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Comparative Effectiveness Review
Number XXX [to be provided by AHRQ]

Comparative Effectiveness of Pain Management Interventions for Hip Fracture

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The investigators have no relevant financial interests in the report. The investigators have no employment, consultancies, honoraria, or stock ownership or options, or royalties from any organization or entity with a financial interest or financial conflict with the subject matter discussed in the report.

Preface

The Agency for Healthcare Research and Quality (AHRQ), through its Evidence-based Practice Centers (EPCs), sponsors the development of evidence reports and technology assessments to assist public- and private-sector organizations in their efforts to improve the quality of health care in the United States. The reports and assessments provide organizations with comprehensive, science-based information on common, costly medical conditions and new health care technologies. The EPCs systematically review the relevant scientific literature on topics assigned to them by AHRQ and conduct additional analyses when appropriate prior to developing their reports and assessments.

To bring the broadest range of experts into the development of evidence reports and health technology assessments, AHRQ encourages the EPCs to form partnerships and enter into collaborations with other medical and research organizations. The EPCs work with these partner organizations to ensure that the evidence reports and technology assessments they produce will become building blocks for health care quality improvement projects throughout the Nation. The reports undergo peer review prior to their release.

AHRQ expects that the EPC evidence reports and technology assessments will inform individual health plans, providers, and purchasers as well as the health care system as a whole by providing important information to help improve health care quality.

We welcome comments on this evidence report. They may be sent by mail to the Task Order Officer named below at: Agency for Healthcare Research and Quality, 540 Gaither Road, Rockville, MD 20850, or by e-mail to epc@ahrq.gov.

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Structured Abstract

Objectives: To review and synthesize the evidence on pain management interventions in nonpathological hip fracture patients following low energy trauma. Key outcomes include pain management (short- and long-term), mortality, functional status, pain medication use, mental status, health-related quality of life, quality of sleep, ability to participate in rehabilitation, return to pre-fracture living arrangements, health services utilization, and adverse effects.
Data Sources: Comprehensive literature searches were conducted in 25 electronic databases from 1990 to present. Searches of the grey literature, trial registries, and reference lists of previous systematic reviews and included studies were conducted to identify additional studies.
Methods: Study selection, quality assessment, data extraction, and grading of the evidence were conducted independently and in duplicate. Discrepancies were resolved by consensus or third-party adjudication. Meta-analyses were conducted where data were available, and deemed appropriate.
Results: In total, 75 studies were included (65 trials, 10 cohorts). Most participants were females over the age of 75 with no cognitive impairment. The methodological quality of cohort studies was generally moderate; most trials were at high or unclear risk of bias. Included studies were grouped into eight intervention categories: systemic analgesia, anesthesia, complementary and alternative medicine, multimodal pain management, nerve blocks, neurostimulation, rehabilitation, and traction.

Most studies examined peri- and postoperative pain management, albeit from few perspectives such as reported pain, mortality, and adverse effects. Long-term pain was not reported and other outcomes were reported infrequently. Nerve blockade was effective for relief of acute pain; however, most studies were limited to either assessing acute pain or use of additional analgesia and did not report on how nerve blockades may affect rehabilitation such as ambulation or mobility if the blockade has both sensory and motor effects. Additionally, acupressure, relaxation therapy, and transcutaneous electrical neurostimulation (TENS) were shown to be associated with clinically meaningful reductions in pain. Postoperative physical conditioning regimens also improved pain control. Intravenous parecoxib, a systemic analgesia, appears to be a reasonable alternative to traditional intramuscular injections of opiates and older NSAIDs. However, the strength of evidence for these intereventions was considered insufficient to make firm conclusions. Preoperative traction and spinal anesthesia (with or without additional agents) were not found to reduce pain or complications in any demonstrable way. Multimodal analgesia (combinations of analgesic interventions) failed to yield improvements over single modalities. Although most studies reported on adverse effects, they were short-term and not adequately powered to identify significant differenences.

None of the included studies exclusively examined participants from institutional settings or with cognitive impairment, which reduces the generalizability of results to the overall hip fracture patient population.
Conclusion: For most interventions in this review there were sparse data available, which precludes firm conclusions for any single approach or for the optimal overall pain management following hip fracture.

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Executive Summary

Introduction

Hip fractures are a source of significant morbidity and mortality. Incidence increases substantially with age, rising, for men and women respectively, from 22.5 and 23.9 per 100,000 population at age 50, to 630.2 and 1,289.3 per 100,000 population by age 80. Short-term mortality rates are high and range from 25 percent for women to 37 percent for men in the first year following a hip fracture. Furthermore, a large proportion of those patients who survive never recover to their pre-fracture level of function, and approximately 25 to 50 percent of elderly patients with hip fractures have not returned home by 1 year postfracture. Up to 25 percent of hip fractures occur in continuing care facilities (i.e., long-term residential care for dependent people).

Pain following hip fracture has been associated with delirium, depression, sleep disturbance, and decreased response to interventions for other disease states. Therefore, it is important to treat and manage complaints of pain adequately during acute treatment for hip fracture. Furthermore, poorly managed postoperative pain is associated with delayed ambulation, pulmonary complications and delayed transition to lower levels of care. The patient's self-report of pain is the gold standard for evaluating its character and intensity. However, those with dementia or acute delirium may have difficulty reporting pain levels. The potential for underreporting of pain has direct ramifications for the hip fracture population, as many patients are frail elderly with postoperative confusion and an impaired ability to communicate.

Key Questions

KQ 1: In older adults (≥50 years) admitted to hospital following acute hip fracture, what is the effectiveness of pharmacologic and/or nonpharmacologic pain management interventions for controlling acute and chronic pain up to 1 year postfracture compared with usual care or other interventions in all settings?

KQ 2: In older adults (≥50 years) admitted to hospital following acute hip fracture, what is the effectiveness of pharmacologic and/or nonpharmacologic pain management interventions on other outcomes up to 1 year postfracture compared with usual care or other interventions in all settings? Other outcomes include:

a. Mortality (30 day and up to 1 year postfracture)
b. Functional status
c. Pain medication use; change in type and quantity
d. Mental status
e. Health-related quality of life
f. Quality of sleep in the hospital
g. Ability to participate in rehabilitation
h. Return to prefracture living arrangements
i. Health services utilization

KQ 3: In older adults (≥50 years) admitted to hospital following acute hip fracture, what is the is the nature and frequency of adverse effects that are directly or indirectly associated with

pharmacologic and nonpharmacologic pain management interventions up to 1 year postfracture compared with usual care or other interventions in all settings?

KQ 4: In older adults (≥50 years) admitted to hospital following acute hip fracture, how do the effectiveness and safety of pharmacologic and nonpharmacologic pain management interventions vary in differing subpopulations following acute hip fracture up to 1 year after fracture compared with usual care or other interventions in all settings?

Methods

Literature Search

The following bibliographic databases were searched systematically for studies published from 1990 to 2009: Academic Search Elite, AMED, BIOSIS Previews®, CINAHL Plus with Full Text, Cochrane Database of Systematic Reviews, Computer Retrieval of Information on Scientific Projects, Conference Papers Index, Database of Abstracts of Reviews of Effects, EBM Reviews – Cochrane Central Register of Controlled Trials, EMBASE, Global Health, Global Health Library, Health Source: Nursing/Academic Edition, International Pharmaceutical Abstracts, OCLC PapersFirst, Ovid MEDLINE®, Pascal, PEDro, ProQuest® Dissertations and Theses – Full Text, ScienceDirect, Scopus®, TOXLINE, CQVIP Chinese Scientific Journals database, and Web of Science. Hand searches were conducted to identify literature from proceedings from the following scientific meetings: American Geriatric Society, American Physical Therapy Association, American Society of Regional Anesthesia and Pain Medicine, European Society of Regional Anesthesia, European Society of Anesthesiology, and International Anesthesia Research Society. Ongoing studies were identified by searching clinical trials registers in addition to contacting experts in the field. Reference lists of relevant reviews were searched to identify additional studies. No language restrictions were applied.

Study Selection

Two reviewers independently screened titles and abstracts using general inclusion criteria. The full text publication of all articles identified as “include” or “unclear” were retrieved for formal review. Each full text article was independently assessed by two reviewers using detailed a priori inclusion criteria and a standardized form. Disagreements were resolved by consensus or by third party adjudication. Randomized controlled trials (RCTs), nonrandomized controlled trials (NRCTs), cohort studies (prospective or retrospective), and case-control studies were included if they were published in 1990 or later, focused on older adults (≥ 50 years) who were admitted to hospital with acute hip fracture due to low energy trauma and examined any pharmacological or nonpharmacological pain management therapy, regardless of mode of administration or time point during the care pathway.

Quality Assessment and Rating the Body of Evidence

Two reviewers independently assessed the methodological quality of included studies with disagreements resolved through discussion or third party adjudication, as needed. The Cochrane Collaboration’s risk of bias tool was used to assess RCTs and NRCTs. Observational analytic

studies were assessed using the cohort and case-control Newcastle Ottawa Scales. In addition, the source of funding was recorded for all studies.

The body of evidence was rated by two reviewers using the AHRQ GRADE approach. The strength of evidence was assessed for key outcomes identified by the clinical investigators to be most clinically important: acute pain, chronic pain, mortality (30 days), and the incidence of serious adverse effects (i.e., stroke, myocardial infarction, delirium, renal failure). The following four major domains were assessed: risk of bias (low, medium, high), consistency (no inconsistency, inconsistency present, unknown or not applicable), directness (direct, indirect), and precision (precise, imprecise).

Data Extraction

Data were independently double-extracted by two reviewers using a standardized form; discrepancies were resolved by consensus or third party adjudication. Extracted data included study characteristics, inclusion/exclusion criteria, participant characteristics, interventions, and outcomes.

Data Analysis

Evidence tables and qualitative description of results were presented for all included studies. Comparative studies were considered appropriate to combine in a meta-analysis if the study design, study population, interventions being compared, and outcomes were deemed sufficiently similar. Results were combined using random effects models. Statistical heterogeneity was quantified using the I-squared (I^2) statistic.

Results

Description of Included Studies

The search strategy identified 8,072 citations; 75 unique studies met the eligibility criteria and were included in the review. The studies included 60 RCTs, 5 NRCTs, and 10 cohort studies. The number of participants in the studies ranged from 14 to 535 (median = 60 [IQR: 40 to 79]). The mean age of study participants ranged from 59.2 to 86.3 years. Based on the interventions reported in each study, the studies were divided into eight groups: systemic analgesia (n = 3), anesthesia (n = 25), complementary and alternative medicine (CAM) (n = 2), multimodal pain management (n = 2), nerve blocks (n = 30), neurostimulation (n = 2), rehabilitation (n = 1), and traction (n = 10).

Methodological Quality of Included Studies

All but two of the RCTs and NRCTs were considered to have a high or unclear risk of bias. The most common sources of potential bias were inadequate description of the randomization procedure, allocation concealment, and external sources of funding. The methodological quality of the cohort studies was moderate, with a median score of 7 stars on a possible score of 9 (IQR:

6 to 8). Common weaknesses in the design of the studies included lack of independent blind outcome assessment and failure to adequately control for potential confounding factors.

Results of Included Studies

The results of the included studies are presented by the type of intervention and by the key questions. A table with the summary of findings for key outcomes for each intervention is presented at the end of the executive summary.

Systemic Analgesia

Three RCTs (n = 214) evaluated different types of systemic analgesia. The mean age ranged from 77.2 to 78.5 years; most were female.

KQ1: Acute pain management. All three trials reported acute pain. Acute pain was measured using the 10cm VAS; the mean baseline measure was 6.5cm. One trial (n = 90) comparing parecoxib intravenous (IV) vs. diclofenac intramuscular (IM) ± pethidine IM found a significant difference in favor of parecoxib IV (MD -0.70; 95% CI -1.04, -0.36; p <0.0001). The second trial (n = 30) comparing intrathecal isotonic clonidine vs. intrathecal hypertonic clonidine reported a significant difference in favor of isotonic clonidine (MD -1.69; 95% CI -2.01, -1.37; p <0.00001). The third trial (n = 94) comparing lysine clonixinate vs. metamizole found no significant difference (MD -0.43; 95% CI -1.30, 0.44; p = 0.33). The strength of the evidence was rated as insufficient.

KQ2: Other outcomes. *Additional pain medication use* was reported in one trial comparing lysine clonixinate vs. metamizole and reported no significant difference between groups (OR 3.00; 95% CI 0.30, 29.94; p = 0.35). *Delirium* was reported in one trial comparing lysine clonixinate vs. metamizole and found no significant difference (OR 0.96; 95% CI 0.06, 15.77; p = 0.98). The strength of the evidence was rated as insufficient.

KQ3: Adverse effects. One trial comparing lysine clonixinate vs. metamizole reported the number of participants with *any adverse event* and found a significant difference in favor of metamizole (OR 3.50; 95% CI 1.04, 11.81; p = 0.04). Similarly, fewer patients in the metamizole group reported any *gastrointestinal disturbance* (OR 11.84; 95% CI 1.45, 96.75; p = 0.02). The remaining reported adverse effects were from single studies and did not demonstrate any significant statistical differences between the pain management interventions.

KQ 4: Efficacy, effectiveness, and safety in subpopulations. No data were reported.

Anesthesia

Twenty RCTs and one NRCT (n = 939) evaluated anesthesia including neuraxial (i.e., continuous vs. single administration) or neuraxial vs. general anesthesia, or another form of anesthesia (i.e., spinal or regional); sample sizes ranged from 20 to 74. Additionally, four cohort studies (n = 716) provided data on spinal anesthesia vs. general anesthesia. The mean age of participants ranged from 70.0 to 86.0 years; most were female. Acute pain was measured using different scales (numeric rating score (1-5) and 10cm VAS). The studies were grouped as follows: spinal vs. epidural or general anesthesia (n = 4); neuraxial anesthesia: addition of clonidine, fentanyl, meperidine, morphine, or sufentanil (n = 15); neuraxial anesthesia: different

doses or modes of administration (n = 12); spinal anesthesia (continuous vs. single administration); and spinal anesthesia (different doses)

KQ1: Acute pain management. The average baseline VAS pain score was 5.0 for the RCTs and 1.9 for nonrandomized studies.

Spinal vs. general anesthesia. One RCT (n = 30) reported a statistically significant difference of additional pain relief in favor of spinal anesthesia (MD = -0.86; 95% CI -1.30, -0.42; p = 0.0001). The strength of the evidence was rated as insufficient.

Neuraxial anesthesia: addition of clonidine, fentanyl, meperidine, morphine, or sufentanil. Three RCTs compared additional fentanyl vs. standard spinal anesthesia (n = 40), additional morphine vs. spinal anesthesia (n = 40), and additional sufentanil vs. spinal anesthesia (n = 50). In the studies comparing the addition of fentanyl or sufentanil, no patients reported feeling pain following the procedure. In the study comparing the addition of morphine, there was no significant difference between groups (MD = -0.36; 95% CI -1.11, 0.39; p = 0.35). One RCT and one NRCT comparing additional fentanyl reported acute pain on day 1 and found no significant difference between groups (OR 1.24; 95% CI 0.34, 4.48; p = 0.75). The strength of the evidence was rated as insufficient.

KQ2: Other outcomes. *Spinal vs. general anesthesia or spinal vs. epidural anesthesia.* Two RCTs reported *30-day mortality* (n = 99) and no statistically significant difference in mortality rates (OR 1.73; 95% CI 0.53, 5.68; p = 0.36). In two cohort studies (n = 650), pooling was not performed due to marked statistical heterogeneity and conflicting results between the studies. The strength of the evidence was rated as insufficient.

In one RCT (n = 30) that reported *delirium* there was no significant difference between groups (OR 0.76; 95% CI 0.18, 3.24; p = 0.71). The strength of the evidence was rated as low.

LOS for acute hospitalization was reported in two RCTs (n = 99). LOS was significantly less in the general anesthesia group (MD 1.69; 0.38, 3.01; p = 0.01).

Neuraxial anesthesia: addition of clonidine, fentanyl, meperidine, morphine, or sufentanil. Additional pain medication use was reported in six RCTs. In one RCT (n = 40) comparing the addition of clonidine vs. spinal anesthesia, all participants required additional pain medication. The pooled estimate from three trials examining the addition of fentanyl (n = 102) showed no significant difference between groups (OR 5.51; 95% CI 0.25, 122.08; p = 0.28). There was no significant difference in additional pain medication use in the RCT (n = 40) that compared the addition of morphine (OR 0.27; 95% CI 0.07, 1.04; p = 0.06). Similarly, three RCTs (n = 132) that compared the addition of sufentanil found no difference between groups (OR 3.15; 95% CI 0.12, 81.74; p = 0.49).

Delirium was reported in one RCT (n = 40) comparing the addition of morphine and found no significant difference between groups (OR 3.15; 95% CI 0.12, 82.16; p = 0.49). The strength of the evidence was rated as low.

Neuraxial anesthesia: different doses and modes of administration (continuous vs. single administration). Three trials (n = 163) reported *30 day mortality*. In two, there were no deaths. In the third, there was no significant difference between groups (OR 0.46; 95% CI 0.07, 3.02; p = 0.42). Additionally, 30 day mortality was reported in one cohort study (n = 291) and found no significant difference between groups (OR 0.96; 95% CI 0.30, 3.00; p = 0.94). The strength of the evidence was rated as insufficient.

Additional pain medication use was reported in two trials (n = 134); there were no events in either group. *LOS for acute hospitalization* was reported in two trials (n = 89). There was no significant difference between groups (MD = -0.98; 95% CI -2.06, 0.10; p = 0.07). In two trials

(n = 134) that reported *delirium*, there was no significant difference between groups (OR 1.27; 95% CI 0.32, 4.99; p = 0.73).

Spinal anesthesia (different doses). One NRCT (n = 182) reported that there was no significant difference in *30 day mortality* rates between groups (OR 0.49; 95% CI 0.12, 2.02; p = 0.32). The strength of the evidence was rated as insufficient.

In one RCT (n = 6) that reported on *additional pain medication use*, there was no significant difference between groups at different doses (4 vs. 5mg, 4 vs. 6mg, or 5 vs. 6mg).

KQ 3: Adverse effects. *Spinal vs. general anesthesia or spinal vs. epidural anesthesia.* Two RCTs (n = 73) and one cohort study (n = 333) reported adverse effects. Overall, the RCTs reported no significant differences in the occurrence of hypotension, myocardial infarcton, or ST segment depression. The cohort study found no difference in the incidence of headaches and hypotension.

Neuraxail anesthesia: addition of clonidine, fentanyl, meperidine, morphine, or sufentanil. Ten RCTs (n = 388) and one NRCT (n = 40) provided data on adverse effects.

a) *Addition of clonidine*. One trial (n = 40) reported no *damage to surrounding structures, headaches,* or *infections*.
b) *Addition of fentanyl*. There was no significant difference in the number of participants reporting an *allergic reaction* in four RCTs. There was no significant difference in the number of participants reporting *bradycardia* in one RCT. Seven trials (n = 284) reported the frequency of *hypotension*. Results were not pooled due to high heterogeneity. Five trials (n = 40) reported *nausea or vomiting* and found no significant difference between groups (OR 1.10; 95% CI 0.06, 20.73; p = 0.95). There were no reports of *neurological complications* in one RCT (n = 40); no reports of *respiratory distress* in three RCTs (n = 124); no reports of *gastrointestinal symptoms* in three RCTs (n = 140); and no reports of *headaches* in one trial (n = 40).
c) *Addition of meperidine*. There were no reports of *headaches* in one RCT (n = 34).
d) *Addition of morphine.* One RCT (n = 40) reported no significant difference in the number of participants reporting *allergic reactions*, *gastrointestinal symptoms*, or *nausea or vomiting*.
e) *Addition of sufentanil.* There was no significant difference in the incidence of *bradycardia* in one trial. Three trials (n = 132) reported a significant lower incidence of *hypotension* in participants receiving sufentanil. In one RCT (n = 42) there were no reports of *allergic reaction, nausea or vomiting*, or *respiratory distress*.

Neuraxial anesthesia: different modes of administration. In one cohort study (n = 291), there were no reports of adverse effects. In one RCT (n = 60) there was no significant difference in the occurrence of *gastrointestinal symptoms*. In two trials (n = 103) that reported on *hypotension* there was a significant difference between groups in favor of continuous spinal anesthesia (OR 0.12; 95% CI 0.03, 0.51; p = 0.004). Similarly, in one cohort study (n = 291) there was a statistically significant difference in favor of continuous spinal anesthesia (OR 0.08; 95% CI 0.04, 0.14; p < 0.00001). There was no significant difference in *myocardial infarction* in one trial (n = 29). There was no significant difference in the occurrence *ST depression* in one trial (n = 29). In one RCT (n = 74) there were no reports of *bradycardia, myocardial ischemia*, or *stroke* and no reports of *headache* in one trial (n = 60) or one cohort study (n = 291).

Neuraxial anesthesia: different doses. In one cohort study (n = 182), there were no reports of adverse effects. In one RCT (n = 60) there was no significant difference in the occurrence of *allergic reaction* for the difference doses of bupivacaine. *Bradycardia* was reported in two trials

(n = 120); there was no significant difference among the different doses of bupivacaine or levobupivacaine). *Hypotension* was reported in four RCTs (n = 190). There was a significant difference following 4mg vs. 6mg of bupivacaine (OR 0.03; 95% CI 0.00, 0.58; p = 0.02), and 5 vs. 6mg of bupivacaine (OR 0.31; 95% CI 0.08, 1.13; p = 0.08). Two NRCTs reported hypotension (n = 207) and found a significant difference following 2.5mg vs. 5mg of bupivacaine (OR 0.08; 95% CI 0.03, 0.23; p <0.00001), and 0.125 vs. 0.5 percent of bupivacaine (OR 0.15; 95% CI 0.03, 0.87; p = 0.03). There were no reports of *nausea or vomiting* in two trials (n = 100); no reports of *residual sensory deficits or motor weakness, respiratory distress, sedation, or urinary retention* in one RCT (n = 60); no reports of *gastrointestinal symptoms* in one trial (n = 40); and no reports of *headache* in one cohort study (n = 182).

KQ 4: Efficacy, effectiveness, and safety in subpopulations. No data were reported.

Complementary and Alternative Medicine

Two RCTs (n = 98) evaluated the administration of CAM interventions vs. no or sham intervention. The mean age ranged from 76.8 to 86.2 years; most were female. One trial (n = 38) compared acupressure vs. sham control delivered pre-operatively. Acute pain was measured using the 10cm VAS; the baseline measure was 6.5cm. The second trial (n = 60) compared the Jacobson relaxation technique (a two-step process of contracting and relaxing specific muscles) vs. no intervention. Pain was measured using a 10-point verbal scale; the baseline measure was not reported.

KQ1: Acute pain. Acupressure reduced pain vs. a sham intervention (MD -3.01; 95% CI -4.53, -1.49; p <0.0001). Relaxation also showed a reduction in pain vs. no relaxation (MD -1.10; 95% CI -1.43, -0.77; p <0.00001). The strength of the evidence was rated as insufficient.

KQ2: Other outcomes. In the RCT that examined relaxation, fewer patients in the relaxation group required *additional pain medication* (e.g., meperidine or morphine) vs. the control group (MD -8.43; 95% CI -15.11, -1.75; p = 0.01).

KQ3: Adverse effects. No data were reported.

KQ 4: Efficacy, effectiveness, and safety in subpopulations. No data were reported.

Multimodal Pain Management

Two cohort studies (n = 226) evaluated multimodal pain management vs. standard care. These studies described the use of multiple pain management strategies (sequential or in parallel) as part of the care map for patients with hip fractures. The mean age was not reported; most participants were female. One study compared a formal postoperative protocol of IV and oral tramadol plus acetaminophen vs. standard care. The second compared a formal pre-operative protocol of skin traction, morphine and acetaminophen vs. standard care.

KQ1: Acute pain. No data were reported.

KQ2: Other outcomes. *Mortality* was reported in one study (n = 106). There was no significant difference between groups after 30 days (OR 0.54; 95% CI 0.16, 1.77; p = 0.31), or at 1 year (OR 0.60; 95% CI 0.25, 1.47; p = 0.26). Both studies reported *delirium* and found no significant difference between groups. The strength of the evidence for both outcomes was rated as insufficient.

KQ 3: Adverse effects. Data were reported in one study (n = 106). There were no significant differences between groups.

KQ 4: Efficacy, effectiveness, and safety in subpopulations. No data were reported.

Nerve Blocks

Twenty-seven RCTs (n = 1,443) evaluated nerve blocks, including 3-in-1 (neurostimulation [NS]/ultrasound-guided [US]), combined lumbar/sacral plexus, fascia iliaca compartment, femoral, lumbar plexus ± sciatic nerve, posterior lumbar plexus, psoas compartment and epidural nerve blocks. These were compared with placebo/standard care, or a different method of nerve blocks. Additionally, three cohort studies (n = 696) evaluated 3-in-1, femoral lumbar plexus plus sciatic nerve blocks vs. analgesia, or comparing different analgesic medications in femoral lumbar plexus plus sciatic block. The mean age of participants ranged from 59.2 to 85.9 years; most were female. Acute pain was measured using different scales (i.e., numeric rating scales and 10cm VAS). Eight studies using the VAS reported mean baseline scores from 1.4cm to 7.3cm. The studies were grouped as follows: nerve blocks vs. standard care; nerve blocks vs. neuraxial anesthesia; ropivacaine vs. bupivacaine; nerve blocks–addition of clonidine; and US vs. NS.

KQ1: Acute pain management. *Nerve blocks vs. no block*. Acute pain was reported in 10 RCTs (n = 653). There was a significant decrease in pain favoring nerve blocks (MD -0.74; 95% CI -1.03, -0.46; p < 0.00001). One trial (n = 50) reported a significant difference in postoperative pain on day 1 favoring nerve blocks (OR 0.10; 95% CI 0.03, 0.36; p = 0.0005). The strength of the evidence was rated as moderate.

Nerve blocks vs. neuraxial anesthesia. Acute pain was reported in three RCTs (n = 109). There was no significant difference between groups (MD -0.35; 95% CI -1.10, 0.39; p = 0.35). The strength of the evidence was rated as low.

KQ 2: Other outcomes. *Nerve blocks vs. no block.* Four RCTs (n = 228) evaluated *30-day mortality*; there was no significant difference between groups (OR 0.28; 95% CI 0.07, 1.12; p = 0.07). The strength of the evidence was rated as low. There was no significant difference in *1-year mortality* in one RCT (OR 1.10; 95% CI 0.20, 6.03; p = 0.92), or in one cohort study (OR 0.73; 95% CI 0.48, 1.10; p = 0.14). Seven RCTs (n = 426) evaluated *additional pain medication use* and found a significant difference favoring nerve blocks (OR 0.37; 95% CI 0.18, 0.79; p = 0.010). Similarly, one cohort study reported a significant difference favoring nerve blocks (OR 0.03; 95% CI 0.00, 0.44; p = 0.01). Pooled results for three RCTs (n = 307) and two cohort studies (n = 634) that provided data on *delirium* showed a significant difference favoring nerve blocks (OR 0.36; 95% CI 0.17, 0.74; p = 0.006 [RCTs]; OR 0.24; 95% CI 0.08, 0.72; p = 0.01[cohorts]). The strength of the evidence was rated as moderate. *LOS for acute hospitalization* (days) was reported in two cohort studies (n = 634) and found no significant difference (MD -3.41; 95% CI -8.41, 1.68; p = 0.19). *Quality of sleep* was reported in one RCT (n = 77) and found no significant difference (MD 0.30; 95% CI -0.46, 1.06; p = 0.44).

Nerve blocks vs. neuraxial anesthesia. *Additional pain medication use* was reported in one RCT (n = 30); there was no significant difference between groups (OR 2.00; 95% CI 0.38, 10.51; p = 0.41). *Delirium* was reported in one RCT (n = 29); there was no significant difference between groups (OR 1.20; 95% CI 0.27, 5.40; p = 0.81). The strength of the evidence was rated as insufficient.

Ropivacaine vs. bupivacaine. *Additional pain medication use* and *delirium* were reported in one cohort study (n = 62). There was no significant difference between groups for either outcome

(OR 1.25; 95% CI 0.42, 3.76; p = 0.69 ; OR 1.93; 95% CI 0.17, 22.50; p = 0.60, respectively). The strength of the evidence was rated as insufficient.

KQ3: Adverse effects. *Nerve blocks vs. no block. Respiratory infection* was reported in five RCTs (n = 268) and found no significant difference (OR 0.43; 95% CI 0.18, 1.04; p = 0.06). There were no significant differences between groups for the following adverse effects: c*ardiac complications* (2 RCTs, n = 128; 1 cohort, n = 99); *damage to surrounding structures* (3 RCTs, n = 224); *deep venous thrombosis* (2 RCTs, n = 100); *myocardial infarction* (2 RCTs, n = 145; 1 cohort, n = 535); *nausea/vomiting* (5 RCTs, n = 315); *pulmonary embolism* (2 RCTs, n = 128); *surgical wound infection* (2 RCTs, n = 110); *urinary retention* (2 RCTs, n = 62; 1 cohort, n = 535). There were no reports of infection in two RCTs (n = 184). The remaining reported adverse effects were from single studies and did not demonstrate any significant statistical differences between the pain management interventions.

Nerve blocks vs. neuraxial anesthesia, Ropivacaine vs. bupivacaine and Addition of clonidine. The reported adverse effects were from single studies and did not demonstrate any significant statistical differences between the pain management interventions.

US vs. NS. Two RCTs (n = 100) reported no significant difference in *damage to surrounding structures* (OR 0.16; 95% CI 0.02, 1.30; p = 0.09). The remaining reported adverse effects were from single studies and did not demonstrate any significant statistical differences between the pain management interventions.

KQ 4: Efficacy, effectiveness, and safety in subpopulations. One RCT recruited patients with pre-existing heart disease. There was a significant reduction in pain favoring nerve blocks (MD -0.55; -0.81, -0.29; p <0.0001). There was no significant difference in 30 day mortality (OR 0.10; 95% CI 0.01, 1.90; p = 0.12) or adverse effects. One RCT recruited participants that were independent prior to their hip fracture. There was no significant difference between nerve blocks vs. standard care for 30 day mortality (OR 1.00; 95% CI 0.06, 16.76; p = 1.00).

Neurostimulation

Two RCTs (n = 123) evaluated transcutaneous electrical neurostimulation (TENS) vs. sham control. One trial administered the TENS pre-operatively, and the other postoperatively. The mean age of participants ranged from 71.2 to 80.5 years; most were female. Pain was measured using the VAS; the mean baseline measure was 8.4 to 8.8.

KQ1: Acute pain. Two RCTs (n = 123) found a significant difference in additional pain relief in favor of TENS (MD -2.79; 95% CI -4.95, -0.64; p = 0.01). Pain on movement was reported in one trial (n = 60) and found a significant difference in favor or TENS (MD -3.90; 95% CI -6.22, -1.58; p = 0.001). The strength of the evidence was rated as insufficient.

KQ2: Other outcomes. One RCT (n = 60) provided data on *HRQOL* and *quality of sleep*. TENS provided significant improvement in HRQOL (MD -4.30; 95% CI -6.86, -1.74; p = 0.001) and quality of sleep (MD -3.60; 95% CI -575, -1.45; p = 0.001).

KQ3: Adverse effects. No data were reported.

KQ 4: Efficacy, effectiveness, and safety in subpopulations. No data were reported.

Rehabilitation

One RCT (n = 37) evaluated rehabilitation (stretching and strengthening of spinal and psoas muscles) vs. standard care. The mean age was 67.1; all participants were female. Pain was measured using the 10cm VAS; the mean baseline measure was 7.9cm.

KQ1: Acute pain. There was a significant difference in additional pain relief following rehabilitation (MD -1.39; 95% CI -2.27, -0.51; p = 0.002). The strength of the evidence was rated as insufficient.

KQ2: Other outcomes. No other outcomes were reported.

KQ3: Adverse effects. No data were reported.

KQ 4: Efficacy, effectiveness, and safety in subpopulations. All participants were female.

Traction

Six RCTs, three NRCTs, and one cohort study evaluated skin or skeletal traction vs. no intervention or other interventions. Sample sizes ranged from 60 to 311. The mean age ranged from 74.0 to 81.0; most participants were female.

KQ1: Acute pain management. Acute pain was measured using the 10cm VAS; the mean baseline measure ranged from 0.3 to 6.6cm. Seven trials compared skin traction (n = 462) vs. no traction (n = 522) and found no significant difference between groups. The strength of the evidence was rated as low. One trial compared skin traction (n = 40) vs. skeletal traction (n = 38) and found no difference between groups. The strength of the evidence was rated as insufficient.

KQ2: Other outcomes: *LOS for acute hospitalization* was reported in two trials comparing skin traction (n = 137) vs. no traction (n = 189) and found no significant difference. *Thirty day mortality* was reported in one RCT (n = 105) and found no difference between skin or skeletal traction vs. no traction. *Additional pain medication use* was reported in one RCT and one NRCT (n = 352). There was no significant difference between groups.

KQ3: Adverse effects. Six RCTs (n = 792) and one cohort study (n = 134) provided data on adverse effects. The reported adverse effects were from single studies, with the exception of difficulty in fracture reduction, and did not demonstrate any significant statistical differences between the pain management interventions.

KQ 4: Efficacy, effectiveness, and safety in subpopulations. No data were reported.

Rating the Body of Evidence

Most of the evidence for the key outcomes (acute pain, chronic pain, mortality (30 days), and the incidence of serious adverse effects (i.e., stroke, myocardial infarction, delirium, renal failure)) came from single trials and cohort studies precluding any conclusions. The strength of evidence was low to moderate to support the use of some interventions for alleviating acute pain, preventing delirium, and decreasing the 30-day mortality rate (Table). The strength of evidence for the remaining outcomes was classified as insufficient due to lack of an adequate number of studies and study power.

Future Research

Multi-center research studies. Adequately powered multi-center research studies are needed to provide a comprehensive assessment of safe, effective, and appropriate pain management following a hip fracture. Studies need to be large enough to allow subgroup analyses by age, gender, comorbidities, or functional groups (e.g., independent vs. dependent ambulates). In addition, researchers need to consider inclusion of common subpopulations of hip fracture patients. In particular, those with altered cognition who make up a substantial proportion

of the overall hip fracture patient population should be included in future studies of pain management following hip fracture.

Outcomes. Standardization of outcomes and outcome measures will allow easier and meaningful comparisons across different interventions and among studies. The types of outcomes reported do not reflect the multi-dimensional nature of pain. Relevant outcomes should include validated pain scores, prescription of opiates and other agents, adverse effects or complications attributable or related to the intervention. Associated outcomes of pain such as function, quality of life, and time to recovery should also be evaluated. The evaluation of pain should include long term followup of outcomes beyond the acute hospital setting to determine the pattern of pain recovery and whether early effective pain management techniques affect ultimate recovery levels.

Methods. Future research should seek to minimize bias by blinding outcome assessors, use of validated and standardized outcome assessment instruments, adequate allocation concealment (where applicable), and appropriate handling and reporting of missing data.

Conclusions

For the majority of interventions, there are sparse data available, which precludes firm conclusions for any single approach or for the optimal overall pain management following nonpathological hip fracture due to low energy trauma. The paucity of evidence related to long-term outcomes and the fact that the majority of the data is derived from studies of low methodological quality or from study designs associated with higher risk of bias (i.e., cohort studies). Overall, the evidence shows that most interventions result in improvements in short-term pain scores; however, few differences of long-term clinical importance are evident when comparisons between interventions are available. The rates of complication were generally low and the majority of complications were not significantly different among the interventions. Well-designed and powered, long-term trials are needed in order to determine the relative effectiveness of pain interventions for hip fracture patients. Until then, pain management in this population will rely heavily on availability of the interventions, staff skills and training, and pre-existing patient comorbidities.

Summary of evidence for key outcomes for pain management following hip fracture

Outcome	Comparison (# studies)	Strength of evidence	Summary
Systemic analgesia			
Acute pain	Parecoxib IV vs. diclofenac ± pethidine IM (1 RCT) Intrathecal isotonic clonidine vs. intrathecal hypertonic clonidine (1 RCT)	Insufficient	Significant effect in favor of parecoxib IV Significant effect in favor of intrathecal isotonic clonidine
Acute pain at rest	Lysine clonixinate vs. metamizole (1 RCT)	Insufficient	No significant difference
Chronic pain	None	Insufficient	No data
30 day mortality	None	Insufficient	No data
Delirium	Lysine clonixinate vs. metamizole (1 RCT)	Insufficient	No significant difference
Stroke	None	Insufficient	No data
Myocardial infarction	None	Insufficient	No data
Renal failure	None	Insufficient	No data
Anesthesia: spinal vs. general anesthesia			
Acute pain	Spinal vs. general anesthesia (1 RCT)	Insufficient	Significant effect in favor of spinal anesthesia
Chronic pain	None	Insufficient	No data
30 day mortality	Spinal vs. general anesthesia (2 RCTs, 2 cohorts)	Low	No significant difference
Delirium	Spinal vs. general anesthesia (1 RCT)	Insufficient	No significant difference
Stroke	None	Insufficient	No data
Myocardial infarction	Spinal vs. general anesthesia (1 RCT)	Insufficient	No significant difference
Renal failure	None	Insufficient	No data
Anesthesia: spinal – continuous vs. single administration			
Acute pain	None	Insufficient	No data
Chronic pain	None	Insufficient	No data
30 day mortality	Continuous vs. single administration (3 RCTs, 1 cohort)	Insufficient	No significant difference
Delirium	Continuous vs. single administration (2 RCTs)	Low	No significant difference
Stroke	Continuous vs. single administration (1 RCT)	Insufficient	No data
Myocardial infarction	Continuous vs. single administration (1 RCT)	Insufficient	No significant difference
Renal failure	None	Insufficient	No data
Anesthesia: spinal – addition of other medications			
Acute pain	Addition of fentanyl vs. standard spinal anesthesia (1 RCT)	Insufficient	No data
Acute pain	Addition of morphine vs. standard spinal anesthesia (1 RCT)	Insufficient	No significant difference
Acute pain	Addition of sufentanil vs. standard spinal anesthesia (1 RCT)	Insufficient	No significant difference
Chronic pain	None	Insufficient	No data
30 day mortality	None	Insufficient	No data
Delirium	Addition of morphine vs. standard spinal anesthesia (1 RCT)	Low	No significant difference
Stroke	None	Insufficient	No data
Myocardial infarction	None	Insufficient	No data
Renal failure	None	Insufficient	No data

IM = intramuscular; IV = intravenous; RCT = randomized controlled trial

Summary of evidence for key outcomes for pain management following hip fracture (continued)

Outcome	Comparison (# studies)	Strength of evidence	Summary
Anesthesia: spinal – ropivacaine vs. bupivacaine			
Acute pain	None	Insufficient	No data
Chronic pain	None	Insufficient	No data
30 day mortality	None	Insufficient	No data
Delirium	Ropivacaine vs. bupivacaine (1 cohort)	Insufficient	No significant difference
Stroke	None	Insufficient	No data
Myocardial infarction	None	Insufficient	No data
Renal failure	None	Insufficient	No data
Anesthesia: spinal –different doses			
Acute pain	Bupivacaine 2.5 mg vs. 5mg (1 cohort)	Insufficient	No significant difference
Chronic pain	None	Insufficient	No data
30 day mortality	None	Insufficient	No data
Delirium	None	Insufficient	No data
Stroke	None	Insufficient	No data
Myocardial infarction	None	Insufficient	No data
Renal failure	None	Insufficient	No data
Complementary and alternative medicine			
Acute pain	Acupressure vs. standard care (1 RCT)	Insufficient	No significant difference
Acute pain	Relaxation vs. standard care (1 RCT)	Insufficient	No significant difference
Chronic pain	None	Insufficient	No data
30 day mortality	None	Insufficient	No data
Delirium	None	Insufficient	No data
Stroke	None	Insufficient	No data
Myocardial infarction	None	Insufficient	No data
Renal failure	None	Insufficient	No data
Multimodal pain management			
Acute pain	None	Insufficient	No data
Chronic pain	None	Insufficient	No data
30 day mortality	Multimodal pain management vs. standard care (1 cohort)	Insufficient	No significant difference
Delirium	Multimodal pain management vs. standard care (2 cohorts)	Insufficient	No significant difference
Stroke	Multimodal pain management vs. standard care (1 cohort)	Insufficient	No significant difference
Myocardial infarction	Multimodal pain management vs. standard care (1 cohort)	Insufficient	No significant difference
Renal failure	None	Insufficient	No data

Summary of evidence for key outcomes for pain management following hip fracture (continued)

Outcome	Comparison (# studies)	Strength of evidence	Summary
Nerve blockade			
Acute pain	Nerve block vs. no nerve block (10 RCTs)	Moderate	Significant effect in favor of nerve block
Pain on movement	Nerve block vs. no nerve block (4 RCTs)	Insufficient	No data
Pain at rest	Nerve block vs. no nerve block (3 RCTs)	Insufficient	No data
Day 1 pain	Nerve block vs. no nerve block (1 RCTs)	Insufficient	No significant difference
Chronic pain	None	Insufficient	No data
30 day mortality	Nerve block vs. no nerve block (4 RCTs)	Low	No significant difference
Delirium	Nerve block vs. no nerve block (3 RCTs, 2 cohorts)	Moderate	Significant effect in favor of nerve block
Stroke	Nerve block vs. no nerve block (1 RCT, 1 cohort)	Insufficient	No significant difference
Myocardial infarction	Nerve block vs. no nerve block (2 RCTs, 1 cohort)	Insufficient	No significant difference
Renal failure	None	Insufficient	No data
Nerve blockade vs. regional anesthesia			
Acute pain	Nerve block vs. regional anesthesia (3 RCTs)	Low	No significant difference
Chronic pain	None	Insufficient	No data
30 day mortality	None	Insufficient	No data
Delirium	Nerve block vs. regional anesthesia (1 RCT)	Insufficient	No significant difference
Stroke	None	Insufficient	No data
Myocardial infarction	None	Insufficient	No data
Renal failure	None	Insufficient	No data
Neurostimulation			
Acute pain	Neurostimulation vs. standard care (2 RCTs)	Insufficient	Significant effect in favor of neurostimulation
Pain on movement	Neurostimulation vs. standard care (1 RCT)	Insufficient	Significant effect in favor of neurostimulation
Chronic pain	None	Insufficient	No data
30 day mortality	None	Insufficient	No data
Delirium	None	Insufficient	No data
Stroke	None	Insufficient	No data
Myocardial infarction	None	Insufficient	No data
Renal failure	None	Insufficient	No data
Rehabilitation			
Acute pain	Rehabilitation vs. standard dare	Insufficient	Significant effect in favor of rehabilitation
Chronic pain	None	Insufficient	No data
30 day mortality	None	Insufficient	No data
Delirium	None	Insufficient	No data
Stroke	None	Insufficient	No data
Myocardial infarction	None	Insufficient	No data
Renal failure	None	Insufficient	No data

Summary of evidence for key outcomes for pain management following hip fracture (continued)

Outcome	Comparison (# studies)	Strength of evidence	Summary
Traction			
Acute pain	Skin traction vs. no traction (7 RCTs)	Low	No significant difference
Acute pain	Skin traction vs. skeletal traction (1 RCT)	Insufficient	No significant difference
Chronic pain	None	Insufficient	No data
30 day mortality	Skin traction vs. no traction (1 RCT)	Insufficient	No significant difference
30 day mortality	Skin traction vs. skeletal traction (1 RCT)	Insufficient	No data
Delirium	None	Insufficient	No data
Stroke	None	Insufficient	No data
Myocardial infarction	None	Insufficient	No data
Renal failure	None	Insufficient	No data

Evidence Report

Chapter 1. Introduction

Background

Hip fractures are a source of significant morbidity and mortality. Incidence increases substantially with age, rising, for men and women respectively, from 22.5 and 23.9 per 100,000 population at age 50, to 630.2 and 1,289.3 per 100,000 population by age 80.[1-4] The impact of hip fractures is far reaching. Short-term mortality rates are high and range from 25 percent for women to 37 percent for men in the first year following a hip fracture.[5] Furthermore, a large proportion of those patients who survive never recover to their pre-fracture level of function,[6-8] and approximately 25 to 50 percent of elderly patients with hip fractures have not returned home by 1 year postfracture.[9] Up to 25 percent of hip fractures occur in continuing care facilities (long-term residential care for dependent people).[10,11] Because of poor functional recovery, health service utilization associated with recovery is substantially increased for at least 1 year, with much of the health care cost attributable to subsequent long-term care.[1,12-14]

Pain following hip fracture has been associated with delirium, depression, sleep disturbance, and decreased response to interventions for other disease states.[15-17] Therefore, it is important to treat and manage complaints of pain adequately during acute treatment for hip fracture. Furthermore, poorly managed postoperative pain is associated with delayed ambulation, pulmonary complications and delayed transition to lower levels of care.[18]

Hip fracture patients require a continuum of pain management from the time of pre-hospital admission through the completion of final rehabilitation. Therefore the interventions administered to relieve pain in this population can be divided according to both the timing of the intervention (e.g., pre-, intra-, and postoperative) and according to their classification (e.g., systemic analgesia, nerve blocks, etc.).

According to the timing of the intervention, pre-operative pain management has traditionally been achieved using systemic analgesia and in some cases, lower limb traction. Recently, nerve blocks, which block the nerve impulses from reaching the sensory cortex, have been introduced .

Intra-operative pain management has also traditionally been achieved with systemic analgesia in association with general anesthesia. Even so, neuraxial anesthesia is gaining momentum as a replacement for general anesthesia.

Postoperative pain management is usually accomplished by a more diverse array of interventions including systemic analgesia, nerve blocks, physiotherapy, and transcutaneous electrical nerve stimulation (TENS).

Interventions

Pain management interventions also can be divided into pharmacological and nonpharmacological interventions. Pharmacological interventions include systemic analgesia and medications used in nerve blocks and neuraxial anesthesia (e.g., bupivacaine). Nonpharmacological interventions include TENS, acupressure, or stabilization of the fracture using traction or a pillow (e.g., Lasse pillow).

Systemic Analgesia

This classification of intervention is broad and encompasses both narcotic and non-narcotic medications. The general goal is to provide pharmacologic analgesia although some also have anti-inflammatory properties.

Opiates (e.g., morphine) can be used at all stages of pain management to treat mild to severe pain.[19] Fentanyl primarily targets the *mu* receptors in the brain and spinal cord and is used in the treatment of severe pain. Sufentanil is 5–10 times more potent than fentanyl and, due to its immediate onset of action and its limited accumulation, it is ideal for short, quick action.

NSAIDs (e.g., diclofenac) and acetaminophen are used for their analgesic and anti-inflammatory properties and act by inhibiting both COX isoenzymes (COX-1 and COX-2).[20] Recently, COX-2 selective inhibitors (e.g., parecoxib) are being used more frequently.[21]

Anesthesia

Anesthesia can generally be divided into general and neuraxial, with the latter constituting spinal and epidural anesthesia. Pain management during general anesthesia is usually accomplished by the use of pharmacological systemic analgesia (e.g., opioids). During neuraxial anesthesia, injection of a local anesthetic into the epidural or subarachnoid space (e.g., spinal anesthesia) causes pain relief and often does not require additional pain medications.

Comparative and alternative medicine (CAM)

According to Traditional Chinese acupuncture, auricular acupressure involves the placing of tiny beads onto the outer ear at acupuncture points thereby stimulating the corresponding acupuncture points. Bilateral auricular acupressure can be performed at sites known to decrease pain and anxiety (e.g., shenmen, hip, valium point).[22] Using these body points, areas can be stimulated to direct energy flow.

Another CAM procedure used for hip fracture patients is the Jacobson relaxation technique. This involves a two step process of contracting and relaxing specific muscles. With practice the patient learns which muscles are related to pain and relaxes them.

Multimodal pain management

Mutimodal pain management is the use of multiple pain management strategies (consecutively or in parallel) as part of the care map for patients with hip fractures. The goal is to decrease pain to a greater extent than with one intervention alone.

Nerve blocks

Nerve blocks include the lateral cutaneous nerve of the thigh, femoral nerve, sciatic nerve, 3-in-1 nerve block (femoral, obturator, and sciatic nerves), psoas (lumbar plexus), or continuous epidural block.[23] Local anesthetics (e.g., bupivacine) are used in regional nerve blocks to prevent the generation and conduction of nerve impulses to the spinal column and brain.[24] Additional medications used with nerve blocks include clonidine, morphine, fentanyl, and sulfetanil.

Rehabilitation

Rehabilitation is a standard part of postoperative care in patients with hip fractures to increase mobility and reduce pain due to muscle atrophy. The goal is to increase muscle strength and range of motion as soon as possible following hip fracture. One of the major factors that can

limit patient participation in rehabilitation is the degree of delirium and pain that the patient may be experiencing.

Traction

Pre-operative skin, or skeletal, traction was traditionally standard care in this patient population. The theory is that by maintaining the lower limb stretched, using 5 to 10 pounds, intracapsular pressure and pain is decreased, and fracture reduction is made easier. However, a recent Cochrane systematic review of 10 randomized controlled trials (1,546 participants) reported no benefits for traction use.[25]

Skin traction is used to stabilize a fractured leg and to decrease pain and the risk of surgical complications prior to any operation. Skin traction is applied by using adhesive tape, bandaging the limb, and placing it on a traction sled with an appropriate weight hung from it.[20,26] Foam boot traction, a form of skin traction, uses a foam boot strapped around the leg and placed on a traction sled with an appropriate weight attached.[26] Skeletal traction involves passing a metal pin through the proximal tibia or distal femur, under local anesthesia. Traction is applied using ropes and weights attached to the end of the pin.[20]

A Lasse pillow is a foam rubber cube with a slit and a hole cut in it. The pillow reduces pressure on the heel and helps keep the lower leg immobilized in a position in which the patient is most comfortable.[26]

Transcutaneous electrical nerve stimulation (TENS)

TENS uses electrodes to apply electrical energy to peripheral nerves to treat acute and chronic musculoskeletal pain. Electrical stimulation can be administered at varying amplitudes and frequencies, depending on the indication.[27]

Outcomes

The patient's self-report of pain is the gold standard for evaluating its character and intensity.[15] However, those with dementia or acute delirium may have difficulty reporting pain levels. The potential for underreporting of pain has direct ramifications for the hip fracture population, as many patients are frail elderly with postoperative confusion and an impaired ability to communicate.[28-31]

The most commonly used measure of pain in clinical settings is the visual analogue scale (VAS).[32] It consists of a 100mm unmarked line printed where the patients are instructed to point to the position on the line to indicate how much pain they are currently feeling. The far left end of the line indicates 'No pain' and the far right end of the line indicates 'Worst pain ever'. It's ease of use, especially with older patients, reproducible results and extensive use in clinical practice makes it one of the first choices among pain measurement scales.[33] Additionally, it has been shown not to be biased by the severity of pain.[34]

Other commonly used pain scales include numerical and verbal scales. The numerical scales usually consist of a number between zero and ten and the patients are instructed to give a number relating to how much pain they are currently feeling, with the higher the number the higher the pain intensity. Many variations of this scale exist including a numerical scale of zero to three, one to five, etc. Numerical scales have been shown to have a linear correlation with the visual analog scale and don't require the use of any printed material.[35,36]

With regards the clinically important effect size differences for pain measurements, no exact cutoff is clear in the medical literature. Even so, it has been widely accepted as ranging from 20 – 30% additional pain reduction. This would reflect an additional 30mm of difference on the VAS.

The need to improve recovery after hip fracture, particularly among frail elderly patients, is a pressing worldwide problem that will only increase in the future as the population ages.[37] Synthesized data are lacking regarding pain management after hip fracture, therefore our review will be of interest to patients and families, the medical community and healthcare decisionmakers. The review will also elucidate evidence on important subgroups of patients and interventions for which further research is needed.

Scope and Key Questions

We have focused the key questions using the PICOTS framework (population, intervention, comparison, outcome, timing, and setting) as follows:

KQ 1: In older adults (≥50 years) admitted to hospital following acute hip fracture, what is the effectiveness of pharmacologic and/or nonpharmacologic pain management interventions for controlling acute and chronic pain up to 1 year postfracture compared with usual care or other interventions in all settings?

KQ 2: In older adults (≥50 years) admitted to hospital following acute hip fracture, what is the effectiveness of pharmacologic and/or nonpharmacologic pain management interventions on other outcomes up to 1 year postfracture compared with usual care or other interventions in all settings? Other outcomes include:

a. Mortality (30 day and up to 1 year postfracture)
b. Functional status
c. Pain medication use; change in type and quantity
d. Mental status
e. Health-related quality of life
f. Quality of sleep in the hospital
g. Ability to participate in rehabilitation
h. Return to prefracture living arrangements
i. Health services utilization

KQ 3: In older adults (≥50 years) admitted to hospital following acute hip fracture, what is the is the nature and frequency of adverse effects that are directly or indirectly associated with pharmacologic and nonpharmacologic pain management interventions up to 1 year postfracture compared with usual care or other interventions in all settings?

KQ 4: In older adults (≥50 years) admitted to hospital following acute hip fracture, how do the effectiveness and safety of pharmacologic and nonpharmacologic pain management interventions vary in differing subpopulations following acute hip fracture up to 1 year after fracture compared with usual care or other interventions in all settings?

Important refinement points regarding the key questions:

- **Population(s):**
  Older adults of either sex who were diagnosed as having an acute hip fracture resulting

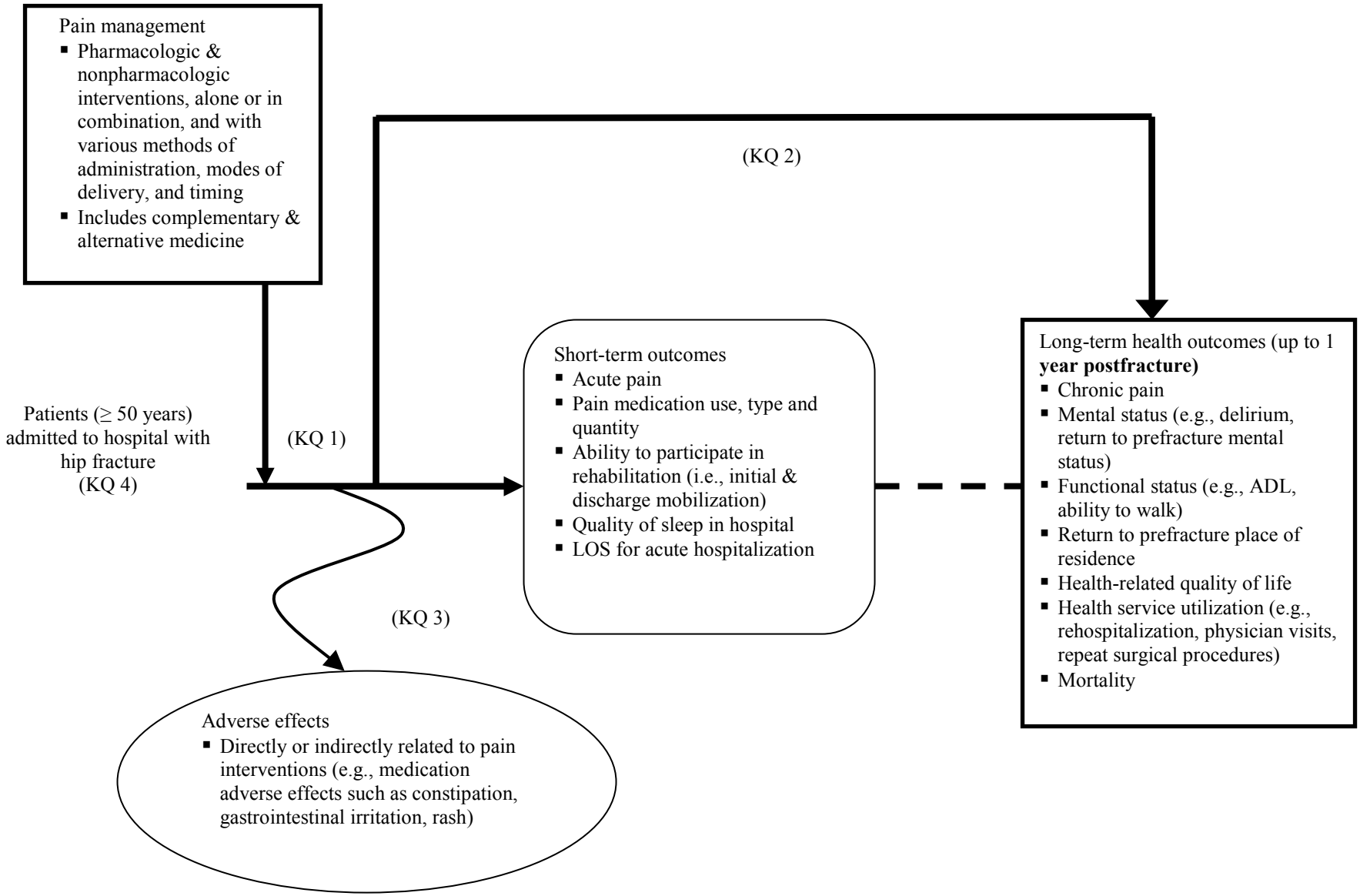
from low energy trauma (e.g., slip and fall) were included. This includes patients with intracapsular (e.g., subcapital and femoral neck) and extracapsular (e.g., basal, trochanteric, intertrochanteric and subtrochanteric) fractures regardless of whether surgical repair was performed. There were no restrictions on comorbidities or baseline functionality.
Patients with hip fracture due to the following etiologies were not considered: pathologic hip fractures (e.g., metastatic fractures, Pagets Disease); femoral head fractures; periprosthetic fractures (i.e., post hip replacement fractures/arthroplasty population); fractures resulting from high energy trauma (e.g., motor vehicle crashes, falls from heights, etc.).

- **Interventions:**
  We considered all interventions, alone or in combination, with various methods of administration and modes of delivery, and at various time points during the care pathway (e.g., preoperative, intraoperative, postoperative, rehabilitation, and following discharge from acute care). The same intervention may be administered at different time points (e.g., epidural block for preoperative analgesia and intraoperatively for anesthesia). Interventions included traditional and nontraditional medications/interventions (e.g., natural health products). Interventions that were directly related to surgical/nonsurgical treatment of the hip fracture (e.g., reduction, fixation, hemiarthroplasty, total hip replacement) were not considered.
- **Comparators:**
  Comparators of interest were defined in the primary studies. This included, but was not limited to, opioid, non-opioid, or nonsteroidal anti-inflammatory drugs (NSAIDS), and nonpharmacological comparators.
- **Outcomes for each question:**
  For KQ1, pain had to be assessed using a validated pain measurement tool—either patient defined or proxy reported.
  For KQ2, all reported outcomes that were directly or indirectly related to the intervention for pain management were investigated.
  For KQ3, all reported adverse effects (AE) that were directly or indirectly associated to the intervention for pain management (e.g., medication complications such as constipation or gastrointestinal bleeding) were investigated. AE of interventions directly related to surgical/nonsurgical/medical treatment of the hip fracture (e.g., AEs of anesthesia, wound infection, etc.) were not investigated.
  For KQ4: Subgroups to be investigated included sex, age, race, marital status, comorbidities, body mass index, prefracture functional status, and family distress.
- **Timing:**
  We included all followup time points from the time of the trauma leading to the hip fracture and thereafter.
- **Settings:**
  Settings included, but were not limited to, emergency department (ED), hospital, rehabilitation facilities, skilled nursing facility, subacute care facility, and place of residence.

Figure 1 provides an analytic framework to illustrate the population, interventions, and outcomes that guided the literature search and synthesis. The figure depicts the key questions

within the context of the PICOTS described in the previous section. In general, the figure illustrates how pharmacologic and nonpharmacologic pain management interventions, alone or in combination, may result in 1) intermediate outcomes such as control of acute pain, pain medication use, the ability to participate in rehabilitation, the quality of sleep in hospital, and length of stay, and 2) long-term outcomes such as chronic pain, changes in the mental status, the functional status (e.g., activities of daily living), the ability to return to prefracture place of residence, health-related quality of life, health service utilization, and mortality. Also, adverse effects may occur at any point after the treatment is received (e.g., medication adverse effects such as constipation, gastrointestinal irritation, rash).

Figure 1. Analytic framework



Chapter 2. Methods

Topic Development

The topic for this comparative effectiveness review (CER) was nominated in a public process. With input from technical experts, the Scientific Resource Center (SRC) for the Agency for Healthcare Research and Quality (AHRQ) Effective Health Care Program selected and refined the questions to be addressed. Initial questions were posted on a website for public feedback. Investigators at the University of Alberta Evidence-based Practice Center (UAEPC), including clinical specialists in relevant fields, further refined the questions with the assistance of the SRC and AHRQ.

Search Strategy

The research librarian, in collaboration with the research team, developed and implemented search strategies designed to identify evidence relevant to the key questions (Appendix B).

For the questions on efficacy and effectiveness, we conducted comprehensive searches in the following electronic databases: Academic Search Elite (1985 to 2009), AMED (1985 to July 2009), BIOSIS Previews® (1926 to 2009), CINAHL Plus with Full Text (1937 to 2009), Cochrane Database of Systematic Reviews (2009 Issue 3), Computer Retrieval of Information on Scientific Projects, Database of Abstracts of Reviews of Effects (2009 Issue 3), EBM Reviews – Cochrane Central Register of Controlled Trials (2009 Issue 2), EMBASE (1980 to 2009), Global Health (1910 to June 2009), Global Health Library, Health Source: Nursing/Academic Edition (1975 to 2009), International Pharmaceutical Abstracts (1970 to 2009), Ovid MEDLINE® (1950 to 2009), Pascal (1987 to Feb 2010), PEDro (1929 to 2009), ProQuest® Dissertations and Theses – Full Text (1861 to 2009), Scopus® (1823 to 2009), CQVIP Chinese Scientific Journals database, and Web of Science (1900 to 2009) (Appendix B-1 to B-14).

For the questions on AE, in addition to the above databases, we also searched TOXLINE (1998 to 2009) (Appendix B-1 to B-15).

In order to identify literature from symposia proceedings, we searched Conference Papers Index (1982 to 2009), OCLC PapersFirst (1993 to 2009) and ScienceDirect Tables of Contents for select journals (Appendix B). We also hand searched proceedings for the following associations: American Geriatric Society (AGS), American Physical Therapy Association (APTA), American Society of Regional Anesthesia and Pain Medicine (ASRA), European Society of Regional Anesthesia (ESRA), European Society of Anesthesiology (ESA), and International Anesthesia Research Society (IARS) (Appendix B-16 to B-19).

Unpublished studies and studies in progress were identified by searches of clinical trials registers (Appendix B-20 to B-25), by contacting experts in the field, and by contacting authors of relevant studies.

The reference lists of reviews and guidelines were reviewed to help identify potential studies for inclusion. Original studies that met the inclusion criteria for this review were searched for citing studies using Scopus™ Citation Tracker.

Search terms were selected by scanning search strategies of systematic reviews on similar topics and by examining index terms of potentially relevant studies. A combination of subject

headings and text words were adapted for each electronic resource. This included terms for hip fracture (fracture* and (hip or intertrochanter* or petrochanter* or subtrochanter* or intracapsular or extracapsular or petrochant* or trochant* or hip or "femoral neck")) and pain terms (pain* or heal or healing or therap* or recover* or "quality of life" or rehabilitat* or "drug therapy" or pharmacological or acupunct* or acupress* or traction or "electrical stimulation" or "passive motion" or morphine or acetaminophen or paracetamol or tylenol or anesth* or analges*). All searches were restricted to studies published from 1990. No language or study design restrictions were applied. The detailed search strategies for each database are presented in Appendix B.

Results from the literature searches were entered into Reference Manager® 11.0.1 (Thomson Reuters, Carlsbad, CA).

Study Selection

The results of the electronic literature searches, hand searches, and expert nominated records were screened using a two-step process. We included studies published as full-text manuscripts, conference abstracts, or other grey literature with no language restrictions. Research published prior to 1990 was not considered based on the rationale that surgical procedures and medical care (particularly as related to aggressive postsurgery mobilization) for this patient population has changed and the earlier research may not be applicable to current care.

Study selection was based on an *a priori* set of criteria for inclusion and exclusion of studies including study design, patient populations, interventions, and outcome measures (Table 1). First, two reviewers independently screened the titles and abstracts (level I screening) to determine if an article met the broad inclusion/exclusion criteria for study design, population, and intervention. Each article was rated independently as: include, exclude or unclear. Records rated as ‘include’ or ‘unclear’ by at least one reviewer were advanced to full-text screening (level II screening).

The full-text of all potentially relevant articles were retrieved for independent formal review by two reviewers (level II screening), applying *a priori* eligibility criteria and using a standardized screening form that was developed and piloted by the review team. Discrepancies regarding inclusion/exclusion of a study were resolved through discussion and consensus, or by third party adjudication if consensus could not be reached. Reviewers were not masked to the study authors, institution or journal.[38]

Table 1. Inclusion and exclusion criteria

A) Inclusion criteria

Study design	Randomized controlled trials , nonrandomized controlled trials , cohort studies (prospective or retrospective), case-control studies
Participants	Older adults (≥50 years old) of either sex admitted to hospital with acute hip fracture due to low energy trauma
Interventions	Pharmacological and/or nonpharmacological pain management monotherapy or combination therapy, regardless of mode of administration or time point during the care pathway
Comparator	Usual care (as defined by study authors) or another intervention(s) for pain management, administered as monotherapy or combination therapy
Outcomes	Primary outcomes: • Acute pain • Chronic pain Secondary outcomes: • Mortality • Functional status • Pain medication use; change in type and quantity Adverse effects: • AE related to the pain management intervention • Mental status • Health-related quality of life • Quality of sleep in hospital • Ability to participate in rehabilitation • Return to prefracture place of residence • Length of stay for acute hospitalization, skilled nursing facility, subacute care facility • Health service utilization
Timing	From time of trauma leading to acute hip fracture and thereafter
Setting	All settings

B) Exclusion criteria

Study design	Observational study designs with no comparison group (case reports, case series, cross-sectional studies)
Participants	Majority (>80%) of participants <50 years, as stated by the study investigators or evident from the study characteristics (e.g., mean/SD of patient population); participants with underlying pathological conditions that may directly lead to fracture; acute hip fractures due to high energy trauma
Interventions	Interventions directly related to surgical/nonsurgical treatment of the hip fracture and not a pain management intervention
Comparator	Initial care for patients is substantially different than the current practices in North America (e.g., based on time to discharge from acute care to subacute care)
Outcomes	None of the aforementioned outcomes were available from the trial report or through communication with the trial's corresponding author

Assessment of Methodological Quality of Individual Studies

The risk of bias of the included studies was assessed using the Cochrane Collaboration's Risk of Bias (RoB) tool[39] for randomized controlled trials (RCTs) and nonrandomized controlled trials (NRCTs). The methodological quality of cohort and case-control studies was assessed using the Newcastle Ottawa Scale (NOS)[40] for cohort and case-control studies, respetively. Decision rules regarding application of the tools were developed *a priori* by the research team. For randomized and nonrandomized controlled trials, we performed a domain-based risk of bias assessment according to the principles of the RoB tool. The domains were: (1) sequence generation (e.g., was the allocation sequence adequately generated?); (2) allocation concealment (e.g., was

allocation adequately concealed?); (3) blinding of participants, personnel and outcome, assessors (e.g., was knowledge of the allocated intervention adequately prevented during the study?); (4) incomplete outcome data (e.g., were incomplete outcome data adequately addressed?); (5) selective outcome reporting (e.g., were reports of the study free of suggestion of selective outcome reporting?); and (6) other sources of bias (e.g., was the study apparently free of other problems that could put it at a high risk of bias?). Other sources of bias included baseline imbalances, source of funding, early stopping for benefit, appropriateness of crossover design. For cohort and case-control studies, the NOS uses a 'star system' in which a study is judged on three broad perspectives: (1) the selection of the study groups; (2) the comparability of the groups; and (3) the ascertainment of either the exposure or outcome of interest for case-control or cohort studies, respectively.

Two reviewers (AMAS, MH, MK, KW) independently performed quality assessment of the included studies with disagreements resolved through discussion or third party adjudication, as needed.

Data Extraction

Published data were independently double-extracted by members of the research team (AMAS, MH, MK, KW, SM). Standardized data extraction forms were developed in Microsoft Word (Microsoft Corporation, Redmond, WA). Data extraction forms were piloted with three studies[41-43] and identified issues were resolved. We extracted data on the following: general study characteristics (e.g., study design); population characteristics (e.g., age, sex); interventions and dosing regimens; numbers of patients allocated into relevant treatment groups; outcomes measured, method of ascertainment, and the results of each outcome, including measures of variability, by relevant intervention arm. Funding source, if reported, was also recorded.

When there were multiple reports of the same study we referenced the primary or most relevant study, and extracted only additional data from companion reports. Corresponding authors were contacted for data clarification and missing data. All data were imported into Microsoft Excel (Microsoft Corporation, Redmond, WA) for data management.

Dichotomous data were extracted as the number (n) of participants with events and the total number of participants (N). Continuous outcomes were extracted as the mean with the accompanying measure of variance for each treatment group, or as a mean difference (MD) between treatments based on the method of outcome measurement (e.g., scale, score system). Continuous data were analyzed as post-treatment score or absolute difference (or change score) from baseline.[44] Multiple scales and scoring systems were used to gauge the outcomes (e.g., pain scores). Therefore, in addition to summary data and measure of variance, the scale and the type of analysis used in the study were extracted (Appendix C).

When data were available only in a graphical format, data were imputed from the available graphs using the distance measurement tool in Adobe Acrobat 8 Professional (Adobe Systems Incorporated, San Jose, CA). When data were not available for the measure of variability for continuous outcomes, the variability was calculated from the computed P-value, and if not available imputed from other studies in the same analysis. When relevant data for multiple followup/observation periods were reported, only the followup data for the reported period that demonstrated the greatest improvement for the intervention arm were extracted.When trials incorporated multiple relevant treatment arms, data from all were extracted. We noted the specific intervention, dosage and intervals of each intervention to determine if arms were

clinically appropriate for pooling. For the purpose of this review, acute outcomes occurred up to 30 days postfracture.

Data Analysis

Evidence tables and qualitative description of results are presented for all included studies. Where appropriate, we conducted meta-analyses to answer the key questions. Meta-analyses were performed in Review Manager 5.0 (The Cochrane Collaboration, Copenhagen, Denmark) using a random effects model.[45] Chi-square tests were used to test for significant heterogeneity reduction in partitioned subgroups. Chi-square test of $p < 0.1$ was considered to be significant. Forest plots were generated and presented for the primary outcomes as long as at least two trials contributed to the synthesis. For secondary outcomes, forest plots were presented only if there were at least five included studies.

In the meta-analyses, RCTs and NRCTs were combined. Cohort studies were synthesized separately, as meta-analysis including both trials and cohort studies is controversial.[46] For continuous summary estimates, when the same measure of analysis was used, the MD was calculated with 95% confidence intervals (CI). When different measures of analysis (e.g., different scales) were used, the standardized mean difference (SMD) was used. Dichotomous summary estimates were reported as odds ratios (OR) with accompanying 95% CI.

Heterogeneity was tested using an I^2 statistic,[47] with an I^2 value 75 percent or greater considered to be substantial, thereby precluding pooling of studies. In the case of substantial statistical heterogeneity, if there were at least 10 studies in the analysis, we explored heterogeneity through meta-regression, subgroup and sensitivity analyses. If the number of included studies was less than 10, we explored heterogeneity qualitatively through subgroup and sensitivity analyses. Effect modifiers that were considered important to explain heterogeneity included specific intervention details (e.g., type and quantity), study design, and risk of bias. In addition, we conducted sensitivity analyses on studies with imputed data to determine if the imputations had any effect on the effect estimate or heterogeneity. *A priori* subgroup analyses included sex, age, race, body mass index, marital status, comorbidities, prefracture functional ability, and family distress.

Almost one fifth (17.6 percent) of the trials had multiple intervention arms comparing different doses or concentrations of the same intervention, or drugs of the same class. When appropriate, data from the available arms were pooled before being included in the meta-analysis.

Dichotomous data with zero values (i.e., no participant experienced an event) in all trial participants were not included in meta-analyses because summary trial results were not estimable, but such trials were reported in the particular narrative synthesis.

Potential publication bias was explored graphically through funnel plots for comparisons for which meta-analyses were conducted and when there were at least 10 studies in the analysis. Additionally, publication bias was quantitatively assessed using the Begg adjusted rank correlation test and Egger regression asymmetry test, if bias was suspected.[48]

Applicability

Applicability of evidence distinguishes between *effectiveness* studies conducted in primary care or office-based settings that use less stringent eligibility criteria, assess health outcomes, and have longer followup periods than most *efficacy* studies.[49] The results of effectiveness studies are more applicable to the spectrum of patients in the community, than efficacy studies, which

usually involved highly selected populations. The applicability of the body of evidence was assessed following the PICOTS (population, intervention, comparator, outcomes, timing of outcome measurement, setting) format used to assess study characteristics. Clinically important outcomes and participant characteristics are reported in the results.

Rating the Body of Evidence

We evaluated the overall strength of the evidence for the primary outcomes. We used the EPC GRADE[50] approach based on the standard GRADE approach developed by the Grading of Recommendation Assessment, Development & Evaluation (GRADE) Working Group.[51] The strength of evidence was assessed for key outcomes identified by the clinical investigators to be most clinically important: acute pain, chronic pain, mortality (30 days), and the incidence of serious adverse effects (e.g., stroke, myocardial infarction, delirium, renal failure). The following four major domains were examined: risk of bias (low, medium, high), consistency (inconsistency not present, inconsistency present, unknown or not applicable), directness (direct, indirect), and precision (precise, imprecise).

Each key outcome on each comparison of interest was given an overall evidence grade based on the ratings for the individual domains. The overall strength of evidence was graded as "high" (indicating high confidence that the evidence reflects the true effect and further research is very unlikely to change our confidence in the estimate of effect); "moderate" (indicating moderate confidence that the evidence reflects the true effect and further research may change our confidence in the estimate of effect and may change the estimate); "low" (indicating low confidence that the evidence reflects the true effect and further research is likely to change our confidence in the estimate of effect and is likely to change the estimate); and (4) "insufficient" (indicating that evidence is either unavailable or does not permit estimation of an effect). When no studies were available for an outcome or comparison of interest, the evidence was graded as insufficient. A detailed explanation of the parameters used to grade the evidence and their operationalization were summarized in Appendix J. The GRADEprofiler (GRADEpro), software (GRADE Working Group) was used on select important outcomes of interest for the key questions and the results modified in accordance with the EPC GRADE model. The body of evidence was graded independently by two reviewers (AMAS, DD); disagreements were resolved through discussion.

Peer Review

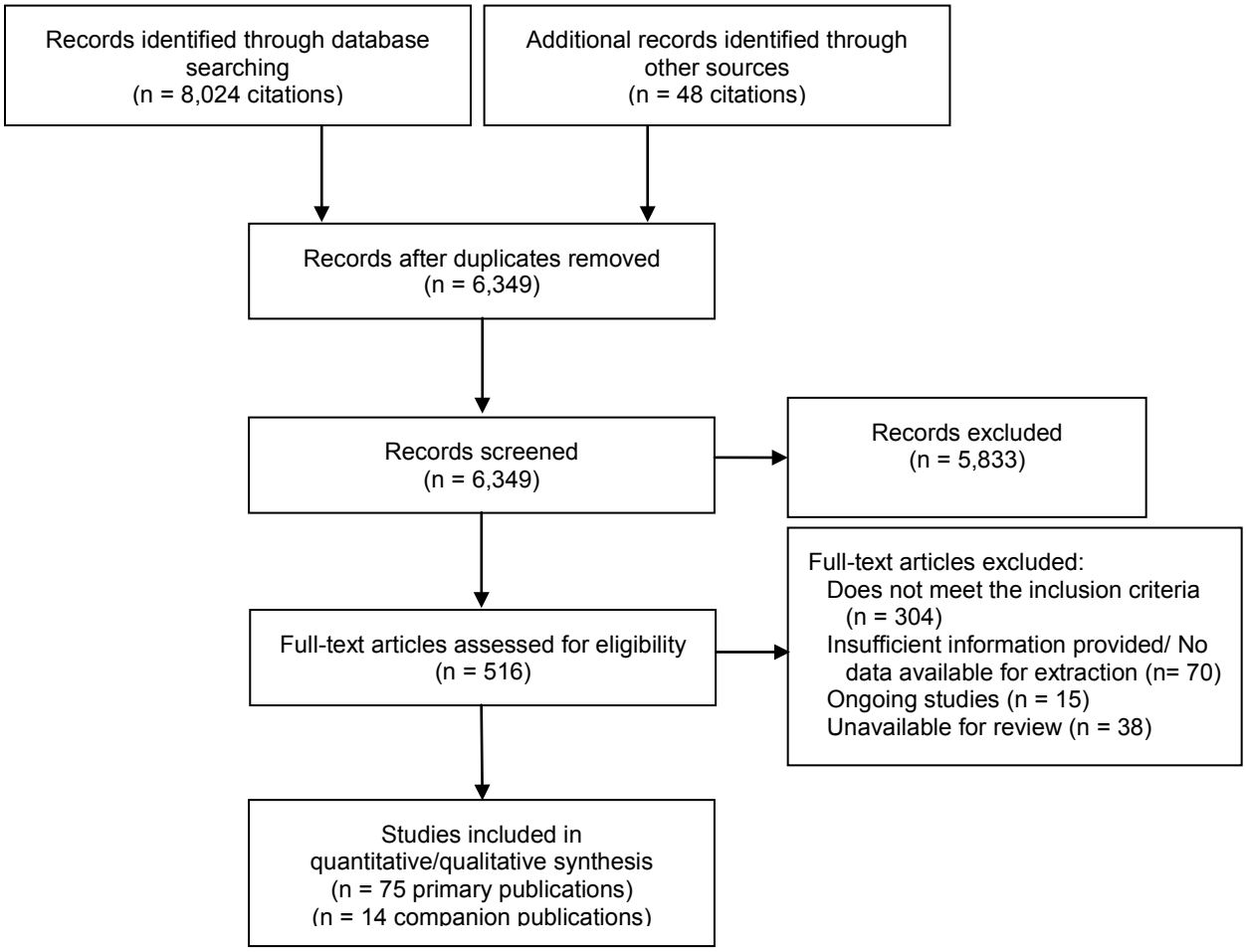
XX experts in the field (Appendix A) agreed to peer review the draft report and provide comments. Reviewer comments were considered by the UAEPC in preparation of the final report. All peer reviewer comments and the UAEPC disposition of comments were submitted to AHRQ for assessment and approval.

Chapter 3. Results

Search Results

All citations generated from electronic or hand searching and expert nominated studies were pooled into a single database (Figure 2).[52] Of these 8,072 citations retrieved, 1,723 were duplicates and 6,349 were considered to be unique study reports. Following level I screening, 5,833 were excluded and 516 were further evaluated for inclusion. Of these, 75 primary publications[26,41-43,53-123] passed level II screening and were included in this CER. An additional 14 companion publications[124-137] were identified and also included. The characteristics of the publications excluded at level II screening are presented in Appendices D. The main exclusion criteria were publication type (e.g., case-report, observational study, review), population characteristics (e.g., average age below 50, fractures other than hip fractures), no details of pain management intervention, and no extractable data related to outcomes of importance to the review (e.g., ongoing studies).

Figure 2. Flow diagram for study retrieval and selection



Description of Included Studies

Based on the interventions reported in each study, the primary publications were divided into eight groups: systemic analgesia (n = 3),[41,42,53] anesthesia (n = 25),[54-78] complementary and alternative medicine (CAM) (n = 2),[43,79] multimodal pain management (n = 2),[80,81] nerve blocks (n = 30),[82-111] neurostimulation (n = 2),[112,113] rehabilitation (n = 1),[114] and traction (n = 10).[26,115-123] The studies were published between 1990 and 2009 (median= 2003 [interquartile range (IQR): 1998 to 2007]). The majority of the studies was RCTs performed in single university settings in Europe, investigated pre- or intra-operative pain management interventions for hip fracture patients, and were published in peer-reviewed journals (Table 2).

Table 2. Characteristics of included studies

Publication type	Published manuscript	66
	Conference proceedings	8
	Dissertation	1
Study design	RCT	60
	NRCT	5
	Retrospective cohort study	6
	Prospective cohort study	4
Setting	General hospital	27
	Orthopedic hospital	1
	University hospital	47
Country	Asia/Australia	7
	Europe	52
	Middle East/North Africa	11
	North America	4
Number of centers	Single center	72
	Two centers	3
Timing of intervention	Pre-operative	31
	Intra-operative	31
	Postoperative	12
	Pre- vs. postoperative	1

NRCT = nonrandomized controlled trial; RCT = randomized controlled trial

Methodological Quality of Included Studies

The risk of bias (RoB) of each included randomized and nonrandomized trial was assessed using the RoB tool by two independent reviewers and the consensus ratings are presented in Appendix G–H. The methodological quality of each included cohort study was assessed using the Newcastle Ottawa Scale (NOS) by two independent reviewers and the consensus ratings are presented in Appendix I. A summary of the overall quality trends by study design is presented below.

Randomized and Nonrandomized Controlled Trials

Of the 65 RCTs and NRCTs, 29 trials[26,54,57,61,67,79,82,84,86,88,89,93,102,106,107,109,111-114,116,118-121] were rated as having high risk of bias (RCTs = 25; NRCTs = 4); 34 RCTs[41-43,53,55,56,58-60,62,64,66,68,69,71,73-77,83,85,92,94-96,98-101,103,104,108,110] were rated as having an unclear risk of bias; and, 2 RCTs[90,91] were considered to have a low risk of bias.

Cohort Studies

Data were prospectively collected in four cohort studies[65,80,81,122] and retrospectively in six.[70,72,78,87,97,105] Overall, the methodological quality of the cohort studies was moderate (median score=7 stars; IQR: 6 to 8).

Results of Included Studies

This section is organized by intervention category (i.e., systemic analgesia, anesthesia, etc.). Within each intervention category, the results are presented for the four key questions addressed in this report: KQ1: Acute and chronic pain management; KQ2: Other outcomes; KQ3: Adverse effects; and, KQ4: Effectiveness and safety in differing subpopulations. For each category, we provide a description of the characteristics and findings of the individual trials and cohort studies and a summary of key findings. Appendix E, F presents detailed evidence tables on each of the included studies.

Systemic Analgesia

Overview of included studies

Three RCTs[41,42,53] evaluated the efficacy and/or harms of different types of systemic analgesia, in a total of 214 participants; sample size ranged from 30 to 94. Two studies[41,42] compared different parenteral analgesics (parecoxib IV and intrathecal isotonic clonidine vs. diclofenac ± pethidine IM and intrathecal hypertonic clonidine, respectively). The third study[53] compared different oral analgesics (lysine clonixinate vs. metamizole). The mean age of participants in the trials ranged from 77.2 to 78.5 years. Most were female (74.5 percent). Acute pain was measured using the 10cm VAS and the mean baseline pain measure was 6.5cm. All three trials had an unclear risk of bias (Appendix G). Summary of the evidence from these trials is provided in Table 3.

Table 3. Evidence addressing key questions: Systemic analgesia

Key Question	Outcome	Evidence availability	Strength of Evidence
KQ1	**Acute pain**	Yes	2 RCTs reported statistically significant effects in favor of parecoxib IV and intrathecal isotonic clonidine vs. diclofenac±pethidine IM and intrathecal hypertonic clonidine, respectively. The strength of the evidence was rated as insufficient. 1 RCT reported no statistically significant difference between lysine clonixinate vs. metamizole. The strength of the evidence was rated as insufficient.
	Chronic pain	No	
KQ2	**Mortality (30 day and up to 1-year postfracture)**	No	
	Functional status	No	
	Pain medication use; change in type and quantity	Yes	1 RCT comparing lysine clonixinate vs. metamizole reported no statistically significant difference.
	Mental status	Yes	1 RCT comparing lysine clonixinate vs. metamizole reported no statistically significant difference. The strength of the evidence was rated as insufficient.
	Health-related quality of life	No	
	Quality of sleep in the hospital	No	
	Ability to participate in rehabilitation	No	
	Return to prefracture living arrangements	No	
	Health services utilization	No	

KQ = key question; RCT = randomized controlled trial

Table 3. Evidence addressing key questions: Systemic analgesia (continued)

KQ3	**Frequency of adverse effects**	Yes	1 RCT comparing intrathecal isotonic vs. hypertonic clonidine reported no events of damage to surrounding structures, headaches, or infections. 1 RCT comparing lysine clonixinate vs. metamizole reported a statistically significant higher incidence of adverse effects and gastrointestinal disturbances in the lysine clonixinate group; other adverse effects were not significant.
KQ4	**Effectiveness and safety in differing subpopulations**	No	

Key Question 1: Acute and chronic pain management

Acute pain (post-treatment means) was reported in all three RCTs[41,42,53] (Table 4). One trial[41] compared parecoxib IV (n = 35) vs. diclofenac IM ± pethidine IM (n = 55). There was a statistically significant effect difference in additional pain relief in favor of parecoxib IV (MD -0.70; 95% CI -1.04, -0.36; p <0.0001). The second trial[42] compared intrathecal isotonic clonidine (n = 15) vs. intrathecal hypertonic clonidine (n = 15). There was a statistically significant effect difference in additional pain relief in favor of isotonic clonidine (MD -1.69; 95% CI -2.01, -1.37; p <0.00001). The third trial[53] compared lysine clonixinate (n = 48) vs. metamizole (n = 46), but no evidence of a significant effect difference was noted (MD -0.43; 95% CI -1.30, 0.44; p = 0.33). The strength of the evidence was rated as insufficient to make any firm conclusions regarding these interventions.

Key Question 2: Other outcomes

Pain medication use. Additional pain medication use was reported in one trial[53] comparing lysine clonixinate (n = 48) vs. metamizole (n = 46) (Table 4). There was no statistically significant difference in the number of participants requiring additional pain medication (OR 3.00; 95% CI 0.30, 29.94; p = 0.35).

Mental status. The incidence of delirium was reported in one trial[53] comparing lysine clonixinate (n = 48) vs. metamizole (n = 46) (Table 4). There was no statistically significant difference in the number of participants developing delirium (OR 0.96; 95% CI 0.06, 15.77; p = 0.98). The strength of the evidence was rated as insufficient to make any firm conclusions regarding these interventions.

Key Question 3: Adverse effects

Data on adverse effects associated with the administration of different types of systemic analgesia were available from two RCTs[42,53] (Table 4). One trial[53] comparing lysine clonixinate (n = 48) vs. metamizole (n = 46) reported the number of participants with any adverse event and found a statistically significant difference in the number of patients experiencing any adverse event, in favor of metamizole (OR 3.50; 95% CI 1.04, 11.81; p = 0.04). Similarly, fewer patients in the metamizole group reported any gastrointestinal disturbance (OR 11.84; 95% CI 1.45, 96.75; p = 0.02). The remaining reported adverse effects were from single studies and did not demonstrate any significant statistical differences between the pain management interventions.

Key Question 4: Efficacy, effectiveness, and safety in subpopulations

No data were reported on subpopulations.

Table 4. Evidence summary table (randomized controlled trials): Systemic analgesia

	Outcome or subgroup	Studies (N)	Participants (N)	Statistical method	Effect estimate	I^2
KQ1	**Acute pain (post-treatment means)**					
	IM Analgesia[41]	1	90	MD (95% CI)	**-0.70 (-1.04, -0.36)***	NA
	Oral analgesia[53]	1	94	MD (95% CI)	-0.43 (-1.30, 0.44)	NA
	Intrathecal analgesia[42]	1	30	MD (95% CI)	**-1.69 (-2.01, -1.37)***	NA
	Acute pain (at rest)					
	Oral analgesia[53]	1	94	MD (95% CI)	-0.43 (-1.30, 0.44)	NA
KQ2	**Additional pain medication use**					
	Oral analgesia[53]	1	94	OR (95% CI)	3.00 (0.30, 29.94)	NA
	Delirium					
	Oral analgesia[53]	1	94	OR (95% CI)	0.96 (0.06, 15.77)	NA
KQ3	**Any adverse event**					
	Oral analgesia[53]	1	94	OR (95% CI)	**3.50 (1.04, 11.81)***	NA
	Damage to surrounding structures					
	Intrathecal analgesia[42]	1	30		NE	
	Gastrointestinal disturbances					
	Oral analgesia[53]	1	94	OR (95% CI)	**11.84 (1.45, 96.75)***	NA
	Headache					
	Intrathecal analgesia[42]	1	30		NE	
	Infection					
	Intrathecal analgesia[42]	1	30		NE	
	Respiratory distress					
	Oral analgesia[53]	1	94	OR (95% CI)	0.96 (0.06, 15.77)	0%

CI = confidence interval; IM = intramuscular; KQ = key question; MD = mean difference; NA = not applicable; NE = not estimable; OR = odds ratio; * = statistically significant difference

Anesthesia

Overview of included studies

Twenty RCTs[54-62,64,66-69,71,73-77] and one NRCT[63] evaluated the efficacy and/or harms of anesthesia including neuraxial (i.e., continuous or single administration spinal or epidural anesthesia) or neuraxial anesthesia vs. general anesthesia in a total of 939 participants; study sample sizes ranged from 20 to 74. Additionally, four cohort studies[65,70,72,78] provided data on spinal anesthesia vs. general anesthesia or other modes of administration of spinal anesthesia in 716 participants. The mean age of participants ranged from 70.0 to 86.0 years. Most were female (range = 38.9 to 99.3 percent). Acute pain was measured using different scales (numeric rating score (1-5) (NRS) and 10cm VAS). The average baseline VAS pain score was 5.0 and the average baseline pain score on the NRS was 1.9.

Three RCTs[54,57,61,67] and one NRCT[63] had a high risk of bias, while the other 17 RCTs[55,56,58-60,62-64,66,68,69,71,73-77] had an unclear risk of bias (Appendix G). The cohort studies were of moderate quality (median = 8) (Appendix I). Summary of the evidence from these trials is provided in Table 5.

Based on the primary interventions and comparison groups, the studies were grouped as follows:

1. Spinal anesthesia vs. epidural or general anesthesia (n = 4);[54,57,62,70]
2. Neuraxial anesthesia: addition of clonidine, fentanyl, meperidine, morphine, or sufentanil (n = 15);[54-56,60,62-64,66-70,74,75,77]
3. Neuraxial anesthesia: different doses or modes of administration (n = 12)[58-61,65,67,71-73,75,76,78]
    a. Spinal anesthesia (continuous vs. single administration)
    b. Spinal anesthesia (different doses)

Table 5. Evidence addressing key questions: Anesthesia

Key Question	Outcome	Evidence availability	Strength of Evidence
KQ 1	**Acute pain**	Yes	1 RCT reported a statistically significant effect difference in favor of spinal anesthesia vs. general anesthesia. The strength of the evidence was rated as insufficient. 4 RCTs and NRCTs reported no significant difference comparing the addition of fentanyl, morphine or sufentanil vs. standard spinal anesthesia. The strength of the evidence was rated as insufficient.
	Chronic pain	No	
KQ2	**Mortality (30 day and up to 1-year postfracture)**	Yes	2 RCTs and 2 cohorts comparing continuous vs. single spinal anesthesia reported no significant difference in mortality at 30 days. The strength of the evidence was rated as insufficient. 3 RCTs and 1 cohort study comparing continuous vs. single spinal anesthesia reported no statistically significant difference. The strength of the evidence was rated as insufficient.
	Functional status	No	

KQ = key question; NRCT = nonrandomized controlled trial; RCT = randomized controlled trial

Table 5. Evidence addressing key questions: Anesthesia (continued)

Key Question	Outcome	Evidence availability	Strength of Evidence
KQ2	**Pain medication use; change in type and quantity**	Yes	6 RCTs comparing the addition of clonidine, fentanyl, morphine or sufentanil with standard spinal anesthesia were indeterminate. 2 RCTs comparing continuous vs. single spinal anesthesia found no statistically significant difference. 1 RCT comparing different doses of spinal anesthesia found no statistically significant difference.
	Mental status	Yes	1 RCT comparing the use of spinal anesthesia vs. general anesthesia found no statistically significant difference. The strength of the evidence was rated as low. 1 RCT comparing the addition of morphine with standard spinal anesthesia found no statistically significant difference. The strength of the evidence was rated as low. 2 RCTs comparing continuous vs. single spinal anesthesia found no statistically significant difference. The strength of the evidence was rated as low.
	Health-related quality of life	No	
	Quality of sleep in the hospital	No	
	Ability to participate in rehabilitation	No	
	Return to prefracture living arrangements	No	
	Health services utilization	Yes	2 RCTs comparing spinal vs. general anesthesia found LOS for acute hospitalization was significantly less in the general anesthesia group. 2 RCTs comparing continuous vs. single spinal anesthesia found no statistically significant difference.
KQ3	**Frequency of adverse effects**	Yes	1 cohort study comparing single dose spinal vs. general anesthesia reported a statistically significant effect difference in hypotension in favor of spinal anesthesia. Evidence for the other outcomes was indeterminate. 1 RCT comparing the addition of sufentanil vs. standard spinal anesthesia reported a significantly higher incidence of hypotension with standard spinal anethesia. Evidence for the other outcomes in 10 RCTs comparing the addition of clonidine, fentanyl, meperidine, morphine or sufentanil vs. standard spinal anesthesia was indeterminate. 1 RCT and 1 cohort study comparing different doses of spinal anesthesia reported the incidence of participants having hypotention was significantly greater with higher doses and higher concentrations of spinal anesthesia.

Table 5. Evidence addressing key questions: Anesthesia (continued)

KQ3	**Frequency of adverse effects**		Other adverse events were examined in single trials and the strength of the evidence for the probability of stroke, myocardial infarction, delirium or renal failure was rated as insufficient.
KQ4	**Effectiveness and safety in differing subpopulations**	No	

Key Question 1: Acute and chronic pain management

Spinal vs. general anesthesia

One RCT[57] comparing (spinal anesthesia (n = 15) vs. general anesthesia (n = 15) reported a statistically significant difference of additional pain relief in favor of spinal anesthesia (MD = -0.86; 95% CI -1.30, -0.42; p = 0.0001) (Table 6). The strength of the evidence was rated as insufficient to make any firm conclusions regarding these interventions.

Neuraxial anesthesia: addition of clonidine, fentanyl, meperidine, morphine, or sufentanil

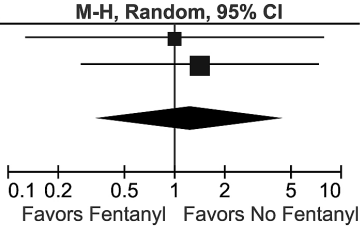
Acute pain (post-treatment means) was reported in three RCTs[64,68,74] comparing additional fentanyl (n = 20) vs. standard spinal anesthesia (n = 20),[68] additional morphine (n = 20) vs. standard spinal anesthesia (n = 20),[64] and additional sufentanil (n = 25) vs. standard spinal anesthesia (n = 25)[74] (Table 6). In the studies comparing the addition of fentanyl or sufentanil, no patients reported feeling pain following the procedure. In the study comparing the addition of morphine, there was no significant difference in pain relief vs. standard spinal anesthesia (MD = -0.36; 95% CI -1.11, 0.39; p = 0.35).

Acute pain on day 1 was reported in one RCT[68] and one NRCT[63] comparing additional fentanyl (n = 40) vs. standard spinal anesthesia (n = 40) (Table 6). There was no significant difference in pain on day 1 following the addition of fentanyl (OR 1.24; 95% CI 0.34, 4.48; p = 0.75) (Figure 3). The strength of the evidence was rated as insufficient to make any firm conclusions regarding these interventions.

Figure 3. Neuraxial anesthesia: Addition of fentanyl – acute pain (day 1)

Study or Subgroup	Fentanyl Events	Fentanyl Total	No Fentanyl Events	No Fentanyl Total	Weight	Odds Ratio M-H, Random, 95% CI
Krobot 2006	2	20	2	20	38.8%	1.00 [0.13, 7.89]
Martyr 2005	4	20	3	20	61.2%	1.42 [0.27, 7.34]
Total (95% CI)		**40**		**40**	**100.0%**	**1.24 [0.34, 4.48]**
Total events	6		5			

Heterogeneity: Tau² = 0.00; Chi² = 0.07, df = 1 (P = 0.80); I² = 0%
Test for overall effect: Z = 0.32 (P = 0.75)



Key Question 2: Other outcomes

Spinal vs. general anesthesia or spinal vs. epidural anesthesia

Mortality (30 day). Thirty day mortality was reported in two RCTs[54,61] (n = 99 participants) (Table 6). There was no significant difference in mortality rates following spinal anesthesia vs. general anesthesia (10/53 vs. 5/46; OR 1.73; 95% CI 0.53, 5.68; p = 0.36).

Additionally, 30 day mortality was reported in two cohorts[70,72] (n = 650 participants) (Table 7). Pooling was not performed because of marked heterogeneity between the included studies.

Subgroup analyses according to the mode of administration of spinal anesthesia revealed a statistically significant difference in the incidence of 30 day mortality for participants receiving continuous spinal anesthesia compared with general anesthesia (8/182 vs. 4/28; OR 0.28; 95% CI 0.08, 0.99; P = 0.05) favoring spinal anesthesia. There was no significant difference in mortality rates following single dose spinal vs. general anesthesia (25/246 vs. 11/194; OR 1.94; 95% CI 0.52, 7.31; p = 0.33). The strength of the evidence was rated as low to make any firm conclusions regarding these interventions.

Mental status. Delirium measured with the Mini Mental State Examination (MMSE) was reported in one RCT[57] comparing spinal anesthesia (n = 15) vs. general anesthesia (n = 15) (Table 6). There was no signicant difference between the the two groups (8/15 vs. 9/15; OR 0.76; 95% CI 0.18, 3.24; p = 0.71). The strength of the evidence was rated as insufficient to make any firm conclusions regarding these interventions.

Health services utilization. LOS for acute hospitalization was reported in two RCTs[54,61] comparing spinal anesthesia (n = 53) vs. general anesthesia (n = 46) (Table 6). The LOS was significantly less in the general anesthesia group (MD 1.69; 0.38, 3.01; p = 0.01).The variance for one trial[61] was imputed from the reported p value, while the variance was for the second trial[54] was imputed from the first trial[61] as no measure of variance was reported.

Neuraxial anesthesia: addition of clonidine, fentanyl, meperidine, morphine, or sufentanil

Additional pain medication use. Additional pain medication use was reported in all six RCTs (Table 6). Differences in effect estimates from one RCT[62] (n = 40 participants) comparing the addition of clonidine vs. standard spinal anesthesia was not estimable because all participants required additional pain medication. The pooled estimate from three trials[56,66,77] comparing the addition of fentanyl vs. standard spinal anesthesia (n = 102 participants) showed no statistically significant difference between groups (2/51 vs. 0/51; OR 5.51; 95% CI 0.25, 122.08; p = 0.28).

There was no significant difference in additional pain medication use in the RCT[64] (n = 40) that compared the addition of morphine to spinal anesthesia vs. standard spinal anesthesia (9/20 vs. 15/20; OR 0.27; 95% CI 0.07, 1.04; p = 0.06). Similarly, there was no difference in reported additional pain medication use between three RCTs[66,74,77] that compared the addition of sufentanil to spinal anesthesia with standard spinal anesthesia (n = 132; 1/66 vs. 0/ 66; OR 3.15; 95% CI 0.12, 81.74; p = 0.49).

Mental status. Delirium (confusion) was reported in one RCT[64] (n = 40) comparing the addition of morphine vs. standard spinal anesthesia (Table 6). Only one event occurred in this trial, therefore there was no significant differences in the number of patients with post-operative delirium between the two groups (1/20 vs. 0/20; OR 3.15; 95% CI 0.12, 82.16; p = 0.49). The strength of the evidence was rated as low to make any firm conclusions regarding these interventions.

Neuraxial anesthesia: Different doses and modes of administration

Spinal anesthesia (continuous vs. single administration)

Mortality (30 day). Three trials[59,61,71] (n = 163) reported 30 day mortality (Table 6). Two of the trials[59,71] did not record any events in either group. In the third trial,[61] there was no significant difference between continuous vs. single administration spinal anesthesia (2/81 vs. 4/82; OR 0.46; 95% CI 0.07, 3.02; p = 0.42). Additionally, it should be noted that 30 day mortality was reported in one other cohort study[72] (n = 291) (Table 7). There was no significant difference

between continuous vs. single administration of spinal anesthesia (8/182 vs. 5/109; OR 0.96; 95% CI 0.30, 3.00; p = 0.94). The strength of the evidence was rated as insufficient to make any firm conclusions regarding these interventions.

Additional pain medication. Additional pain medication use was reported in two trials[59,71] (n = 134) (Table 6). The MD in additional pain medication use was not estimable as there were no events in either group.

Health services utilization. LOS for acute hospitalization was reported in two trials[59,61] (n = 89) (Table 6). There was no significant difference between groups (MD = -0.98; 95% CI -2.06, 0.10; p = 0.07). The variance for one trial[61] was imputed from the reported p value.

Mental status. Delirium (confusion) was reported in two trials[59,71] (n = 134) (Table 6). There was no significant difference between groups in the occurrence of delirium (5/67 vs. 4/67; OR 1.27; 95% CI 0.32, 4.99; p = 0.73). The strength of the evidence was rated as low to make any firm conclusions regarding these interventions.

Spinal anesthesia (different doses)

Mortality (30 day). One NRCT[72] (n = 182) reported that there was no significant difference in 30 day mortality rates between the two groups (4/121 vs. 4/61; OR 0.49; 95% CI 0.12, 2.02; p = 0.32) (Table 6). The strength of the evidence was rated as insufficient to make any firm conclusions regarding these interventions.

Pain medication use. Additional pain medication use was reported in one RCT[60] (n =60) (Table 6). There was no significant difference between groups following spinal anesthesia at different doses (4 vs. 5mg, 4 vs. 6mg, or 5 vs. 6mg).

Key Question 3: Adverse effects

Spinal vs. general anesthesia or spinal vs. epidural anesthesia

Two RCTs[57,61] (n = 73) and one cohort study[72] (n = 333) evaluated the nature and frequency of adverse effects associated with the administration of spinal anesthesia vs. general anesthesia (Table 6, 7). There were no significant differences in the occurrence of hypotension in the RCTs.[57,61] The incidence of hypotension from the different arms of the cohort study[72] were not pooled because of marked heterogeneity among the included cohorts. There was no significant differences in the incidence of hypotension in the continuous spinal anesthesia groups compared with general anesthesia (OR 0.35; 95% CI 0.10, 1.28; p = 0.11). There was a significantly lower incidence of hypotension with single dose spinal anesthesia compared with general anesthesia (OR 0.04; 0.01, 0.13; p < 0.00001). The remaining reported adverse effects were from single studies and did not demonstrate any significant statistical differences between the pain management interventions.

Neuraxail anesthesia: addition of clonidine, fentanyl, meperidine, morphine, or sufentanil

A total of 10 RCTs[56,62,64,66-69,74,75,77] (n = 388) evaluated the harms of the administration of clonidine, fentanyl, meperidine, morphine, or sufentanil during neuraxaial anesthesia (Table 6). Additionally, one NRCT[63] provided data on 40 participants (Table 7).

Addition of clonidine

The reported adverse effects were from a single trial[62] and did not demonstrate any significant statistical differences (Table 6).

Addition of fentanyl

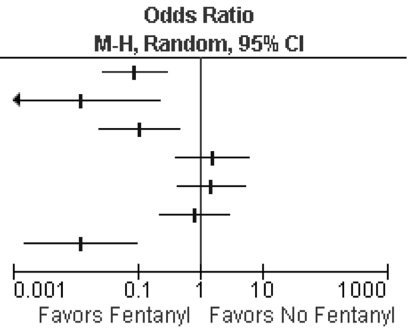
Allergic reaction. There was no statistically significant difference in the number of participants reporting an allergic reaction in four trials[63,66-68] (14/81 in the group with fetany vs. l5/83 in the group with no fentanyl).

Gastrointestinal (GI) symptoms. There were no reports of GI symptoms in three trials[63,68,75] (n = 140).

Hypotension. Seven trials[55,56,63,66-68,77] (n = 284) reported the frequency of hypotension (Figure 4). Results of the studies were not pooled due to high heterogeneity (I^2 = 83 percent) which was not explained by study design (i.e., removal of the NRCT[63]), risk of bias (i.e., removal of the trials[63,67] with a high risk of bias), or specific intervention details (i.e., type and quantity).

Figure 4. Neuraxial anesthesia: Addition of fentanyl – hypotension

Study or Subgroup	Fentanyl Events	Fentanyl Total	No Fentanyl Events	No Fentanyl Total	Odds Ratio M-H, Random, 95% CI
Alonso Chico 2003	6	30	22	30	0.09 [0.03, 0.30]
Ben-David 2000	1	10	9	10	0.01 [0.00, 0.23]
Krobot 2006	4	20	14	20	0.11 [0.03, 0.46]
Malek 2004	7	21	5	21	1.60 [0.41, 6.19]
Martyr 2001	13	20	12	22	1.55 [0.45, 5.37]
Martyr 2005	7	20	8	20	0.81 [0.22, 2.91]
Said-Ahmed 2006	2	20	18	20	0.01 [0.00, 0.10]

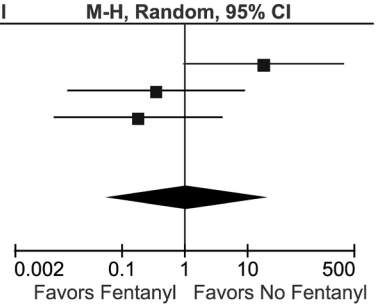


Nausea/ vomiting. In the five trials[56,66-68,75] (n = 40) that reported the frequency of nausea or vomiting there was no statistically significant difference between the groups (6/111 vs. 3/93; OR 1.10; 95% CI 0.06, 20.73; p = 0.95).

Figure 5. Neuraxial anesthesia: Addition of fentanyl – nausea/vomiting

Study or Subgroup	Fentanyl Events	Fentanyl Total	No Fentanyl Events	No Fentanyl Total	Weight	Odds Ratio M-H, Random, 95% CI
Ben-David 2000	0	10	0	10		Not estimable
Malek 2004	6	21	0	21	34.6%	18.03 [0.94, 344.40]
Martyr 2001	0	20	1	22	32.1%	0.35 [0.01, 9.08]
Martyr 2005	0	20	2	20	33.3%	0.18 [0.01, 4.01]
Qamarul Hoda 2007	0	40	0	20		Not estimable
Total (95% CI)		**111**		**93**	**100.0%**	**1.10 [0.06, 20.73]**
Total events	6		3			

Heterogeneity: Tau² = 4.25; Chi² = 5.40, df = 2 (P = 0.07); I² = 63%
Test for overall effect: Z = 0.06 (P = 0.95)



Respiratory distress. There were no reports of respiratory distress in three trials[63,66,67] (n = 124).

Other adverse effects. The remaining reported adverse effects were from single trials and did not demonstrate any statistically significant differences.

Addition of meperidine

Adverse effects were reported from a single trial and did not demonstrate any significant statistical differences.

Addition of morphine

Adverse effects. The reported adverse effects were from single trials and did not demonstrate any significant statistical differences.

Addition of sufentanil

Hypotension. Three trials[66,74,77] (n = 132) reported a significant lower incidence of hypotension in participants receiving sufentanil (8/66 in the group with sufentanil vs. 45/66 in the group with no sulfentantil).

Other adverse effects. The remaining reported adverse effects were from single studies and did not demonstrate any significant statistical differences.

Neuraxial anesthesia: Different doses and modes of administration (i.e., continuous vs. single administration)

Spinal anesthesia (continuous vs. single administration)

Hypotension. Hypotension was reported for two trials[61,71] (n = 103). There was a statistically significant difference between groups continuous spinal anesthesia (13/51 vs. 37/52; OR 0.12; 95% CI 0.03, 0.51; p = 0.004). Similarly, hypotension was reported in one cohort study[72] (n = 291) and found a statistically significant difference continuous spinal anesthesia (26/182 vs. 74/109; OR 0.08; 95% CI 0.04, 0.14; p < 0.00001).

Other adverse effects. The remaining reported adverse effects were from single trials and studies and did not demonstrate any significant statistical differences between the pain management interventions.

Spinal anesthesia (different doses)

Bradycardia. Bradycardia was reported in two trials[58,60] (n = 120). There was no significant difference for different doses of spinal anesthesia (Bupivacaine: 4 vs. 5mg: 0/30 vs. 0/30; 4 vs. 6mg: 0/30 vs. 0/30; 5 vs. 6 mg: 3/29 vs. 3/31; Levobupivacaine: 3/29 vs. 3/31).

Hypotension. Hypotension was reported for four trials[58,60,73,76] in 190 participants. There were statistically significant differences in hypotension following spinal anesthesia with 4 vs. 6mg of bupivacaine (0/30 vs. 10/30; OR 0.03; 95% CI 0.00, 0.58; p = 0.02), and 5 vs. 6mg of bupivacaine (4/30 vs. 10/30; OR 0.31; 95% CI 0.08, 1.13; p = 0.08). However, there was no statistically significant reductions in hypotension following spinal anesthesia with 0.15-0.25% vs.0.5% of bupivacaine (3/15 vs. 8/15), 0.5% vs. 0.75% of levobupivacaine (13/29 vs. 10/31), with 4 vs. 5mg of bupivacaine (0/30 vs. 4/30), and with 2.5 vs. 5mg of bupivacaine (7/20 vs. 8/20).

Two controlled clinical studies[65,72] reported hypotension in 207 evaluable participants. There was a statistically significant reduction in hypotension following spinal anesthesia with 2.5 vs. 5mg of bupivacaine (5/121 vs. 21/61; OR 0.08; 95% CI 0.03, 0.23; p <0.00001), and 0.125% vs. 0.5% of bupivacaine (4/12 vs. 10/13; OR 0.15; 95% CI 0.03, 0.87; p = 0.03).

Nausea/vomiting. There were no reports of nausea or vomiting in two trials[60,75] (n = 100).

Other adverse effects. The remaining reported adverse effects were from single studies and cohorts and did not demonstrate any significant statistical differences between the pain management interventions.

Key question 4: Efficacy, effectiveness, and safety in subpopulations

No data were reported on subpopulations.

Table 6. Evidence summary table (randomized and nonrandomized controlled trials): Anesthesia

Table 6-A. Epidural (continuous) vs. spinal anesthesia (continuous): (RCT/NRCT)

	Outcome or Subgroup	Studies	Participants	Statistical Method	Effect Estimate	I^2
KQ3	**Damage to surrounding structures**[62]	1	40		NE	NA

KQ = key question; NA = not applicable; NE = not estimable; RCT/NRCT = randomized and nonrandomized controlled trials

Table 6-B. Spinal vs. general anesthesia: (RCT/NRCT)

	Outcome or Subgroup	Studies	Participants	Statistical Method	Effect Estimate	I^2
KQ1	**Acute pain (post-treatment means)**					
	Spinal anesthesia (single)[57]	1	30	MD (95% CI)	**-0.86 (-1.30, -0.42)***	NA
KQ2	**Delirium**					
	Spinal anesthesia (single)[57]	1	30	OR (95% CI)	0.76 (0.18, 3.24)	NA
	LOS	2	99	MD (95% CI)	**1.69 (0.38, 3.01)***	0%
	Spinal anesthesia (incremental)[61]	1	21	MD (95% CI)	2.00 (-0.16, 4.16)	NA
	Spinal anesthesia (single)[54,61]	2	78	MD (95% CI)	1.55 (-0.20, 3.31)	7%
	Mortality 30 days	2	416	OR (95% CI)	**2.48 (1.28, 4.79)***	0%
	Spinal anesthesia (incremental)[61]	1	21	OR (95% CI)	1.00 (0.07, 13.37)	NA
	Spinal anesthesia (single)[54,61]	2	78	OR (95% CI)	2.01 (0.53, 5.68)	0%
KQ3	**Hypotension**	2	73	OR (95% CI)	0.36 (0.04, 2.92)	72%
	Spinal anesthesia (incremental)[61]	1	21	OR (95% CI)	**0.07 (0.01, 0.61)***	0%
	Spinal anesthesia (single)[57,61]	2	52	OR (95% CI)	0.76 (0.06, 9.90)	75%
	Myocardial Infarction	1	43	OR (95% CI)	1.55 (0.06, 42.91)	NA
	Spinal anesthesia (incremental)[61]	1	21		NE	
	Spinal anesthesia (single)[61]	1	22	OR (95% CI)	1.55 (0.06, 42.91)	NA
	ST depression	1	43	OR (95% CI)	0.56 (0.11, 2.81)	NA
	Spinal anesthesia (incremental)[61]	1	21	OR (95% CI)	0.22 (0.03, 1.85)	NA
	Spinal anesthesia (single)[61]	1	22	OR (95% CI)	1.17 (0.19, 7.12)	NA

CI = confidence intervals; KQ = key question; LOS = length of stay; MD = mean difference; NA = not applicable; NE = not estimable; OR = odds ratio; RCT/NRCT = randomized and nonrandomized controlled trials; * = statistically significant

Table 6-C. Spinal anesthesia (continuous vs. single administration): (RCT/NRCT)

	Outcome or Subgroup	Studies	Participants	Statistical Method	Effect Estimate	I^2
KQ2	**Additional pain medication use**[59,71]	2	134		NE	
	Delirium[59,71]	2	134	OR (95% CI)	1.27 (0.32, 4.99)	0%
	LOS[59,61]	2	89	MD (95% CI)	0.01 (-7.75, 7.77)	0%

CI = confidence intervals; KQ = key question; LOS = length of stay; MD = mean difference; MI = myocardial infarction; NE = not estimable; OR = odds ratio; * = statistically significant; RCT/NRCT = randomized and nonrandomized controlled trials

Table 6-C. Spinal anesthesia (continuous vs. single administration): (RCT/NRCT) (continued)

	Outcome or Subgroup	Studies	Participants	Statistical Method	Effect Estimate	I^2
KQ2	**Mortality 30 days**[59,61,71]	3	163	OR (95% CI)	0.46 (0.07, 3.02)	0%
KQ3	**Bradycardia**[71]	1	74		NE	
	GI symptoms[59]	1	60	OR (95% CI)	1.00 (0.06, 16.76)	NA
	Headache[59]	1	60		NE	
	Hypotension[61,71]	2	103	OR (95% CI)	**0.12 (0.03, 0.51)***	50%
	MI[61]	1	29	OR (95% CI)	0.33 (0.01, 8.88)	NA
	Myocardial Ischemia[71]	1	74		NE	
	ST depression[61]	1	29	OR (95% CI)	0.19 (0.03, 1.16)	NA
	Stroke[71]	1	74		NE	

Table 6-D. Neuraxial anesthesia (addition of clonidine): RCT/NRCT

	Outcome or Subgroup	Studies	Participants	Statistical Method	Effect Estimate	I^2
KQ2	**Additional pain medication use**[62]	1	40		NE	
	Epidural anesthesia (continuous)[62]	1	20		NE	
	Spinal anesthesia (continuous)[62]	1	20		NE	
KQ3	**Damage to surrounding structures**[62]	1	40		NE	
	Epidural anesthesia (continuous)[62]	1	20		NE	
	Spinal anesthesia (continuous)[62]	1	20		NE	
	Headache[62]	1	40		NE	
	Epidural anesthesia (continuous)[62]	1	20		NE	
	Spinal anesthesia (continuous)[62]	1	20		NE	
	Infection	1	40		NE	
	Epidural anesthesia (continuous)[62]	1	20		NE	
	Spinal anesthesia (continuous)[62]	1	20		NE	

KQ = key question; NE = not estimable; RCT/NRCT = randomized and nonrandomized controlled trials

Table 6-E. Spinal (single) anesthesia (addition of fentanyl): RCT/NRCT

	Outcome or Subgroup	Studies	Participants	Statistical Method	Effect Estimate	I^2
KQ1	**Acute pain (post-treatment means)**[68]	1	40		NE	
	Day 1 Pain[63,68]	2	80	OR (95% CI)	1.24 (0.34, 4.48)	0%
KQ2	**Additional pain medication use**[56,66,77]	3	102	OR (95% CI)	5.51 (0.25, 122.08)	
KQ3	**Allergic reaction**[63,66-68]	4	164	OR (95% CI)	2.86 (0.83, 9.80)	16%
	Bradycardia[66]	1	42	OR (95% CI)	8.14 (0.39, 167.98)	NA
	GI symptoms[63,68,75]	3	140		NE	
	Headache[63]	1	40		NE	

CI = confidence intervals; KQ = key question; NA = not applicable; NP = not pooled; NE = not estimable OR = odds ratio; RCT/NRCT = randomized and nonrandomized controlled trials

Table 6-E. Spinal (single) anesthesia (addition of fentanyl): RCT/NRCT

	Outcome or Subgroup	Studies	Participants	Statistical Method	Effect Estimate	I^2
KQ3	**Hypotension**[55,56,63,66-68,75]	7	284		NP	83%
	Nausea/ vomiting[56,66-68,75]	5	204	OR (95% CI)	1.10 (0.06, 20.73)	63%
	Neurological complications[63]	1	40		NE	
	Respiratory distress[63,66,67]	3	124		NE	

Table 6-F. Spinal (continuous)anesthesia (addition of meperidine): RCT/NRCT

	Outcome or Subgroup	Studies	Participants	Statistical Method	Effect Estimate	I^2
KQ3	**Headache**[69]	1	34		NE	

KQ = key question; NE = not estimable; RCT/NRCT = randomized and nonrandomized controlled trials

Table 6-G. Spinal (single)anesthesia (addition of morphine): RCT/NRCT

	Outcome or Subgroup	Studies	Participants	Statistical Method	Effect Estimate	I^2
KQ1	**Acute pain (post-treatment means)**[64]	1	40	MD (95% CI)	-0.36 (-1.11, 0.39)	NA
KQ2	**Additional pain medication use**[64]	1	40	OR (95% CI)	0.27 (0.07, 1.04)	NA
	Delirium[64]	1	40	OR (95% CI)	3.15 (0.12, 82.16)	NA
KQ3	**Allergic reaction**[64]	1	40	OR (95% CI)	1.00 (0.06, 17.18)	NA
	Any adverse event[64]	1	40	OR (95% CI)	4.75 (0.48, 46.91)	NA
	GI symptoms[64]	1	40	OR (95% CI)	11.18 (0.56, 222.98)	NA
	Headache[64]	1	40		NE	
	Hypopnoea[64]	1	40		NE	
	Hypotension[64]	1	40		NE	
	Nausea/ vomiting[64]	1	40	OR (95% CI)	11.18 (0.56, 222.98)	NA
	Respiratory distress[64]	1	40		NE	

CI = confidence intervals; KQ = key question; MD = mean difference; NA = not applicable; NE = not estimable; OR = odds ratio; RCT/NRCT = randomized and nonrandomized controlled trials

Table 6-H. Spinal (single) anesthesia (addition of sufentanil): RCT/NRCT

	Outcome or Subgroup	Studies	Participants	Statistical Method	Effect Estimate	I^2
KQ1	**Acute pain (post-treatment means)**[74]	1	50		NE	
KQ2	**Additional pain medication use)**[66,74,77]	3	132	OR (95% CI)	3.15 (0.12, 81.74)	0%
KQ3	**Allergic reaction**[66]	1	42		NE	
	Bradycardia[66]	1	42	OR (95% CI)	11.06 (0.56, 219.68)	NA
	Hypotension[66,74,77]	3	132	OR (95% CI)	**0.05 (0.01, 0.34)***	71%
	Nausea/ vomiting[66]	1	42		NE	
	Respiratory distress[66]	1	42		NE	

CI = confidence intervals; KQ = key question; NA = not applicable; NE = not estimable; OR = odds ratio; * = statistically significant; RCT/NRCT = randomized and nonrandomized controlled trials

Table 6-I. Spinal anesthesia (Different doses): RCT/NRCT

	Outcome or Subgroup	Studies	Participants	Statistical Method	Effect Estimate	I^2
KQ2	**Additional pain medication use**					
	Bupivacaine: 4 vs. 5mg[60]	1	60	OR (95% CI)	2.36 (0.63, 8.92)	NA
	Bupivacaine: 4 vs. 6mg[60]	1	60	OR (95% CI)	3.27 (0.77, 13.83)	NA
	Bupivacaine: 5 vs. 6mg[60]	1	60	OR (95% CI)	1.38 (0.28, 6.80)	NA
KQ3	**GI symptoms**					
	Bupivacaine: 6 vs. 8mg[75]	1	40		NE	
	Bupivacaine: 6 vs.10mg[75]	1	40		NE	
	Bupivacaine: 8 vs.10mg[75]	1	40		NE	
	Allergic reaction					
	Bupivacaine: 4 vs. 5mg[60]	1	60	OR (95% CI)	0.62 (0.15, 2.45)	NA
	Bupivacaine: 4 vs. 6mg[60]	1	60	OR (95% CI)	0.62 (0.15, 2.45)	NA
	Bupivacaine: 5 vs. 6mg[60]	1	60	OR (95% CI)	1.00 (0.28, 3.54)	NA
	Respiratory distress					
	Bupivacaine: 4 vs. 5mg[60]	1	60		NE	
	Bupivacaine: 4 vs. 6mg[60]	1	60		NE	
	Bupivacaine: 5 vs. 6mg[60]	1	60		NE	
	Bradycardia					
	Bupivacaine: 4 vs. 5mg[60]	1	60		NE	
	Bupivacaine: 4 vs. 6mg[60]	1	60		NE	
	Bupivacaine: 5 vs. 6mg[60]	1	60		NE	
	Levobupivacaine: 0.5% vs. 0.75%[58]	1	60	OR (95% CI)	1.08 (0.20, 5.82)	NA
	Hypotension					
	Bupivacaine: 2.5 vs. 5mg[76]	1	40	OR (95% CI)	0.81 (0.22, 2.91)	NA
	Bupivacaine: 4 vs. 5mg[60]	1	60	OR (95% CI)	0.10 (0.00, 1.88)	NA
	Bupivacaine: 4 vs. 6mg[60]	1	60	OR (95% CI)	**0.03 (0.00, 0.58)***	NA
	Bupivacaine: 5 vs. 6mg[60]	1	60	OR (95% CI)	0.31 (0.08, 1.13)	NA
	Bupivacaine: 0.15 – 0.25% vs. 0.5%[73]	1	30	OR (95% CI)	0.22 (0.04, 1.11)	NA
	Levobupivacaine: 0.5% vs. 0.75%[58]	1	60	OR (95% CI)	1.71 (0.60, 4.88)	NA
	Nausea/vomiting					
	Bupivacaine: 4 vs. 5mg[60]	1	60		NE	
	Bupivacaine: 4 vs. 6mg[60]	1	60		NE	

CI = confidence intervals; KQ = key question; NA = not applicable; NE = not estimable; OR = odds ratio; RCT/NRCT = randomized and nonrandomized controlled trials

Table 6-I. Spinal anesthesia (Different doses): RCT/NRCT (continued)

	Outcome or Subgroup	Studies	Participants	Statistical Method	Effect Estimate	I^2
KQ3	Bupivacaine: 5 vs. 6mg[60]	1	60		NE	
	Bupivacaine: 6 vs. 8mg[75]	1	40		NE	
	Bupivacaine: 6 vs.10mg[75]	1	40		NE	
	Bupivacaine: 8 vs.10mg[75]	1	40		NE	
	Residual sensory deficits/motor weakness					
	Levobupivacaine: 0.5% vs. 0.75%[58]	1	60		NE	
	Sedation					
	Bupivacaine: 4 vs. 5mg[60]	1	60		NE	
	Bupivacaine: 4 vs. 6mg[60]	1	60		NE	
	Bupivacaine: 5 vs. 6mg[60]	1	60		NE	
	Urinary retention					
	Bupivacaine: 4 vs. 5mg[60]	1	60		NE	
	Bupivacaine: 4 vs. 6mg[60]	1	60		NE	
	Bupivacaine: 5 vs. 6mg[60]	1	60		NE	

Table 7. Evidence summary table (cohort studies): Anesthesia

Table 7-A. Spinal vs. general anesthesia: Cohort studies

	Outcome or Subgroup	Studies	Participants	Statistical Method	Effect Estimate	I^2
KQ2	**Mortality 30 days**	2	650		NP	80%
	Spinal anesthesia (continuous)[72]	1	210	OR (95% CI)	**0.28 (0.08, 0.99)***	NA
	Spinal anesthesia (single)[70,72]	2	440	OR (95% CI)	0.63 (0.07, 5.77)	NA
KQ3	**Headache**[72]	1	333		NE	
	Spinal anesthesia (continuous)[72]	1	203		NE	
	Spinal anesthesia (single)[72]	1	130		NE	
	Hypotension[72]	1	333		NP	84%
	Spinal anesthesia (incremental)[72]	1	130	OR (95% CI)	0.35 (0.10, 1.28)	NA
	Spinal anesthesia (single)[72]	1	203	OR (95% CI)	**0.04 (0.01, 0.13)***	NA

CI = confidence intervals; KQ = key question; NA = not applicable; NE = not estimable; NP = not pooled; OR = odds ratio; * = statistically significant

Table 7-B. Spinal anesthesia (continuous vs. single administration): Cohort studies

	Outcome or Subgroup	Studies	Participants	Statistical Method	Effect Estimate	I^2
KQ2	Mortality 30 days[72]	1	291	OR (95% CI)	0.96 (0.30, 3.00)	NA
KQ3	Any adverse event[72]	1	291		NE	
	Headache[72]	1	291		NE	
	Hypotension[72]	1	291	OR (95% CI)	**0.08 (0.04, 0.14)***	NA

CI = confidence intervals; KQ = key question; NA = not applicable; NE = not estimable; OR = odds ratio; * = statistically significant

Table 7-C. Spinal (single) anesthesia (lateral vs. supine position): Cohort studies

	Outcome or Subgroup	Studies	Participants	Statistical Method	Effect Estimate	I^2
KQ3	**Bradycardia**[78]	1	41	OR (95% CI)	0.55 (0.15, 1.98)	NA
	Hypotension[78]	1	41	OR (95% CI)	**0.22 (0.06, 0.86)***	NA

CI = confidence intervals; KQ = key question; NA = not applicable; NE = not estimable; OR = odds ratio; * = statistically significant

Table 7-D. Spinal anesthesia (Different doses): Cohort studies

	Outcome or Subgroup	Studies	Participants	Statistical Method	Effect Estimate	I^2
KQ2	**Mortality 30 days**					
	Bupivacaine 2.5 vs. 5mg[72]	1	182	OR (95% CI)	0.49 (0.12, 2.02)	NA
KQ3	**Any adverse event**					
	Bupivacaine 2.5 vs. 5mg[72]	1	182		NE	
	Headache					
	Bupivacaine 2.5 vs. 5mg[72]	1	182		NE	
	Hypotension					
	Bupivacaine: 2.5 vs. 5mg[72]	1	182	OR (95% CI)	0.08 (0.03, 0.23)	NA
	Bupivacaine: 0.125% vs. 0.5%[65]	1	25	OR (95% CI)	0.15 (0.03, 0.87)	NA

CI = confidence intervals; KQ = key question; NE = not estimable; OR = odds ratio

Complementary and Alternative Medicine (CAM)

Overview of included studies

Two RCTs[43,79] evaluated the efficacy and/or harms of the administration of complementary and alternative medicine (CAM) interventions vs. no intervention or sham intervention (n = 98 participants). The mean age ranged from 76.8 to 86.2 years. Most were female (81.7 to 86.7 percent). One trial[43] compared acupressure (n = 18 participants) to sham control (n = 20) delivered pre-operatively. Acute pain was measured using the VAS and the baseline pain measure was 6.5cm. The second trial[79] compared the Jacobson relaxation technique (n = 30 participants) with no intervention (n = 30). Acute pain was measured using the 10-point verbal "Sensation of Pain and Distress Scale". Baseline pain measure was not reported.

One RCT[43] had an unclear risk of bias, while the other[79] had a high risk of bias (Appendix G). Summary of the evidence from these trials is provided in Table 8.

Table 8. Evidence addressing key questions: Complementary and alternative medicine

Key Question	Outcome	Evidence availability	Strength of Evidence
KQ 1	Acute pain	Yes	2 RCTs reported a statistically significant effect in favor of the CAM interventions. The strength of the evidence was rated as insufficient.
	Chronic pain	No	
KQ2	Mortality (30 day and up to 1-year postfracture)	No	
	Functional status	No	
	Pain medication use; change in type and quantity	Yes	1 RCT reported a statistically significant effect in favor of relaxation.
	Mental status	No	
	Health-related quality of life	No	
	Quality of sleep in the hospital	No	
	Ability to participate in rehabilitation	No	
	Return to prefracture living arrangements	No	
	Health services utilization	No	
KQ3	Frequency of adverse effects	No	
KQ4	Effectiveness and safety in differing subpopulations	No	

KQ = key question; RCT = randomized controlled trial

Key Question 1: Acute and chronic pain management

Acute pain (post-treatment means)

Acupressure reduced hip pain compared with a sham intervention[43] (MD -3.01; 95% CI -4.53, -1.49; p <0.0001) (Table 9). It should be noted that the variance was imputed from the reported p value presented in this study. Relaxation also showed a reduction in hip pain compared with no relaxation (Sensation of Pain Scale (0-10): MD -1.10; 95% CI -1.43, -0.77; p <0.00001) (Table 9). The strength of the evidence was rated as insufficient to make any firm conclusions regarding these interventions.

Key Question 2: Other outcomes

In the RCT[79] that compared relaxation vs. no intervention, patients in the relaxation group required less additional pain medication (e.g., meperidine (mg) or morphine (mg)) compared with the control group (MD -8.43; 95% CI -15.11, -1.75; p = 0.01) (Table 9).

Key Question 3: Adverse effects

No data were reported on adverse effects.

Key Question 4: Efficacy, effectiveness and safety in subpopulations

No data were reported on subpopulations.

Table 9. Evidence summary table (randomized controlled trials): Complementary and alternative medicine

	Outcome or Subgroup	Studies	Participants	Statistical Method	Effect Estimate	I^2
KQ1	**Acute pain (post-treatment means)**					
	Acupressure[43]	1	38	MD (95% CI)	**-3.01 (-4.53, -1.49)***	NA
	Relaxation[79]	1	60	MD (95% CI)	**-1.10 (-1.43, -0.77)***	NA
KQ2	**Additional pain medication**					
	Relaxation[79]	1	60	MD (95% CI)	**-8.43 (-15.11, -1.75)***	NA

KQ = key question; CI = confidence intervals; MD = mean difference; NA = not applicable; * = statistically significant

Multimodal Pain Management

Overview of included studies

Two prospective cohort studies[80,81] evaluated the effectiveness and/or harms of the administration of multimodal pain management vs. standard care in 226 participants; sample size ranged from 106 to 120. The mean age for the cohorts was not reported. Most were female (79.2 percent). One study[80] compared a formal post-operative protocol of IV and oral tramadol plus acetaminophen vs. standard care (Study 1). The second study[81] compared a formal pre-operative protocol of skin traction, morphine and acetaminophen vs. standard care (Study 2).

Based on the NOS, the study quality for both studies was moderate (5 to 7 stars) (Appendix I). Summary of the evidence from these studies is provided in Table 10.

Table 10. Evidence addressing key questions: Multimodal pain management

Key Question	Outcome	Evidence avaiability	Strength of Evidence
KQ 1	**Acute pain**	No	
	Chronic pain	No	
KQ2	**Mortality (30 day and up to 1-year postfracture)**	Yes	1 prospective cohort study comparing multimodal pain management with standard care reported no statistically significant difference. The strength of the evidence was rated as insufficient.
	Functional status	No	
	Pain medication use; change in type and quantity	No	
	Mental status	Yes	2 prospective cohort studies comparing multimodal pain management with standard care reported no statistically significant difference. The strength of the evidence was rated as insufficient.
	Health-related quality of life	No	
	Quality of sleep in the hospital	No	
	Ability to participate in rehabilitation	No	
	Return to prefracture living arrangements	No	
	Health services utilization	No	
KQ3	**Frequency of adverse effects**	Yes	1 prospective cohort study comparing multimodal pain management with standad care reported no statistically significant difference. The strength of the evidence for the probability of stroke, myocardial infarction, delirium or renal failure was rated as insufficient.
KQ4	**Effectiveness and safety in differing subpopulations**	No	

KQ = key question

Key Question 1: Acute and chronic pain management.

There were no data on pain management.

Key Question 2: Other outcomes

Mortality (30 day and one year). Mortality was reported in one prospective cohort study[81] (n = 106) (Table 11). There was no significant difference between groups after 30 days (5/55 vs. 8/51; OR 0.54; 95% CI 0.16, 1.77; p = 0.31), or at 1 year (11/55 vs. 15/51; OR 0.60; 95% CI 0.25, 1.47; p = 0.26). The strength of the evidence was rated as insufficient to make any firm conclusions regarding these interventions.

Delirium. Delirium was reported in two prospective cohort studies [80,81] (n = 226) (Table 11). There was no significant difference between groups in the number of patients with delirium (12/60 vs. 14/60; OR 0.82; 95% CI 0.34, 1.96; p = 0.66);[80] 1/55 vs. 2/51; OR 0.45; 95% CI 0.04, 5.16; p = 0.52)).[81] The strength of the evidence was rated as insufficient to make any firm conclusions regarding these interventions.

Key Question 3: Adverse effects

Data on adverse effects were reported in one prospective cohort study[81] and were not statistically significant (Table 11).

Key Question 4: Efficacy, effectiveness and safety in subpopulations

No data were reported on subpopulations.

Table 11. Evidence summary table (cohort studies): Multimodal pain management

	Outcome or Subgroup	Studies	Participants	Statistical Method	Effect Estimate	I^2
KQ2	**Delirium**					
	Study 1[80]	1	120	OR (95% CI)	0.82 (0.34, 1.96)	NA
	Study 2[81]	1	106	OR (95% CI)	0.45 (0.04, 5.16)	NA
	Mortality 30 days					
	Study 2[81]	1	106	OR (95% CI)	0.54 (0.16, 1.77)	NA
	Mortality 1 year					
	Study 2[81]	1	106	OR (95% CI)	0.60 (0.25, 1.47)	NA
KQ3	**Angina**					
	Study 2[81]	1	106	OR (95% CI)	0.30 (0.01, 7.62)	NA
	Deep venous thrombosis					
	Study 2[81]	1	106	OR (95% CI)	2.83 (0.11, 71.18)	NA
	Dehydration					
	Study 2[81]	1	106	OR (95% CI)	0.93 (0.06, 15.20)	NA
	GI bleeding					
	Study 2[81]	1	106	OR (95% CI)	2.83 (0.11, 71.18)	NA
	Hyponatremia					
	Study 2[81]	1	106	OR (95% CI)	2.83 (0.11, 71.18)	NA
	Myocardial infarction					
	Study 2[81]	1	106	OR (95% CI)	0.45 (0.04, 5.16)	NA
	Postoperative ileus					
	Study 2[81]	1	106	OR (95% CI)	0.30 (0.01, 7.62)	NA
	Pulmonary edema					
	Study 2[81]	1	106	OR (95% CI)	2.83 (0.11, 71.18)	NA
	Pulmonary embolism					
	Study 2[81]	1	106	OR (95% CI)	0.45 (0.04, 5.16)	NA
	Respiratory infection					
	Study 2[81]	1	106	OR (95% CI)	0.30 (0.01, 7.62)	NA
	Sepsis					
	Study 2[81]	1	106	OR (95% CI)	2.83 (0.11, 71.18)	NA
	Stroke					
	Study 2[81]	1	106	OR (95% CI)	0.30 (0.01, 7.62)	NA
	Urinary retention					
	Study 2[81]	1	106	OR (95% CI)	0.10 (0.00, 1.81)	NA
	Urinary tract infection					
	Study 2[81]	1	106	OR (95% CI)	0.45 (0.04, 5.16)	NA

CI = confidence intervals; KQ = key question; NA = not applicable; OR = odds ratio

Nerve Blocks

Overview of included studies

Twenty-seven RCTs[82-86,88-96,98-104,106-111] (n = 1,443) evaluated the efficacy and/or harms of the administration of nerve blocks, including 3-in-1 (neurostimulation [NS]/ultrasound-guided [US]), combined lumbar/sacral plexus, fascia iliaca compartment, femoral, lumbar plexus ± sciatic nerve, posterior lumbar plexus, psoas compartment and epidural nerve blocks. These were compared with placebo/standard care, or a different method of nerve blocks. Sample size ranged from 14 to 207 participants. Additionally, three retrospective cohort studies[87,97,105] (n = 696) evaluated 3-in-1, femoral lumbar plexus plus sciatic nerve blocks vs. systemic analgesia, or comparing different analgesic medications in femoral lumbar plexus plus sciatic block. Sample size ranged from 62 to 535 participants. The mean age ranged from 59.2 to 85.9 years. Most were female (43.3 to 90.0 percent). Acute pain was measured using different scales (i.e., NRS (0-3, 1-5 and 1-10) and 10cm VAS. Eight studies using the 10cm VAS reported mean baseline pain scores ranging from 1.4cm to 7.3cm.

Two RCTs[90,91] had a low risk of bias, 15 RCTs[83-85,92,94-96,98-101,103,104,108,110] had an unclear risk of bias, while the remaining 10[82,86,88,89,93,102,106,107,109,111] had a high risk of bias (Appendix G). Summary of the evidence from these trials is provided in Table 12.

Based on the primary interventions and comparison groups, the studies were grouped as follows:

1. Nerve blocks vs. standard care
2. Nerve blocks vs. neuraxial anesthesia
3. Nerve blocks: ropivacaine vs. bupivacaine
4. Nerves blocks: addition of clonidine
5. Nerve blocks: US vs. NS

Table 12. Evidence addressing key questions: Nerve blocks

Key Question	Outcome	Evidence availability	Strength of Evidence
KQ 1	**Acute pain**	Yes	10 RCTs reported a statistically significant effect in favor of the nerve blocks compared with standard care. Additional analyses of pain at rest and on movement were not performed due to marked statistical heterogeneity. One RCT reported a statistically significant reduction in number of participants with pain on day 1. The strength of the evidence was rated as moderate. 3 RCTs reported no significant difference between the use of nerve blocks vs. neuraxial anesthesia on acute pain reduction. The strength of the evidence was rated as low.
	Chronic pain	No	
KQ2	**Mortality (30 day and up to 1-year postfracture)**	Yes	4 RCTs and 1 retrospective cohort reported no statistically significant difference between nerve blocks and standard care. The strength of the evidence was rated as low.
	Functional status	No	

KQ = key question; LOS = length of stay; RCT = randomized controlled trial

Table 12. Evidence addressing key questions: Nerve blocks (continued)

KQ2	**Pain medication use; change in type and quantity**	No	7 RCTs and 1 retrospective cohort reported statistically significantly fewer participants requiring additional pain medications when nerve blocks were administered.
	Mental status	Yes	3 RCTs and 2 retrospective cohorts reported a statistically significant difference in participants developing delirium in favor of the nerve blocks. The strength of the evidence was rated as moderate.
	Health-related quality of life	No	
	Quality of sleep in the hospital	Yes	1 RCT reported no statistically significant difference between nerve blocks and standard care.
	Ability to participate in rehabilitation	No	
	Return to prefracture living arrangements	No	
	Health services utilization	No	2 retrospective cohorts reported conflicting results with one demonstrating a statistically significant decrease in hospital LOS while the other showed no difference.
KQ3	**Frequency of adverse effects**	Yes	19 RCTs and 2 retrospective cohorts reported on different adverse effects with no statistically significant difference between nerve blocks and standard care except for urinary tract and respiratory infections, drowsiness and dizziness which occurred less frequently in the nerve block groups. The strength of the evidence for the probability of stroke, myocardial infarction, or renal failure was rated as insufficient.
KQ4	**Effectiveness and safety in differing subpopulations**	Yes	1 RCT included only participants with heart disease and 1 RCT included only participants who were independent prior to the hip fracture.

Key Question 1: Acute and chronic pain management

Nerve blocks vs. no block

Acute pain (post-treatment) was reported in 10 RCTs[83,85,89,94,95,102-104,106,109] (Table 13). There was a statistically significant decrease in acute pain favoring nerve blocks (MD -0.74; 95% CI -1.03, -0.46; p < 0.00001; Figure 6). Publication bias assessment did not reveal any obvious publication bias.

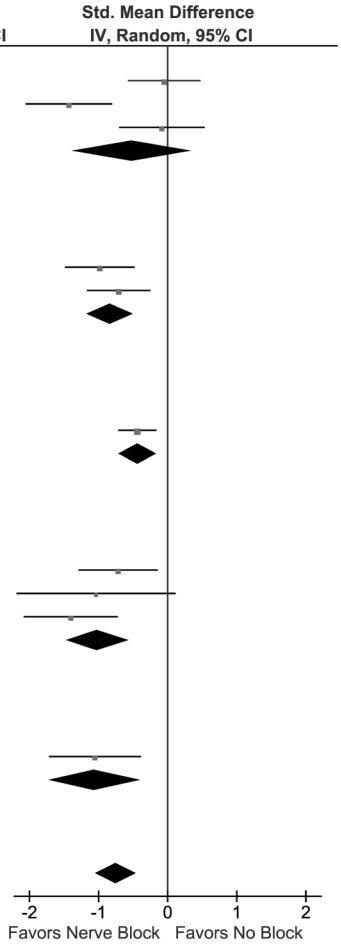
Day 1 pain. One trial[96] (n = 50) reported a statistically significant difference in the frequency of patients who reported post-operative pain on day 1 favoring nerve blocks (7/25 vs. 20/25; OR 0.10; 95% CI 0.03, 0.36; p = 0.0005) (Table 13).

Pain on movement. Pain on movement (post-treatment means) was reported in four trials[89,92,102,109] (n = 258) (Table 13). Studies were not pooled due to significant heterogeneity (I^2 = 95 percent) (Figure 7). Meta-analysis restricted to two trials[89,109] using 3-in-1 nerve block vs. no block showed a significant reduction in pain on movement favoring nerve blocks (SMD -1.02; 95% CI -1.83, -0.21; p = 0.01). One trial[89] investigated pre-operative pain relief (numeric rating scale (0-3)) while the other trial[109] investigated post-operative pain (10cm VAS) relief. Both trials had a high risk of bias.

One trial[102] examined pre-operative epidural analgesia vs. no block and showed a significant increase in pain relief (10cm VAS) on movement favoring nerve blocks (MD -2.01; 95% CI -2.42, -1.60; p <0.00001). The trial had a high risk of bias.

Figure 6. Nerve blocks vs. no block – acute pain (post-treatment)

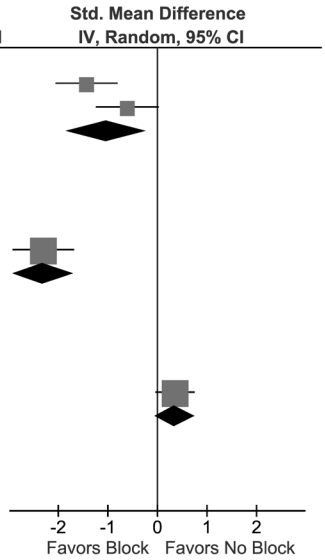
Study or Subgroup	Nerve Block Mean	Nerve Block SD	Nerve Block Total	Standard Care (no block) Mean	Standard Care (no block) SD	Standard Care (no block) Total	Weight	Std. Mean Difference IV, Random, 95% CI
12.1.1 3-in-1 nerve block								
Cuvillon 2007	0.64	0.93	21	0.68	0.7	41	10.9%	-0.05 [-0.58, 0.48]
Fletcher 2003	0.57	0.53	24	1.34	0.53	26	9.4%	-1.43 [-2.06, -0.80]
Tuncer 2003	0.24	0.93	20	0.31	0.7	20	9.5%	-0.08 [-0.70, 0.54]
Subtotal (95% CI)			**65**			**87**	**29.8%**	**-0.51 [-1.38, 0.35]**
Heterogeneity: Tau² = 0.49; Chi² = 12.94, df = 2 (P = 0.002); I² = 85%								
Test for overall effect: Z = 1.16 (P = 0.25)								
12.1.2 Epidural analgesia								
Matot 2003	1.16	0.45	34	1.71	0.64	34	11.2%	-0.98 [-1.49, -0.48]
Scheinin 2000	2.2	1.6	38	3.5	2	39	11.9%	-0.71 [-1.17, -0.25]
Subtotal (95% CI)			**72**			**73**	**23.0%**	**-0.83 [-1.17, -0.49]**
Heterogeneity: Tau² = 0.00; Chi² = 0.61, df = 1 (P = 0.43); I² = 0%								
Test for overall effect: Z = 4.80 (P < 0.00001)								
12.1.3 Fascia iliaca nerve block								
Mouzopoulos 2009	6.46	1.6	102	7.26	2	105	14.7%	-0.44 [-0.72, -0.16]
Subtotal (95% CI)			**102**			**105**	**14.7%**	**-0.44 [-0.72, -0.16]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 3.12 (P = 0.002)								
12.1.4 Femoral nerve block								
Haddad 1995	3.7	3.02	25	5.9	3.02	25	10.2%	-0.72 [-1.29, -0.14]
Henderson 2008	2.7	3.07	6	6.1	3.07	8	4.6%	-1.04 [-2.19, 0.11]
Murgue 2006	2.1	2.1	16	6.45	3.45	29	8.7%	-1.40 [-2.08, -0.72]
Subtotal (95% CI)			**47**			**62**	**23.5%**	**-1.01 [-1.46, -0.57]**
Heterogeneity: Tau² = 0.02; Chi² = 2.28, df = 2 (P = 0.32); I² = 12%								
Test for overall effect: Z = 4.45 (P < 0.00001)								
12.1.5 Psoas compartment nerve block								
Chudinov 1999	1.4	0.6	20	2.1	0.7	20	8.9%	-1.05 [-1.72, -0.39]
Subtotal (95% CI)			**20**			**20**	**8.9%**	**-1.05 [-1.72, -0.39]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 3.10 (P = 0.002)								
Total (95% CI)			**306**			**347**	**100.0%**	**-0.74 [-1.03, -0.46]**
Heterogeneity: Tau² = 0.13; Chi² = 24.68, df = 9 (P = 0.003); I² = 64%								
Test for overall effect: Z = 5.06 (P < 0.00001)								



One trial[109] examined pre-operative femoral nerve block vs. no block and showed no significant difference in pain relief (5-point Verbal Rating Scale) on movement (MD 0.25; 95% CI -0.02, 0.52; p = 0.07).

Figure 7. Nerve blocks vs. no block – pain on movement (post-treatment)

Study or Subgroup	Nerve Block Mean	Nerve Block SD	Nerve Block Total	Standard care (no block) Mean	Standard care (no block) SD	Standard care (no block) Total	Weight	Std. Mean Difference IV, Random, 95% CI
12.2.1 3-in-1 nerve block								
Fletcher 2003	0.57	0.53	24	1.34	0.53	26	50.2%	-1.43 [-2.06, -0.80]
Tuncer 2003	0.97	4.81	20	3.95	4.81	20	49.8%	-0.61 [-1.24, 0.03]
Subtotal (95% CI)			**44**			**46**	**100.0%**	**-1.02 [-1.83, -0.21]**
Heterogeneity: Tau² = 0.23; Chi² = 3.26, df = 1 (P = 0.07); I² = 69%								
Test for overall effect: Z = 2.48 (P = 0.01)								
12.2.2 Epidural analgesia								
Matot 2003	1.45	0.64	34	3.46	1.04	34	100.0%	-2.30 [-2.92, -1.68]
Subtotal (95% CI)			**34**			**34**	**100.0%**	**-2.30 [-2.92, -1.68]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 7.27 (P < 0.00001)								
12.2.3 Femoral nerve block								
Gille 2006	2.64	0.78	50	2.39	0.6	50	100.0%	0.36 [-0.04, 0.75]
Subtotal (95% CI)			**50**			**50**	**100.0%**	**0.36 [-0.04, 0.75]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 1.77 (P = 0.08)								

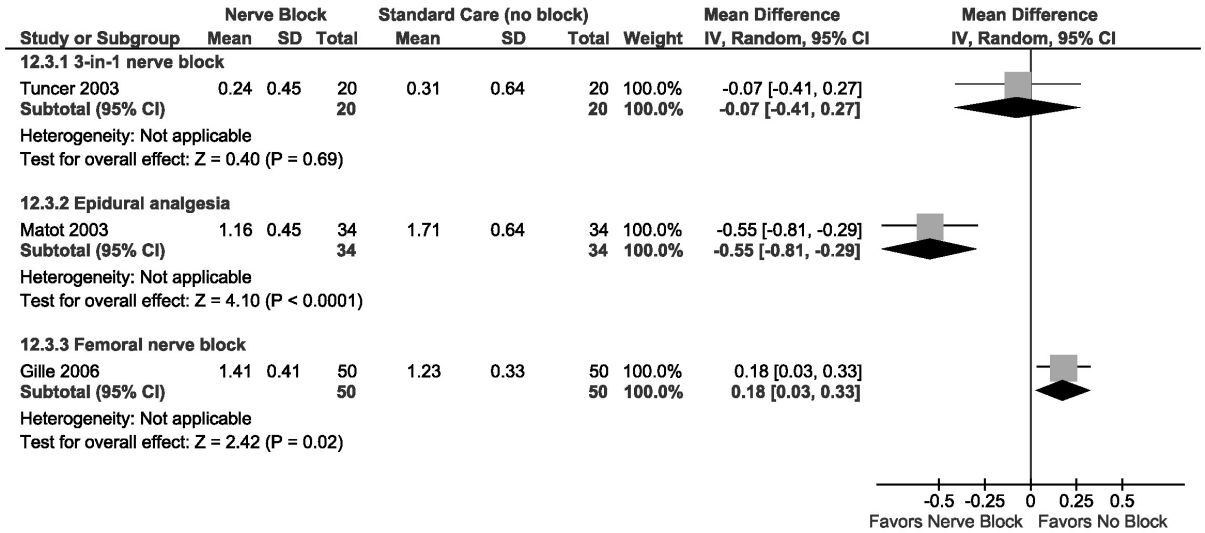


Pain on rest. Pain on rest (post-treatment means) was reported in three trials[92,102,109] (n = 208) (Table 13). Studies were not pooled due to significant heterogeneity (I^2 = 91 percent) (Figure 8). One trial[109] examined post-operative 3-in-1 nerve block vs. standard care and found no significant difference in pain relief (10cm VAS) (MD -0.07; 95% CI -0.41, 0.27; p = 0.69). This study had a high risk of bias.

One trial[102] examined pre-operative epidural analgesia vs. standard care and found a statistically difference in pain relief in favor of the nerve blocks (10cm VAS) (MD -0.55; 95% CI -0.81, -0.29; p < 0.0001). This study had a high risk of bias.

One trial[92] examined pre-operative femoral nerve block vs. standard care and reported a statistically difference in pain relief in favor of standard care (5-point Verbal Rating Scale) (MD 0.18; 95% CI 0.03, 0.33; p = 0.02). This study had an unclear risk of bias.

Figure 8. Nerve blocks vs. no block – pain on rest (post-treatment)



Nerve blocks vs. neuraxial anesthesia

Acute pain (post-treatment) was reported in three RCTs[86,88,110] (n = 109) (Table 13). There was no statistically significant difference in pain between the two groups (MD -0.35; 95% CI -1.10, 0.39; p = 0.35).

Key Question 2: Other outcomes

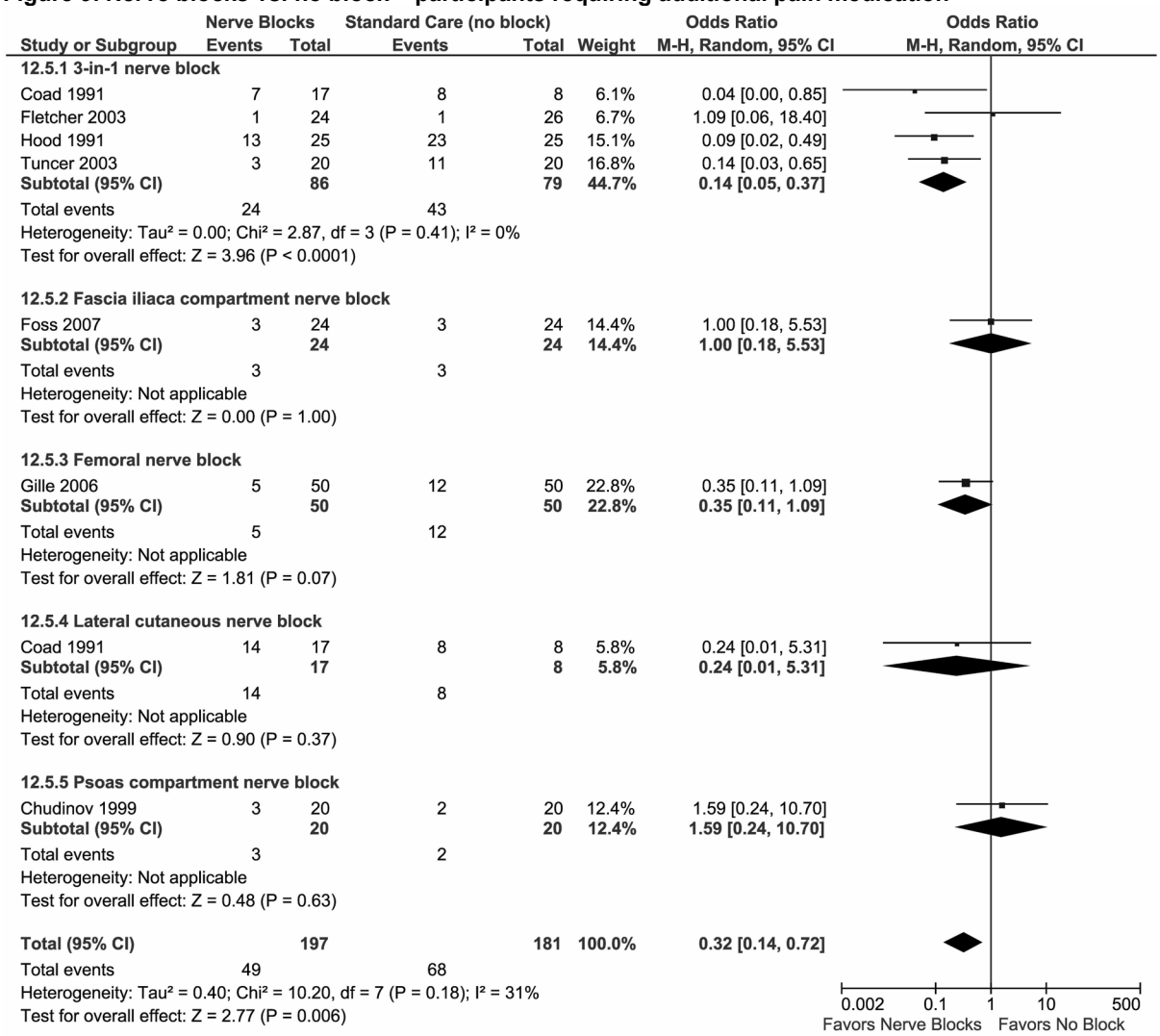
Nerve blocks vs. no block

30-day mortality. A total of four RCTs[90,94,96,102] evaluated 30-day mortality in a total of 228 participants (Table 13). Meta-analysis did not provide evidence of a significant difference in 30-day mortality (2/114 vs. 10/114; OR 0.28; 95% CI 0.07, 1.12; p = 0.07).

1-year mortality. One RCT[89] evaluated 1-year mortality in a total of 50 participants (Table 13). Additionally, one retrospective cohort study[105] reported data for 535 participants (Table 14). There was no evidence of a significant difference in mortality in the RCT[89] (3/24 vs. 3/26; OR 1.10; 95% CI 0.20, 6.03; p = 0.92), or in the cohort study[105] (41/178 vs. 104/357; OR 0.73; 95% CI 0.48, 1.10; p = 0.14).

Additional pain medication use. Seven RCTs[83,84,89,91,92,96,109] evaluated additional pain medication use in a total of 426 participants (Table 13). Additionally, one retrospective cohort study[86] compared femoral nerve block vs. no block, reporting data for 99 participants (Table 14). Meta-analysis of the six trials[83,84,89,91,92,96,109] resulted in a significant difference in additional pain medication use, favoring nerve blocks (52/331 vs. 71/205; OR 0.37; 95% CI 0.18, 0.79; p = 0.010) (Figure 10). The retrospective cohort study[86] reported a statistically significant effect difference favoring nerve blocks (0/49 vs. 14/50; OR 0.03; 95% CI 0.00, 0.44; p = 0.01).

Figure 9. Nerve blocks vs. no block – participants requiring additional pain medication



Delirium. Three RCTs[90,93,103] (n = 307) and two cohort studies[86,105] (n = 634) reported the occurrence of delirium (Table 13, 14). Meta-analysis of the trials[90,93,103] showed a significant difference favoring nerve blocks (11/150 vs. 29/157; OR 0.36; 95% CI 0.17, 0.74; p = 0.006). The pooled results of the cohort studies[86,105] also showed a significant difference in favor of nerve blocks (11/227 vs. 55/407; OR 0.24; 95% CI 0.08, 0.72; p = 0.01).

Length of stay for acute hospitalization. LOS for acute hospitalization (days) was reported in two cohort studies[86,105] (n = 634) (Table 14). There was no significant difference between the two groups (MD -3.41; 95% CI -8.41, 1.68; p = 0.19).

Quality of sleep. Quality of sleep (10cm VAS) (post-treatment means) was reported in one RCT[106] (n = 77) (Table 13). There was no significant difference between groups (MD 0.30; 95% CI -0.46, 1.06; p = 0.44).

Nerve blocks vs. neuraxial anesthesia

Additional pain medication use. Additional pain medication use was reported in one RCT[110] (n = 30) (Table 13). There was no significant difference between the two groups (5/15 vs. 3/15; OR 2.00; 95% CI 0.38, 10.51; p = 0.41).

Delirium. Delirium (MMSE) was reported in one RCT[86] (n = 29) (Table 13). There was no significant difference between the two groups (6/15 vs. 5/14; OR 1.20; 95% CI 0.27, 5.40; p = 0.81).

Nerve blocks: ropivacaine vs. bupivacaine

Additional pain medication use. Additional pain medication use was reported in one cohort study[97] (n = 62) (Table 14). There was no significant difference between the two groups (10/32 vs. 8/30; OR 1.25; 95% CI 0.42, 3.76; p = 0.69).

Delirium. Delirium (user defined) was reported in one cohort study[97] (n = 62) (Table 14). There was no significant difference between the two groups (2/32 vs. 1/30; OR 1.93; 95% CI 0.17, 22.50; p = 0.60).

Key Question 3: Adverse effects

Nerve blocks vs. no block

Any adverse event. Any adverse effects were reported in four RCTs[82,92,93,95] (n = 238) and there was a significant difference favoring no block (19/123 vs. 6/115; OR = 4.49; 95% CI 1.61, 12.55; p = 0.004; Table 13). Two retrospective cohorts[87,105] (n = 634) found no significant effect difference between the two groups (62/227 vs. 76/407; OR 1.64; 95% CI 0.79, 3.42; p = 0.18; Table 13).

Cardiac complications. Cardiac complications were reported in two RCTs[90,102] (n = 128) (Table 13). There was no significant difference between the two groups (3/64 vs. 8/64; OR 0.35; 95% CI 0.08, 1.44; p = 0.15). One retrospective cohort [87] (n = 99) found no significant difference between the two groups (0/49 vs. 1/50; OR 0.33; 95% CI 0.01, 8.38; p = 0.50; Table 14).

Damage to surrounding structures. Damage to surrounding structures was reported in three RCTs[82,92,111] (n = 224) and found no significant difference between the two groups (3/119 vs. 0/105; OR = 7.44; 95% CI 0.37, 147.92; p = 0.19; Table 13).

Deep venous thrombosis. Deep venous thrombosis was reported in two RCTs[89,94] (n = 100) (Table 13). There was no significant difference between the two groups (4/49 vs. 3/51; OR 1.40; 95% CI 0.29, 6.72; p = 0.67).

Infection. There were no reports of infection in two RCTs[82,92] (n = 184) (Table 13).

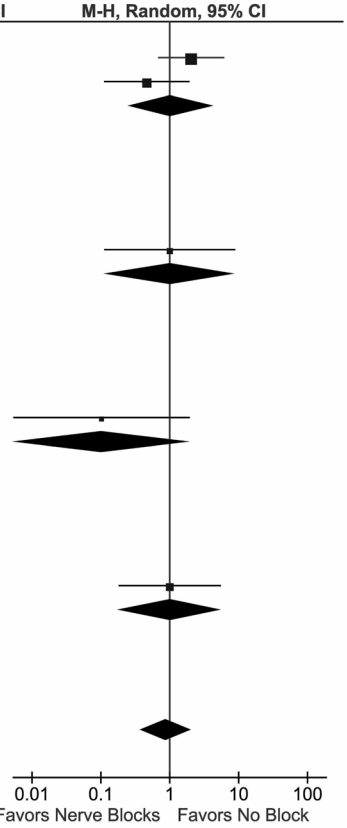
Myocardial infarction. Myocardial infarction was reported in two RCTs[102,106] (n = 145) (Table 13). One trial[106] reported no events. For the other trial[102] there was no significant difference between the two groups (1/72 vs. 1/73; OR 1.00; 95% CI 0.06, 16.67; p = 1.00; Table

13). One retrospective cohort [105] (n = 535) found no significant difference between the two groups (1/178 vs. 3/357; OR 0.67; 95% CI 0.07, 6.46; p = 0.73; Table 14).

Nausea/vomiting. Nausea/vomiting was reported in five RCTs[85,91,92,108,109] (n = 270) and found no evidence of a significant difference between the two groups (18/125 vs. 27/145; OR 0.90; 95% CI 0.39, 2.08; p = 0.28; Table 13; Figure 10).

Figure 10. Nerve blocks vs. no block – nausea/vomiting

Study or Subgroup	Nerve Blocks Events	Nerve Blocks Total	Standard care (no block) Events	Standard care (no block) Total	Weight	Odds Ratio M-H, Random, 95% CI
12.28.1 3-in-1 nerve block						
Cuvillon 2007	9	21	11	41	35.4%	2.05 [0.68, 6.18]
Tuncer 2003	4	20	7	20	25.2%	0.46 [0.11, 1.94]
Subtotal (95% CI)		**41**		**61**	**60.6%**	**1.05 [0.25, 4.45]**
Total events	13		18			
Heterogeneity: Tau² = 0.68; Chi² = 2.59, df = 1 (P = 0.11); I² = 61%						
Test for overall effect: Z = 0.06 (P = 0.95)						
12.28.2 Lumbar plexus block						
Spansberg 1996	2	10	2	10	12.7%	1.00 [0.11, 8.95]
Subtotal (95% CI)		**10**		**10**	**12.7%**	**1.00 [0.11, 8.95]**
Total events	2		2			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.00 (P = 1.00)						
12.28.3 Femoral nerve block						
Gille 2006	0	50	4	50	7.5%	0.10 [0.01, 1.95]
Subtotal (95% CI)		**50**		**50**	**7.5%**	**0.10 [0.01, 1.95]**
Total events	0		4			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.52 (P = 0.13)						
12.28.4 Fascia iliaca compartment nerve block						
Foss 2007	3	24	3	24	19.2%	1.00 [0.18, 5.53]
Subtotal (95% CI)		**24**		**24**	**19.2%**	**1.00 [0.18, 5.53]**
Total events	3		3			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.00 (P = 1.00)						
Total (95% CI)		**125**		**145**	**100.0%**	**0.90 [0.39, 2.08]**
Total events	18		27			
Heterogeneity: Tau² = 0.20; Chi² = 5.11, df = 4 (P = 0.28); I² = 22%						
Test for overall effect: Z = 0.26 (P = 0.80)						



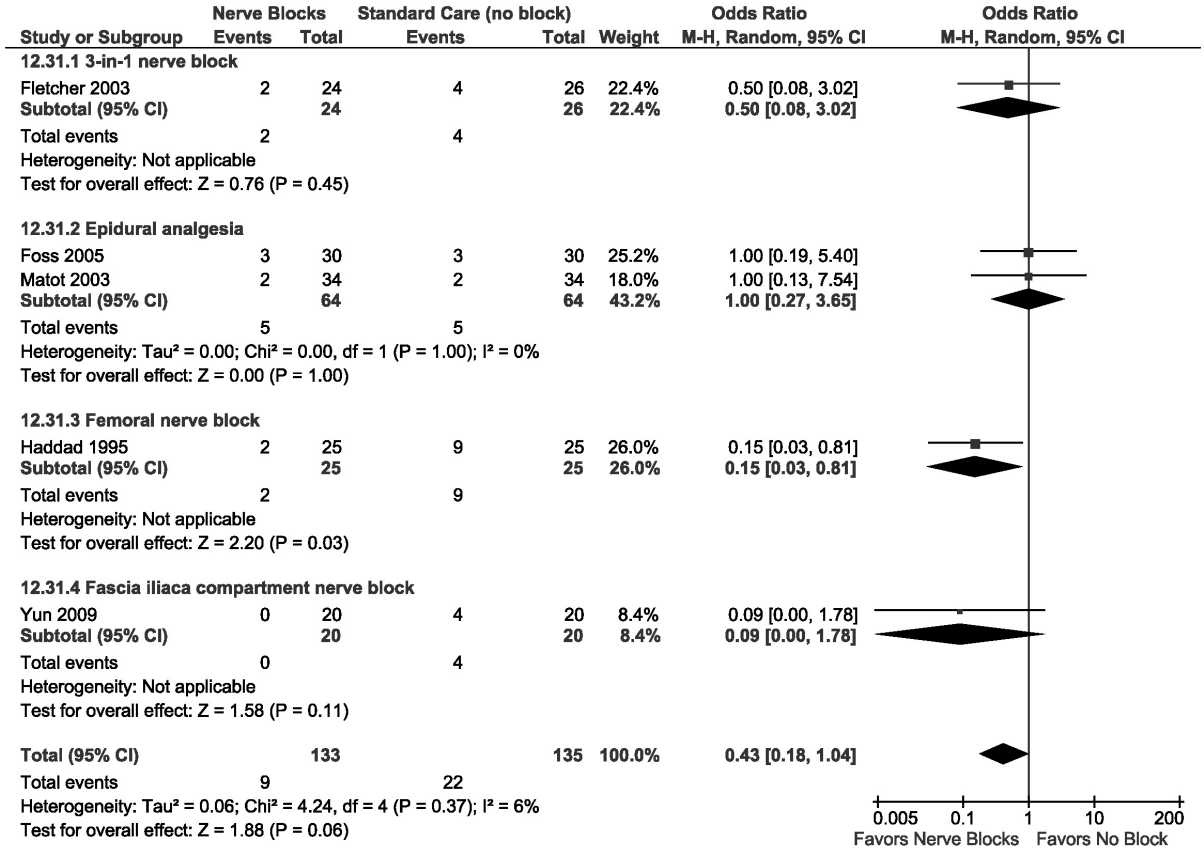
Pulmonary embolism. Pulmonary embolism was reported in two RCTs[90,102] (n = 128) and found no significant difference between the two groups (2/64 vs. 1/64; OR 1.63; 95% CI 0.19, 13.61; p = 0.65; Table 13).

Respiratory infection. Respiratory infection was reported in five RCTs[89,90,94,102,111] (n = 268) and found no significant difference between the two groups (9/133 vs. 18/135; OR 0.43; 95% CI 0.18, 1.04; p = 0.06; Table 13; Figure 11). One retrospective cohort[105] (n = 535) found a statistically significant difference favoring nerve blocks (9/178 vs. 39/357; OR 0.43; 95% CI 0.21, 0.92; p = 0.03; Table 14).

Stroke. Stroke was reported in one RCT[94] (n = 50) and found no significant effect between the two groups (1/25 vs. 0/25; OR 3.12; 95% CI 0.12, 80.39; p = 0.49; Table 13). Stroke was also reported in one retrospective cohort [105] (n =535) and found no significant difference between the two groups (1/178 vs. 8/357; OR 0.25; 95% CI 0.03, 1.99; p = 0.19; Table 14).

Surgical wound infection. Surgical wound infection was reported in two RCTs[90,94] (n = 110) and found no significant difference between the two groups (3/55 vs. 4/55; OR 0.77; 95% CI 0.11, 5.63; p = 0.80; Table 13).

Figure 11. Nerve blocks vs. no block – respiratory infection



Urinary retention. Urinary retention was reported in two RCTs[108,110] (n = 62) and found no significant difference between the two groups (3/31 vs. 1/31; OR 2.23; 95% CI 0.27, 18.71; p = 0.46; Table 13). One retrospective cohort study[105] (n = 535) and found no significant difference between the two groups (4/178 vs. 17/357; OR 0.46; 95% CI 0.15, 1.39; p = 0.17; Table 14).

Urinary tract infection. Urinary tract infection was reported in one RCT[94] (n = 50) and found no significant difference between the two groups (4/25 vs.6/25; OR 0.60; 95% CI 0.15, 2.47; p = 0.48; Table 13). One retrospective cohort study[105] (n = 535) found a statistically significant difference favoring nerve blocks (12/178 vs. 63/357; OR 0.34; 95% CI 0.18, 0.64; p = 0.0010; Table 14).

Other adverse effects. The remaining reported adverse effects were from single trials and cohort studies and did not demonstrate any significant statistical differences between the pain management interventions (Table 13, 14).

Nerve blocks vs. neuraxial anesthesia

Adverse effects. The reported adverse effects were from single trials and did not demonstrate any significant statistical differences between the pain management interventions (Table 13).

Nerve blocks: ropivacaine vs. bupivacaine

Adverse effects. The reported adverse effects were from single trials and cohort studies did not demonstrate any significant statistical differences between the pain management interventions (Table 13, 14).

Nerve blocks: addition of clonidine

Adverse effects. The reported adverse effects were from single trials and did not demonstrate any significant statistical differences between the pain management interventions (Table 13).

Nerve blocks: US vs. NS

Damage to surrounding structures. Damage to surrounding structures was reported in two RCTs[99,100] (n = 100) (Table 13). There was no statistically significant difference between the two groups (0/40 vs. 7/60; OR 0.16; 95% CI 0.02, 1.30; p = 0.09).

Other adverse effects. The remaining reported adverse effects were from a single trial and did not demonstrate any significant statistical differences between the pain management interventions.

Key Question 4: Efficacy, effectiveness and safety in subpopulations

One RCT[102] only recruited patients with pre-existing heart disease. There was a significant reduction in acute pain (MD -0.55; -0.81, -0.29; p <0.0001) favoring nerve blocks. There was no significant difference in 30 day mortality (0/34 vs. 4/34; OR 0.10; 95 % CI 0.01, 1.90; p = 0.12) or adverse effects: participants with any cardiac complications (2/34 vs. 7/34; OR 0.24; 95% CI 0.05, 1.26; p = 0.09), congestive heart failure (1/34 vs. 2/34; OR 0.48; 95% CI 0.04, 5.61; p = 0.56); myocardial infarction (1/34 vs. 1/34; OR 1.00; 95 % CI 0.06, 16.67; p = 1.00); respiratory infection (2/34 vs. 2/34; OR 1.00; 95% CI 0.13, 7.54; p = 1.00), pulmonary embolism (1/34 vs. 1/34; OR 1.00; 95% CI 0.06, 16.67; p = 1.00).

One RCT[90] only recruited participants that were independent prior to their hip fracture. There was no significant difference between nerve blocks vs. standard care for 30 day mortality (1/30 vs. 1/30; OR 1.00; 95 % CI 0.06, 16.76; p = 1.00).

Table 13. Evidence summary table (randomized controlled trials): Nerve blocks

Table 13-A. Nerve blocks vs. no block: RCT/NRCT

	Outcome or Subgroup	Studies	Participants	Statistical Method	Effect Estimate	I^2
KQ1	**Acute pain (post-treatment means)**[83,85,89,94,95,102-104,106,109]	10	653	SMD (95% CI)	**-0.74 (-1.03, -0.46)***	64%
	3-in-1 NB[85,89,109]	3	152	SMD (95% CI)	NP	85%
	Epidural analgesia[102,106]	2	145	SMD (95% CI)	**-0.83 (-1.17, -0.49)***	0%
	Fascia iliaca NB[103]	1	207	SMD (95% CI)	**-0.44 (-0.72, -0.16)***	NA
	Femoral NB[94,95,104]	3	109	SMD (95% CI)	**-1.01 (-1.46, -0.57)***	12%
	Psoas compartment NB[83]	1	40	SMD (95% CI)	**-1.05 (-1.72, -0.39)***	NA
	Day 1 Pain					
	3-in-1 NB[96]	1	50	OR (95% CI)	0.10 (0.03, 0.36)	NA
	Pain on movement (post-treatment)[89,92,102,109]	4	258		NP	95%
	3-in-1 NB[89,109]	2	90	SMD (95% CI)	**-1.02 (-1.83, -0.21)***	69%
	Epidural analgesia[102]	1	68	MD (95% CI)	**-2.01 (-2.42, -1.60)***	NA
	Femoral NB[109]	1	100	MD (95% CI)	0.25 (-0.02, 0.52)	NA
	Pain on rest (post-treatment)[92,102,109]	3	208		NP	95%
	3-in-1 NB[109]	1	40	MD (95% CI)	-0.07 (-0.41, 0.27)	69%
	Epidural analgesia[102]	1	68	MD (95% CI)	**-0.55 (-0.81, -0.29)***	NA
	Femoral NB[92]	1	100	MD (95% CI)	**0.18 (0.03, 0.33)***	NA
KQ2	**Additional pain medication use**[83,84,89,91,92,96,109]	7	378	OR (95% CI)	**0.32 (0.14, 0.72)***	**31%**
	3-in-1 NB[84,89,96,109]	4	165	OR (95% CI)	**0.14 (0.05, 0.37)***	0%
	Fascia iliaca NB[91]	1	48	OR (95% CI)	1.00 (0.18, 5.53)	NA
	Femoral NB[92]	1	100	OR (95% CI)	0.35 (0.11, 1.09)	NA
	Lateral cutaneous NB[84]	1	25	OR (95% CI)	0.24 (0.01, 5.31)	NA
	Psoas compartment NB[83]	1	40	OR (95% CI)	1.59 (0.24, 10.70)	NA
	Delirium[90,93,103]	3	307	OR (95% CI)	**0.36 (0.17, 0.74)***	0%
	3-in-1 NB[93]	1	40	OR (95% CI)	0.22 (0.01, 4.92)	NA
	Epidural analgesia[90]	1	60	OR (95% CI)	0.19 (0.01, 4.06)	NA
	Fascia iliaca NB[103]	1	207	OR (95% CI)	**0.39 (0.18, 0.84)***	NA
	Mortality 30 days[90,96]	4	228	OR (95% CI)	0.28 (0.07, 1.12)	0%
	3-in-1 NB[96]	1	50	OR (95% CI)	0.32 (0.01, 8.25)	NA
	Epidural analgesia[90,102]	2	128	OR (95% CI)	0.33 (0.03, 3.34)	23%
	Femoral NB[94]	1	50	OR (95% CI)	0.22 (0.02, 2.11)	NA
	Mortality 1 year					
	3-in-1 NB[85,89]	2	112	OR (95% CI)	0.82 (0.07, 1.12)	0%
	Quality of sleep					
	Epidural analgesia[106]	1	77	MD (95% CI)	0.30 (-0.46, 1.06)	NA
KQ3	**Allergic reaction**					
	3-in-1 NB[109]	1	40	OR (95% CI)	0.07 (0.00, 1.34)	NA
	Any adverse event[82,92,93,95]	4	238	OR (95% CI)	**4.49 (1.61, 12.55)***	NA
	3-in-1 NB[93]	1	40	OR (95% CI)	NE	NA
	Femoral NB[82,92,95]	3	198	OR (95% CI)	**4.49 (1.61, 12.55)***	NA

KQ: key question; CI = confidence intervals; MD = mean difference; NA = not applicable; NB = nerve block; NP = not pooled; OR = odds ratio: randomized and nonrandomized controlled trials; SMD = standardized mean difference; * = statistically significant

Table 13-A. Nerve blocks vs. no block: RCT/NRCT (continued)

	Outcome or Subgroup	Studies	Participants	Statistical Method	Effect Estimate	I^2
KQ3	**Cardiac complications**					
	Epidural analgesia[90,102]	2	128	OR (95% CI)	0.35 (0.08, 1.44)	NA
	Cardiovascular complications					
	Femoral NB[94]	1	50	OR (95% CI)	1.00 (0.13, 7.72)	NA
	Cardiovascular or neurological toxicity					
	Femoral NB[82]	1	84		NE	
	Congestive heart failure					
	Epidural analgesia[102]	1	68	OR (95% CI)	0.48 (0.04, 5.61)	NA
	Constipation					
	3-in-1 NB[85]	1	42	OR (95% CI)	3.86 (0.97, 15.44)	NA
	Damage to surrounding structures[82,92,111]	3	224	OR (95% CI)	7.44 (0.37, 147.92)	0%
	Fascia iliaca compartment NB[111]	1	40		NE	
	Femoral NB[82,92]	2	184	OR (95% CI)	7.44 (0.37, 147.92)	0%
	Deep venous thrombosis[89,94]	2	100	OR (95% CI)	1.40 (0.29, 6.72)	0%
	3-in-1 NB[89]	1	50	OR (95% CI)	1.09 (0.06, 18.40)	NA
	Femoral NB[94]	1	50	OR (95% CI)	1.57 (0.24, 10.30)	NA
	Direct skin damage					
	Femoral NB[94]	1	50	OR (95% CI)	0.17 (0.02, 1.55)	NA
	Dizziness					
	Fascia iliaca compartment NB[111]	1	40	OR (95% CI)	0.00 (0.00, 0.03)	NA
	Drowsiness					
	Fascia iliaca compartment NB[111]	1	40	OR (95% CI)	0.02 (0.00, 0.31)	NA
	Hematoma					
	Lumbar plexus block[108]	1	20		NE	
	Hematemesis					
	Fascia iliaca NB[91]	1	48	OR (95% CI)	3.13 (0.12, 80.68)	NA
	Hypotension					
	3-in-1 NB[96]	1	50	OR (95% CI)	0.52 (0.17, 1.61)	NA
	Infection					
	Femoral NB[82,92]	2	184		NE	
	Major medical complications					
	Epidural analgesia[90]	1	60	OR (95% CI)	0.69 (0.21, 2.30)	NA
	Myocardial infarction					
	Epidural analgesia[102,106]	2	145	OR (95% CI)	1.00 (0.06, 16.67)	0%
	Myocardial ischemia					
	Epidural analgesia[106]	1	77	OR (95% CI)	0.92 (0.36, 2.40)	NA
	Nausea/vomiting[85,91,92,108,109]	5	270	OR (95% CI)	0.90 (0.39, 2.08)	31%
	3-in-1 NB[85,109]	2	102	OR (95% CI)	1.05 (0.25, 4.45)	61%
	Lumbar plexus block[108]	1	20	OR (95% CI)	1.00 (0.11, 8.95)	NA
	Femoral NB[92]	1	100	OR (95% CI)	0.10 (0.01, 1.95)	NA
	Fascia iliaca NB[91]	1	48	OR (95% CI)	1.00 (0.18, 5.53)	NA
	Paresthesia	2	140	OR (95% CI)	5.21 (0.24, 111.24)	NA
	Femoral NB[92]	1	100	OR (95% CI)	5.21 (0.24, 111.24)	NA
	Fascia iliaca compartment NB[111]	1	40		NE	
	Pulmonary embolism					
	Epidural analgesia[90,102]	2	128	OR (95% CI)	1.63 (0.19, 13.61)	0%
	Respiratory infection[89,90,94,102,111]	5	268	OR (95% CI)	0.43 (0.18, 1.04)	6%
	3-in-1 NB[89]	1	50	OR (95% CI)	0.50 (0.08, 3.02)	NA
	Epidural analgesia[90,102]	2	128	OR (95% CI)	1.00 (0.27, 3.65)	0%
	Femoral NB[94]	1	50	OR (95% CI)	**0.15 (0.03, 0.81)***	NA

Table 13-A. Nerve blocks vs. no block: RCT/NRCT (continued)

	Outcome or Subgroup	Studies	Participants	Statistical Method	Effect Estimate	I^2
KQ3	Fascia iliaca compartment NB[111]	1	40	OR (95% CI)	0.09 (0.00, 1.78)	NA
	Stroke					
	Femoral NB[94]	1	50	OR (95% CI)	3.12 (0.12, 80.39)	NA
	Surgical wound infection[90,94]	2	110	OR (95% CI)	0.77 (0.11, 5.63)	0%
	Epidural analgesia[90]	1	60	OR (95% CI)	0.19 (0.01, 4.06)	NA
	Femoral NB[94]	1	50	OR (95% CI)	1.57 (0.24, 10.30)	NA
	Urinary retention[85,108]	2	62	OR (95% CI)	2.23 (0.27, 18.71)	0%
	Lumbar plexus block[108]	1	20	OR (95% CI)	1.00 (0.05, 18.57)	NA
	3-in-1 NB[85]	1	42	OR (95% CI)	5.51 (0.25, 122.08)	NA
	Urinary tract infection					
	Femoral NB[94]	1	50	OR (95% CI)	0.60 (0.15, 2.47)	NA

Table 13-B. Nerve blocks vs. neuraxial anesthesia: RCT/NRCT

	Outcome or Subgroup	Studies	Participants	Statistical Method	Effect Estimate	I^2
KQ1	**Acute pain (post-treatment means)**[86,88,110]	3	109	MD (95% CI)	-0.35 (-1.10, 0.39)	0%
	Psoas compartment NB vs. epidural anesthesia (single)[110]	1	30	MD (95% CI)	0.34 (-1.22, 1.90)	NA
	Posterior lumbar plexus NB vs. spinal anesthesia (single)[88]	1	50	MD (95% CI)	-0.60 (-1.73, 0.53)	NA
	Combined lumbar + sacral plexus NB vs. spinal anesthesia (single)[86]	1	29	MD (95% CI)	-0.50 (-1.78, 0.78)	NA
KQ2	**Additional pain medication use**					
	Psoas compartment NB vs. epidural anesthesia (single)[110]	1	30	OR (95% CI)	2.00 (0.38, 10.51)	NA
	Delirium					
	Combined lumbar + sacral plexus NB vs. spinal anesthesia (single)[86]	1	29	OR (95% CI)	1.20 (0.27, 5.40)	NA
KQ3	**Allergic reaction**					
	Psoas compartment NB vs. epidural anesthesia (single)[110]	1	30	OR (95% CI)	0.23 (0.04, 1.41)	NA
	Cardiac arrest					
	Psoas compartment NB vs. epidural anesthesia (single)[110]	1	30		NE	
	Damage to surrounding structures					
	Psoas compartment NB vs. epidural anesthesia (single)[110]	1	30		NE	
	Deep venous thrombosis					
	Psoas compartment NB vs. epidural anesthesia (single)[110]	1	30		NE	
	GI symptoms					
	Psoas compartment NB vs. epidural anesthesia (single)[110]	1	30	OR (95% CI)	0.06 (0.00, 1.24)	NA

KQ: key question; CI = confidence intervals; MD = mean difference; NB = nerve block; NA = not applicable; NE = not estimable; OR = odds ratio: randomized and nonrandomized controlled trials; * = statistically significant

Table 13-B. Nerve blocks vs. neuraxial anesthesia: RCT/NRCT (Continued)

	Outcome or Subgroup	Studies	Participants	Statistical Method	Effect Estimate	I^2
KQ3	**Hematoma**					
	Psoas compartment NB vs. epidural anesthesia (single)[110]	1	30		NE	
	Hypotension					
	Psoas compartment NB vs. epidural anesthesia (single)[110]	1	30	OR (95% CI)	0.11 (0.01, 1.04)	NA
	Infection					
	Psoas compartment NB vs. epidural anesthesia (single)[110]	1	30		NE	
	Urinary retention					
	Psoas compartment NB vs. epidural anesthesia (single)[110]	1	30	OR (95% CI)	**0.04 (0.00, 0.72)***	NA

Table 13-C. Nerve blocks (Ropivacaine vs. bupivacaine): RCT/NRCT

	Outcome or Subgroup	Studies	Participants	Statistical Method	Effect Estimate	I^2
KQ3	**Infection**					
	3-in-1 NB[101]	1	50		NE	

KQ: key question; CI = confidence intervals; NB = nerve block; NE = not estimable: randomized and nonrandomized controlled trials

Table 13-D. Nerve block (addition of clonidine) : RCT/NRCT

	Outcome or Subgroup	Studies	Participants	Statistical Method	Effect Estimate	I^2
KQ3	**Bradycardia**					
	Psoas compartment NB: clonidine IV vs. no clonidine[98]	1	24	OR (95% CI)	1.40 (0.28, 7.02)	NA
	Psoas compartment NB: clonidine Intra-catheter vs. no clonidine[98]	1	24	OR (95% CI)	1.40 (0.28, 7.02)	NA
	Psoas compartment NB: clonidine IV vs. clonidine intra-catheter[98]	1	24	OR (95% CI)	1.00 (0.20, 4.95)	NA
	Hypotension					
	Psoas compartment NB: clonidine IV vs. no clonidine[98]	1	24	OR (95% CI)	1.00 (0.12, 8.56)	NA
	Psoas compartment NB: clonidine intra-catheter vs. no clonidine[98]	1	24	OR (95% CI)	1.00 (0.12, 8.56)	NA
	Psoas compartment NB: clonidine IV vs. clonidine Intra-catheter[98]	1	24	OR (95% CI)	1.00 (0.12, 8.56)	NA
	Nausea/vomiting					
	Psoas compartment NB: clonidine IV vs. no clonidine[98]	1	24	OR (95% CI)	1.50 (0.25, 8.84)	NA
	Psoas compartment NB: Clonidine Intra-catheter vs. no clonidine[98]	1	24	OR (95% CI)	0.27 (0.02, 3.09)	NA

KQ: key question; CI = confidence intervals; NA = not applicable; NB = nerve block; OR = odds ratio: randomized and nonrandomized controlled trials

Table 13-D. Nerve block (addition of clonidine) : RCT/NRCT (continued)

	Outcome or Subgroup	Studies	Participants	Statistical Method	Effect Estimate	I^2
KQ3	Psoas compartment NB: clonidine IV vs. clonidine intra-catheter[98]	1	24	OR (95% CI)	5.50 (0.51, 59.01)	NA

Table 13-E. Nerve blocks (US vs. NS): RCT/NRCT

	Outcome or Subgroup	Studies	Participants	Statistical Method	Effect Estimate	I^2
KQ3	**Damage to surrounding structures**[99,100]	2	100	OR (95% CI)	0.16 (0.02, 1.30)	NA
	Infection[99]	1	40		NE	

KQ = key question; CI = confidence intervals; NA = not applicable; NE = not estimable; OR = odds ratio: randomized and nonrandomized controlled trials

Table 14. Evidence summary table (cohort studies): Nerve blocks

Table 14-A. Nerve blocks vs. no block: Cohort studies

	Outcome or Subgroup	Studies	Participants	Statistical Method	Effect Estimate	I^2
KQ2	**Additional pain medication use**					
	Femoral NB[87]	1	99	OR (95% CI)	**0.03 (0.00, 0.44)***	NA
	Delirium[87,105]	2	634	OR (95% CI)	**0.24 (0.08, 0.72)***	60%
	3-in-1 NB[105]	1	535	OR (95% CI)	**0.39 (0.17, 0.90)***	NA
	Femoral NB[87]	1	99	OR (95% CI)	**0.12 (0.04, 0.39)***	NA
	LOS[87,105]	2	634		NP	93%
	3-in-1 NB[105]	1	535	MD (95% CI)	**-6.10 (-8.40, -3.80)***	NA
	Femoral NB[87]	1	99	MD (95% CI)	-0.90 (-2.18, 0.38)	NA
	Mortality 1 year					
	3-in-1 NB[105]	1	535	OR (95% CI)	0.73 (0.48, 1.10)	NA
KQ3	**Acute heart failure**					
	3-in-1 NB[105]	1	535	OR (95% CI)	0.70 (0.33, 1.47)	NA
	Any adverse event	2	634	OR (95% CI)	1.64 (0.79, 3.42)	28%
	3-in-1 NB[105]	1	535	OR (95% CI)	**1.96 (1.31, 2.94)***	NA
	Femoral NB[87]	1	99	OR (95% CI)	0.75 (0.16, 3.54)	NA
	Cardiac complications					
	Femoral NB[87]	1	99	OR (95% CI)	0.33 (0.01, 8.38)	NA
	GI bleeding					
	3-in-1 NB[105]	1	535	OR (95% CI)	1.00 (0.18, 5.53)	NA
	Myocardial Infarction					
	3-in-1 NB[105]	1	535	OR (95% CI)	0.67 (0.07, 6.46)	NA
	Renal disease					
	Femoral NB[87]	1	99	OR (95% CI)	2.09 (0.18, 23.77)	NA
	Respiratory distress					
	Femoral NB[87]	1	99	OR (95% CI)	0.50 (0.04, 5.70)	NA
	Respiratory infection					
	3-in-1 NB[105]	1	535	OR (95% CI)	**0.43 (0.21, 0.92)***	NA
	Stroke					
	3-in-1 NB[105]	1	535	OR (95% CI)	0.25 (0.03, 1.99)	NA
	Urinary retention					
	3-in-1 NB[105]	1	535	OR (95% CI)	0.46 (0.15, 1.39)	NA

KQ = key question; CI = confidence intervals; LOS: length of stay; MD = mean difference; NA = not applicable; NB: nerve block; NP = not pooled; OR = odds ratio

Table 14-A. Nerve blocks vs. no block: Cohort studies (continued)

	Outcome or Subgroup	Studies	Participants	Statistical Method	Effect Estimate	I^2
KQ3	**Urinary tract infection**					
	3-in-1 NB[105]	1	535	OR (95% CI)	**0.34 (0.18, 0.64)***	NA

Table 14-B. Nerve blocks (Ropivacaine vs. bupivacaine): Cohort studies

	Outcome or Subgroup	Studies	Participants	Statistical Method	Effect Estimate	I^2
KQ2	**Additional pain medication use**					
	Lumbar plexus + sciatic plexus NB[97]	1	62	OR (95% CI)	1.25 (0.42, 3.76)	NA
	Deleirium					
	Combined lumbar + sacral plexus NB[97]	1	62	OR (95% CI)	1.93 (0.17, 22.50)	NA
KQ3	**Any adverse event**					
	Lumbar plexus + sciatic plexus NB[97]	1	62		NE	

KQ = key question; CI = confidence intervals; NA = not applicable; NB: nerve block; NE = not estimable; OR = odds ratio

Neurostimulation

Overview of included studies

Two RCTs[112,113] evaluated the efficacy and/or harms of the administration of transcutaneous electrical neurostimulation (TENS) vs. sham control in 123 participants; sample size ranged from 60 to 63. One trial administered the TENS pre-operatively,[113] and the other post-operatively.[112] The mean age ranged from 71.2 to 80.5 years. Most were female (66.7 to 92.1 percent). Acute pain was measured using the VAS and the average baseline pain measure 8.4 to 8.8.

Both RCTs had a high risk of bias (Appendix G). Summary of the evidence from these trials is provided in Table 15.

Table 15. Evidence addressing key questions: Neurostimulation

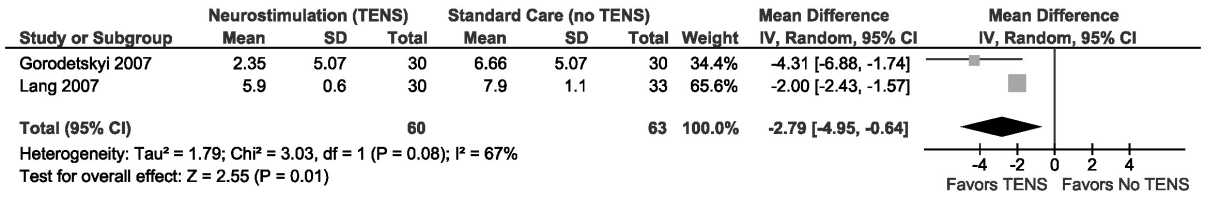
Key Question	Outcome	Evidence avaiability	Strength of Evidence
KQ 1	**Acute pain**	Yes	2 RCTs reported a statistically significant effect in favor of neurostimulation compared with sham control. The strength of the evidence was rated as insufficient.
	Chronic pain	No	
KQ2	**Mortality (30 day and up to 1-year postfracture)**	No	
	Functional status	No	
	Pain medication use; change in type and quantity	No	
	Mental status	No	
	Health-related quality of life	Yes	1 RCT reported a statistically significant difference in favor of neurostimulation.
	Quality of sleep in the hospital	Yes	1 RCT reported a statistically significant difference in favor of neurostimulation.
	Ability to participate in rehabilitation	No	
	Return to prefracture living arrangements	No	
	Health services utilization	No	
KQ3	**Frequency of adverse effects**	No	
KQ4	**Effectiveness and safety in differing subpopulations**	No	

KQ = key question; RCT = randomized controlled trial

Key Question 1: Acute and chronic pain management

Acute pain (post-treatment means) was reported in both RCTs[112,113] (n = 123) (Table 16). It should be noted that the variance was imputed from the reported p value presented in one of the trials.[112] The pooled results showed a significant difference in additional pain relief in favor of TENS (MD -2.79; 95% CI -4.95, -0.64; p = 0.01) (Figure 12).

Figure 12. Neurostimulation acute pain (post-treatment means)



Pain on movement. Pain on movement (post-treatment means) was reported in one trial[112] (n = 60) (Table 16). Neurostimulation provided significantly more pain relief vs. sham control (MD -3.90; 95% CI -6.22, -1.58; p = 0.001). The variance was imputed from the reported p value presented in the trial.[112]

Key Question 2: Other outcomes

One RCT[112] comparing TENS (n = 30) vs. sham control (n = 30) provided data on HRQOL (10cm VAS) and quality of sleep (10cm VAS) (Table 16). Neurostimulation provided significant improvement in HRQOL vs. sham control (MD -4.30; 95% CI -6.86, -1.74; p = 0.001). Similarly neurostimulation provided significant improvement in quality of sleep (MD -3.60; 95% CI -575, -1.45; p = 0.001). The variance was imputed from the reported p value in the trial for both outcomes.[112]

Key Question 3: Adverse effects

No data were reported on adverse effects.

Key Question 4: Efficiacy, effectiveness and safety in subpopulations

No data were reported on subpopulations.

Table 16. Evidence summary table (randomized controlled trials): Neurostimulation

	Outcome or Subgroup	Studies	Participants	Statistical Method	Effect Estimate	I^2
KQ1	Acute pain (post-treatment)[112,113]	2	123	MD (95% CI)	-2.79 (-4.95, -0.64)	67%
	Pain on movement (post-treatment)[112]	1	60	MD (95% CI)	-3.90 (-6.22, -1.58)	NA
KQ2	HRQOL[112]	1	60	MD (95% CI)	-4.30 (-6.86, -1.74)	NA
	Quality of sleep[112]	1	60	MD (95% CI)	-3.60 (-5.75, -1.45)	NA

KQ = key question; CI = confidence intervals; MD = mean difference; NA = not applicable

Rehabilitation

Overview of included studies

One RCT[114] evaluated the efficacy and/or harms of the administration of rehabilitation (stretching and strengthening of spinal and psoas muscles (n = 18) vs. standard care (n = 19)). The mean age was 67.1 years and all participants were female. Acute pain was measured using the 10cm VAS and the mean baseline pain measure was 7.9cm.

The trial had a high risk of bias (Appendix G). Summary of the evidence from these trials is provided in Table 17.

Table 17. Evidence addressing key questions: Rehabilitation

Key Question	Outcome	Evidence avaiability	Strength of Evidence
KQ 1	**Acute pain**	Yes	1 RCT reported a statistically significant effect in favor of rehabilitation vs. standard care. The strength of the evidence was rated as insufficient.
	Chronic pain	No	
KQ2	**Mortality (30 day and up to 1-year postfracture)**	No	
	Functional status	No	
	Pain medication use; change in type and quantity	No	
	Mental status	No	
	Health-related quality of life	No	
	Quality of sleep in the hospital	No	
	Ability to participate in rehabilitation	No	
	Return to prefracture living arrangements	No	
	Health services utilization	No	
KQ3	**Frequency of adverse effects**	No	
KQ4	**Effectiveness and safety in differing subpopulations**	No	

KQ = key question; RCT = randomized controlled trial

Key Question 1: Acute and chronic pain management

Acute pain (post-treatment means)

There was a statistically significant difference in additional pain relief following stretching-strengthening of spinal and psoas muscles vs. standard care (MD -1.39; 95% CI -2.27, -0.51; p = 0.002) (Table 18).

Key Question 2: Other outcomes

No other outcomes were reported.

Key Question 3: Adverse effects

No data were reported for adverse effects.

Key Question 4: Efficacy, effectiveness and safety in subpopulations

All participants in this trial were female.

Table 18. Evidence summary table (randomized controlled trials): Rehabilitation

	Outcome or Subgroup	Studies	Participants	Statistical Method	Effect Estimate	I^2
KQ1	**Acute pain (post-treatment means)**[114]	1	37	MD (95% CI)	**-1.39 (-2.27, -0.51)***	NA

KQ = key question; CI = confidence intervals; MD = mean difference; NA = not applicable

Traction

Overview of included studies

Six RCTs[26,116,118-121] and three NRCTs[115,117,123] (n = 1,167) evaluated the efficacy and/or harms of the administration of traction vs. no intervention or other interventions; sample size ranged from 60 to 311 participants. Additionally, one prospective cohort[122] (n = 134) provided data. The mean age ranged from 74.0 to 81.0 years. Most were female (66.2 to 84.7 percent). Acute pain was measured using the VAS and the mean baseline pain measure ranged from 0.3 to 6.6.

All the RCTs and NRCTs had a high risk of bias; the cohort study had a moderate score (n = 6 stars) on the NOS (Appendix G, I). Summary of the evidence from these trials is provided in Table 19.

Table 19. Evidence addressing key questions: Traction

Key Question	Outcome	Evidence avaiability	Strength of Evidence
KQ 1	**Acute pain**	Yes	7 RCTs reported no statistically significant difference between skin, skeletal, and no traction. The strength of the evidence was rated as low. 1 RCT reported no statistically significant difference between skin and skeletal traction. The strength of the evidence was rates as insufficient.
	Chronic pain	No	
KQ2	**Mortality (30 day and up to 1-year postfracture)**	Yes	1 RCT reported no statistically significant difference between skin, skeletal, and no traction. The strength of the evidence was rated as insufficient.
	Functional status	No	
	Pain medication use; change in type and quantity	Yes	2 RCTs reported no statistically significant difference between skin traction and no traction.
	Mental status	No	
	Health-related quality of life	No	
	Quality of sleep in the hospital	No	
	Ability to participate in rehabilitation	No	
	Return to prefracture living arrangements	No	
	Health services utilization	Yes	2 RCTs reported no statistically significant difference between skin traction and no traction.
KQ3	**Frequency of adverse effects**	Yes	6 RCTs and 1 cohort study demonstrated no statistically significant difference in any adverse event, peroneal palsy, damage to surrounding structures, difficult reduction, pressure sores, direct skin damage, deep venous thrombosis, or failure to heal.
KQ4	**Effectiveness and safety in differing subpopulations**	No	

KQ = key question; RCT = randomized controlled trial

Key Question 1: Acute and chronic pain management

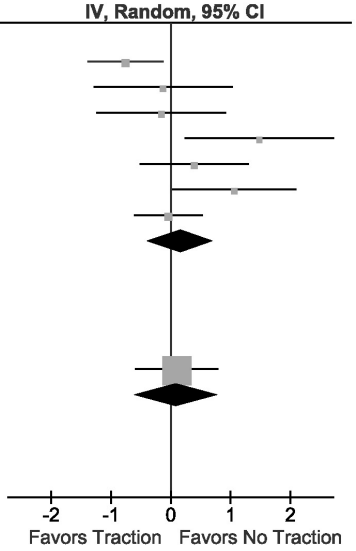
Acute pain (post-treatment means)

Seven trials[26,115,117-119,121,123] compared skin traction (n = 462) vs. no traction (n = 522) (Table 20). There was no significant difference in pain relief between the groups (MD 0.17; 95% CI -0.38, 0.72; p = 0.54) (Figure 13). The variance was imputed for one of the trials[121] using the reported p value in the original publication and from the other included trials for four trials.[115,117,119,123]

In the trial[120] that compared skin traction (n = 40) vs. skeletal traction (n = 38), there was no significant difference between the two groups (MD 0.10; 95% CI -0.60, 0.80; p = 0.78).

Figure 13. Traction - acute pain (post-treatment means)

Study or Subgroup	Traction Mean	Traction SD	Traction Total	No Traction Mean	No Traction SD	No Traction Total	Weight	Mean Difference IV, Random, 95% CI
19.1.1 Skin traction vs. no traction								
Anderson 1993	4.24	2.4	101	5	2.7	151	18.3%	-0.76 [-1.40, -0.12]
Ghnaimat 2005	5.13	2.4	36	5.26	2.7	38	11.6%	-0.13 [-1.29, 1.03]
Jerre 2000	3.02	2.19	30	3.18	2.09	30	12.5%	-0.16 [-1.24, 0.92]
Needoff 1993	4.32	2.4	30	2.84	2.7	34	10.7%	1.48 [0.23, 2.73]
Resch 2005	3.9	2.4	49	3.51	2.7	74	14.6%	0.39 [-0.52, 1.30]
Rosen 2001	-1.76	2.58	50	-2.82	2.7	50	13.0%	1.06 [0.02, 2.10]
Yip 2002	0.88	2.4	166	0.92	2.7	145	19.3%	-0.04 [-0.61, 0.53]
Subtotal (95% CI)			**462**			**522**	**100.0%**	**0.17 [-0.38, 0.72]**
Heterogeneity: Tau² = 0.32; Chi² = 15.75, df = 6 (P = 0.02); I² = 62%								
Test for overall effect: Z = 0.61 (P = 0.54)								
19.1.2 Skin traction vs. skeletal traction								
Resch 1998	3.4	2	40	3.3	1	38	100.0%	0.10 [-0.60, 0.80]
Subtotal (95% CI)			**40**			**38**	**100.0%**	**0.10 [-0.60, 0.80]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.28 (P = 0.78)								



Key Question 2: Other outcomes

Health services utilization. LOS for acute hospitalization was reported in two trials[115,117] comparing skin traction (n = 137) vs. no traction (n = 189) (Table 20). In one trial[115] there was no significant difference between the groups (MD 1.20; 95% CI -0.93, 3.33; p = 0.27). The MD was not estimable in the other study[117] as no measure of variance was reported; however, the authors reported that the difference was not statistically significant. In order to allow pooling of the two trials, the variance was imputed from the available study variance.[115] There was no significant difference between the LOS between the two groups (MD 1.08; 95% CI -0.78, 2.95; p = 0.26).

Mortality (30 day). Thirty day mortality was reported in one RCT[116] (n = 105) (Table 20). There was no difference in mortality between skin or skeletal traction vs. no traction (0/55 vs. 4/50; OR 0.17; 95% CI 0.02, 1.49; p = 0.11). There were no reports of mortality when comparing skin vs. skeletal traction.

Pain medication use. Additional pain medication use was reported in one RCT[121] and one NRCT[115] (n = 352) (Table 20). There was no significant difference in pain medication use

following skin traction vs. no traction (99/151 vs. 111/201; OR 1.47; 95% CI 0.83, 2.61; p = 0.18).

Key Question 3: Adverse effects

Six RCTs[115,117,118,120,121,123] (n = 792) evaluated the nature and frequency of adverse effects associated with the administration of skin or skeletal traction vs. no traction (Table 20). Additionally, one cohort study[122] (n = 134) compared pillow vs. metal frame (Table 21). In two trials[120,123] (n = 389) no adverse effects were reported in either the intervention or control group. For the following specific adverse effects, there were no significant differences between the study groups: damage to surrounding structures,[121] deep venous thrombosis,[118] difficult reduction,[115,117] direct skin damage,[117] failure to heal,[118] peroneal palsy,[121,122] and pressure sores.[118]

Key Question 4: Efficacy, effectiveness and safety in subpopulations

One NRCT[123] was conducted in Oriental participants comparing skin traction (n = 166) vs. no traction (n = 145). Acute pain reduction was not significantly different between the two groups (MD -0.04; 95% CI -0.61, 0.53; p = 0.89). No adverse effects were recorded (0/166 vs. 0/145).

Table 20. Evidence summary table (randomized controlled trials): Traction

	Outcome or Subgroup	Studies	Participants	Statistical Method	Effect Estimate	I^2
KQ1	**Acute pain (post-treatment means)**					
	Skin traction vs. no traction[26,115,117-119,121,123]	7	984	MD (95% CI)	0.17 (-0.38, 0.72)	62%
	Skin traction vs. skeletal traction[26]	1	78	MD (95% CI)	0.10 (-0.60, 0.80)	NA
KQ2	**Additional pain medication use**					
	Skin traction vs. no traction[115,121]	2	352	OR (95% CI)	1.47 (0.83, 2.61)	17%
	Length of stay for acute hospitalization					
	Skin traction vs. no traction[115,117]	2	326	MD (95% CI)	1.08 (-0.78, 2.95)	0%
	Mortality 30 days					
	Traction vs. no traction[116]	1	105	OR (95% CI)	0.17 (0.02, 1.49)	NA
	Skin traction vs. no traction[116]	1	51	OR (95% CI)	0.18 (0.01, 3.89)	NA
	Skeletal traction vs. no traction[116]	1	54	OR (95% CI)	0.16 (0.01, 3.48)	NA
	Skin traction vs. skeletal traction[116]	1	55		NE	
KQ3	**Any adverse event**					
	Skin traction vs. no traction[123]	1	311		NE	
	Skin traction vs. skeletal traction[120]	1	78		NE	
	Damage to surrounding structures					
	Skin traction vs. no traction[121]	1	100	OR (95% CI)	5.21 (0.24, 111.24)	NA
	Difficult reduction					
	Skin traction vs. no traction[115,117]	2	183	OR (95% CI)	0.90 (0.42, 1.96)	0%
	Peroneal palsy					
	Skin traction vs. no traction[121]	1	100	OR (95% CI)	3.06 (0.12, 76.95)	NA
	Pressure sores					
	Skin traction vs. no traction[118]	1	120	OR (95% CI)	11.99 (0.65, 221.86)	NA

KQ = key question; CI = confidence intervals; NA = not applicable; NE = not estimable; OR = odds ratio

Table 21. Evidence summary table (cohort studies): Traction

	Outcome or Subgroup	Studies	Participants	Statistical Method	Effect Estimate	I^2
KQ3	**Peroneal palsy**					
	Skin traction vs. no traction[122]	1	134	OR (95% CI)	0.09 (0.00, 1.60)	NA

KQ = key question; CI = confidence intervals; NA = not applicable; OR = odds ratio

Chapter 4. Discussion

Overview

Hip fracture due to low energy trauma (e.g., slip and fall) is a common condition in the geriatric population. Today, nearly all hip fractures in the developed world are surgically treated and represent one of the most common emergency orthopedic procedures. Even so, the associated morbidity and mortality of hip fracture are significant. One year mortality for hip fracture is estimated to be up to 37 percent, and a large proportion of those patients who do survive will never recover to their prefracture level of function.[5]

Hip fractures are frequently characterized by acute pre-, peri- and postoperative pain. Pain is manifested on a number of fronts. Preoperative pain arises from injury to the muscles and joint capsule from the serrated edges of broken bone and the associated release of local inflammatory factors. Immediate postoperative pain is attributed to the procedures required for the surgical fixation of the femur (e.g., skin incision, femur stabilization). Patients with greater postoperative pain are slower to mobilize and have longer hospital stays.[138] Additionally, pain at all stages is aggravated by psychological stress and anxiety.

Pain that is not properly managed in older patients can have deleterious effects in terms of increased risk of cardiovascular adverse effects and postoperative delirium. While little is known about the impact of postoperative pain in older adults, physicians are hesitant to prescribe opioid analgesics for fear of adverse effects such as delirium, nausea, respiratory depression, drowsiness, hypotension, and constipation as these events have been demonstrated to occur more frequently in the geriatric population.[138,139] Others have reported that postoperative pain management in older adults is more commonly undertreated and untreated than in younger patients.[140] This may reflect a belief among patients and health professionals that pain in the elderly is a natural phenomenon that is self-limiting and should be left to take its course without any intervention.[19]

This comparative effectiveness review (CER) identified, summarized, critically appraised, and compared the evidence on pain management interventions following hip fracture. We conducted a comprehensive search of over 25 electronic databases for published studies, ongoing trials, and conference proceedings. In addition, we hand searched major conference proceedings in order to identify additional relevant studies. Finally, we did not exclude studies on the basis of their published language. All these safeguards were implemented to help identify the evidence and limit the possibility of publication bias. To reduce the possibility of selection bias, we performed duplicate, independent study selection, and all data were independently extracted by two reviewers.

Summary of Findings

Table 22 summarizes the findings for key outcomes for each intervention. Many studies within this review included small numbers of participants and reported only a small number of outcome measures. Several studies had a poor level of methodological rigor, in particular regarding their inherent risk of bias. Of the 65 included trials, the majority were assessed with an unclear risk for bias. Twenty-seven trials were considered to be at high risk of bias while only two were considered to be of low risk of bias., The strength of the evidence for most key outcomes was considered insufficient or low. This is a reflection of the general poor

methodological quality, lack of study power, and number of studies investigating each intervention in this population.

The majority of studies included in this review fell into the categories of nerve blocks (n = 30),[82-111] and anesthesia (n = 25),[54-78] while fewer studies dealt with traction (n = 10),[26,115-123] systemic analgesia (n = 3),[41,42,53] CAM (n = 2),[43,79] multimodal pain management (n = 2),[80,81] neurostimulation (n = 2),[112,113] and rehabilitation (n = 1).[114] Although we restricted the publication of studies from 1990, there appears to be a trend for more recent studies to examine pain management following hip fracture (median publication date = 2003; IQR: 1998 to 2007). Most studies included in this review were RCTs conducted in single university settings in Europe with few studies included from North American sites.

Most studies examined the pharmaceutical management of peri- and postoperative pain in this patient population. Short-term (inhospital) postoperative pain was the most frequent pain examined. None of the studies examined the long-term pain associated with hip fracture. Management of pain was often evaluated from few perspectives such as reported pain, mortality and adverse effects. The ramifications of pain were infrequently examined in terms of function, HRQOL, and health services.

Although predominantly elderly women fracture their hips, this patient population consists of subgroups that warrant further investigation. For instance, almost half of the studies (n = 30) reported excluding patients with any cognitive impairment, or inability to cooperate. Researchers have reported that approximately 35 percent of the elderly hip fracture population includes patients with some degree of cognitive impairment, be it, dementia, delirium, or acute confusion.[141] None of the included studies in this CER was exclusively examined participants from institutional settings or with cognitive impairment, which reduces the external validity or generalizability of our findings to the overall hip fracture patient population.

Regardless of these limitations, some general consensus can be made from this review.

Key Questions 1 and 2: Pain management and other outcomes. The available evidence suggests that, in general, the **nerve blockade** is effective for the relief of the acute pain of hip fracture. The nerve supply to the hip joint comes from more than one major nerve and, not surprisingly, the more of these that are blocked, the greater the relief. Thus, epidural blockade is more effective than the so called '3-in-1' block (simultaneous blockade of the femoral nerve, obturator nerve, and lateral cutaneous nerve of thigh), which in turn is more effective than isolated blockade of the femoral nerve. Nerve blockade also reduces the need for supplemental systemic analgesia, and may reduce the risk of delirium, a common and dangerous complication of hip fracture. However, most studies were limited to either assessing acute pain or examining use of additional analgesia and did not report on how nerve blockades may affect rehabilitation such as ambulation or mobility if the blockade has both sensory and motor effects. Furthermore, our decision to extract followup data demonstrating the greatest improvement for the intervention arm may have introduced a bias favoring the intervention. However, we do not expect this to have had a major impact because most studies presented data for only time point. Nerve blockade of the types described in this CER are within the repertoire of most practicing anesthesiologists, but many institutions are deterred from providing them due to the additional time, effort and supervision they require if they are if they are to work well.

This review also calls into question some commonly held beliefs about the care of those with hip fracture. **Preoperative traction**, for instance, does not reduce pain or complications in any demonstrable way. Spinal **anesthesia** used during the operation to fix the fracture, while effective and safe, does not reduce mortality, delirium, or other medical complications of the

fracture. Adding other agents to plain local anesthetic for spinal anesthesia does not seem to make any difference to outcome outside the operating room. Furthermore, bigger doses of spinal anesthetic cause more hemodynamic issues without improving pain control or outcome.[142]

The evidence guiding the selection of **systemic drugs** for hip fracture analgesia is very scant. Intravenous parecoxib emerges as a reasonable alternative to traditional intramuscular injections of opiate and older NSAIDs. Parenteral medications cause fewer gastrointestinal side effects than oral ones.

This review also finds that **acupressure, relaxation therapy,** and **TENS** are safe interventions that are associated with clinically meaningful reductions in pain after hip fracture, with effect sizes surpassing those of systemic drug and anesthetic interventions. The obvious drawback of these is the amount of skilled health provider time that must be used to apply and/or teach these modalities correctly. **Physical conditioning regimens** improve pain control in the postoperative period.

No evidence could be found that any analgesic intervention attenuated the progression of acute to chronic pain. Furthermore, **multimodal analgesia** (combinations of analgesic interventions) failed to yield improvements over single modalities. Further research in this area might profitably focus on combinations of interventions that are known to be effective in isolation.

Key Question 3: Adverse effects. Although most studies reported on adverse effects associated with the specific interventions being evaluated, the included studies were small; thus most studies reported few, if any, adverse effects. Moreover, the horizon for adverse effects was over a short period of time, usually within the acute care setting, and did not examine the development of adverse effects outside of the acute care setting.

Key Question 4: Effectiveness and safety of pain management in differing subpopulations. This question was addressed by limited data from two RCTs of nerve blocks—one was restricted participants with heart disease and to participants who were independent prior to the hip fracture. The only significant difference reported was a reduction in acute pain in participants with heart disease who received a nerve block.

Applicability

The study populations in this body of evidence were relatively homogeneous. Studies included patients with all types of hip fractures due to low energy trauma. All participants were over 50 years of age; the mean age in most studies clustered between 77 and 82 years. Most patients were female. Studies generally included a mixture of hip fracture types and minimal data for specific fracture types were available. A majority of studies excluded patients on the basis of mental status (i.e., patients with dementia or other cognitive disorders). Studies did not generally provide information of the pre-fracture dwelling (i.e., community vs. institution) or social status/support of participants (e.g., married, living with relatives). Interventions were provided across the spectrum of the care pathway from pre-operative to postoperative; however, no studies provided data on long term followup for this patient population.

The other issue regarding applicability for this body of evidence relates to the practitioners administering the interventions (e.g., anesthetists, surgeons, physical therapists, or other healthcare providers). Outcome effects may differ between the trials and real life practice based on practitioners' skills and experience, volume of surgery, and variations or rigor surrounding cointerventions or procedural protocols.

Limitations of Existing Evidence

To our knowledge, no specific evidence-based guidelines for pain management in hip fracture are available; however, this may be indirectly related to the fact that currently there are no committees or task force groups for pain management in hip fracture. Further, there are no recommended standardized outcomes for assessing pain specific to this patient population. This patient population is different from other surgical patients in that they are older and predominantly women with significant number of co-existing conditions, commonly including altered cognition.

Evaluations of common subpopulations found within the overall hip fracture patient populations were infrequent. A large proportion of the included studies excluded patients with altered cognition due to delirium or dementia, despite the high prevalence of dementia in the hip fracture population. In addition, although multiple comorbidities are common in patients who experience a hip fracture, risk adjustment for illness/health severity were not reported, nor were most of the subpopulations that we intended to investigate (e.g., pre-fracture functional status). These are all factors that could potentially affect reported pain levels.

Included studies were primarily pharmacologic interventions and represented evaluation by a single discipline (e.g., anesthesiology, rehabilitation) despite evidence in other clinical areas that optimal chronic pain management is multidisciplinary.[19,143] In addition to the fact that all studies examined acute pain from one discipline's perspective, studies were primarily conducted in single centers in Europe or Asia with small samples sizes; minimal evidence was available from centers in North America. Study quality was low to moderate and thus, clear evidence to support clinical decisionmaking for interventions is limited.

In addition, lack of standardized outcome reporting or use of standardized measures limits the interpretation and applicability of the results. Although pain and function are correlated,[138] most outcomes focused on pain relief and did not evaluate if the intervention had any positive or negative effects on the patients' ability to mobilize postoperatively, a factor that is linked to recovery levels following hip fracture.[144] There was no evidence about managing pain after hospital discharge or examining the long-term effects of early postoperative management on subsequent recovery.

Finally, because of the low incidence of complications following surgery, no individual included study had adequate numbers to detect associated adverse effects with the interventions. For example, the rationale for using a nerve block for pain management following a hip fracture is primarily to enable pain to be controlled with lower doses of systemic analgesia. Although the studies demonstrated a reduced requirement for systemic analgesics, this is only clinically useful if it associated with a reduction in the adverse effects of such analgesic use.

Recommendations for Future Research

Multi-center research studies. Adequately powered multi-center research studies are needed to provide a comprehensive assessment of safe, effective, and appropriate pain management following a hip fracture. Studies need to be large enough to allow subgroup analyses by age, gender, comorbidities, or functional groups (e.g., independent vs. dependent ambulates). In addition, researchers need to consider inclusion of common subpopulations of hip

fracture patients. In particular, those with altered cognition who make up a substantial proportion of the overall hip fracture patient population should be included in future studies of pain management following hip fracture.

Outcomes. Standardization of outcomes and outcome measures will allow easier and meaningful comparisons across different interventions and among studies. The types of outcomes reported do not reflect the multi-dimensional nature of pain. Relevant outcomes should include validated pain scores, prescription of opiates and other agents, adverse effects or complications attributable or related to the intervention. Associated outcomes of pain such as function, quality of life, and time to recovery should also be evaluated. The evaluation of pain should include long term followup of outcomes beyond the acute hospital setting to determine the pattern of pain recovery and whether early effective pain management techniques affects ultimate recovery levels.

Methods. Future research should seek to minimize bias by blinding outcome assessors, use of validated and standardized outcome assessment instruments, adequate allocation concealment (where applicable), and appropriate handling and reporting of missing data.

Conclusions

For the majority of interventions, there are only sparse data available, which precludes firm conclusions for any single approach or for the optimal overall pain management following nonpathological hip fracture due to low energy trauma. The paucity of evidence related to long-term outcomes and the fact that the majority of the data is derived from studies of low methodological quality or from study designs associated with higher risk of bias (i.e., cohort studies). Overall, the evidence shows that most interventions result in improvements in short-term pain scores; however, few differences of long-term clinical importance are evident when comparisons between interventions are available. The rates of complication were generally low and the majority of complications were not significantly different among the interventions. Well-designed and powered, long-term trials are needed in order to determine the relative effectiveness of pain interventions for hip fracture patients. Until then, pain management in this population will rely heavily on availability of the interventions, staff skills and training and pre-existing patient comorbidities.

Table 22. Summary of evidence for key outcomes for pain management following hip fracture

Outcome	Comparison (# studies)	Strength of evidence	Summary
Systemic analgesia			
Acute pain	Parecoxib IV vs. diclofenac ±pethidine IM (1 RCT) Intrathecal isotonic clonidine vs. intrathecal hypertonic clonidine (1 RCT)	Insufficient	Significant effect in favor of parecoxib IV Significant effect in favor of intrathecal isotonic clonidine
Acute pain at rest	Lysine clonixinate vs. metamizole (1 RCT)	Insufficient	No significant difference
Chronic pain	None	Insufficient	No data
30 day mortality	None	Insufficient	No data
Stroke	None	Insufficient	No data
Myocardial infarction	None	Insufficient	No data
Delirium	Lysine clonixinate vs. metamizole (1 RCT)	Insufficient	No significant difference
Renal failure	None	Insufficient	No data
Anesthesia: spinal vs. general anesthesia			
Acute pain	Spinal vs. general anesthesia	Insufficient	Significant effect in favor of spinal anesthesia
Chronic pain	None	Insufficient	No data
30 day mortality	Spinal vs. general anesthesia (2 RCTs, 2 cohorts)	Low	No significant difference
Stroke	None	Insufficient	No data
Myocardial infarction	Spinal vs. general anesthesia (1 RCT)	Insufficient	No significant difference
Delirium	Spinal vs. general anesthesia (1 RCT)	Insufficient	No significant difference
Renal failure	None	Insufficient	No data
Anesthesia: spinal – continuous vs. single administration			
Acute pain	None	Insufficient	No data
Chronic pain	None	Insufficient	No data
30 day mortality	Continuous vs. single administration (3 RCTs, 1 cohort)	Insufficient	No significant difference
Stroke	Continuous vs. single administration (1 RCT)	Insufficient	No data
Myocardial infarction	Continuous vs. single administration (1 RCT)	Insufficient	No significant difference
Delirium	Continuous vs. single administration (2 RCTs)	Low	No significant difference
Renal failure	None	Insufficient	No data
Anesthesia: spinal – addition of other medications			
Acute pain	Addition of fentanyl vs. standard spinal anesthesia (1 RCT)	Insufficient	No data
Acute pain	Addition of morphine vs. standard spinal anesthesia (1 RCT)	Insufficient	No significant difference
Acute pain	Addition of sufentanil vs. standard spinal anesthesia (1 RCT)	Insufficient	No significant difference
Chronic pain	None	Insufficient	No data
30 day mortality	None	Insufficient	No data
Stroke	None	Insufficient	No data
Myocardial infarction	None	Insufficient	No data
Delirium	Addition of morphine vs. standard spinal anesthesia (1 RCT)	Low	No significant difference
Renal failure	None	Insufficient	No data

IV = intravenous; IM = intramuscular; RCT = randomized controlled trial

Table 22. Summary of evidence for key outcomes for pain management following hip fracture (continued)

Outcome	Comparison (# studies)	Strength of evidence	Summary
Anesthesia: spinal – ropivacaine vs. bupivacaine			
Acute pain	None	Insufficient	No data
Chronic pain	None	Insufficient	No data
30 day mortality	None	Insufficient	No data
Stroke	None	Insufficient	No data
Myocardial infarction	None	Insufficient	No data
Delirium	Ropivacaine vs. bupivacaine (1 cohort)	Insufficient	No significant difference
Renal failure	None	Insufficient	No data
Anesthesia: spinal – different doses			
Acute pain	Bupivacaine 2.5 mg vs. 5mg (1 cohort)	Insufficient	No significant difference
Chronic pain	None	Insufficient	No data
30 day mortality	None	Insufficient	No data
Stroke	None	Insufficient	No data
Myocardial infarction	None	Insufficient	No data
Delirium	None	Insufficient	No data
Renal failure	None	Insufficient	No data
Complementary and alternative medicine			
Acute pain	Acupressure vs. standard care (1 RCT)	Insufficient	No significant difference
Acute pain	Relaxation vs. standard care (1 RCT)	Insufficient	No significant difference
Chronic pain	None	Insufficient	No data
30 day mortality	None	Insufficient	No data
Stroke	None	Insufficient	No data
Myocardial infarction	None	Insufficient	No data
Delirium	None	Insufficient	No data
Renal failure	None	Insufficient	No data
Multimodal pain management			
Acute pain	None	Insufficient	No data
Chronic pain	None	Insufficient	No data
30 day mortality	Multimodal pain management vs. standard care (1 cohort)	Insufficient	No significant difference
Stroke	Multimodal pain management vs. standard care (1 cohort)	Insufficient	No significant difference
Myocardial infarction	Multimodal pain management vs. standard care (1 cohort)	Insufficient	No significant difference
Delirium	Multimodal pain management vs. standard care (1 cohort)	Insufficient	No significant difference
Delirium	Multimodal pain management vs. standard care (1 cohort)	Insufficient	No significant difference
Renal failure	None	Insufficient	No data

Table 22. Summary of evidence for key outcomes for pain management following hip fracture (continued)

Outcome	Comparison (# studies)	Strength of evidence	Summary
Nerve blockade			
Acute pain	Nerve block vs. no nerve block (10 RCTs)	Moderate	Significant effect in favor of nerve block
Pain on movement	Nerve block vs. no nerve block (4 RCTs)	Insufficient	No data
Pain at rest	Nerve block vs. no nerve block (3 RCTs)	Insufficient	No data
Day 1 pain	Nerve block vs. no nerve block (1 RCTs)	Insufficient	No significant difference
Chronic pain	None	Insufficient	No data
30 day mortality	Nerve block vs. no nerve block (4 RCTs)	Low	No significant difference
Stroke	Nerve block vs. no nerve block (1 RCT, 1 cohort)	Insufficient	No significant difference
Myocardial infarction	Nerve block vs. no nerve block (2 RCTs, 1 cohort)	Insufficient	No significant difference
Delirium	Nerve block vs. no nerve block (3 RCTs, 2 cohorts)	Moderate	Significant effect in favor of nerve block
Renal failure	None	Insufficient	No data
Nerve blockade vs. regional anesthesia			
Acute pain	Nerve block vs. regional anesthesia (3 RCTs)	Low	No significant difference
Chronic pain	None	Insufficient	No data
30 day mortality	None	Insufficient	No data
Stroke	None	Insufficient	No data
Myocardial infarction	None	Insufficient	No data
Delirium	Nerve block vs. regional anesthesia (1 RCT)	Insufficient	No significant difference
Renal failure	None	Insufficient	No data
Neurostimulation			
Acute pain	Neurostimulation vs. standard care (2 RCTs)	Insufficient	Significant effect in favor of neurostimulation
Pain on movement	Neurostimulation vs. standard care (1 RCT)	Insufficient	Significant effect in favor of neurostimulation
Chronic pain	None	Insufficient	No data
30 day mortality	None	Insufficient	No data
Stroke	None	Insufficient	No data
Myocardial infarction	None	Insufficient	No data
Delirium	None	Insufficient	No data
Renal failure	None	Insufficient	No data
Rehabilitation			
Acute pain	Rehabilitation vs. standard dare	Insufficient	Significant effect in favor of rehabilitation
Chronic pain	None	Insufficient	No data
30 day mortality	None	Insufficient	No data
Stroke	None	Insufficient	No data
Myocardial infarction	None	Insufficient	No data
Delirium	None	Insufficient	No data
Renal failure	None	Insufficient	No data

Table 22. Summary of evidence for key outcomes for pain management following hip fracture (continued)

Outcome	Comparison (# studies)	Strength of evidence	Summary
Traction			
Acute pain	Skin traction vs. no traction (7 RCTs)	Low	No significant difference
Acute pain	Skin traction vs. skeletal traction (1 RCT)	Insufficient	No significant difference
Chronic pain	None	Insufficient	No data
30 day mortality	Skin traction vs. no traction (1 RCT)	Insufficient	No significant difference
30 day mortality	Skin traction vs. skeletal traction (1 RCT)	Insufficient	No data
Stroke	None	Insufficient	No data
Myocardial infarction	None	Insufficient	No data
Delirium	None	Insufficient	No data
Renal failure	None	Insufficient	No data

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Abbreviations

Abbreviation	Description
AE	Adverse Event
AEs	Adverse Events
AHRQ	Agency for Healthcare Research and Quality
AGS	American Geriatric Society
APTA	American Physical Therapy Association
ASRA	American Society of Regional Anesthesia and Pain Medicine
CER	Comparative Effectiveness Review
CAM	Complementary and Alternative Medicines
CI	Confidence Interval
COX-2	cyclooxygenase 2
ESA	European Society of Anesthesiology
ESRA	European Society of Regional Anesthesia
EPC	Evidence-based Practice Centre
EPCs	Evidence-based Practice Centres
GI	Gastrointestinal
GRADE	Grading of Recommendation Assessment, Development & Evaluation
HRQOL	Health Related Quality of Life
IM	Intermuscular
IARS	International Anesthesia Research Society
IQR	Interquartile Range
IV	Intravenous
KQ	Key Question
LOS	Length of Stay
MD	Mean Difference
mg	Milligrams
MMSE	Mini Mental State Examination
MI	Myocardial Infarction
NB	Nerve Block
NS	Neurostimulation
NOS	Newcastle Ottawa Scale
NSAIDS	Non Steroidal Anti-Inflammatory Drugs
NRCT	Nonrandomized Controlled Trials
NA	Not Applicable
NE	Not Estimable
NP	Not Pooled
NRS	Numeric Rating Score
PICOTS	Population, Intervention, Comparison, Outcome, Timing, and Setting
RCT	Randomized Controlled Trial
RoB	Risk of Bias
SRC	Scientific Resource Center
SD	Standard Deviation
SMD	Standardized Mean Difference

TENS	Transcutaneous Electrical Neurostimulation
US	Ultrasound
UAEPC	University of Alberta Evidence-based Practice Centre
VAS	Visual Analog Scale