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Intra-Articular Analgesia After Knee Arthroscopy: A Rapid Review

Health Quality Ontario

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Evidence Development and Standards Branch at Health Quality Ontario

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Conflict of Interest Statement

All authors in the Evidence Development and Standards branch at Health Quality Ontario are impartial. There are no competing interests or conflicts of interest to declare.

Rapid Review Methodology

Rapid reviews are completed in 2-4–week time frames. Clinical questions are developed by the Evidence Development and Standards branch at Health Quality Ontario, in consultation with experts, end users, and/or applicants in the topic area. A systematic literature search is then conducted to identify relevant systematic reviews, health technology assessments, and meta-analyses. The methods prioritize systematic reviews, which, if found, are rated by AMSTAR to determine the methodological quality of the review. If the systematic review has evaluated the included primary studies using the GRADE Working Group criteria (http://www.gradeworkinggroup.org/index.htm), the results are reported and the rapid review process is complete. If the systematic review has not evaluated the primary studies using GRADE, the primary studies in the systematic review are retrieved and the GRADE criteria are applied to 2 outcomes. If no systematic review is found, then RCTs or observational studies are included, and their risk of bias is assessed. All rapid reviews are developed and finalized in consultation with experts.

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Health Quality Ontario strives to promote health care that is supported by the best available scientific evidence. The Evidence Development and Standards branch works with expert advisory panels, clinical experts, scientific collaborators, and field evaluation partners to conduct evidence-based reviews that evaluate the effectiveness and cost-effectiveness of health interventions in Ontario.

Based on the evidence provided by Evidence Development and Standards and its partners, the Ontario Health Technology Advisory Committee—a standing advisory subcommittee of the Health Quality Ontario Board—makes recommendations about the uptake, diffusion, distribution, or removal of health interventions to Ontario's Ministry of Health and Long-Term Care, clinicians, health system leaders, and policy-makers.

Health Quality Ontario's research is published as part of the *Ontario Health Technology Assessment Series,* which is indexed in MEDLINE/PubMed, Excerpta Medica/Embase, and the Centre for Reviews and Dissemination database. Corresponding Ontario Health Technology Advisory Committee recommendations and other associated reports are also published on the Health Quality Ontario website. Visit http://www.hqontario.ca for more information.

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In addition, Evidence Development and Standards collects and analyzes information about how a health intervention fits within current practice and existing treatment alternatives. Details about the diffusion of the intervention into current health care practices in Ontario add an important dimension to the review. Information concerning the health benefits, economic and human resources, and ethical, regulatory, social, and legal issues relating to the intervention may be included to assist in making timely and relevant decisions to optimize patient outcomes.

Disclaimer

This rapid review is the work of the Evidence Development and Standards branch at Health Quality Ontario, and is developed from analysis, interpretation, and comparison of published scientific research. It also incorporates, when available, Ontario data and information provided by experts. As this is a rapid review, it may not reflect all the available scientific research and is not intended as an exhaustive analysis. Health Quality Ontario assumes no responsibility for omissions or incomplete analysis resulting from its rapid reviews. In addition, it is possible that other relevant scientific findings may have been reported since completion of the review. This report is current as of the date of the literature search specified in the Research Methods section. Health Quality Ontario makes no representation that the literature search captured every publication that was or could be applicable to the subject matter of the report. This rapid review may be superseded by an updated publication on the same topic. Please check the Health Quality Ontario website for a list of all publications: http://www.hqontario.ca/evidence/publications-and-ohtac-recommendations.

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List of Abbreviations

AMSTAR	Assessment of Multiple Systematic Reviews
IA	Intra-articular
GRADE	Grading of Recommendations Assessment, Development, and Evaluation
RCT	Randomized controlled trial
RR	Relative risk
SMD	Standardized mean difference
VAS	Visual Analogue Scale

Background

As legislated in Ontario's *Excellent Care for All Act*, Health Quality Ontario's mandate includes the provision of objective, evidence-informed advice about health care funding mechanisms, incentives, and opportunities to improve quality and efficiency in the health care system. As part of its Quality-Based Procedures (QBP) initiative, Health Quality Ontario works with multidisciplinary expert panels (composed of leading clinicians, scientists, and administrators) to develop evidence-based practice recommendations and define episodes of care for selected disease areas or procedures. Health Quality Ontario's recommendations are intended to inform the Ministry of Health and Long-Term Care's Health System Funding Strategy.

For more information on Health Quality Ontario's Quality-Based Procedures initiative, visit www.hqontario.ca.

Objective of Analysis

The objective of this analysis was to determine the effectiveness of intra-articular (IA) analgesics after arthroscopic knee surgery.

Clinical Need and Target Population

Ambulatory arthroscopic surgery of the knee has been shown to result in moderate to severe pain after surgery, (1) and pain from arthroscopic surgery has been suggested as a cause for delay in patient recovery and return to daily activity. Effective pain management options are therefore required for patients receiving arthroscopic surgery of the knee.

Technology/Technique

Intra-articular (IA) analgesic agents have been used to improve pain relief and the duration and quality of analgesia after arthroscopic knee surgery. Intra-articular analgesics are delivered to patients by injection into the knee joint at the end of surgery, and include both local anesthetics such as bupivacaine, lidocaine, and ropivacaine, as well as analgesics such as opioids and steroids.

Rapid Review

Research Question

What is the effectiveness of intra-articular analgesia for patients undergoing arthroscopic knee surgery?

Research Methods

Literature Search

Search Strategy

A literature search was performed on December 20, 2013, using Ovid MEDLINE, Ovid MEDLINE In-Process and Other Non-Indexed Citations, and EBM Reviews for studies published from January 1, 2003, to December 20, 2013. (Appendix 1 provides details of the search strategies.) Abstracts were reviewed by a single reviewer and, for those studies meeting the eligibility criteria, full-text articles were obtained. Reference lists were also examined for any additional relevant studies not identified through the search.

Inclusion Criteria

- English-language full-text publications
- published between January 1, 2003, and December 20, 2013
- systematic reviews (SRs), meta-analyses (MAs), and health technology assessments
- studies evaluating IA analgesia given at the conclusion of surgery compared with no IA analgesia
- reports on 1 or more outcomes of interest
- approved by Health Canada as an analgesic

Exclusion Criteria

- studies where relevant data could not be extracted
- studies comparing different types of IA analgesics

Outcomes of Interest

- pain
- additional analgesics required
- return to daily activity

Expert Panel

In December 2013, an Expert Advisory Panel for Patients Undergoing Knee Arthroscopic Surgery was struck. Members of the panel included physicians, personnel from the Ministry of Health and Long-Term Care, health care administrators, and allied health professionals.

The role of the expert advisory panel was to provide advice on primary patient groupings; to review the evidence, guidance, and publications related to defined patient populations; to identify and prioritize

interventions for review; and to advise on the development of a care pathway model. The role of panel members was to provide advice on the scope of the project, the methods used, and the findings. However, the statements, conclusions, and views expressed in this report do not necessarily represent the views of the expert panel members.

Quality of Evidence

The Assessment of Multiple Systematic Reviews (AMSTAR) measurement tool was used to assess the methodological quality of systematic reviews. (2)

The quality of the body of evidence for each outcome was examined according to the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) Working Group criteria. (3) The overall quality was determined to be high, moderate, low, or very low using a step-wise, structural methodology.

Study design was the first consideration; the starting assumption was that randomized controlled trials (RCTs) are high quality, whereas observational studies are low quality. Five additional factors—risk of bias, inconsistency, indirectness, imprecision, and publication bias—were then taken into account. Limitations in these areas resulted in downgrading the quality of evidence. Finally, 3 main factors that may raise the quality of evidence were considered: large magnitude of effect, dose response gradient, and accounting for all residual confounding factors. (3) For more detailed information, please refer to the latest series of GRADE articles. (3)

When fewer than 10 studies were included in a SR, the original studies referenced within the review were obtained and assessed for risk of bias. Alternatively, when 10 or more studies were included within the review risk of bias was based solely on data provided and available within the SR.

As stated by the GRADE Working Group, the final quality score can be interpreted using the following definitions:

High	High confidence in the effect estimate—the true effect lies close to the estimate of the effect
Moderate	Moderate confidence in the effect estimate—the true effect is likely to be close to the estimate of the effect, but may be substantially different
Low	Low confidence in the effect estimate—the true effect may be substantially different from the estimate of the effect
Very Low	Very low confidence in the effect estimate—the true effect is likely to be substantially different from the estimate of effect

Results of Rapid Review

The database search yielded 238 citations published between January 1, 2003, and December 20, 2013, (with duplicates removed). Articles were excluded based on information in the title and abstract. The full texts of potentially relevant articles were obtained for further assessment.

Three SRs with MAs met the inclusion criteria. (4-6) The reference lists of the included studies and health technology assessment websites were hand-searched to identify other relevant studies, and no additional citations were identified. The search did not identify any studies that reported on return to daily activity as an outcome measure.

The efficacy of single-dose IA bupivacaine was evaluated in 1 SR (5) with an AMSTAR score of 8 out of a possible 11 (Table A1, Appendix 2). Two SRs evaluated the efficacy of single-dose IA morphine (4;6) with AMSTAR scores of 5 and 8 (Table A1, Appendix 2). Given that the SR by Zeng et al (6) had a higher AMSTAR rating and included 7 studies published since the 2004 search date of the Rosseland et al (4) review, only the results from the review by Zeng et al were included for the analysis of IA morphine in the present rapid review. No systematic reviews were identified that evaluated the combined effectiveness of all IA analgesics or assessed combinations of IA analgesics in comparison to no IA analgesia. A summary of the SRs meeting the inclusion criteria and selected for final inclusion are shown in Table 1.

Table 1. Summary of Systematic Reviews Evaluating Intra-articular Analgesics After Knee Arthroscopy

Author, Year	Type of Review	Search Dates	Selection Criteria	No. RCTs	AMSTAR Score
Wei, 2013 (5)	SR and MA	Up to April 2013	• RCTs • Arthroscopic knee surgery • Single-dose IA bupivacaine or placebo after surgery • Experimental group received no other analgesic with bupivacaine • Ability to extract data	23	8
Zeng, 2013 (6)	SR and MA	1966 to 2013	• RCTs • Arthroscopic knee surgery • IA use of morphine for post-operative pain control • Experimental injection with morphine only (not mixed with other analgesics) • Control receiving isotonic saline • Ability to extract data	26	8

Abbreviations: AMSTAR, Assessment of Multiple Systematic Reviews; IA, intra-articular; MA, meta-analysis; No., number; RCT, randomized controlled trial; SR, systematic review.

Studies included in both reviews varied in terms of the type of arthroscopic surgery conducted (e.g., any arthroscopic surgery, meniscal repairs only, or ACL repairs only), dose and concentration of IA analgesia used (50–150 mg bupivacaine and 1–15 mg morphine), and IA injection time (5–15 minutes before release of tourniquet). Four of the 23 studies in the single-dose IA morphine review by Wei et al (5) included epinephrine. Maximum length of follow-up ranged from 8 to 48 hours in the Zeng et al (6) review, and 4 to 48 hours in the Wei et al (5) review.

Postoperative Pain

Both Zeng et al (6) and Wei et al (5) evaluated and meta-analyzed postoperative pain intensity subsequent to IA analgesia as measured on the Visual Analogue Scale (VAS). Results from the meta-analyses on pain intensity are shown in Table 2.

Table 2. Summary of Meta-Analysis Results for Pain After Arthroscopic Knee Surgery With IA Analgesia in Comparison With No IA Analgesia

Author, Year	No. RCTs included in MA	Sample Size (Intervention /Control)	Summary of Study findings for Post-operative Pain	Mean Difference in VAS Pain Scores (95% CI)	I^2	GRADE
IA Bupivacaine versus Placebo						
Wei, 2013 (5)	14	825 (262/263)	6 found a significant improvement; 8 found no significant difference	WMD[a] -1.08 (95% CI, -1.69 to -0.47)	85%	Very Low
IA Morphine versus Placebo						
Zeng, 2013 (6)	11	568 (NR/NR)	5 found a significant improvement; 6 found no significant difference	SMD -1.16 (95% CI, -1.79 to -0.53)	89.8%	Very Low

Abbreviations: CI, confidence interval; IA, intra-articular; No., number; NR, not reported; RCT, randomized controlled trial; SMD, standardized mean difference; VAS, visual analogue scale; WMD, weighted mean difference.
[a]VAS scores were converted to a score between 1 and 10.

IA Bupivacaine

Wei et al (5) found a significant improvement in VAS pain scores among patients receiving IA bupivacaine in comparison to placebo ($P < 0.001$); however, there was considerable and significant statistical heterogeneity (Table 2). The GRADE for this body of evidence was assessed as very low (Table A2, Appendix 2).

Sensitivity analyses consistently found statistically significant improvements in VAS values with bupivacaine in comparison to placebo after removing studies that mixed bupivacaine with epinephrine, used spinal anaesthesia, had a small sample size (<10 in control group), or included mild pain (VAS $\leq$ 3), and studies that were supported by industry. The authors also excluded those studies with poor methodological quality, and results remained consistent (WMD −1.05, 95% CI −1.69 to −0.41). None of the hypotheses, however, were able to explain the observed inconsistency in results, with heterogeneity ranging from 81% to 88%.

IA Morphine

Zeng et al (6) found a significant improvement in pain, with a large effect size, with IA morphine in comparison to placebo after knee arthroscopy ($P < 0.001$). These results were associated with considerable and significant statistical heterogeneity (Table 2). Of the 11 studies included in the meta-analysis, only 2 were reported as having a perfect methodological score, but these 2 presented inconsistent results. The GRADE for this body of evidence was assessed as very low (Table A3, Appendix 2).

Meta-regression analysis found SMDs for VAS postoperative pain intensity to be positively correlated with the last follow-up point (coefficient 0.11, $P = 0.38$; adjusted $R^2 = 38\%$) and explained 56.7% of the heterogeneity. (6) This analysis suggests that benefit may diminish with longer term follow-up; however, no combined effect estimate from the meta-regression analysis was provided, and therefore conclusions

from the original analysis of the review are limited. Scatter plots found no correlation between dose and the standardized mean difference for VAS, although limited raw data was provided to further assess the significance of this factor.

Additional Analgesics Required

The number of patients requiring additional analgesia after knee arthroscopy was assessed by both SRs (Table 3). From the SRs, it was not stated how individual studies defined "supplementary analgesia," or what types of analgesia were considered. Additionally, the additional analgesia dosages required were not reported.

Table 3. Summary of Meta-Analysis Results for Additional Analgesics Required After Arthroscopic Knee Surgery With IA Analgesia in Comparison With No IA Analgesia

Author, Year	No. RCTs included in MA	Sample Size (Intervention /Control)	Summary of RCT findings for Postoperative Pain	RR of additional analgesia required (95% CI)	I^2	GRADE
IA Bupivacaine Versus Placebo						
Wei, 2013 (5)	12	432/422	2 found a significant decrease; 10 found no significant difference	0.83 (0.74, 0.94)	41%	Very Low
IA Morphine Versus Placebo						
Zeng, 2013 (6)	8	NR	1 found a significant decrease; 7 found no significant different	0.82 (0.71, 0.95)	0%	Low

Abbreviations: CI, confidence interval; IA, intra-articular; No., number; NR, not reported; RCT, randomized controlled trial; RR, relative risk.

IA Bupivacaine

Wei et al (5) found a significant decrease in the number of patients requiring supplementary analgesia after receiving IA bupivacaine in comparison to placebo ($P = 0.002$). The GRADE for this body of evidence was very low.

Sensitivity analyses consistently found statistically significant reductions in use of supplementary analgesia with bupivacaine in comparison to placebo after removing studies mixed bupivacaine with epinephrine, had a small sample size (<10 in control group), or that were supported by industry. Removal of those studies with poor methodological quality also resulted in no difference to the effect estimate; however, the GRADE for the body of evidence would remain low.

IA Morphine

Zeng et al (6) identified a significant reduction in the need for supplementary analgesia among patients receiving IA morphine in comparison to placebo after knee arthroscopy ($P = 0.008$). None of the included studies had a perfect methodological score, as assessed by the study authors. Only 1 individual randomized controlled trial (RCT) found a significant impact of IA morphine on additional analgesia required, and the overall relative risk (RR) became non-significant once this study was removed in a sensitivity analysis (RR 0.85; 95% confidence interval [CI], 0.72 – 1.01). Although not explored by the review authors, this RCT had the lowest methodological quality among those included in the meta-analysis. No correlation was determined between dose and relative risk of additional analgesia (correlation coefficient -0.372, $P = 0.266$). The GRADE for this body of evidence was very low.

Limitations

In addition to the limitations stated for individual outcomes, both SRs were further limited in their ability to meta-analyse results due to heterogeneous qualities of the studies and outcomes. Factors that may have had an impact on heterogeneity, such as the type of arthroscopic surgery, early postoperative pain intensity, or preoperative analgesic usage, were not accounted for in any of the reviewed meta-analyses. Other important factors, such as the length of follow-up measurement and the dosage and concentration of IA analgesics, either were not adequately assessed or were not reported in the results. Given the significant heterogeneity of study designs and the small sample sizes available for subgroup analyses, the results may not have been appropriate for meta-analysis.

Conclusions

Based on results from 2 SRs that were limited in their ability to meta-analyse because of their heterogeneous studies and outcome measures, the following conclusions were made in regards to IA analgesia for knee arthroscopy:

- There is very low quality evidence of an improvement in pain with IA-bupivacaine or IA-morphine in comparison to placebo.
- There is low to very low quality evidence of a reduction in the number of additional analgesics required with IA-bupivacaine or IA-morphine in comparison to placebo.

No systematic reviews were identified that reported on the effectiveness of IA analgesia on return to daily activity.

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HQO's Expert Advisory Panel on Episode of Care for Patients Undergoing Knee Arthroscopic Surgery

Name	Affiliation(s)	Appointment(s)
Chair		
Dr James Waddell	St. Michaels Hospital; University of Toronto	Orthopaedic Surgeon Professor, Division of Orthopaedic Surgery
Orthopaedic and Reconstructive Surgery		
Dr Mark MacLeod	Victoria Hospital, London Health Sciences Centre	Orthopaedic Surgery
Dr Steven Charles Reed	Humber River Regional Hospital	Orthopaedic Surgery
Dr John Semple	Women's College Hospital	Chief of Surgery
Primary Care		
Dr Christopher Jyu	Rouge Valley Health System The Scarborough Hospital	Primary Care Lead
Anesthesiology		
Dr Nick Lo	St. Michael's Hospital University of Toronto	Staff Anesthesiologist Assistant Professor
Dr Jean Wong	Women's College Hospital University Health Network	Staff Anesthesiologist
Physiotherapy and Rehabilitation		
Rhona McGlasson	Bone and Joint Canada North Simcoe Muskoka LHIN	Executive Director Surgical Coordinator
Anne-Marie MacLeod	Holland Musculoskeletal Program, Sunnybrook Health Science Centre	Operations Director
Executive Administration		
Tiziana Silveri	North Bay Regional Health Centre	Vice President of Clinical Services
Leslie Gauthier	Hamilton Health Sciences	Director, Perioperative Services
Winnie Doyle	St Joseph's Healthcare, Hamilton	VP President Patient Services, Chief Nursing Executive

Appendices

Appendix 1: Literature Search Strategies

Database: EBM Reviews - Cochrane Database of Systematic Reviews 2005 to November 2013, **EBM Reviews - ACP Journal Club** 1991 to November 2013**, EBM Reviews - Database of Abstracts of Reviews of Effects** 4th Quarter 2013, **EBM Reviews - Cochrane Central Register of Controlled Trials** November 2013, **EBM Reviews - Cochrane Methodology Register** 3rd Quarter 2012, **EBM Reviews - Health Technology Assessment** 4th Quarter 2013, **EBM Reviews - NHS Economic Evaluation Database** 4th Quarter 2013, **Ovid MEDLINE(R)** 1946 to November Week 3 2013**, Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations** December 19, 2013

Search Strategy

#	Searches	Results
1	exp Knee Joint/ or exp Knee Injuries/ or Anterior Cruciate Ligament/ or Medial Collateral Ligament, Knee/ or Posterior Cruciate Ligament/ or Anterior Cruciate Ligament Reconstruction/	60371
2	Arthroscopy/	17602
3	1 and 2	7532
4	exp Orthopedic Procedures/	214460
5	Anterior Cruciate Ligament/ or Medial Collateral Ligament, Knee/ or Posterior Cruciate Ligament/	12170
6	4 and 5	5285
7	(arthroscop* and (anterior cruciate ligament? or knee* or meniscal or menisci or meniscus or menisectom* or semilunar cartilage? or ACL or PCL or MCL)).ti,ab.	9862
8	(arthroscop* and (((medial or tibial*) adj3 ligament?) or posterior cruciate ligament?)).ti,ab.	801
9	or/3,6-8	14673
10	Injections, Intra-Articular/	6372
11	Analgesia/ or exp Analgesics/ or exp Anesthetics, Local/ or Anesthesia, Local/ or exp "Hypnotics and Sedatives"/ or exp Glucocorticoids/	831849
12	((intra-articular* or intraarticular* or ((knee adj3 joint*) and inject*) or local infiltration) adj5 (anesthesia* or anaesthesia* or anesthetic* or anaesthetic* or analgesi* or opiod? or glucocorticoid? or steroid*)).ti,ab.	2030
13	((intra-articular* or intraarticular* or ((knee adj3 joint*) and inject*) or local infiltration) adj5 (bupivacaine or dexmedetomidine or ketorolac or lidocaine or midazolam or prilocaine or ropivacaine or tramadol)).ti,ab.	833
14	((intra-articular* or intraarticular* or ((knee adj3 joint*) and inject*) or local infiltration) adj5 (alfentanil or alphaprodine or buprenorphine or butorphanol or codeine or dextromoramide or dextropropoxyphene or dihydromorphine or diphenoxylate or enkephalin* or ethylketocyclazocine or ethylmorphine or etorphine or fentanyl or heroin or hydrocodone or hydromorphone or levorphanol or meperidine or meptazinol or methadone or methadyl acetate or morphine or nalbuphine or opiate alkaloid? or opium or oxycodone or oxymorphone or pentazocine or phenazocine or phenoperidine or pirinitramide or promedol or sufentanil or tilidine or tramadol)).ti,ab.	517
15	or/10-14	836195
16	9 and 15	1391
17	limit 16 to english language [Limit not valid in CDSR,ACP Journal Club,DARE,CCTR,CLCMR; records were retained]	1287
18	limit 17 to yr="2003 -Current" [Limit not valid in DARE; records were retained] EBM Reviews - Cochrane Database of Systematic Reviews <2005 to November 2013> (2) EBM Reviews - ACP Journal Club <1991 to November 2013> (1) EBM Reviews - Database of Abstracts of Reviews of Effects <4th Quarter 2013> (3) EBM Reviews - Cochrane Central Register of Controlled Trials <November 2013> (199) EBM Reviews - Cochrane Methodology Register <3rd Quarter 2012> (0) EBM Reviews - Health Technology Assessment <4th Quarter 2013> (0)	579

	EBM Reviews - NHS Economic Evaluation Database <4th Quarter 2013> (0) Ovid MEDLINE(R) <1946 to November Week 3 2013> (360) Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations <December 19, 2013> (14)	
19	(Meta Analysis or Controlled Clinical Trial or Randomized Controlled Trial).pt.	936844
20	Meta-Analysis/ or exp Technology Assessment, Biomedical/	62967
21	(meta analy* or metaanaly* or pooled analysis or (systematic* adj2 review*) or published studies or published literature or medline or embase or data synthesis or data extraction or cochrane or ((health technolog* or biomedical technolog*) adj2 assess*)).ti,ab.	214422
22	exp Random Allocation/ or exp Double-Blind Method/ or exp Control Groups/ or exp Placebos/	351014
23	(random* or RCT or placebo* or sham* or (control* adj2 clinical trial*)).ti,ab.	1266511
24	exp Standard of Care/ or exp Guideline/ or exp Guidelines as Topic/	142360
25	(guideline* or guidance or consensus statement* or standard or standards).ti.	117946
26	or/19-25	1944905
27	9 and 15 and 26	1028
28	limit 27 to english language [Limit not valid in CDSR,ACP Journal Club,DARE,CCTR,CLCMR; records were retained]	988
29	limit 28 to yr="2003 -Current" [Limit not valid in DARE; records were retained] EBM Reviews - Cochrane Database of Systematic Reviews <2005 to November 2013> (1) EBM Reviews - ACP Journal Club <1991 to November 2013> (1) EBM Reviews - Database of Abstracts of Reviews of Effects <4th Quarter 2013> (3) EBM Reviews - Cochrane Central Register of Controlled Trials <November 2013> (197) EBM Reviews - Cochrane Methodology Register <3rd Quarter 2012> (0) EBM Reviews - Health Technology Assessment <4th Quarter 2013> (0) EBM Reviews - NHS Economic Evaluation Database <4th Quarter 2013> (0) Ovid MEDLINE(R) <1946 to November Week 3 2013> (232) Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations <December 19, 2013> (10)	444
30	from 18 keep 1-205	205
31	from 29 keep 203-444	242
32	30 or 31	447
33	remove duplicates from 32	255

Appendix 2: Evidence Quality Assessment

Table A1: AMSTAR Scores of Included Systematic Reviews

Author, Year	AMSTAR Score[a]	(1) Provided Study Design	(2) Duplicate Study Selection	(3) Broad Literature Search	(4) Considered Status of Publication	(5) Listed Excluded Studies	(6) Provided Characteristics of Studies	(7) Assessed Scientific Quality	(8) Considered Quality in Conclusion	(9) Methods to Combine Appropriate	(10) Assessed Publication Bias	(11) Stated Conflict of Interest
Zeng et al, 2013 (6)	8	Yes	Yes	Yes	No	No	Yes	Yes	No	Yes	Yes	Yes
Wei et al, 2013 (5)	8	Yes	Yes	Yes	No	No	Yes	Yes	No	Yes	Yes	Yes
Rosseland et al, 2005 (4)	5	Yes	No	Yes	No	Yes	No	Yes	Yes	No	No	No

Abbreviations: AMSTAR, Assessment of Multiple Systematic Reviews; RCT, randomized controlled trial.
[a]Maximum possible score is 11. Details of AMSTAR score are described in Shea et al. (2)

Table A2: GRADE Evidence Profile for Comparison of IA Analgesia and Placebo

Number of Studies (Design)	Risk of Bias[a]	Inconsistency	Indirectness	Imprecision	Publication Bias[b]	Upgrade Considerations	Quality
Pain – Bupivacaine							
14 (RCTs)	Serious limitations (–1)[c]	Very serious limitations (–2)[d]	No serious limitations	No serious limitations	Not Detected	none	⊕ Very Low
Pain – Morphine							
11 (RCTs)	No serious limitations (-1)[e]	Very serious limitations (–2)[f]	No serious limitations	No serious limitations	Detected[g]	none	⊕ Very Low
Number of Additional Analgesics Required - Bupivacaine							
12 (RCTs)	Serious limitations (–1)[h]	No serious limitations	Serious limitations (–1)[i]	No serious limitations	Detected[j]	none	⊕ Very Low
Number of Additional Analgesics Required - Morphine							
8 (RCTs)	Serious limitations (-1)[k]	No serious limitations	Serious limitations (–1)[l]	No serious limitations	Not Detected	none	⊕⊕ Low

Abbreviations: GRADE, Grading of Recommendations Assessment, Development, and Evaluation; IA, intra-articular; RCT, randomized controlled trial.

[a]Risk of bias was assessed based on the data and analyses provided within the Wei et al (5) and Zeng et al (5) systematic reviews. The original studies were not retrieved for further review.

[b]Publication bias was assessed and reported by Wei et al (5) and Zeng et al (6). Assessment of publication bias was based on conclusions derived from the systematic reviews only.

[c]10 of 14 RCTs did not use allocation concealment, and no RCTs used an intention-to-treat analysis.

[d]The meta-analysis had considerable, unexplained, statistical heterogeneity.

[e]5 of 11 studies had limitations with their randomization, 8 had limitations with allocation concealment, and 2 had limitations with study blinding.

[f]The meta-analysis had considerable statistical heterogeneity.

[g]Zeng et al (6) identified some asymmetry in Begg's funnel plot, and Begg's rank correlation test found a high risk of publication bias.

[h]7 RCTs did not use allocation concealment and 12 RCTS did not use an intention-to-treat analysis.

[i]Number of additional analgesics required is a surrogate measure for pain. It was unclear from the study how additional analgesics were defined, what dosages were required, or whether results were appropriately combined. The study authors stated that only 3 studies reported person-time during various time periods after surgery, and therefore they did not know the exact number of patients who required supplementary analgesia.

[j]Wei et al (5) stated that the Begg's rank correlation test found a high risk of publication bias.

[k]5 of 8 studies had limitations to randomization, all 8 had limitations to allocation concealment, and 2 had limitations to study blinding. Additionally, the single study that had a significant effect and that is driving the meta-analysis in favour of morphine, had the lowest methodological quality of all studies (score of 4 of 7 on the Modified Oxford Score).

[l]Number of additional analgesics required is a surrogate measure for pain. It was unclear from the study how additional analgesics were defined, or if appropriately combined.

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