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# Pre-emptive Oral Non-Steroidal Anti-Inflammatory Drugs or Acetaminophen for Knee Arthroscopy: A Rapid Review

Health Quality Ontario

August 2014

*Evidence Development and Standards Branch at Health Quality Ontario*

Pre-emptive Oral Non-Steroidal Anti-Inflammatory Drugs or Acetaminophen for Knee Arthroscopy: A Rapid Review. August 2014; pp. 1–18

## Suggested Citation

This report should be cited as follows:

Health Quality Ontario. Pre-emptive oral non-steroidal anti-inflammatory drugs or acetaminophen for knee arthroscopy: a rapid review. Toronto: Health Quality Ontario; 2014 August. 18 p. Available from: http://www.hqontario.ca/evidence/evidence-process/episodes-of-care#knee-arthroscopy.

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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.

## About Health Quality Ontario Publications

To conduct its rapid reviews, Evidence Development and Standards and its research partners review the available scientific literature, making every effort to consider all relevant national and international research; collaborate with partners across relevant government branches; consult with expert advisory panels, clinical and other external experts, and developers of health technologies; and solicit any necessary supplemental information.

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.

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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.

# Table of Contents

# List of Abbreviations

| | |
|---|---|
| **COX** | Cyclooxygenase |
| **GRADE** | Grading of Recommendations Assessment, Development, and Evaluation |
| **HQO** | Health Quality Ontario |
| **NSAID** | Non-steroidal anti-inflammatory drug |
| **OHTAC** | Ontario Health Technology Advisory Committee |
| **RCT** | Randomized controlled trial |

# 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 is to determine the effectiveness of pre-emptive oral non-steroidal anti-inflammatory drugs (NSAIDs) or acetaminophen for pain management after arthroscopic knee surgery.

## Clinical Need and Target Population

Arthroscopic surgery of the knee has been shown to result in moderate to severe pain 24 hours post-operatively in over 40% of patients. (1) Effective pain management options are therefore required to reduce post-operative pain.

## Technology/Technique

Various definitions of pre-emptive analgesia exist in the literature, (2) but for the purposes of this review, pre-emptive analgesia is defined as analgesics given prior to surgical incision.

The most commonly used oral analgesics for short-term management of moderate to severe pain after orthopedic surgery are acetaminophen; conventional NSAIDs such as ibuprofen and naproxen; and the newer selective cyclooxygenase (COX-2) inhibitor NSAIDs such as celecoxib. The effectiveness of these agents as pre-emptive analgesics for post-operative pain control after knee arthroscopy is assessed in this rapid review.

# Rapid Review

## Research Questions

1. What is the effectiveness of pre-emptive oral acetaminophen for relief of post-operative pain after knee arthroscopy?
2. What is the effectiveness of pre-emptive oral non-steroidal anti-inflammatory drugs (NSAIDs) for relief of post-operative pain after knee arthroscopy?

## Research Methods

### Literature Search

#### *Search Strategy*

A literature search was performed on January 31, 2014, using Ovid MEDLINE, Ovid MEDLINE In-Process and Other Non-Indexed Citations, and EMBASE and EBM Reviews for studies published from January 1, 2003, to January 30, 2014. (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

- published between January 1, 2003 and January 30, 2014
- systematic reviews, meta-analyses, health technology assessments, and randomized controlled trials (RCTs)
- evaluating pre-emptive (pre-incisional) administration of 1) oral acetaminophen or 2) oral NSAIDs
- comparing the intervention to placebo prior to surgery (or usual care)
- reporting on 1 or more outcomes of interest
- reporting on drugs approved as analgesics by Health Canada

### Exclusion Criteria

- studies evaluating only the timing of analgesic administration
- studies where relevant data could not be extracted
- studies only comparing different types of pre-emptive analgesics

### Outcomes of Interest

- pain
- return to daily activity
- need for additional analgesics

# 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 methodology for a rapid review of primary studies assesses the quality of the evidence through a GRADE risk of bias assessment of the individual studies in the review including allocation concealment, blinding, accounting of patients and outcome events, selective reporting bias and other limitations. (3)

# Results of Rapid Review

The database search yielded 671 citations published between January 1, 2003, and January 30, 2014, (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.

### Research Question 1: Pre-emptive Oral Acetaminophen

No RCTs were identified that evaluated the use of pre-emptive oral acetaminophen prior to knee arthroscopy.

### Research Question 2: Pre-emptive Oral NSAIDs

Two RCTs were identified that met the inclusion criteria. (4;5) However, no studies were identified that evaluated the use of conventional NSAIDs. 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.

Both included RCTs evaluated the pre-emptive use of oral celecoxib, a COX-2 inhibitor NSAID. The study by Boonriong et al (5) was designed to evaluate the effectiveness of etoricoxib in comparison with celecoxib or placebo; however, given that etoricoxib is not approved for use in Canada, relevant data was extracted from the celecoxib and placebo arms only. Table 1 summarizes the included studies.

**Table 1: Summary of Included Randomized Controlled Trials**

| Author, Year, Country | Sample Size | Population | Intervention | Comparator | Additional Anesthesia and Analgesia |
|---|---|---|---|---|---|
| Mardani-Kivi et al, 2013 (4)<br>Iran | 130 | Arthroscopic knee surgery (isolated ACL reconstruction or partial meniscectomy) | 400 mg celecoxib, 2 hours prior to operation | Placebo, 2 hours prior to operation | - No other analgesics or sedatives within 2 days prior to surgery<br>- General anesthesia<br>- Post-operative pethidine (0.5 mg/kg) injection |
| Boonriong et al, 2010 (5)<br>Thailand | 67[a] | Arthroscopic ACL reconstruction | 400 mg celecoxib, 1 hour prior to incision | Placebo, 1 hour prior to incision | - No NSAIDs, opioids, or salicylates within 7 days prior to surgery<br>- Spinal anesthesia with 0.5% hyperbaric bupivacaine without intrathecal opioid<br>- Oral paracetamol,1000 mg as needed every 6 hours; and/or IV fentanyl 1 µg/kg every 3 hours as requested |

Abbreviations: ACL, anterior cruciate ligament; IV, intravenous; NSAID, non-steroidal anti-inflammatory drug.
[a] Excluded 35 patients in the etoricoxib arm.

The studies varied in the timing of pre-emptive celecoxib administration and the type of anesthesia provided, as well as the length of surgery, with Mardani-Kivi et al (4) excluding patients with operation times over 1 hour.

### *Post-operative Pain*

Both studies evaluated post-operative pain intensity as the primary outcome measure. Results are presented in Table 2.

**Table 2: Summary of Results for Pain after Arthroscopic Knee Surgery with Pre-emptive Oral Celecoxib in Comparison to Placebo**

| Author, Year | Measure of Pain | Subgroup (Sample Size ) | Post-operative Pain |
|---|---|---|---|
| Mardani-Kivi et al, 2013 (4) | Mean VAS score [a] (SD) | Overall (117) | **6 hrs:** 5.0 (NR) vs. 7.2 (NR)<br>**24 hrs**: 4.88 (NR) vs. 6.7 (NR)<br>*P* < 0.001[b] |
| | | Meniscectomy (57) | **6 hrs:** 4.3 (1) vs. 5.6 (2); *P* < 0.001<br>**24 hrs:** 3.8 (2) vs. 6.3 (1); *P* < 0.001 |
| | | ACL Reconstruction (60) | **6 hrs:** 5.7 (2) vs. 7.5 (2); *P* < 0.001<br>**24 hrs:** 5.3 (1) vs. 6.9 (2); *P* < 0.001 |
| Boonriong et al, 2010 (5) | Mean VbAPS | Overall (67) | No statistically significant difference between celecoxib and placebo at any time point (measured between 0 and 48 hours) |

Abbreviations: hrs, hours; NR, not reported; SD, standard deviation; VAS, visual analog scale; VbAPS, verbal analog pain scale; vs., versus.
[a] Scores range from 1 to 10. [b] It was unclear from the text which measurement, or both, the significance related to.

Mardani-Kivi et al (4) found a statistically significant reduction in pain with pre-emptive celecoxib, versus placebo, at both 6- and 24-hour follow-ups, although no confidence intervals were reported. They found similar results for both the meniscectomy and ACL reconstruction groups, though the study was not designed or powered to assess these subgroups. Additionally, the results at 6-hour follow-up for the meniscectomy group did not reach 1.6—the minimum difference in VAS scores that Mardani-Kivi et al had pre-defined as clinically significant.

Boonriong et al (5) found no significant difference in pain intensity between celecoxib and placebo recipients at any time point measured, but did not provide specific values.

The impact of *pre*-operative pain was not evaluated in either study.

This rapid review assessed both studies as having serious limitations due to risk of bias (see Appendix 2, Table A1).

### *Additional Analgesics Required*

The number of patients requiring additional analgesia after knee arthroscopy was assessed by both included RCTs, with results presented in Table 3.

**Table 3: Summary of Results for Additional Analgesics Required After Arthroscopic Knee Surgery With Pre-emptive Oral Celecoxib in Comparison to Placebo**

| Author, Year | Measure of Pain | Subgroup (Sample Size ) | Post-operative Pain |
|---|---|---|---|
| Mardani-Kivi et al, 2013 (4) | Mean opioid consumption (pethidine injection, 0.5 mg/kg) (SD) | Overall (117) | **6 hrs:** 21.2 (NR) vs. 38.8 (NR)<br>**24 hrs**: 18.8 (NR) vs. 34.1 (NR)<br>$P < 0.05$[a] |
| | | Meniscectomy (57) | **6 hrs:** 19.2 (NR) vs 42 (NR); $P < 0.0001$<br>**24 hrs:** 11.4 (NR) vs 28.4 (NR); $P = 0.001$ |
| | | ACL Reconstruction (60) | **6 hrs:** 23 (NR) vs. 35.8 (NR); $P = 0.004$<br>**24 hrs**: 26 (NR) vs. 39.2 (NR); $P = 0.02$ |
| Boonriong et al, 2010 (5) | Mean number of 500 mg paracetamol | Overall (67) | No significant difference between groups |
| | Mean amount of fentanyl (μg) | Overall (67) | No significant difference between groups |

Abbreviations: ACL, anterior cruciate ligament; hrs, hours; NR, not reported; SD, standard deviation; vs., versus.
[a] It was unclear from the text which measurement, or both, the significance related to.

The results are contradictory, with Mardani-Kivi et al (4) finding a significant decrease in mean pethidine injection at both 6-hour and 24-hour follow-ups, and Boonriong et al (5) finding no statistically significant difference in the mean amount of paracetamol or fentanyl required. As noted previously, both studies were assessed as having serious limitations due to risk of bias (see Appendix 2, Table A1).

### *Return to Daily Activity*

Neither study reviewed assessed the effectiveness of pre-emptive analgesia on return to daily activity.

# Conclusions

- Based on 2 RCTs, both with limitations due to risk of bias, there were inconsistent results regarding the effectiveness of pre-emptive oral celecoxib, a selective COX-2 inhibitor NSAID, for post-operative pain control in patients undergoing knee arthroscopy.
- No evidence was identified that evaluated the oral pre-emptive use of acetaminophen or conventional NSAIDs for post-operative pain control in patients undergoing knee arthroscopy.

# Acknowledgements


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**Medical Information Services**
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| Dr Steven Charles Reed | Humber River Regional Hospital | Orthopaedic Surgery |
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# Appendices

## Appendix 1: Literature Search Strategies

**Database:** EBM Reviews - Cochrane Database of Systematic Reviews <2005 to December 2013>, EBM Reviews - ACP Journal Club <1991 to January 2014>, EBM Reviews - Database of Abstracts of Reviews of Effects <4th Quarter 2013>, EBM Reviews - Cochrane Central Register of Controlled Trials <December 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>, Embase <1980 to 2014 Week 04>, Ovid MEDLINE(R) <1946 to January Week 4 2014>, Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations <January 30, 2014>

**Search Strategy:**

| # | Searches | Results |
|---|---|---|
| 1 | Arthroscopy/ use mesz,acp,cctr,coch,clcmr,dare,clhta,cleed | 17006 |
| 2 | exp Knee Joint/ use mesz,acp,cctr,coch,clcmr,dare,clhta,cleed or exp Knee Injuries/ use mesz,acp,cctr,coch,clcmr,dare,clhta,cleed | 53142 |
| 3 | and/1-2 | 6452 |
| 4 | Anterior Cruciate Ligament/ use mesz,acp,cctr,coch,clcmr,dare,clhta,cleed or Medial Collateral Ligament, Knee/ use mesz,acp,cctr,coch,clcmr,dare,clhta,cleed or Posterior Cruciate Ligament/ use mesz,acp,cctr,coch,clcmr,dare,clhta,cleed or Anterior Cruciate Ligament Reconstruction/ use mesz,acp,cctr,coch,clcmr,dare,clhta,cleed or exp Menisci, Tibial/ use mesz,acp,cctr,coch,clcmr,dare,clhta,cleed | 16883 |
| 5 | exp knee arthroscopy/ use emez or exp anterior cruciate ligament reconstruction/ use emez or exp knee ligament surgery/ use emez or exp meniscal surgery/ use emez or anterior cruciate ligament/ use emez | 16358 |
| 6 | (((arthroscop* or reconstruct* or repair* or surg* or orthop*) and (anterior cruciate ligament* or posterior cruciate ligament* or meniscal or menisci or meniscus or menisectom* or semilunar cartilage* or ACL or PCL or MCL)) or (arthroscop* and knee*)).ti,ab. | 41852 |
| 7 | or/3-6 | 54155 |
| 8 | exp Analgesia/ | 138401 |
| 9 | exp Analgesics/ use mesz,acp,cctr,coch,clcmr,dare,clhta,cleed or exp Anesthetics, Local/ use mesz,acp,cctr,coch,clcmr,dare,clhta,cleed or exp Anesthesia, Local/ use mesz,acp,cctr,coch,clcmr,dare,clhta,cleed or exp Sulfonamides/ use mesz,acp,cctr,coch,clcmr,dare,clhta,cleed or exp Pyrazoles/ use mesz,acp,cctr,coch,clcmr,dare,clhta,cleed or exp Anti-Inflammatory Agents/ use mesz,acp,cctr,coch,clcmr,dare,clhta,cleed or exp Anti-Inflammatory Agents, Non-Steroidal/ use mesz,acp,cctr,coch,clcmr,dare,clhta,cleed | 899915 |
| 10 | exp analgesic agent/ use emez or exp local anesthetic agent/ use emez or exp local anesthesia/ use emez or exp sulfonamide/ use emez or exp pyrazole derivative/ use emez or exp antiinflammatory agent/ use emez or exp nonsteroid antiinflammatory agent/ use emez or exp salicylic acid derivative/ use emez or exp prostaglandin synthase inhibitor/ use emez | 1692023 |
| 11 | (NSAID* or ((non-steroidal or nonsteroidal) adj3 agent*) or antiinflammator* or anti inflammator* or ibuprofen or aspirin or tylenol or n-acetyl-p-aminophenol or parcetamol or anacin or acamol or acetaco or apap or acetaminophen or acetominophen or acephen or acetamidophenol or hydroxyacetanilide or panadol or algotropyl or datril or ip 82 or ip82 or ibumetin or motrin or brufen or trauma-dolgit gel or traumadolgit gel or salprofen or nuprin or rufen or alpha-methyl-4-2-methylpropyl benzeneacetic acid or (acetylsalicylic adj acid*) or dispril or polopiryna or zorprin or polopirin or colfarit or aloxiprimum or micristin or easprin or magnecyl or solprin or ecotrin or 2-acetyloxy benzoic acid or endosprin or acylpyrin or solupsan or acetysal or ketorolac or salicylate* or (salicylic adj acid*) or naproxen or proxen or anaprox or naprosin or synflex or mnpa or naprosyn or methoxypropiocin or aleve or ((cyclooxygenase or cyclo oxygenase) adj inhibitor*) or celecoxib or COX-1 inhibitor* or COX-2 inhibitor* or etoricoxib or celebrex or celebra or onsenal or (prostaglandin adj2 (synthase or synthesis)) or diclofenac or orthofen or feloran or dicrofenac or dichlofenal or novapirina or sr-38 or sr38 or diclophenac or orthophen or voltarol or gp 45840 or gp45840 or ortofen or voltaren or diclonate or ((preemptive or pre emptive or preventative or prophylactic) adj analgesi*)).ti,ab. | 470307 |
| 12 | or/8-11 | 2820231 |
| 13 | 7 and 12 | 4109 |
| 14 | (Meta Analysis or Controlled Clinical Trial).pt. | 214103 |

| | | |
|---|---|---|
| 15 | Meta-Analysis/ use mesz,acp,cctr,coch,clcmr,dare,clhta,cleed or exp Technology Assessment, Biomedical/ use mesz,acp,cctr,coch,clcmr,dare,clhta,cleed | 52824 |
| 16 | Meta Analysis/ use emez or Biomedical Technology Assessment/ use emez | 91445 |
| 17 | (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. | 395482 |
| 18 | exp Randomized Controlled Trial/ | 725352 |
| 19 | exp Random Allocation/ use mesz,acp,cctr,coch,clcmr,dare,clhta,cleed or exp Double-Blind Method/ use mesz,acp,cctr,coch,clcmr,dare,clhta,cleed or exp Control Groups/ use mesz,acp,cctr,coch,clcmr,dare,clhta,cleed or exp Placebos/ use mesz,acp,cctr,coch,clcmr,dare,clhta,cleed | 338544 |
| 20 | exp Randomization/ use emez or exp RANDOM SAMPLE/ use emez or Double Blind Procedure/ use emez or exp Triple Blind Procedure/ use emez or exp Control Group/ use emez or exp PLACEBO/ use emez | 418137 |
| 21 | (random* or RCT or placebo* or sham* or (control* adj2 clinical trial*)).ti,ab. | 2225077 |
| 22 | exp Standard of Care/ use mesz,acp,cctr,coch,clcmr,dare,clhta,cleed or exp Guideline/ use mesz,acp,cctr,coch,clcmr,dare,clhta,cleed or exp Guidelines as Topic/ use mesz,acp,cctr,coch,clcmr,dare,clhta,cleed | 134892 |
| 23 | exp Practice Guideline/ use emez or exp Professional Standard/ use emez | 590105 |
| 24 | (guideline* or guidance or consensus statement* or standard or standards).ti. | 247852 |
| 25 | or/14-24 | 3818471 |
| 26 | 13 and 25 | 2111 |
| 27 | limit 26 to english language [Limit not valid in CDSR,ACP Journal Club,DARE,CCTR,CLCMR; records were retained] | 1973 |
| 28 | limit 27 to yr="2003 -Current" [Limit not valid in DARE; records were retained] | 1139 |
| 29 | remove duplicates from 28 | 671 |

# Appendix 2: Evidence Quality Assessment

**Table A1: Risk of Bias Among RCTs for the Comparison of Pre-emptive Oral NSAIDs Versus No Pre-emptive Oral NSAIDs for Post-Surgical Pain Control for Knee Arthroscopy Patients**

| Author, Year | Allocation Concealment | Blinding | Complete Accounting of Patients and Outcome Events | Selective Reporting Bias | Other Limitations |
|---|---|---|---|---|---|
| Mardani-Kivi et al, 2013 (4) | Limitations[a] | No limitations | Limitations[b] | No limitations | No limitations |
| Boonriong et al, 2010 (5) | No limitations | No limitations | Limitations[c] | No limitations | No limitations |

Abbreviations: NSAID, non-steroidal anti-inflammatory drug; RCT, randomized controlled trial.

[a] No allocation concealment stated.

[b] No intent-to-treat analysis stated, and some patients were excluded from the study after randomization.

[c] Not stated if any patients were lost to follow-up, or if an intention-to-treat analysis was conducted.

# References


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