213380) planning to measure delirium post-operatively (Appendix B). No interim data was available.

Study, population and intervention characteristics

Given the large number of studies identified, only the 18 studies reporting the primary outcome of post-operative delirium have been described in detail (Table 1).

Primary Outcome

Post-operative delirium

Fourteen studies reporting unadjusted results are represented in the forest plot (Figure 2), including three of the four RCTs. Based on these 14 studies, only one study found a statistically significant benefit in favour of regional anaesthesia [49] and overall there is no evidence of a benefit of one type of anaesthesia over another. Four further studies not represented in the forest plot (one RCT, [35] two retrospective analyses reported as

abstracts only, [47,50] and one prospective study [31]), also found no significant differences in delirium based on Abbreviated Mental Test (AMT) or DSM-IV.

None of the RCTs that were quality assessed reported all relevant details (Table 2a). Details were lacking on the assessment tools used [38] and method of randomisation. [35,36,38] Blinding of outcome assessment was either not undertaken [38] or unclear, [36] with only one RCT having a clear statement on blinding. [35] There appeared to be no loss to follow-up in two RCTs [36,38], but this was unclear for the other RCT. [35] The RCT by Kamitani 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 was not well described (Table 2b). There were no details on characteristics of completers compared with those lost to follow up. There was also a lack of detail on the type of assessment tool used and/or where the cut-off for a "positive" diagnosis of delirium was.

Most studies did not adjust for potential confounders, but four studies [31,41,49,50], one of which is also represented in the above plot [49], did present adjusted results. There was some variation in terms of which confounders were adjusted for (see Table 2b for details). Three studies reported these in full; all included age, gender and ASA score as well as a range of factors including co-morbidities, surgery type and physical functioning. None found that type of anaesthesia was predictive of post-operative delirium.

There was substantial heterogeneity across the 18 studies regarding assessment tools, assessment time-points and anaesthetic protocol. Many assessment tools were poorly defined. Only 6 out of 18 studies used either DSM-IV criteria [18,46,50,51] or AMT. [35,47] Delirium or cognitive impairment was frequently not a primary outcome, but listed as one of several complications.

Secondary outcomes

Mortality

Two RCTs reported mortality (Table 3). One found a small and statistically significant survival benefit at 120 days and one year for GA; but no such benefit was evident at 30 or 90 days follow-up. [38] Ten observational studies reported adjusted results or results based on a matched analysis (Table 3). Two of these [20,62] 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 40 studies (results not shown) reporting unadjusted mortality results only, six [52,56,61,67,68,70] found statistically significant results in favour of RA. The remainder found no statistically significant differences and no consistent trend of benefit.

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-one [21,36,38,41,44,48,53,54,62,64,65,69,72,74–77,89,91–93] studies reported length of hospital stay; nine could be included in a forest plot (Figure 3, supplementary data). There was no difference in length of hospital stay based on one RCT. [38] The adjusted results, based on three retrospective studies, [21,62,75] showed a slight trend towards a shorter length of stay with RA; whilst this was statistically significant in two studies, [21,62] 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, [65,69,74] and two finding a benefit from RA. [76,91]

Of the remaining twelve studies [36,41,44,48,53,54,64,72,77,89,92,100], neither the RCT [36] nor the four prospective studies [41,44,54,92] showed any significant differences. Results from the seven retrospective studies were also inconsistent (three

studies [53,64,77] reported no difference, two studies [48,72] found a statistically significant benefit for RA [72] and one [89] a statistically significant benefit for GA.)

Most studies reported mean length of stay, but some also reported the median, which may be more appropriate. Of ten studies [21,36,44,48,53,64,65,77,89,92] reporting the median, eight studies [21,36,44,53,64,65,77,92] found no statistically significant differences. Two studies found a statistically significant difference in medians favouring RA [48] or GA [89] respectively.

Adverse Events

Twenty-five studies reported adverse events (Table 4, supplementary data). 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 (8 studies). [21,35,45,54,62,63,75,89] 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 [62], respiratory failure [20,62] and 'overall pulmonary' adverse events [20,48]). There were no differences in occurrences of pneumonia [35,45,49,89] or hypoxia. [69,91] The most commonly reported cardiovascular adverse events were myocardial infarction [45,62,89] and thromboembolic events. [35,54,63,75,89] No differences were found for myocardial infarction. [45,49,62,69,89] Three studies [63,75,89] 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 (e.g. fewer incidences of 'all complications', [48,63] ITU admissions, [62] stroke [62] or requirement for blood transfusion). Three studies [94,96,97] found higher incidences of hypotension in the GA group.

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

Functional outcomes

Eight studies reported functional outcomes using a variety of outcome measures. A small RCT reported a significantly quicker time to ambulation in the RA group (3.3 days RA vs 5.5 days GA). [35] A further RCT [36] reported a statistically significant earlier discharge time from PACU (post-anaesthesia care unit) in the RA group (RA 15 (5-30) min vs. GA 55 (15-80) min, p=0.0005). No differences were found in the non-randomised studies regarding time to ambulation, [98,99] walking speed, [58] time to rise from chair, [41] mean Barthel's score [67] or ambulation at 3, 6 and 12 month post-surgery. [44] 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

Three non-randomised studies described discharge locations of patients following hip fracture. [21,42,45] One study with only 14 patients reported that more patients returned home in the RA group [45]. However, two larger studies [21,97] 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 post-operative 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 one year post-operatively. 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 was limited for functional outcomes and discharge data. Two small RCTs suggested a benefit from RA for immediate post-anaesthetic mobilization. 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 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 the WHO's ICD-10 classification of diseases. [7,101] However in clinical practice the criteria can be difficult to apply [102] and tools such as the confusion assessment method (CAM), Delirium Rating Scale revised-98 (DRS-R-98), Neelon and Champagne (NEECHAM) confusion scale [103] or 4AT have been advocated as validated screening tools. (4 'A's' Test) [6,102,104] No consensus exists in the literature as to which tool should be the gold standard. [6,105,106] 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. [107] No significant differences were found for the incidence of post-operative delirium, based on four 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 pre-dispose the patient to post-operative delirium. [11,108,109] Pre-existing patient risk factors including age > 70 years, pre-existing cognitive impairment, history of post-operative delirium, visual impairment, cerebrovascular disease and renal impairment [110,111] 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. [111] Specific perioperative risk factors include intraoperative blood loss, post-operative transfusions and severe acute pain. [112,113] The studies that adjusted for confounders and reported delirium [31,41,49,50] found no association between type of anaesthesia and post-operative delirium. Confounders adjusted for included demographics, ASA classification, co-morbidities, nutritional status, fracture type, pre-operative blood transfusion and readmission. [41,49,50] 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, intra-operative hypotension and sedation, can also influence outcome but were less frequently included as variables. Given the lack of consistency across studies in 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 [3,114] and acute pain is a well-recognised precipitating factor of delirium but both were poorly reported. Whilst 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 means that many studies were likely underpowered. [35,36,45,91]. 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 hip fracture patients demonstrated increased risk of death associated with intraoperative hypotension. In our review, three studies [94,96,97] examined hypotension all of which found higher incidences of hypotension in the GA group. Four studies [49,63,94,97] 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 sub-groups. It is possible that there are some patients who may, in some circumstances, benefit from RA compared to 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 post-operatively due to age-related physiological decline, multiple co-morbidities and polypharmacy. [115] Principles of care for older patients in the peri-operative setting should employ an anaesthetic technique that leads to rapid recovery, dosing of drugs specific to individual pharmacokinetic variation and appropriate pain management strategies. [116] Most recently, the European Society of Anaesthestiology consensus-guideline on post-

operative 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. [117] 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 health care providers. Future research examining post-operative 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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Data sharing statement: There are no unpublished data from this review.

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 1985 DENMARK	General: ASA 1: 2 ASA 2: 14 ASA 3: 4 Spinal: ASA 1: 2 ASA 2: 15 ASA 3: 3	General (n=20) v 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 2003 ITALY	General: ASA 2: 7 ASA 3: 8 Spinal: ASA 2: 6 ASA 3: 9	General (n=15) v 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 2003 JAPAN	ASA not reported. Comparable 'physical status' between GA and RA groups	General (n=21) v 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
Parker & Griffiths 2015 UK	General: ASA Grade 1 or 2: 98	General (n=164) v Spinal (n=158)	Patients with acute hip fracture	Patients over 49 years of age Mean age General: 83.0 years (range 59-99)	Primary: -Mortality Secondary: -Surgical outcomes

	Spinal: ASA Grade 1 or 2: 94.9			Spinal: 82.9 years (range 52-105) M/F: 87/235	-General complications -Hospital stay
PROSPECTIVE STUDIES					
Atay 2012 TURKEY	Unable to obtain full translation.	General (n=30) v Spinal (n=40)	Patients with hip fractures	Patients aged 60 years and over Mean age M/F:	-Postoperative delirium -Postoperative cognitive function
Bitsch 2006 DENMARK	ASA 1=2 ASA 2=33 ASA 3=51 ASA 4=10	General (n=13) v Regional (n=83)	Hip fracture patients	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 pre, intra and post-operative cognitive dysfunction
Bjorkelund 2010 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) v 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	General:	General (n=311) v	Patients with an acute	Age 65 years and older	-Complications (in-hospital and

2000 USA	ASA 1-2: 105 ASA 3-4: 194 Spinal: ASA 1-2: 109 ASA 3-4: 309	Spinal (n=430)	hip fracture	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	surgical) -Functioning (daily, social, mental)
Ilango 2015 AUSTRALIA	Not reported	General (n=167) v Spinal (n=151)	Hip fracture patients	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 -Post-discharge mortality
Juliebo 2009 NORWAY	ASA 1 or 2 = 182	General (n=20) v 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 1999 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) v 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
RETROSPECTIVE STUDIES					

Bellelli 2013 ITALY Abstract	Not reported	General v Spinal v 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
Kim 2013 KOREA	ASA 1: 6 ASA 2: 311 ASA 3: 189	General (n=246) v Spinal (n=249) v Epidural (n=11)	Hip fracture surgery patients	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 2006 FINLAND	ASA 3: 8 ASA 4: 6	General (n=3) v 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 -Post-op discharge location -Pain management -Haemodynamics -Mental status -Mobilisation -Mortality
Luger 2014 AUSTRIA	Mean ASA: Group 1 (post-op delirium): 2.9 +/- 0.6 Group 2 (unspecified cognitive dysfunction): 88.4 +/- 5.2 Control: 2.8 +/- 0.6	General (n=116) v 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 and post nursing home stay -Comorbidities -Perioperative Complications

Michael 2014 UK Abstract	Not reported	General v Spinal (704 patients included in analysis, but unclear how many received which anaesthesia)	Hip fracture patients	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	Pre and post-operative cognitive function
O'Hara 2000 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) v Regional (n=3219, spinal n=3078 and epidural n=141)	Hip fracture patients	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
Shih 2010 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 is American Society of Anesthiologists Physical Status Classification System; SD is standard deviation. SEM is standard error of the mean

Table 2a: Quality assessment of RCT studies reporting delirium

AMT is Abbreviated mental test
CAM is Confusion assessment method
DRS is Delirium Rating Scale
DSM-IV is Diagnostic and Statistical Manual of Mental Disorders, 4th Edition
MMSE is Mini mental state examination

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								
Parker & Griffiths 2015 N=322	UNCLEAR	LOW	Groups similar for all baseline characteristics measured, except for proportion of male patients (35% in GA group, 19% in RA group).	HIGH	LOW	Unclear-no details	Unclear	UNCLEAR
	Randomisation undertaken by opening sealed opaque numbered envelopes prepared by a person independent to the trial.			No blinding of outcome assessors	Appears post-operative delirium measured in all patients allocated to respective treatments			Insufficient information to permit judgement.
Casati 2003	UNCLEAR	LOW	Groups similar for all baseline characteristics measured.	UNCLEAR	LOW	MMSE good validity for cognitive function	No	UNCLEAR
N=30	*"Using a sealed envelope technique, patients were randomly allocated…"*			Clinical criteria for patient's discharge applied by staff blinded to anaesthetic technique-but no details for applying MMSE.	MMSE for all 30 patients at 1 and 7 days.			Insufficient information to permit judgement.
Bigler1985	UNCLEAR	UNCLEAR	Groups similar for all baseline characteristics measured except for vasopressors being administered more frequently in spinal group.	LOW	UNCLEAR	AMT good validity for cognitive dysfunction	No	UNCLEAR
N=40	No details (other than *"patients randomly allocated"*)	No details		Surgeon undertaking AMT unaware of anaesthesia given	No details on proportion that AMT was undertaken in at 7 days and 3 months.			Insufficient information to permit judgement.

NB Quality assessment was not performed for Kamitani [37] as a full translation was not available. Blinding of patients and surgeons/anaesthetists not possible.

Table 2b: Quality assessment of observational studies reporting delirium

AMT is Abbreviated mental test
CAM is Confusion assessment method
DRS is Delirium Rating Scale
DSM-IV is Diagnostic and Statistical Manual of Mental Disorders, 4th Edition
MMSE is Mini mental state examination

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						
Atay 2010 (Abstract only in English)		Likely LOW for adjusted data. Multivariate analysis-variables not stated in abstract.		LOW DSM-IV, MMSE and DRS	Yes	
Belleli 2013 (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 multivariate analysis for confounders(age, gender, Charlson Comorbidity Index, ASA score, pre-fracture disability in Activities of Daily Living (Katz's ADL Index), and pre-fracture dementia)	No details	DSM-IV-TR criteria		Patients with incomplete data in medical records were excluded from this study. Proportion not stated.
Bitsch 2006	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 day 4 and 7 respectively. Nursing home patients considered stable and those achieving independent ambulation discharged earlier.

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
Björkelund 2010	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
Gilbert 2000	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 multivariate analyses for all outcomes. Variables were age, sex, race, comorbidities, pre-fracture physical function, ASA score, fracture type, surgical procedure and physiologic status.	No details	Mental confusion not further defined; MMSE		No details-only how many included in final analysis
Ilango 2015	LOW	HIGH	UNCLEAR	HIGH	Unclear	UNCLEAR
PROSPECTIVE	All hip fracture patients admitted over a year	Similar baseline characteristics (age, gender, pre-op 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.
Juliebo 2009	LOW	HIGH	LOW	LOW	Yes	HIGH
PROSPECTIVE	All eligible hip fracture patients 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	CAM		No statistically significant differences between patients enrolled and not enrolled for age/sex. No details on the 79 who refused to take part. Pre-operative delirium an exclusion criterion; 127/364 (35%) included not assessed pre-operatively and excluded. No details on their characteristics.

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
			patients			
Kim 2013	LOW	HIGH	UNCLEAR	LOW	Yes	LOW
RETROSPECTIVE	Consecutive sample of hip fracture patients	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
Kontinnen 2006	LOW	HIGH	UNCLEAR	UNCLEAR	Unclear	UNCLEAR
RETROSPECTIVE	All patients over 100 years old undergoing emergency Surgery in one hospital	No adjusted analyses.	No details	Not clearly defined		No details on missing data/exclusions.
Koval 1999	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 pre-determined.	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 2014	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 2014 (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.

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 2000	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 multivariate 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
Shih 2010	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.

NB Quality assessment was not performed for Atay [31] as a full translation was not available.

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 1985	In-hospital	1/19	1/19	**RR=1.00 (0.07, 14.6)**		No statistically significant difference in in-hospital mortality.
Parker & Griffiths 2015	30 day	8/156	5/153	**RR=1.54 (0.52, 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 & Griffiths 2015	90 day	12/152	12/146	**RR=0.96 (0.45, 2.07)**		
Parker & Griffiths 2015	120 day	12/152	15/143	**RR=0.77 (0.61, 0.91)**		
Parker & Griffiths 2015	1 year	19/145	32/126	**RR=0.57 (0.34, 0.96)**		
Prospective cohort						
Withey 1995	1 year	Total only reported: 303	Total only reported: 161	Not reported.	**OR 1.28 (0.76, 2.14)**	No statistically significant difference in mortality (adjusted data).
Zhao 2015	Unknown	65/166	22/238	Not reported.	**OR 0.687 (0.248, 1.906)**	No statistically significant difference in mortality (adjusted data).
Retrospective cohort						
Chu 2015	In-hospital	1363/ 50681	1107/ 50937	Not reported.	**OR 1.24 (1.15, 1.35)**	Statistically significant difference in mortality (adjusted data) in favour of RA.
Neuman 2012	In-hospital	325/12579	110/5144	Not reported.	**OR 0.710 (0.541, 0.932)**	Statistically significant difference in in-hospital mortality in favour of RA (OR<1 indicates benefit from RA).
Patorno 2014	In-hospital	1477/66345	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 2000	7 day	82/6124	53/3076	**OR 0.80 (0.56-1.13)**	**OR 0.90 (0.59-1.39)**	No statistically significant difference in mortality (adjusted or unadjusted).
Basques 2015	30 day	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 2000	30 day	272/5934	174/2955	**OR 0.80 (0.66-0.97)**	**OR 1.08 (0.84-1.38)**	No statistically significant difference in mortality (adjusted or unadjusted).
Seitz 2014	30 day	1044/7774	1450/10705	**RR 0.99 (0.92, 1.07)** (calculated	**RR 1.04 (0.94, 1.15)** (calculated based on raw	No statistically significant difference in 30 day mortality (matched or unmatched).

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
				based on raw data reported)	data reported)	
Whiting 2015	30 day	Total only stated: 5840	Total only stated:1924	Not reported.	Spinal and regional nerve blocks **OR 1.18 (0.91, 1.53)** Spinal only **OR 1.20 (0.92–1.56)** Regional only **OR 1.22 (0.54–2.76)**	No statistically significant difference in 30 day mortality (adjusted data).

OR is odds ratio; RR is relative risk

Table 4: Summary findings table of studies reporting adverse events. *OR = Odds Ratio GA vs. RA; NR = not reported; NS = not significant

POMS categories	Study	Adverse event description	GA	RA	Summary statistic*/p-value
Pulmonary	Basques 2015	*Ventilatory support*	58/7253 (0.8%)	13/2589 (0.5%)	NR
		Pneumonia	261/7253 (3.6%)	108/2589 (4.2%)	NR
	Bigler 1985	*Pneumonia*	2/20	1/20	NR
	Chu 2015	*Respiratory Failure*	868/52043 (1.61%)	328/52044 (0.63%)	OR 2.71 (95%CI 2.38 to 3.01), p<0.001 Favours RA
		Ventilatory support	4008/52043 (7.70%)	338/52044 (1.44%)	OR 6.08 (95%CI 5.59 to 6.61), p<0.001 Favours RA
	Konttinen 2006	*Pneumonia*	0/3	2/11	NR
	Le Liu 2014	*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 2012	*Overall pulmonary*	17/235 (6%)	1/73 (1%)	OR 2.2 (95%CI 0.7 to 7.2) P=0.0841 Favours RA
	Naja 2000	*Hypoxia*	2/30 (6%)	0/30 (0%)	NR
	Neuman 2012	*Overall pulmonary*	1030/12904 (8.1%)	359/5254 (6.8%)	P=0.005 Favours RA
		Respiratory Failure	1040/12904 (5%)	178/5254 (3.4%)	P<0.0001 Favours RA

	O'Hara 2000	*Pneumonia*	174/6206 (2.8%)	84/3219 (2.6%)	OR 1.21 (95%CI 0.87 to 1.68) NS
	Shih 2010	*Overall pulmonary*	11/167 (6.6%)	3/168 (1.8%)	P<0.03 Favours RA
Cardiovascular	Basques 2015	*Myocardial infarction*	137/7253 (1.9%)	49/2859 (1.9%)	NR
		Thromboembolic	138/7253 (1.9%)	25/2589 (1.0%)	NR
	Bigler 1985	*Cardiovascular decompensation*	1/20	1/20	NR
		Pulmonary embolism	1/20	1/20	NR
	Chu 2015	*Myocardial infarction*	188/52043 (0.36%)	169/52044 (0.32%)	OR 1.11 (95%CI 0.9 o 1.37), p=0.31 NS
	Fields 2015	*Thromboembolism*	1.64%	0.72%	P=0.004 Favours RA
	Konttinen 2006	*Myocardial infarction*	0/3	1/11	NR
	Le Wendling 2012	*All cardiovascular complications*	NR	NR	OR 1.7 (95%CI 0.4 to 6.3) NS
	Seitz 2014	*Deep vein thrombosis*	47/8818 (0.5%)	41/12155 (0.3%)	P=0.03 NS when matched
		Pulmonary Embolism	100/8818 (1.1%)	93/12155 (0.8%)	P=0.006 NS when matched
	Sutcliffe 1994	*Deep vein thrombosis*	16/950 (1.7%)	14/383 (3.7%)	P<0.05 NS
		Pulmonary Embolism	NR	NR	NS
Infectious	Bigler 1985	*Wound infection*	1/20	0/20	NR
	Fields 2015	*Urinary Tract infection*	5.76%	8.87%	P<0.0001 Favours GA

	Rashid 2013	*Urinary Tract infection*	NR	NR	NS
	Basques 2015	*Wound infection*	94/7253 (1.3%)	39/2589 (1.5%)	NS
Renal	Basques 2015	*Acute Renal Failure*	29/7253 (0.4%)	10/2589 (0.4%)	NS
	Bigler 1985	*Urinary retention*	4/20	5/20	NS
	Chu 2015	*Acute Renal Failure*	78/52043 (0.15%)	56/52044 (0.11%)	P=0.06 NS
	Naja 2000	*Acute Renal Failure*	2/30 (6%)	0/30 (0%)	NS
Overall complications	Gilbert 2000	*Serious medical complications*	55/311 (17.7%)	79/430 (18.4%)	OR 0.92 (95%CI 0.61 to 1.4) NS
	Gilbert 2000 Whiting 2015	*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 1.16-1.77) NS
	Whiting 2015 Fields 2015	*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 2012	*All complications*	NR	NR	NS
	Ilango 2015	*All complications*	NR	NR	NS
	Koval 1999	*All complications*	41/362 (11.3%)	32/280 (11.4%)	NS
	Le Liu 2014	*All complications*	17/72 (23.6%)	50/145 (34.5%)	P=0.165 NS

	Le Wendling 2012	*All complications*	NR	NR	OR 1.7 (95%CI 0.7 to 4.1) NS
	Radcliffe 2013	*All complications*	22%	19%	Log regression model p=0.002 Favours RA
	Shih 2010	*All complications*	21/167 (12.6%)	9/168 (5.4%)	P<0.02 Favours RA
	Chu 2015	ITU admissions	5743/52043 (11.03%)	3205/52044 (6.16%)	OR 1.95 (95%CI 1.87 to 2.05), p<0.001 Favours RA
Specific complications	Chu 2015	ITU stay >3 days	1206/52043 (2.32%)	411/52044 (0.79%)	P<0.001 Favours RA
	Baumgarten 2012	Pressure ulcers	10/328 (3.0%)	18/313 (5.8%)	OR 1.3 (1.0-1.6) Favours GA
	Casati 2003	Hypotension requiring crystalloid infusion	12/15 (80%)	7/15 (46%)	P=0.05 NS
	Maia 2014	Intraoperative hypotension	25/50	80/173	P=0.014 Favours RA
	Minville 2008	Intraoperative hypotension	35/42 (83%)	74/109 (68%)	NS
	Messina 2013	Haemodynamic changes first 10min	Mean arterial blood pressure, heart rate, systemic vascular resistance index changes. More disturbance in GA		Favours RA
	Basques 2015	Blood transfusion	2843/7253 (39.2%)	851/2589 (32.9%)	Matched OR 1.34 (1.22 to 1.49), p<0.001 Favours RA
	Fields 2015	Blood transfusion	45.49%	39.34%	P<0.0001

					Favours RA
	Minville 2008	Blood transfusion	23%	4%	P<0.05 Favours RA
	Shih 2010	Blood loss	Median 250 (0-1600) ml	Median 200 (0-1200) ml	P=0.01 Favours RA
	Chu 2015	Stroke	840/52043 (1.61%)	717/52044 (1.38%)	OR 1.18 (95%CI 1.07 to 1.31), p=0.001 Favours RA
	Le Liu 2014	Stroke	5/72 (5.9%)	4/145 (2.8%)	P=0.145 NS

POMS is Post-operative morbidity survey
OR is odds ratio
NS is not significant; NR is not reported

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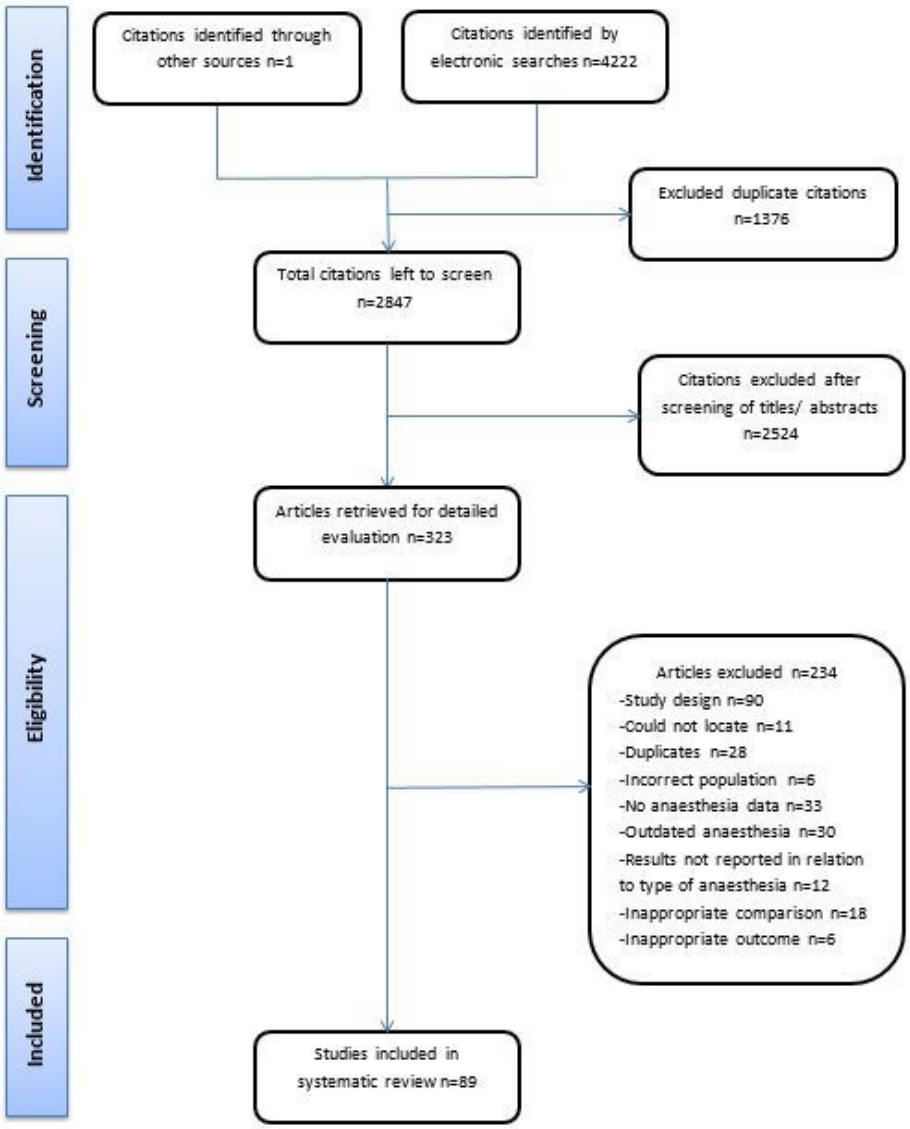
Figure Legends

Figure 1: PRISMA Flow Diagram. Legend: The PRIMSA diagram details our search and selection process applied during the review.

Figure 2: Forest plot of studies reporting the unadjusted relative risk of post-operative delirium with GA compared to spinal anaesthesia. Some studies are represented more than once to show results for different definitions of delirium, or for different assessment time-points. RR= relative risk, CI=confidence interval, MMSE= mini mental state examination, CAM= confusion assessment method, DSM-IV= Diagnostic and statistical manual of mental disorders 5, UCD = unspecified cognitive dysfunction.

Figure 3: Forest plot of studies reporting length of hospital stay. WMD=weighted mean difference, CI=confidence interval



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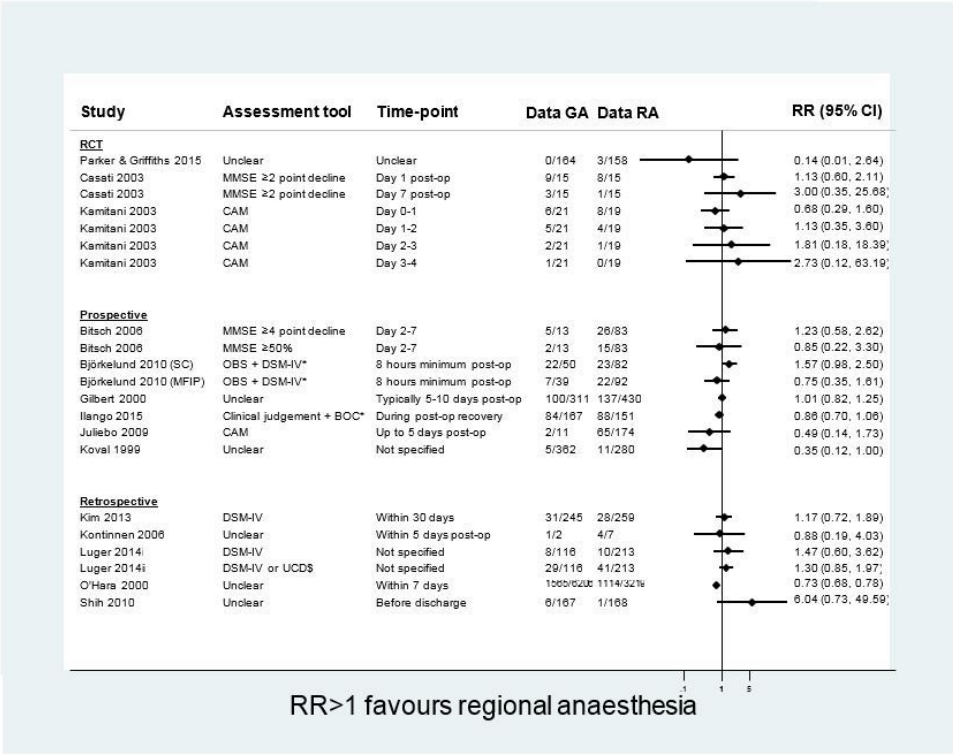

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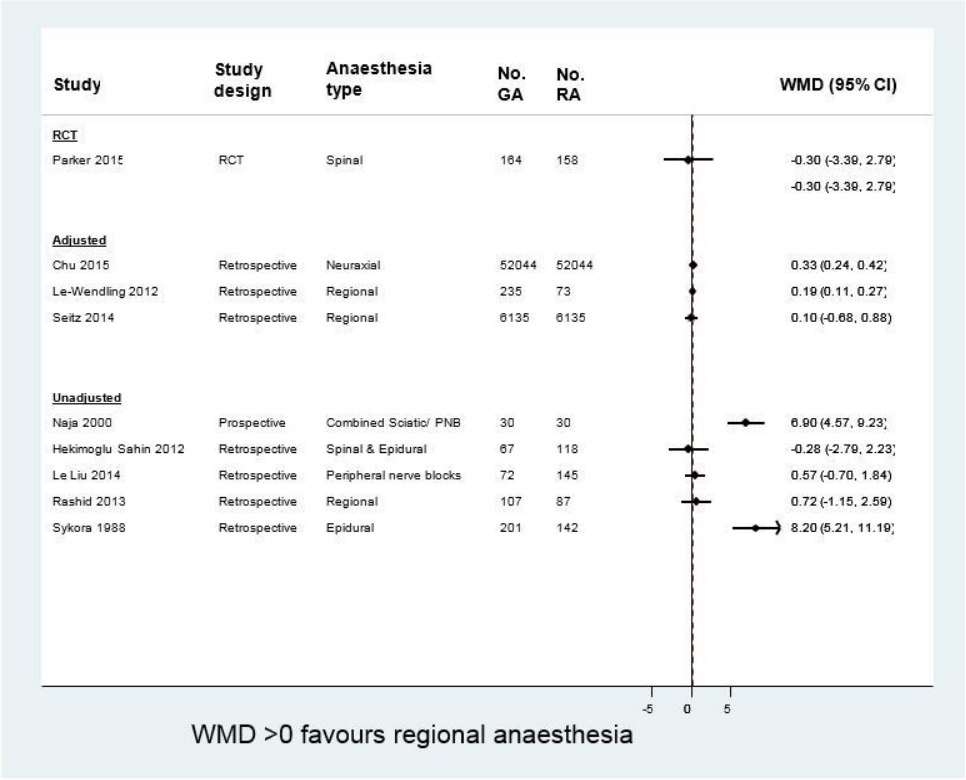

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Appendix A: Example of search strategy

1 exp Hip fracture/
2 hip fracture.mp.
3 (fracture$ adj2 (hip or femur$ or femor$)).tw.
4 or/1-3
5 exp an$esthesia/
6 an$esthesia.mp.
7 (anesthe$ or anaesthe$).tw.
8 an$ethetic.mp.
9 exp anesthetics/
10 exp general an$esthesia/
11 general an$esthesia.mp.
12 Anesthesia/ (43366)
13 exp Anesthesia, General/
14 general an$esthesia.mp.
15 sedation.mp. (28516)
16 exp regional an$esthesia/
17 regional an$esthesia.mp.
18 peripheral an$esthesia.mp.
19 central blockade.mp.
20 central block.mp.
21 exp spinal an$esthesia/
22 spinal an$esthesia.mp.
23 exp epidural an$esthesia/
24 epidural an$esthesia.mp.
25 exp local an$esthesia/
26 local an$esthesia.mp.
27 infiltrative an$esthesia.mp.
28 peripheral nerve block.mp.
29 intravenous regional an$esthesia.mp.
30 systemic local an$esthesia.mp.
31 exp nerve block$/
32 nerve block$.mp.
33 neuroaxial blockade.mp.
34 Anesthesia/ or exp Anesthesia, Intravenous/
35 exp inhalation an$esthesia/
36 inhalation an$esthesia.mp.
37 or/5-36
38 4 and 37

Appendix B: Table of eligible on-going studies

Title	ID	Comparison	Status	Design	Contact	Country
ClinicalTrials.gov						
Variations in Anaesthesia care for hip fracture surgery	NCT02787031	General v Neuraxial	Recruitment completed but no results available	Retrospective observational cohort	Ottawa Hospital Research Institute	Canada
A trial to assess the risk of delirium in older adults undergoing hip fracture surgery with spinal or general anaesthesia	NCT02190903	General v Spinal	Recruitment completed but no results available	Open label randomised trial	Mark D Neuman	USA
Regional versus general anaesthesia for promoting independence after hip fracture	NCT02507505	General v Regional	Recruiting patients	Double blind randomised trial	Mark Powell/ Mark Neuman	USA
Effect of anaesthesia on post-operative delirium in elderly patients undergoing	NCT02213380	General v Regional	Recruiting patients	Open label randomised controlled trial	ing Li/ Sishi hen	China

hip fracture surgery						
The safety of anaesthesia management for traumatic hip surgery in elderly	NCT02692989	General v Regional	Ongoing, but not recruiting patients	Retrospective observational cohort	Doubhi M Alghanem	Jordan
Anaesthesia and post-operative mortality after proximal femur fractures	NCT02406300	Peripheral nerve block/ General v Subarachnoid anaesthesia	Enrolling patients by invite only	Double blind randomised controlled trial	Raul Carvalho	Portugal
Effect of anaesthesia in fracture healing	NCT02621255	General v Regional	Recruiting patients	Double blind randomised trial	Ebru Biricik	Turkey
Mortality following surgery for proximal femoral fractures	NCT01807039	General vs. Subarachnoid anaesthesia	Study has been completed	Retrospective observational cohort	Petr Štourač	Czech Republic
Practice survey on femoral neck fractures and the incidence of type of anaesthesia on	NCT02198820	General v Regional	**WITHDRAWN	Prospective observational cohort	Eric P Deflandre	Belgium

patient outcome						
ICTRP						
Hemodynamic effects of general and spinal anaesthesia for hip fracture surgery	IRCT201308316280N4	General v Spinal	Completed	Double blind randomised trial	Mohammad Haghighi	Iran

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2,3
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	5,6
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	6
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	6
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	6
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	6
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Appendix A
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	7
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	7
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	8
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	23-27
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	8
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	8

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	23-27
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	NA
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	8, Figure 1
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	18-22
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	23-27
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	Table 2a/b,3,4, Figure 2,3
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	NA
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	23-27
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	NA
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	13,14
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	15, 16
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	16
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	16

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TITLE PAGE

The effect of regional versus general anaesthesia on post-operative 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 post-operative delirium. It is unclear whether different types of anaesthesia may reduce the incidence of post-operative delirium. This systematic review will investigate the impact of anaesthetic technique on post-operative 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 on-going 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 post-operative 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 post-operative 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

Whilst there was no evidence to suggest that anaesthesia types influences post-operative delirium, the evidence base is lacking. There is a need to ascertain the impact of type of anaesthesia on outcomes with an adequately powered, methodological rigorous study.

This review is registered with PROSPERO (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 post-operative 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 £2billion. [1] This is projected to rise and reach 100 000 patients a year and costing £3.6-5.6billion by 2033. [2]

Patients undergoing hip fracture surgery are often frail with inter-current 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 (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] Post-operative delirium has been reported to affect between 32%-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 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 peri-operative 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 percent 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 post-operative 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 post-operative outcomes in hip fracture patients are broadly suggestive of improved outcomes [3,5,23,24] and reduced incidence of post-operative delirium in patients having RA. [3,5,22,25,26] However some studies included in these reviews reported use of out-dated 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 (e.g. 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 post-operative 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 (PRISMA) 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 key words relating to the population, intervention and comparator (see 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 on-going trials. (Appendix B) Endnote 7 (Thomson Reuters) was used to store records and facilitate screening.

Study selection

Studies were eligible for inclusion if they met the following pre-defined 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: post-operative 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 'post-operative delirium' were: anaesthetic technique or drug not considered current standard practice (e.g. outdated anaesthesic agents - halothane, enflurane, xenon); patients undergoing hip fracture surgery alongside other surgery (e.g. multiple trauma injuries); and 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 is 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). 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 (such as study design or timing of assessment) have been highlighted. Where studies did not report sufficient data for inclusion into a Forest plot (e.g. 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 odds ratios; length of stay (days) was reported as a mean difference. Adverse events were tabulated, where possible, according to the post-operative 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 post-operative delirium. The research programme has received input from patient partner and Clinical Research Ambassador Group at Heart of England NHS 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 [42,45,56–65] and 45 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 [21,51,57,68,70,71,75,78,80–83,95,104,105,98,99]); 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]) and 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 post-operatively (Appendix B). No interim data was available.

Study, population and intervention characteristics

Given the large number of studies identified, only the 22 studies reporting the primary outcome of post-operative delirium have been described in detail (Table 1).

Primary Outcome

Post-operative delirium

Fifteen studies reporting unadjusted results are represented in the forest plot (Figure 2), including four of the five RCTs. One RCT[Neuman] was a small pilot study with 12 patients. Based on these 15 studies, only one study found a statistically significant benefit in favour of regional anaesthesia [49] and overall there is no evidence of a benefit of one type of anaesthesia over another. Five further studies not represented in

the forest plot (one RCT, [35] two retrospective analyses reported as abstracts only, [50,53] and one prospective study [31]) also found no significant differences in delirium based, where stated, on Abbreviated Mental Test (AMT) or DSM-IV (one RCT, [35] two retrospective analyses reported as abstracts only, [50,53] and two prospective studies [31,46], one of which [46] was reported as an abstract).

One retrospective study [55] found a statistically significant difference in immediate (within 24 hours) delirium with GA for both adjusted and unadjusted results (based on CAM); there was no difference for delayed delirium. A further study [47] also found that delirium was more common with GA, but this did not remain statistically significant on multivariate analysis. The assessment tool for delirium was not stated. Four other studies [42,52,53,115] also presented adjusted results, two of which are also represented in the above plot [42,52](Figure 2). None found that type of anaesthesia was predictive of post-operative delirium.

None of the RCTs that were quality assessed reported all relevant details (Table 2a). Details were lacking on the assessment tools used [38] and method of randomisation. [35,36,38,39] Blinding of outcome assessment was either not undertaken [38] or unclear, [36] although two RCTs had a clear statement on blinding. [35,39] 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 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 was not well described (Table 2b). There was variation in terms of which confounders were adjusted for. Five studies reported details; all included ASA score as well as a range of factors including age, gender, co-morbidities, surgery type, time to surgery and physical functioning. There were no details on characteristics of completers compared with those lost to follow up. There was also a lack of detail on the type of assessment tool used and/or where the cut-off for a "positive" diagnosis of delirium was. This lack of detail is likely to be due in part to the fact that several studies were reported in abstract form only.

Most studies did not adjust for potential confounders, but four studies [31,42,52,53], one of which is also represented in the above plot [52], did present adjusted results. There was some variation in terms of which confounders were adjusted for (see Table 2b for details). Three studies reported these in full; all included age, gender and ASA score as well as a range of factors including co-morbidities, surgery type and physical functioning. None found that type of anaesthesia was predictive of post-operative delirium.

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 [18,31,49,53,54] or AMT. [35,50] Delirium or cognitive impairment was frequently not a primary outcome, but listed as one of several complications.

Secondary outcomes

Mortality

Two RCTs reported mortality (Table 3). One found a small and statistically significant survival benefit at 120 days and one year for GA; but no such benefit was evident at 30 or 90 days 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 and no consistent trend of benefit.

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 [21,36,38,42,45,51,57,58,68,70,71,75,78,80–83,95,101–105,98,99] 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] The matched/adjusted results, based on three retrospective studies, [21,68,81] showed a slight trend towards a shorter length of stay with RA; whilst 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]

Of the remaining sixteen studies [36,42,45,51,57,58,70,78,83,95,102–105,98,99], neither the RCT [36] nor the five prospective studies [42,45,58,102,103] showed any significant differences. Results from the ten retrospective studies were also inconsistent (three studies [57,70,83] reported no difference, four studies [51,78,104,99] found a statistically significant benefit for RA [78] (only for proportion staying up to 6 days [104]) and one [95] 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 LOS 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 twelve studies [21,36,45,51,57,70,71,83,95,102,103,99] 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 favouring RA [51,99] or GA [95] respectively.

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 (e.g. fewer incidences of 'all complications', [51,69] 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 post-operative 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 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 was slower to be discharged from PACU (Mean time to discharge GA 35.04min (SD 3.39) vs RA 41.26min (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 month 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 to RA (16695 patients, return home adjusted OR 0.91 (95%CI 0.84, 0.97); healthcare facility admission OR 1.10 (95%CI 1.03, 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, 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 post-operative 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 one year post-operatively. 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 was limited for functional outcomes and discharge data. Two small RCTs suggested

a benefit from RA for immediate post-anaesthetic mobilization. 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 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 the WHO's ICD-10 classification of diseases. [7,116] However in clinical practice the criteria can be difficult to apply [117] and tools such as the confusion assessment method (CAM), Delirium Rating Scale revised-98 (DRS-R-98), Neelon and Champagne (NEECHAM) confusion scale [118] or 4AT have been advocated as validated screening tools. (4 'A's' Test) [6,117,119] No consensus exists in the literature as to which tool should be the gold standard. [6,120,121] 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. [122] No significant differences were found for the incidence of post-operative delirium, based on four 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 pre-dispose the patient to post-operative

delirium. [11,123,124] Pre-existing patient risk factors including age > 70 years, pre-existing cognitive impairment, history of post-operative delirium, visual impairment, cerebrovascular disease and renal impairment [125,126] 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. [126] Specific perioperative risk factors include intraoperative blood loss, post-operative transfusions and severe acute pain. [127,128] The studies that adjusted for confounders and reported delirium [31,42,52,53] found no association between type of anaesthesia and post-operative delirium. Confounders adjusted for included demographics, ASA classification, co-morbidities, nutritional status, fracture type, pre-operative 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, intra-operative hypotension and sedation, can also influence outcome but were less frequently included as variables. Given the lack of consistency across studies in 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 [3,129] and acute pain is a well-recognised precipitating factor of delirium but both were poorly reported. Whilst 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 means 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 hip fracture patients 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 sub-groups. It is possible that there are some patients who may, in some circumstances, benefit from RA compared to 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 post-operatively due to age-related physiological decline, multiple co-morbidities and polypharmacy. [130] Principles of care for older patients in the peri-operative setting should employ an anaesthetic technique that leads to rapid recovery, dosing of drugs specific to individual pharmacokinetic variation and appropriate pain management strategies. [131] Most recently, the European Society of Anaesthestiology consensus-guideline on post-operative 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. [132] 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 health care providers.

Future research examining post-operative 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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Conflicts of interest

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Author Contributions

All authors have made substantial contributions to the manuscript. JY: the conception and design of the study, VP/RC/JD/JY acquisition of data, analysis and interpretation of data, VP/RC/JD/JY drafting the article or revising it critically for important intellectual content, VP/RC/JD/JY final approval of the version to be submitted. We would like to thank Mrs Preeti Pulgari for her assistance with the review.

Data sharing statement

There are no unpublished data from this review.

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 1985 DENMARK	General: ASA 1: 2 ASA 2: 14 ASA 3: 4 Spinal: ASA 1: 2 ASA 2: 15 ASA 3: 3	General (n=20) v 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 2003 ITALY	General: ASA 2: 7 ASA 3: 8 Spinal: ASA 2: 6 ASA 3: 9	General (n=15) v 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 2003 JAPAN	ASA not reported. Comparable 'physical status' between GA and RA groups	General (n=21) v 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 2016	No details	General (n=6) v spinal (n=6)	Femoral neck or pertrochanteric hip fracture surgery	Patients aged 18 and over Median age(GA): 62.5 (57-88)	Primary: -Postoperative delirium

USA Feasibility study/Letter				Median age (RA): 80.5 (62-92) M/F: 9/3	Secondary: -Mortality
Parker & Griffiths 2015 UK	General: ASA Grade 1 or 2: 98 Spinal: ASA Grade 1 or 2: 94.9	General (n=164) v 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 2012 TURKEY	Unable to obtain full translation.	General (n=30) v Spinal (n=40)	Patients with hip fractures	Patients aged 60 years and over Mean age M/F:	-Postoperative delirium -Postoperative cognitive function
Bitsch 2006 DENMARK	ASA 1=2 ASA 2=33 ASA 3=51 ASA 4=10	General (n=13) v Regional (n=83)	Hip fracture patients	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 pre, intra and post-operative cognitive dysfunction
Bjorkelund 2010 SWEDEN	Intervention group (new care plan): ASA 1=17 ASA 2=59 ASA 3=48 ASA 4=7 Control group	General (n=89) v 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

	(existing care plan: ASA 1=10 ASA 2=77 ASA 3=42 ASA 4=3				
Gilbert 2000 USA	General: ASA 1-2: 105 ASA 3-4: 194 Spinal: ASA 1-2: 109 ASA 3-4: 309	General (n=311) v 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 2015 AUSTRALIA	Not reported	General (n=167) v Spinal (n=151)	Hip fracture patients	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 -Post-discharge mortality
Juliebo 2009 NORWAY	ASA 1 or 2 = 182	General (n=20) v 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 1999	General: ASA 1 or 2: 236	General (n=362) v Spinal (n=280)	Patients who sustained a hip fracture	Patients 65 years of age and older	-Inpatient medical complication rate -Hospital mortality rate

USA	ASA 3 or 4: 120 Spinal: ASA 1 or 2: 131 ASA 3 or 4: 137			Mean age General: 78.5 years Spinal: 81.0 years M/F: 129/513	-1 year mortality rate
Mohamed 2017 UK Abstract	No details	Total n=85 Numbers in GA, GA +block, spinal and spinal + block groups not stated	Hip fracture patients	No details.	-Delirium
Ojeda 2018 Spain Abstract	No details	Total n=303 Numbers in GA and RA groups not stated.	Hip fracture patients	Patients aged 70 years and over. Mean age 84 (SD 6) M/F: 39%/61%	-Delirium -In-hospital complications -Mortality
RETROSPECTIVE STUDIES					
Bellelli 2013 ITALY Abstract	Not reported	General v Spinal v 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 2017 Republic of Korea	For those who developed delirium: ASA 2: 10 ASA 3: 97	Total n=356 For those who developed delirium: General (n=81) v Spinal (n=29)	Patients with femoral neck fracture	Patients aged 70 years and over M/F: 66/290	-Immediate and delayed delirium

	ASA 4: 3				
Kim 2013 KOREA	ASA 1: 6 ASA 2: 311 ASA 3: 189	General (n=246) v Spinal (n=249) v Epidural (n=11)	Hip fracture surgery patients	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 2006 FINLAND	ASA 3: 8 ASA 4: 6	General (n=3) v 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 -Post-op discharge location -Pain management -Haemodynamics -Mental status -Mobilisation -Mortality
Luger 2014 AUSTRIA	Mean ASA: Group 1 (post-op delirium): 2.9 +/- 0.6 Group 2 (unspecified cognitive dysfunction): 88.4 +/- 5.2 Control: 2.8 +/- 0.6	General (n=116) v 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 and post nursing home stay -Comorbidities -Perioperative Complications
Michael 2014 UK Abstract	Not reported	General v Spinal (704 patients included in analysis, but unclear how many received which anaesthesia)	Hip fracture patients	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	Pre and post-operative cognitive function

				M/F: 178/526	
O'Hara 2000 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) v Regional (n=3219, spinal n=3078 and epidural n=141)	Hip fracture patients	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
Shih 2010 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 is American Society of Anesthiologists Physical Status Classification System; SD is standard deviation. SEM is standard error of the mean

Table 2a: Quality assessment of RCT studies reporting delirium

AMT is Abbreviated mental test
CAM is Confusion assessment method
DRS is Delirium Rating Scale
DSM-IV is Diagnostic and Statistical Manual of Mental Disorders, 4th Edition
MMSE is Mini mental state examination

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 2016	UNCLEAR	UNCLEAR	Groups similar for age, gender and comorbidities.	LOW	LOW	CAM good validity for identifying delirium	Yes	UNCLEAR
N=12 (Letter)	No details.			Blinded research coordinators assessed outcomes.	Results reported for all patients.			Insufficient information to permit judgement.
Parker & Griffiths 2015 N=322	UNCLEAR	LOW	Groups similar for all baseline characteristics measured, except for proportion of male patients (35% in GA group, 19% in RA group).	HIGH	LOW	Unclear-no details	Unclear	UNCLEAR
	Randomisation undertaken by opening sealed opaque numbered envelopes prepared by a person independent to the trial.			No blinding of outcome assessors	Appears post-operative delirium measured in all patients allocated to respective treatments			Insufficient information to permit judgement.
Casati 2003	UNCLEAR	LOW	Groups similar for all baseline characteristics measured.	UNCLEAR	LOW	MMSE good validity for cognitive function	No	UNCLEAR
N=30	*"Using a sealed envelope technique, patients were randomly allocated…"*			Clinical criteria for patient's discharge applied by staff blinded to anaesthetic technique-but no details for applying MMSE.	MMSE for all 30 patients at 1 and 7 days.			Insufficient information to permit judgement.
Bigler1985	UNCLEAR	UNCLEAR	Groups similar for all baseline characteristics measured except for vasopressors being administered more frequently in spinal group.	LOW	UNCLEAR	AMT good validity for cognitive dysfunction	No	UNCLEAR
N=40	No details (other than *"patients randomly allocated"*)	No details		Surgeon undertaking AMT unaware of anaesthesia given	No details on proportion that AMT was undertaken in at 7 days and 3 months.			Insufficient information to permit judgement.

NB Quality assessment was not performed for Kamitani [37] as a full translation was not available. Blinding of patients and surgeons/anaesthetists not possible.

Table 2b: Quality assessment of observational studies reporting delirium

AMT is Abbreviated mental test
CAM is Confusion assessment method
DRS is Delirium Rating Scale
DSM-IV is Diagnostic and Statistical Manual of Mental Disorders, 4th Edition
MMSE is Mini mental state examination

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 2013 (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 multivariate analysis for confounders(age, gender, Charlson Comorbidity Index, ASA score, pre-fracture disability in Activities of Daily Living (Katz's ADL Index), and pre-fracture dementia)	No details	DSM-IV-TR criteria		Patients with incomplete data in medical records were excluded from this study. Proportion not stated.
Bitsch 2006	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 day 4 and 7 respectively. Nursing home patients considered stable and those achieving independent ambulation discharged earlier.
Björkelund 2010	LOW	HIGH	UNCLEAR	LOW	No for Organic Brain Syndrome Scale Yes for DSM-	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		Appears to be no loss to follow-up from included patients for delirium assessment

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
				criteria	IV criteria	
Choi 2017	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 2000	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 multivariate analyses for all outcomes. Variables were age, sex, race, comorbidities, pre-fracture physical function, ASA score, fracture type, surgical procedure and physiologic status.	No details	Mental confusion not further defined; MMSE		No details-only how many included in final analysis
Ilango 2015	LOW	HIGH	UNCLEAR	HIGH	Unclear	UNCLEAR
PROSPECTIVE	All hip fracture patients admitted over a year	Similar baseline characteristics (age, gender, pre-op 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.
Juliebo 2009	LOW	HIGH	LOW	LOW	Yes	HIGH
PROSPECTIVE	All eligible hip fracture patients 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	Staff performing assessments were not involved in the care of	CAM		No statistically significant differences between patients enrolled and not enrolled for age/sex. No details on the 79 who refused to take part. Pre-operative delirium an exclusion criterion; 127/364 (35%) included not assessed pre-operatively

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
		anaesthetic as a variable.	enrolled patients			and excluded. No details on their characteristics.
Kim 2013	LOW	HIGH	UNCLEAR	LOW	Yes	LOW
RETROSPECTIVE	Consecutive sample of hip fracture patients	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
Kontinnen 2006	LOW	HIGH	UNCLEAR	UNCLEAR	Unclear	UNCLEAR
RETROSPECTIVE	All patients over 100 years old undergoing emergency Surgery in one hospital	No adjusted analyses.	No details	Not clearly defined		No details on missing data/exclusions.
Koval 1999	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 pre-determined.	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 2014	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 2014 (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 2016	UNCLEAR	HIGH	UNCLEAR	UNCLEAR	Unclear	LOW

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
(Abstract)						
PROSPECTIVE	Patients from 6 hospitals; no further details	No details on baseline characteristics between groups. No adjusted analyses.	No details.	No details.		Data from enrolled patients analysed.
O'Hara 2000	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 multivariate 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 *(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 multivariate analysis were time to surgery, ASA status and comorbidities).	No details.	No details		No details.
Shih 2010	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.

NB Quality assessment was not performed for Atay [31] as a full translation was not available.

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 1985	In-hospital	1/19	1/19	**RR=1.00 (0.07, 14.6)**		No statistically significant difference in in-hospital mortality.
Parker & Griffiths 2015	30 day	8/156	5/153	**RR=1.54 (0.52, 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 & Griffiths 2015	90 day	12/152	12/146	**RR=0.96 (0.45, 2.07)**		
Parker & Griffiths 2015	120 day	12/152	15/143	**RR=0.77 (0.61, 0.91)**		
Parker & Griffiths 2015	1 year	19/145	32/126	**RR=0.57 (0.34, 0.96)**		
Prospective cohort						
Withey 1995	1 year	Total only reported: 303	Total only reported: 161	Not reported.	**OR 1.28 (0.76, 2.14)**	No statistically significant difference in mortality (adjusted data).
Zhao 2015	Unknown	65/166	22/238	Not reported.	**OR 0.687 (0.248, 1.906)**	No statistically significant difference in mortality (adjusted data).
Retrospective cohort						
Chu 2015	In-hospital	1363/ 50681	1107/ 50937	Not reported.	**OR 1.24 (1.15, 1.35)**	Statistically significant difference in mortality (adjusted data) in favour of RA.
Neuman 2012	In-hospital	325/12579	110/5144	Not reported.	**OR 0.710 (0.541, 0.932)**	Statistically significant difference in in-hospital mortality in favour of RA (OR<1 indicates benefit from RA).
Patorno 2014	In-hospital	1477/66345	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 2000	7 day	82/6124	53/3076	**OR 0.80 (0.56-1.13)**	**OR 0.90 (0.59-1.39)**	No statistically significant difference in mortality (adjusted or unadjusted).
Basques 2015	30 day	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 2000	30 day	272/5934	174/2955	**OR 0.80 (0.66-0.97)**	**OR 1.08 (0.84-1.38)**	No statistically significant difference in mortality (adjusted or unadjusted).
Qiu 2018	In hospital	226/9629	111/6597	Not reported	**HR 1.38 (1.10-1.73)**	No statistically significant difference in mortality
Seitz 2014	30 day	1044/7774	1450/10705	**RR 0.99 (0.92,**	**RR 1.04 (0.94, 1.15)**	No statistically significant difference in 30 day mortality

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
				1.07) (calculated based on raw data reported)	(calculated based on raw data reported)	(matched or unmatched).
Whiting 2015	30 day	Total only stated: 5840	Total only stated:1924	Not reported.	Spinal and regional nerve blocks **OR 1.18 (0.91, 1.53)** Spinal only **OR 1.20 (0.92–1.56)** Regional only **OR 1.22 (0.54–2.76)**	No statistically significant difference in 30 day mortality (adjusted data).

OR is odds ratio; RR is relative risk

Table 4: Summary findings table of studies reporting adverse events. *OR = Odds Ratio GA vs. RA; NR = not reported; NS = not significant

POMS categories	Study	Adverse event description	GA	RA	Summary statistic*/p-value
Pulmonary	Basques 2015	*Ventilatory support*	58/7253 (0.8%)	13/2589 (0.5%)	NR
		Pneumonia	261/7253 (3.6%)	108/2589 (4.2%)	NR
	Bigler 1985	*Pneumonia*	2/20	1/20	NR
	Chu 2015	*Respiratory Failure*	868/52043 (1.61%)	328/52044 (0.63%)	OR 2.71 (95%CI 2.38 to 3.01), p<0.001 Favours RA
		Ventilatory support	4008/52043 (7.70%)	338/52044 (1.44%)	OR 6.08 (95%CI 5.59 to 6.61), p<0.001 Favours RA
	Konttinen 2006	*Pneumonia*	0/3	2/11	NR
	Le Liu 2014	*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 2012	*Overall pulmonary*	17/235 (6%)	1/73 (1%)	OR 2.2 (95%CI 0.7 to 7.2) P=0.0841 Favours RA
	Naja 2000	*Hypoxia*	2/30 (6%)	0/30 (0%)	NR
	Neuman 2012	*Overall pulmonary*	1030/12904 (8.1%)	359/5254 (6.8%)	P=0.005 Favours RA
		Respiratory Failure	1040/12904 (5%)	178/5254 (3.4%)	P<0.0001 Favours RA

	O'Hara 2000	*Pneumonia*	174/6206 (2.8%)	84/3219 (2.6%)	OR 1.21 (95%CI 0.87 to 1.68) NS
	Shih 2010	*Overall pulmonary*	11/167 (6.6%)	3/168 (1.8%)	P<0.03 Favours RA
Cardiovascular	Basques 2015	*Myocardial infarction*	137/7253 (1.9%)	49/2859 (1.9%)	NR
		Thromboembolic	138/7253 (1.9%)	25/2589 (1.0%)	NR
	Bigler 1985	*Cardiovascular decompensation*	1/20	1/20	NR
		Pulmonary embolism	1/20	1/20	NR
	Chu 2015	*Myocardial infarction*	188/52043 (0.36%)	169/52044 (0.32%)	OR 1.11 (95%CI 0.9 o 1.37), p=0.31 NS
	Fields 2015	*Thromboembolism*	1.64%	0.72%	P=0.004 Favours RA
	Konttinen 2006	*Myocardial infarction*	0/3	1/11	NR
	Neuman 2016	*Myocardial infarction*	1/6	0/6	NR
	Le Wendling 2012	*All cardiovascular complications*	NR	NR	OR 1.7 (95%CI 0.4 to 6.3) NS
	Seitz 2014	*Deep vein thrombosis*	47/8818 (0.5%)	41/12155 (0.3%)	P=0.03 NS when matched
		Pulmonary Embolism	100/8818 (1.1%)	93/12155 (0.8%)	P=0.006 NS when matched
	Sutcliffe 1994	*Deep vein thrombosis*	16/950 (1.7%)	14/383 (3.7%)	P<0.05 NS
		Pulmonary Embolism	NR	NR	NS
Infectious	Bigler 1985	*Wound infection*	1/20	0/20	NR

	Fields 2015	*Urinary Tract infection*	5.76%	8.87%	P<0.0001 Favours GA
	Rashid 2013	*Urinary Tract infection*	NR	NR	NS
	Basques 2015	*Wound infection*	94/7253 (1.3%)	39/2589 (1.5%)	NS
Renal	Basques 2015	*Acute Renal Failure*	29/7253 (0.4%)	10/2589 (0.4%)	NS
	Bigler 1985	*Urinary retention*	4/20	5/20	NS
	Chu 2015	*Acute Renal Failure*	78/52043 (0.15%)	56/52044 (0.11%)	P=0.06 NS
	Naja 2000	*Acute Renal Failure*	2/30 (6%)	0/30 (0%)	NS
Overall complications	Gilbert 2000	*Serious medical complications*	55/311 (17.7%)	79/430 (18.4%)	OR 0.92 (95%CI 0.61 to 1.4) NS
	Gilbert 2000 Whiting 2015	*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 1.16-1.77) NS
	Whiting 2015 Fields 2015	*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 2012	*All complications*	NR	NR	NS
	Ilango 2015	*All complications*	NR	NR	NS
	Koval 1999	*All complications*	41/362 (11.3%)	32/280 (11.4%)	NS

	Le Liu 2014	*All complications*	17/72 (23.6%)	50/145 (34.5%)	P=0.165 NS
	Le Wendling 2012	*All complications*	NR	NR	OR 1.7 (95%CI 0.7 to 4.1) NS
	Radcliffe 2013	*All complications*	22%	19%	Log regression model p=0.002 Favours RA
	Shih 2010	*All complications*	21/167 (12.6%)	9/168 (5.4%)	P<0.02 Favours RA
	Chu 2015	ITU admissions	5743/52043 (11.03%)	3205/52044 (6.16%)	OR 1.95 (95%CI 1.87 to 2.05), p<0.001 Favours RA
Specific complications	Chu 2015	ITU stay >3 days	1206/52043 (2.32%)	411/52044 (0.79%)	P<0.001 Favours RA
	Baumgarten 2012	Pressure ulcers	10/328 (3.0%)	18/313 (5.8%)	OR 1.3 (1.0-1.6) Favours GA
	Casati 2003	Hypotension requiring crystalloid infusion	12/15 (80%)	7/15 (46%)	P=0.05 NS
	Maia 2014	Intraoperative hypotension	25/50	80/173	P=0.014 Favours RA
	Minville 2008	Intraoperative hypotension	35/42 (83%)	74/109 (68%)	NS
	Gadsden 2016	Intraoperative hypotension	569/745	1144/1528	Favours RA P<0.0001
	Messina 2013	Haemodynamic changes first 10min	Mean arterial blood pressure, heart rate, systemic vascular resistance index changes. More disturbance in GA		Favours RA
	Basques	Blood transfusion	2843/725	851/2589	Matched OR 1.34 (1.22 to 1.49),

	2015		3 (39.2%)	(32.9%)	p<0.001 Favours RA
	Fields 2015	Blood transfusion	45.49%	39.34%	P<0.0001 Favours RA
	Minville 2008	Blood transfusion	23%	4%	P<0.05 Favours RA
	Shih 2010	Blood loss	Median 250 (0-1600) ml	Median 200 (0-1200) ml	P=0.01 Favours RA
	Chu 2015	Stroke	840/52043 (1.61%)	717/52044 (1.38%)	OR 1.18 (95%CI 1.07 to 1.31), p=0.001 Favours RA
	Le Liu 2014	Stroke	5/72 (5.9%)	4/145 (2.8%)	P=0.145 NS

POMS is Post-operative morbidity survey
OR is odds ratio
NS is not significant; NR is not reported

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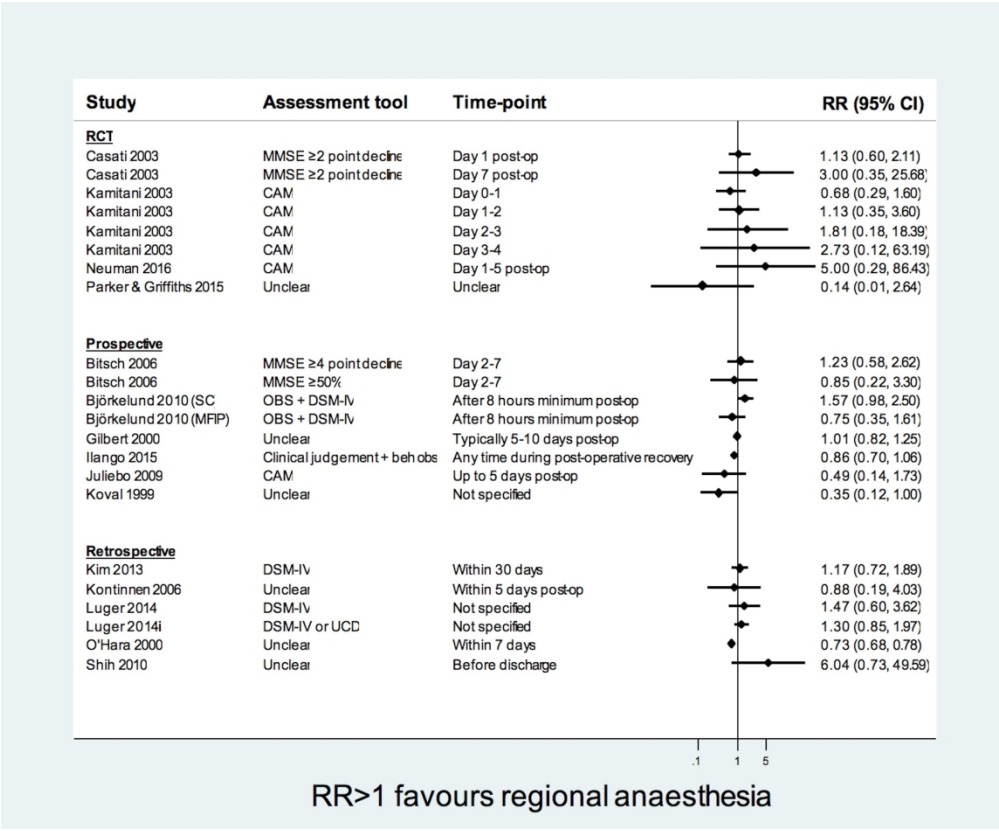
Figure Legends

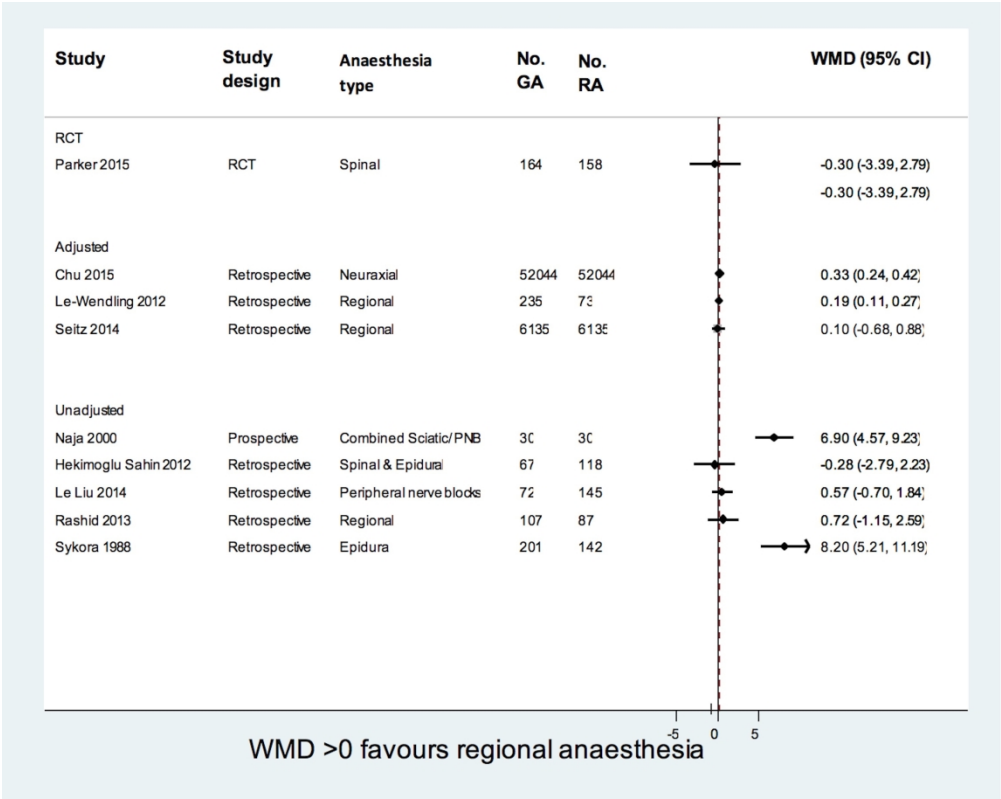
Figure 1: PRISMA Flow Diagram. Legend: The PRIMSA diagram details our search and selection process applied during the review.

Figure 2: Forest plot of studies reporting the unadjusted relative risk of post-operative delirium with GA compared to spinal anaesthesia. Some studies are represented more than once to show results for different definitions of delirium, or for different assessment time-points. RR= relative risk, CI=confidence interval, MMSE= mini mental state examination, CAM= confusion assessment method, DSM-IV= Diagnostic and statistical manual of mental disorders 5, UCD = unspecified cognitive dysfunction.

Figure 3: Forest plot of studies reporting length of hospital stay. WMD=weighted mean difference, CI=confidence interval



248x205mm (300 x 300 DPI)



252x201mm (300 x 300 DPI)

Appendix A: Example of search strategy

1 exp Hip fracture/
2 hip fracture.mp.
3 (fracture$ adj2 (hip or femur$ or femor$)).tw.
4 or/1-3
5 exp an$esthesia/
6 an$esthesia.mp.
7 (anesthe$ or anaesthe$).tw.
8 an$ethetic.mp.
9 exp anesthetics/
10 exp general an$esthesia/
11 general an$esthesia.mp.
12 Anesthesia/ (43366)
13 exp Anesthesia, General/
14 general an$esthesia.mp.
15 sedation.mp. (28516)
16 exp regional an$esthesia/
17 regional an$esthesia.mp.
18 peripheral an$esthesia.mp.
19 central blockade.mp.
20 central block.mp.
21 exp spinal an$esthesia/
22 spinal an$esthesia.mp.
23 exp epidural an$esthesia/
24 epidural an$esthesia.mp.
25 exp local an$esthesia/
26 local an$esthesia.mp.
27 infiltrative an$esthesia.mp.
28 peripheral nerve block.mp.
29 intravenous regional an$esthesia.mp.
30 systemic local an$esthesia.mp.
31 exp nerve block$/
32 nerve block$.mp.
33 neuroaxial blockade.mp.
34 Anesthesia/ or exp Anesthesia, Intravenous/
35 exp inhalation an$esthesia/
36 inhalation an$esthesia.mp.
37 or/5-36
38 4 and 37

Appendix B: Table of eligible on-going studies

Title	ID	Comparison	Status	Design	Contact	Country
ClinicalTrials.gov						
Comparison of Combined Lumbar and Sacral Plexus Block With Sedation Versus General Endotracheal Anesthesia on Postoperative Outcomes in Elderly Patients Undergoing Hip Fracture Surgery(CLSB-HIPELD): Rationale and Design of a Prospective, Multicenter, Randomized Controlled Trial	NCT03318133	General vs Combined lumbar plexus and sacral plexus block(CLSB)	Not yet recruiting patients	Double blind randomised trial	Xiaofeng Wang	China
The Comparative Effects of Regional or General Anesthesia on the Prognosis of Hip	NCT03116490	General vs Regional	Recruiting patients	Prospective observational cohort	ging Li	China

Fracture Surgery on Elderly Patients						
Variations in Anaesthesia care for hip fracture surgery	NCT02787031	General vs Neuraxial	Recruitment completed but no results available	Retrospective observational cohort	Ottawa Hospital Research Institute	Canada
Regional versus general anaesthesia for promoting independence after hip fracture	NCT02507505	General vs Regional	Recruiting patients	Double blind randomised trial	Mark Powell/ Mark Neuman	USA
Effect of anaesthesia on post-operative delirium in elderly patients undergoing hip fracture surgery	NCT02213380	General vs Regional	Recruiting patients	Open label randomised controlled trial	ing Li/ Sishi Chen	China
The safety of anaesthesia management for traumatic hip surgery in elderly	NCT02692989	General vs Regional	Ongoing, but not recruiting patients	Retrospective observational cohort	ubhi M Alghanem	Jordan
Anaesthesia and post-operative mortality after proximal femur fractures	NCT02406300	Peripheral nerve block/ General vs Subarachnoid anaesthesia	Enrolling patients by invite only	Double blind randomised controlled trial	Raul Carvalho	Portugal

Effect of anaesthesia in fracture healing	NCT02621255	General vs Regional	Recruiting patients	Double blind randomised trial	Ebru Biricik	Turkey
Mortality following surgery for proximal femoral fractures	NCT01807039	General vs. Subarachnoid anaesthesia	Study has been completed	Retrospective observational cohort	Petr Štourač	Czech Republic
ICTRP						
Hypobaric Lateral Spinal Anesthesia Versus General Anesthesia: Hemodynamic Stability and Short Term Cardiovascular Complications in Elderly Patients Undergoing Hip Fracture Surgery.	NCTNCT03373864	General vs Hypobaric lateral spinal	Recruiting patients	Randomised controlled trial	Claire Delsuc	France
Effects of different anesthesia methods on postoperative complications and hospital mortality in elderly patients	ChiCTR-RRC-17013545	General vs Regional	Recruiting patients	Prospective cohort	Xu Mao	China

with hip fracture						
Hemodynamic effects of general and spinal anaesthesia for hip fracture surgery	IRCT201308316280N4	General vs Spinal	Completed	Double blind randomised trial	Mohammad Daghighi	Iran
ISRCTN						
A Feasibility Randomised Controlled Trial to compare REgional versus General Anaesthesia in Reducing Delirium in patients with Hip Fractures	ISRCTN15165914	General vs Regional	Recruiting patients	Randomised controlled trial	Joyce Yeung	UK

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2,3
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	5,6
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	6
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	6
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	6
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	6
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Appendix A
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	7
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	7
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	8
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	23-27
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	8
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	8

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	23-27
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	NA
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	8, Figure 1
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	18-22
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	23-27
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	Table 2a/b,3,4, Figure 2,3
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	NA
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	23-27
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	NA
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	13,14
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	15, 16
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	16
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	16

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The effect of regional versus general anaesthesia on post-operative delirium in elderly patients undergoing surgery for hip fracture: a systematic review

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TITLE PAGE

The effect of regional versus general anaesthesia on post-operative 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 post-operative delirium. It is unclear whether different types of anaesthesia may reduce the incidence of post-operative delirium. This systematic review will investigate the impact of anaesthetic technique on post-operative 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 on-going 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 post-operative 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 post-operative 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

Whilst there was no evidence to suggest that anaesthesia types influences post-operative 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.

This review is registered with PROSPERO (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 post-operative 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 £2billion. [1] This is projected to rise and reach 100 000 patients a year and costing £3.6-5.6billion by 2033. [2]

Patients undergoing hip fracture surgery are often frail with inter-current 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 (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] Post-operative delirium has been reported to affect between 32%-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 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 peri-operative 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 percent 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 post-operative 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 post-operative outcomes in hip fracture patients are broadly suggestive of improved outcomes [3,5,23,24] and reduced incidence of post-operative delirium in patients having RA. [3,5,22,25,26] However some studies included in these reviews reported use of out-dated 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 (e.g. 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 post-operative 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 (PRISMA) 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 key words relating to the population, intervention and comparator (see 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 on-going trials. (Appendix B) Endnote 7 (Thomson Reuters) was used to store records and facilitate screening.

Study selection

Studies were eligible for inclusion if they met the following pre-defined 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: post-operative 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 'post-operative delirium' were: anaesthetic technique or drug not considered current standard practice (e.g. outdated anaesthesic agents - halothane, enflurane, xenon); patients undergoing hip fracture surgery alongside other surgery (e.g. multiple trauma injuries); and 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 is 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 (such as study design or timing of assessment) have been highlighted. Where studies did not report sufficient data for inclusion into a Forest plot (e.g. 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 odds ratios; length of stay (days) was reported as a mean difference. Adverse events were tabulated, where possible, according to the post-operative 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 post-operative delirium. The research programme has received input from patient partner and Clinical Research Ambassador Group at Heart of England NHS 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 [42,45,56–65] 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 [21,51,57,68,70,71,75,78,80–83,95,104,105,98,99]); 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]) and 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 post-operatively (Appendix B). No interim data was available.

Study, population and intervention characteristics

Given the large number of studies identified, only the 22 studies reporting the primary outcome of post-operative delirium have been described in detail (Table 1).

Primary Outcome

Post-operative delirium

Fifteen studies (4 RCTs [36-39], 6 prospective studies [18, 41- 45] and 5 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 24hrs of surgery) compared to RA but GA was not associated with delayed delirium (after 24hrs 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 AMT. [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 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 ASA score, age, gender, co-morbidities, 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 one year for GA; but no such benefit was evident at 30 or 90 days 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; whilst 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 was not available from the remaining sixteen studies due to lack of data (3 studies [57, 70, 98] were abstracts only, 6 studies [36, 42, 78, 99, 104, 105] did not provide raw data, 2 studies [45, 95] did not linked data with types of anaesthesia, and 5 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] did not show any significant differences. Results from the ten retrospective studies were also inconsistent: three studies [57,70,83] reported no difference, four studies [51,78,104,99] 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 LOS 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 twelve studies [21,36,45,51,57,70,71,83,95,102,103,99] 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 (e.g. fewer incidences of 'all complications', [51,69] 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 post-operative 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 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 was slower to be discharged from PACU (Mean time to discharge GA 35.04min (SD 3.39) vs RA 41.26min (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 month 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 to RA (16695 patients, return home adjusted OR 0.91 (95%CI 0.84, 0.97); healthcare facility admission OR 1.10 (95%CI 1.03, 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, 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 post-operative 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 one year post-operatively. 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 was limited for functional outcomes and discharge data. Two small RCTs suggested a benefit from RA for immediate post-anaesthetic mobilization. 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 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 the 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 (CAM), Delirium Rating Scale revised-98 (DRS-R-98), Neelon and Champagne (NEECHAM) confusion scale [117] or 4AT have been advocated as validated screening tools. (4 'A's' Test) [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 post-operative delirium, based on four 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 pre-dispose the patient to post-operative delirium. [11,122,123] Pre-existing patient risk factors including age > 70 years, pre-existing cognitive impairment, history of post-operative 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, post-operative 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 post-operative delirium. Confounders adjusted for included demographics, ASA classification, co-morbidities, nutritional status, fracture type, pre-operative 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, intra-operative hypotension and sedation, can also influence outcome but were less frequently included as variables. Given the lack of consistency across studies in 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. Whilst 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 means 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 hip fracture patients 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 sub-groups. It is possible that there are some patients who may, in some circumstances, benefit from RA compared to 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 post-operatively due to age-related physiological decline, multiple co-morbidities and polypharmacy. [129] Principles of care for older patients in the peri-operative 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, the European Society of Anaesthestiology consensus-guideline on post-operative 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 health care providers. Future research examining post-operative 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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Conflicts of interest

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Author Contributions

All authors have made substantial contributions to the manuscript. JY: the conception and design of the study, VP/RC/JD/JY acquisition of data, analysis and interpretation of data, VP/RC/JD/JY drafting the article or revising it critically for important intellectual content, VP/RC/JD/JY final approval of the version to be submitted. We would like to thank Mrs Preeti Pulgari for her assistance with the review.

Data sharing statement

There are no unpublished data from this review.

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 1985 DENMARK	General: ASA 1: 2 ASA 2: 14 ASA 3: 4 Spinal: ASA 1: 2 ASA 2: 15 ASA 3: 3	General (n=20) v 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 2003 ITALY	General: ASA 2: 7 ASA 3: 8 Spinal: ASA 2: 6 ASA 3: 9	General (n=15) v 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 2003 JAPAN	ASA not reported. Comparable 'physical status' between GA and RA groups	General (n=21) v 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 2016 USA	No details	General (n=6) v 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)	Primary: -Postoperative delirium Secondary:

Feasibility study/Letter				M/F: 9/3	-Mortality
Parker & Griffiths 2015 UK	General: ASA Grade 1 or 2: 98 Spinal: ASA Grade 1 or 2: 94.9	General (n=164) v 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 2012 TURKEY	Unable to obtain full translation.	General (n=30) v Spinal (n=40)	Patients with hip fractures	Patients aged 60 years and over Mean age M/F:	-Postoperative delirium -Postoperative cognitive function
Bitsch 2006 DENMARK	ASA 1=2 ASA 2=33 ASA 3=51 ASA 4=10	General (n=13) v Regional (n=83)	Hip fracture patients	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 pre, intra and post-operative cognitive dysfunction
Bjorkelund 2010 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	General (n=89) v 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

	ASA 2=77 ASA 3=42 ASA 4=3				
Gilbert 2000 USA	General: ASA 1-2: 105 ASA 3-4: 194 Spinal: ASA 1-2: 109 ASA 3-4: 309	General (n=311) v 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 2015 AUSTRALIA	Not reported	General (n=167) v Spinal (n=151)	Hip fracture patients	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 -Post-discharge mortality
Juliebo 2009 NORWAY	ASA 1 or 2 = 182	General (n=20) v 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 1999 USA	General: ASA 1 or 2: 236 ASA 3 or 4: 120 Spinal:	General (n=362) v 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

	ASA 1 or 2: 131 ASA 3 or 4: 137				
Mohamed 2017 UK Abstract	No details	Total n=85 Numbers in GA, GA +block, spinal and spinal + block groups not stated	Hip fracture patients	No details.	-Delirium
Ojeda 2018 Spain Abstract	No details	Total n=303 Numbers in GA and RA groups not stated.	Hip fracture patients	Patients aged 70 years and over. Mean age 84 (SD 6) M/F: 39%/61%	-Delirium -In-hospital complications -Mortality
RETROSPECTIVE STUDIES					
Bellelli 2013 ITALY Abstract	Not reported	General v Spinal v 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 2017 Republic of Korea	For those who developed delirium: ASA 2: 10 ASA 3: 97	Total n=356 For those who developed delirium: General (n=81) v Spinal (n=29)	Patients with femoral neck fracture	Patients aged 70 years and over M/F: 66/290	-Immediate and delayed delirium

	ASA 4: 3				
Kim 2013 KOREA	ASA 1: 6 ASA 2: 311 ASA 3: 189	General (n=246) v Spinal (n=249) v Epidural (n=11)	Hip fracture surgery patients	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 2006 FINLAND	ASA 3: 8 ASA 4: 6	General (n=3) v 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 -Post-op discharge location -Pain management -Haemodynamics -Mental status -Mobilisation -Mortality
Luger 2014 AUSTRIA	Mean ASA: Group 1 (post-op delirium): 2.9 +/- 0.6 Group 2 (unspecified cognitive dysfunction): 88.4 +/- 5.2 Control: 2.8 +/- 0.6	General (n=116) v 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 and post nursing home stay -Comorbidities -Perioperative Complications
Michael 2014 UK Abstract	Not reported	General v Spinal (704 patients included in analysis, but unclear how many received which anaesthesia)	Hip fracture patients	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	Pre and post-operative cognitive function

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O'Hara 2000 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) v Regional (n=3219, spinal n=3078 and epidural n=141)	Hip fracture patients	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
Shih 2010 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 is American Society of Anesthiologists Physical Status Classification System; SD is standard deviation. SEM is standard error of the mean

Table 2a: Quality assessment of RCT studies reporting delirium

AMT is Abbreviated mental test
CAM is Confusion assessment method
DRS is Delirium Rating Scale
DSM-IV is Diagnostic and Statistical Manual of Mental Disorders, 4th Edition
MMSE is Mini mental state examination

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 2016	UNCLEAR	UNCLEAR	Groups similar for age, gender and comorbidities.	LOW	LOW	CAM good validity for identifying delirium	Yes	UNCLEAR
N=12 (Letter)	No details.			Blinded research coordinators assessed outcomes.	Results reported for all patients.			Insufficient information to permit judgement.
Parker & Griffiths 2015 N=322	UNCLEAR	LOW	Groups similar for all baseline characteristics measured, except for proportion of male patients (35% in GA group, 19% in RA group).	HIGH	LOW	Unclear-no details	Unclear	UNCLEAR
	Randomisation undertaken by opening sealed opaque numbered envelopes prepared by a person independent to the trial.			No blinding of outcome assessors	Appears post-operative delirium measured in all patients allocated to respective treatments			Insufficient information to permit judgement.
Casati 2003	UNCLEAR	LOW	Groups similar for all baseline characteristics measured.	UNCLEAR	LOW	MMSE good validity for cognitive function	No	UNCLEAR
N=30	*"Using a sealed envelope technique, patients were randomly allocated…"*			Clinical criteria for patient's discharge applied by staff blinded to anaesthetic technique-but no details for applying MMSE.	MMSE for all 30 patients at 1 and 7 days.			Insufficient information to permit judgement.
Bigler1985	UNCLEAR	UNCLEAR	Groups similar for all baseline characteristics measured except for vasopressors being administered more frequently in spinal group.	LOW	UNCLEAR	AMT good validity for cognitive dysfunction	No	UNCLEAR
N=40	No details (other than *"patients randomly allocated"*)	No details		Surgeon undertaking AMT unaware of anaesthesia given	No details on proportion that AMT was undertaken in at 7 days and 3 months.			Insufficient information to permit judgement.

NB Quality assessment was not performed for Kamitani [37] as a full translation was not available. Blinding of patients and surgeons/anaesthetists not possible.

Table 2b: Quality assessment of observational studies reporting delirium

AMT is Abbreviated mental test
CAM is Confusion assessment method
DRS is Delirium Rating Scale
DSM-IV is Diagnostic and Statistical Manual of Mental Disorders, 4th Edition
MMSE is Mini mental state examination

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 2013 (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, pre-fracture disability in Activities of Daily Living (Katz's ADL Index), and pre-fracture dementia)	No details	DSM-IV-TR criteria		Patients with incomplete data in medical records were excluded from this study. Proportion not stated.
Bitsch 2006	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 day 4 and 7 respectively. Nursing home patients considered stable and those achieving independent ambulation discharged earlier.
Björkelund 2010	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 2017	LOW	HIGH for unadjusted data	LOW	LOW	Yes	LOW

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
		LOW for adjusted data				
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 2000	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 physiologic status.	No details	Mental confusion not further defined; MMSE		No details-only how many included in final analysis
Ilango 2015	LOW	HIGH	UNCLEAR	HIGH	Unclear	UNCLEAR
PROSPECTIVE	All hip fracture patients admitted over a year	Similar baseline characteristics (age, gender, pre-op 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.
Juliebo 2009	LOW	HIGH	LOW	LOW	Yes	HIGH
PROSPECTIVE	All eligible hip fracture patients 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. Pre-operative delirium an exclusion criterion; 127/364 (35%) included not assessed pre-operatively and excluded. No details on their characteristics.
Kim 2013	LOW	HIGH	UNCLEAR	LOW	Yes	LOW

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
RETROSPECTIVE	Consecutive sample of hip fracture patients	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
Kontinnen 2006	LOW	HIGH	UNCLEAR	UNCLEAR	Unclear	UNCLEAR
RETROSPECTIVE	All patients over 100 years old undergoing emergency Surgery in one hospital	No adjusted analyses.	No details	Not clearly defined		No details on missing data/exclusions.
Koval 1999	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 pre-determined.	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 2014	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 2014 (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 2016 *(Abstract)*	UNCLEAR	HIGH	UNCLEAR	UNCLEAR	Unclear	LOW
PROSPECTIVE	Patients from 6 hospitals; no further details	No details on baseline characteristics between	No details.	No details.		Data from enrolled patients analysed.

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
		groups. No adjusted analyses.				
O'Hara 2000	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		942/9598 < 2% missing
Ojeda 2018 *(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 2010	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.

NB Quality assessment was not performed for Atay [31] as a full translation was not available.

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 1985	In-hospital	1/19	1/19	**RR=1.00 (0.07, 14.6)**		No statistically significant difference in in-hospital mortality.
Parker & Griffiths 2015	30 day	8/156	5/153	**RR=1.54 (0.52, 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 & Griffiths 2015	90 day	12/152	12/146	**RR=0.96 (0.45, 2.07)**		
Parker & Griffiths 2015	120 day	12/152	15/143	**RR=0.77 (0.61, 0.91)**		
Parker & Griffiths 2015	1 year	19/145	32/126	**RR=0.57 (0.34, 0.96)**		
Prospective cohort						
Withey 1995	1 year	Total only reported: 303	Total only reported: 161	Not reported.	**OR 1.28 (0.76, 2.14)**	No statistically significant difference in mortality (adjusted data).
Zhao 2015	Unknown	65/166	22/238	Not reported.	**OR 0.687 (0.248, 1.906)**	No statistically significant difference in mortality (adjusted data).
Retrospective cohort						
Chu 2015	In-hospital	1363/ 50681	1107/ 50937	Not reported.	**OR 1.24 (1.15, 1.35)**	Statistically significant difference in mortality (adjusted data) in favour of RA.
Neuman 2012	In-hospital	325/12579	110/5144	Not reported.	**OR 0.710 (0.541, 0.932)**	Statistically significant difference in in-hospital mortality in favour of RA (OR<1 indicates benefit from RA).
Patorno 2014	In-hospital	1477/66345	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 2000	7 day	82/6124	53/3076	**OR 0.80 (0.56-1.13)**	**OR 0.90 (0.59-1.39)**	No statistically significant difference in mortality (adjusted or unadjusted).
Basques 2015	30 day	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 2000	30 day	272/5934	174/2955	**OR 0.80 (0.66-0.97)**	**OR 1.08 (0.84-1.38)**	No statistically significant difference in mortality (adjusted or unadjusted).
Qiu 2018	In hospital	226/9629	111/6597	Not reported	**HR 1.38 (1.10-1.73)**	No statistically significant difference in mortality
Seitz 2014	30 day	1044/7774	1450/10705	**RR 0.99 (0.92, 1.07)** (calculated based on raw data reported)	**RR 1.04 (0.94, 1.15)** (calculated based on raw data reported)	No statistically significant difference in 30 day mortality (matched or unmatched).

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 2015	30 day	Total only stated: 5840	Total only stated:1924	Not reported.	Spinal and regional nerve blocks **OR 1.18 (0.91, 1.53)** Spinal only **OR 1.20 (0.92–1.56)** Regional only **OR 1.22 (0.54–2.76)**	No statistically significant difference in 30 day mortality (adjusted data).

OR is odds ratio; RR is relative risk

Table 4: Summary findings table of studies reporting adverse events. *OR = Odds Ratio GA vs. RA; NR = not reported; NS = not significant

POMS categories	Study	Adverse event description	GA	RA	Summary statistic*/p-value
Pulmonary	Basques 2015	*Ventilatory support*	58/7253 (0.8%)	13/2589 (0.5%)	NR
		Pneumonia	261/7253 (3.6%)	108/2589 (4.2%)	NR
	Bigler 1985	*Pneumonia*	2/20	1/20	NR
	Chu 2015	*Respiratory Failure*	868/52043 (1.61%)	328/52044 (0.63%)	OR 2.71 (95%CI 2.38 to 3.01), p<0.001 Favours RA
		Ventilatory support	4008/52043 (7.70%)	338/52044 (1.44%)	OR 6.08 (95%CI 5.59 to 6.61), p<0.001 Favours RA
	Konttinen 2006	*Pneumonia*	0/3	2/11	NR
	Le Liu 2014	*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 2012	*Overall pulmonary*	17/235 (6%)	1/73 (1%)	OR 2.2 (95%CI 0.7 to 7.2) P=0.0841 Favours RA
	Naja 2000	*Hypoxia*	2/30 (6%)	0/30 (0%)	NR
	Neuman 2012	*Overall pulmonary*	1030/12904 (8.1%)	359/5254 (6.8%)	P=0.005 Favours RA

		Respiratory Failure	1040/12904 (5%)	178/5254 (3.4%)	P<0.0001 Favours RA
	O'Hara 2000	*Pneumonia*	174/6206 (2.8%)	84/3219 (2.6%)	OR 1.21 (95%CI 0.87 to 1.68) NS
	Shih 2010	*Overall pulmonary*	11/167 (6.6%)	3/168 (1.8%)	P<0.03 Favours RA
Cardiovascular	Basques 2015	*Myocardial infarction*	137/7253 (1.9%)	49/2859 (1.9%)	NR
		Thromboembolic	138/7253 (1.9%)	25/2589 (1.0%)	NR
	Bigler 1985	*Cardiovascular decompensation*	1/20	1/20	NR
		Pulmonary embolism	1/20	1/20	NR
	Chu 2015	*Myocardial infarction*	188/52043 (0.36%)	169/52044 (0.32%)	OR 1.11 (95%CI 0.9 o 1.37), p=0.31 NS
	Fields 2015	*Thromboembolism*	1.64%	0.72%	P=0.004 Favours RA
	Konttinen 2006	*Myocardial infarction*	0/3	1/11	NR
	Neuman 2016	*Myocardial infarction*	1/6	0/6	NR
	Le Wendling 2012	*All cardiovascular complications*	NR	NR	OR 1.7 (95%CI 0.4 to 6.3) NS
	Seitz 2014	*Deep vein thrombosis*	47/8818 (0.5%)	41/12155 (0.3%)	P=0.03 NS when matched
		Pulmonary Embolism	100/8818 (1.1%)	93/12155 (0.8%)	P=0.006 NS when matched

	Sutcliffe 1994	*Deep vein thrombosis*	16/950 (1.7%)	14/383 (3.7%)	P<0.05 NS
		Pulmonary Embolism	NR	NR	NS
Infectious	Bigler 1985	*Wound infection*	1/20	0/20	NR
	Fields 2015	*Urinary Tract infection*	5.76%	8.87%	P<0.0001 Favours GA
	Rashid 2013	*Urinary Tract infection*	NR	NR	NS
	Basques 2015	*Wound infection*	94/7253 (1.3%)	39/2589 (1.5%)	NS
Renal	Basques 2015	*Acute Renal Failure*	29/7253 (0.4%)	10/2589 (0.4%)	NS
	Bigler 1985	*Urinary retention*	4/20	5/20	NS
	Chu 2015	*Acute Renal Failure*	78/52043 (0.15%)	56/52044 (0.11%)	P=0.06 NS
	Naja 2000	*Acute Renal Failure*	2/30 (6%)	0/30 (0%)	NS
Overall complications	Gilbert 2000	*Serious medical complications*	55/311 (17.7%)	79/430 (18.4%)	OR 0.92 (95%CI 0.61 to 1.4) NS
	Gilbert 2000 Whiting 2015	*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 1.16-1.77) NS
	Whiting 2015 Fields 2015	*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 2012	*All complications*	NR	NR	NS
	Ilango 2015	*All complications*	NR	NR	NS
	Koval 1999	*All complications*	41/362 (11.3%)	32/280 (11.4%)	NS
	Le Liu 2014	*All complications*	17/72 (23.6%)	50/145 (34.5%)	P=0.165 NS
	Le Wendling 2012	*All complications*	NR	NR	OR 1.7 (95%CI 0.7 to 4.1) NS
	Radcliffe 2013	*All complications*	22%	19%	Log regression model p=0.002 Favours RA
	Shih 2010	*All complications*	21/167 (12.6%)	9/168 (5.4%)	P<0.02 Favours RA
	Chu 2015	ITU admissions	5743/52043 (11.03%)	3205/52044 (6.16%)	OR 1.95 (95%CI 1.87 to 2.05), p<0.001 Favours RA
Specific complications	Chu 2015	ITU stay >3 days	1206/52043 (2.32%)	411/52044 (0.79%)	P<0.001 Favours RA
	Baumgarten 2012	Pressure ulcers	10/328 (3.0%)	18/313 (5.8%)	OR 1.3 (1.0-1.6) Favours GA
	Casati 2003	Hypotension requiring crystalloid infusion	12/15 (80%)	7/15 (46%)	P=0.05 NS

	Maia 2014	Intraoperative hypotension	25/50	80/173	P=0.014 Favours RA
	Minville 2008	Intraoperative hypotension	35/42 (83%)	74/109 (68%)	NS
	Gadsden 2016	Intraoperative hypotension	569/745	1144/1528	Favours RA P<0.0001
	Messina 2013	Haemodynamic changes first 10min	Mean arterial blood pressure, heart rate, systemic vascular resistance index changes. More disturbance in GA		Favours RA
	Basques 2015	Blood transfusion	2843/7253 (39.2%)	851/2589 (32.9%)	Matched OR 1.34 (1.22 to 1.49), p<0.001 Favours RA
	Fields 2015	Blood transfusion	45.49%	39.34%	P<0.0001 Favours RA
	Minville 2008	Blood transfusion	23%	4%	P<0.05 Favours RA
	Shih 2010	Blood loss	Median 250 (0-1600) ml	Median 200 (0-1200) ml	P=0.01 Favours RA
	Chu 2015	Stroke	840/52043 (1.61%)	717/52044 (1.38%)	OR 1.18 (95%CI 1.07 to 1.31), p=0.001 Favours RA
	Le Liu 2014	Stroke	5/72 (5.9%)	4/145 (2.8%)	P=0.145 NS

POMS is Post-operative morbidity survey
OR is odds ratio
NS is not significant; NR is not reported

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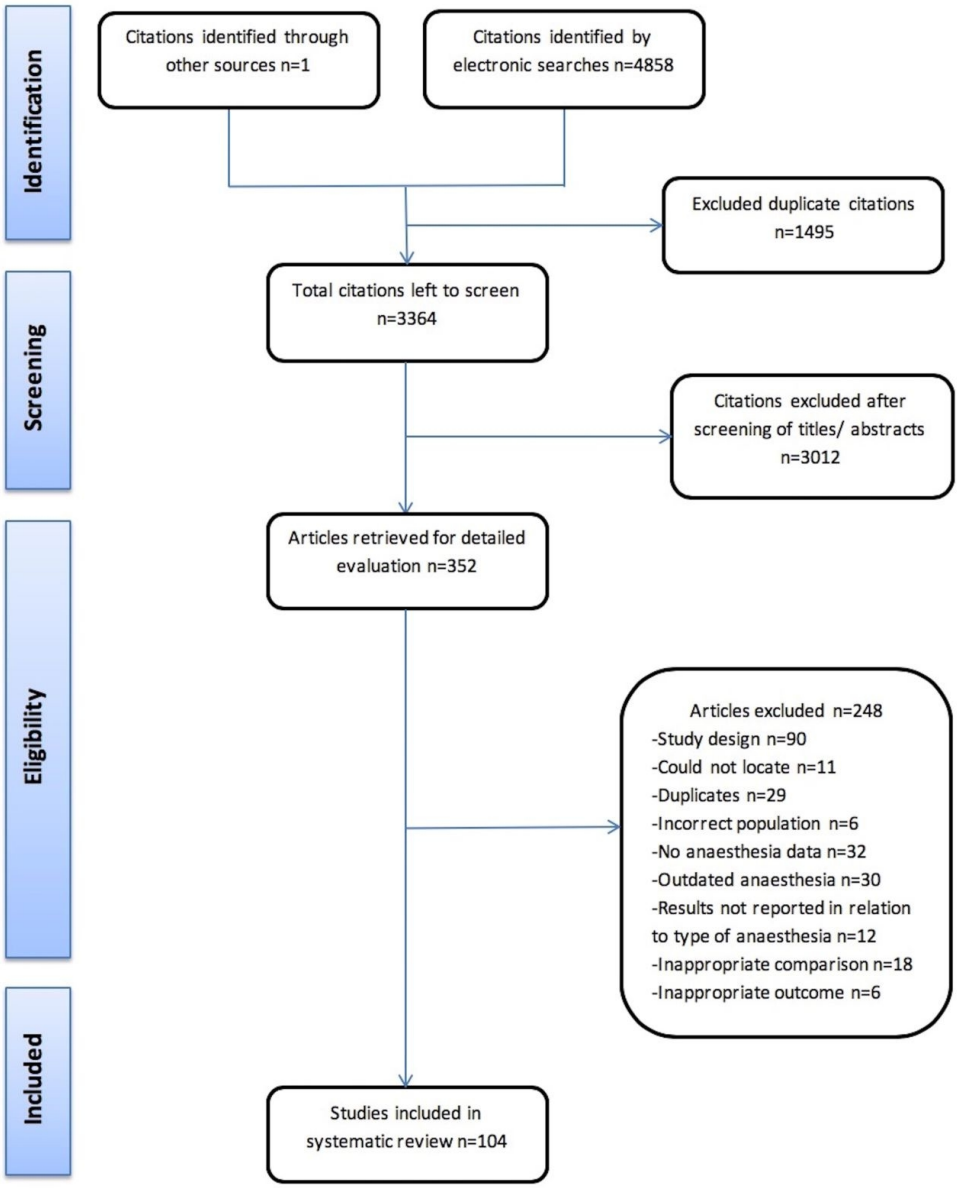
Figure Legends

Figure 1: PRISMA Flow Diagram. Legend: The PRIMSA diagram details our search and selection process applied during the review.

Figure 2: Forest plot of studies reporting the unadjusted relative risk of post-operative delirium with GA compared to spinal anaesthesia. Some studies are represented more than once to show results for different definitions of delirium, or for different assessment time-points. RR= relative risk, CI=confidence interval, MMSE= mini mental state examination, CAM= confusion assessment method, DSM-IV= Diagnostic and statistical manual of mental disorders 5, UCD = unspecified cognitive dysfunction.

Figure 3: 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. WMD=weighted mean difference, CI=confidence interval



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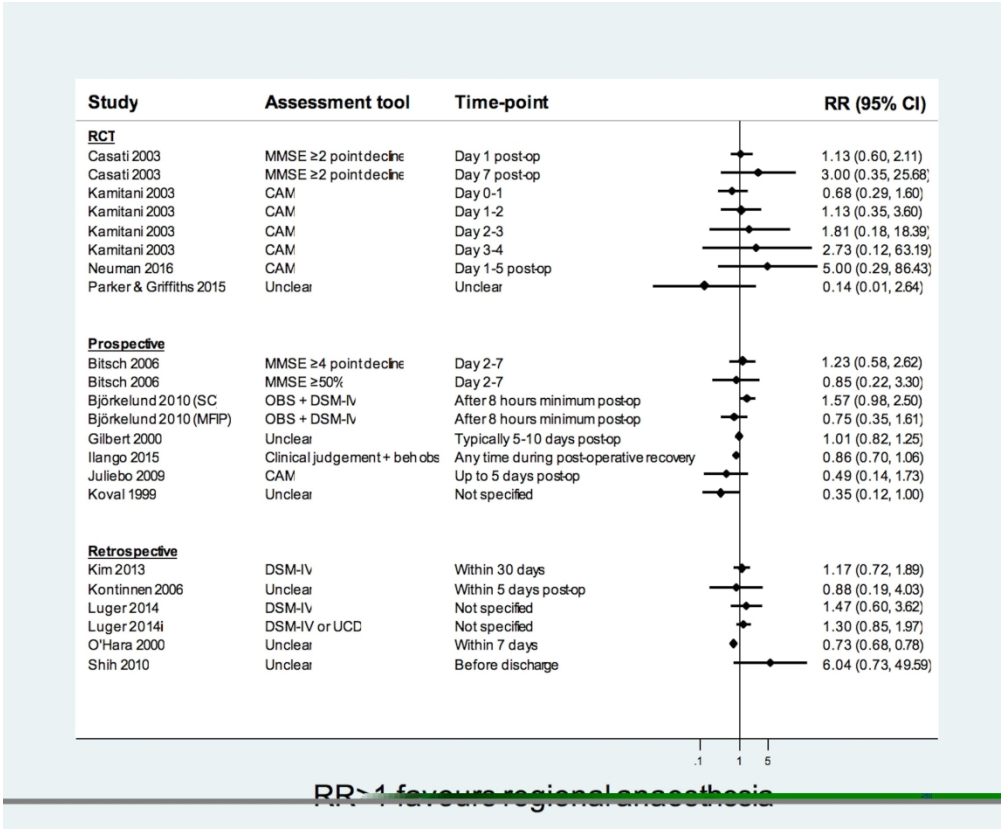

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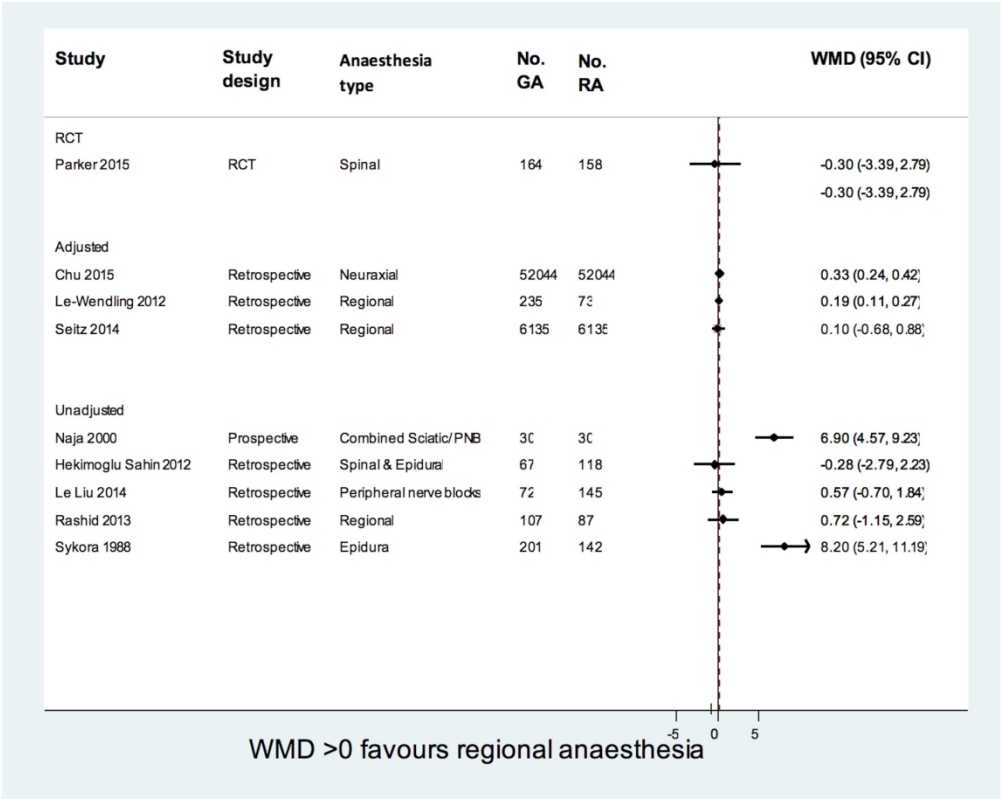

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Appendix A: Example of search strategy

1 exp Hip fracture/
2 hip fracture.mp.
3 (fracture$ adj2 (hip or femur$ or femor$)).tw.
4 or/1-3
5 exp an$esthesia/
6 an$esthesia.mp.
7 (anesthe$ or anaesthe$).tw.
8 an$ethetic.mp.
9 exp anesthetics/
10 exp general an$esthesia/
11 general an$esthesia.mp.
12 Anesthesia/ (43366)
13 exp Anesthesia, General/
14 general an$esthesia.mp.
15 sedation.mp. (28516)
16 exp regional an$esthesia/
17 regional an$esthesia.mp.
18 peripheral an$esthesia.mp.
19 central blockade.mp.
20 central block.mp.
21 exp spinal an$esthesia/
22 spinal an$esthesia.mp.
23 exp epidural an$esthesia/
24 epidural an$esthesia.mp.
25 exp local an$esthesia/
26 local an$esthesia.mp.
27 infiltrative an$esthesia.mp.
28 peripheral nerve block.mp.
29 intravenous regional an$esthesia.mp.
30 systemic local an$esthesia.mp.
31 exp nerve block$/
32 nerve block$.mp.
33 neuroaxial blockade.mp.
34 Anesthesia/ or exp Anesthesia, Intravenous/
35 exp inhalation an$esthesia/
36 inhalation an$esthesia.mp.
37 or/5-36
38 4 and 37

Appendix B: Table of eligible on-going studies

Title	ID	Comparison	Status	Design	Contact	Country
ClinicalTrials.gov						
Comparison of Combined Lumbar and Sacral Plexus Block With Sedation Versus General Endotracheal Anesthesia on Postoperative Outcomes in Elderly Patients Undergoing Hip Fracture Surgery(CLSB-HIPELD): Rationale and Design of a Prospective, Multicenter, Randomized Controlled Trial	NCT03318133	General vs Combined lumbar plexus and sacral plexus block(CLSB)	Not yet recruiting patients	Double blind randomised trial	Xiaofeng Wang	China
The Comparative Effects of Regional or General Anesthesia on the Prognosis of Hip	NCT03116490	General vs Regional	Recruiting patients	Prospective observational cohort	ging Li	China

Fracture Surgery on Elderly Patients						
Variations in Anaesthesia care for hip fracture surgery	NCT02787031	General vs Neuraxial	Recruitment completed but no results available	Retrospective observational cohort	Ottawa Hospital Research Institute	Canada
Regional versus general anaesthesia for promoting independence after hip fracture	NCT02507505	General vs Regional	Recruiting patients	Double blind randomised trial	Mark Powell/ Mark Neuman	USA
Effect of anaesthesia on post-operative delirium in elderly patients undergoing hip fracture surgery	NCT02213380	General vs Regional	Recruiting patients	Open label randomised controlled trial	ing Li/ Sishi Chen	China
The safety of anaesthesia management for traumatic hip surgery in elderly	NCT02692989	General vs Regional	Ongoing, but not recruiting patients	Retrospective observational cohort	ubhi M Alghanem	Jordan
Anaesthesia and post-operative mortality after proximal femur fractures	NCT02406300	Peripheral nerve block/ General vs Subarachnoid anaesthesia	Enrolling patients by invite only	Double blind randomised controlled trial	Raul Carvalho	Portugal

Effect of anaesthesia in fracture healing	NCT02621255	General vs Regional	Recruiting patients	Double blind randomised trial	Ebru Biricik	Turkey
Mortality following surgery for proximal femoral fractures	NCT01807039	General vs. Subarachnoid anaesthesia	Study has been completed	Retrospective observational cohort	Petr Štourač	Czech Republic
ICTRP						
Hypobaric Lateral Spinal Anesthesia Versus General Anesthesia: Hemodynamic Stability and Short Term Cardiovascular Complications in Elderly Patients Undergoing Hip Fracture Surgery.	NCTNCT03373864	General vs Hypobaric lateral spinal	Recruiting patients	Randomised controlled trial	Claire Delsuc	France
Effects of different anesthesia methods on postoperative complications and hospital mortality in elderly patients	ChiCTR-RRC-17013545	General vs Regional	Recruiting patients	Prospective cohort	Xu Mao	China

with hip fracture						
Hemodynamic effects of general and spinal anaesthesia for hip fracture surgery	IRCT201308316280N4	General vs Spinal	Completed	Double blind randomised trial	Mohammad Daghighi	Iran
ISRCTN						
A Feasibility Randomised Controlled Trial to compare REgional versus General Anaesthesia in Reducing Delirium in patients with Hip Fractures	ISRCTN15165914	General vs Regional	Recruiting patients	Randomised controlled trial	Joyce Yeung	UK

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2,3
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	5,6
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	6
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	6
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	6
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	6
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Appendix A
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	7
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	7
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	8
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	23-27
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	8
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	8

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	23-27
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	NA
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	8, Figure 1
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	18-22
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	23-27
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	Table 2a/b,3,4, Figure 2,3
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	NA
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	23-27
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	NA
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	13,14
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	15, 16
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	16
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	16

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

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