Effects of peri-operative nonsteroidal anti-inflammatory drugs on postoperative kidney function for adults with normal kidney function

Bell, Samira; Marwick, Charis A.; Rennie, Trijntje; Davey, Peter

Published in:
Cochrane Database of Systematic Reviews

DOI:
10.1002/14651858.CD011274

Publication date:
2014

Document Version
Publisher's PDF, also known as Version of record

Cochrane Library

Cochrane Database of Systematic Reviews

Effects of peri-operative nonsteroidal anti-inflammatory drugs on postoperative kidney function for adults with normal kidney function (Protocol)

Bell S, Marwick CA, Rennie T, Davey P

Bell S, Marwick CA, Rennie T, Davey P.
Effects of peri-operative nonsteroidal anti-inflammatory drugs on postoperative kidney function for adults with normal kidney function.
Cochrane Database of Systematic Reviews 2014, Issue 8. Art. No.: CD011274.
DOI: 10.1002/14651858.CD011274.

www.cochranelibrary.com

WILEY

TABLE OF CONTENTS

[Intervention Protocol]

Effects of peri-operative nonsteroidal anti-inflammatory drugs on postoperative kidney function for adults with normal kidney function

Samira Bell[1], Charis A Marwick[2], Trijntje Rennie[1], Peter Davey[2]

[1]Renal Unit, NHS Tayside, Ninewells Hospital, Dundee, UK. [2]Population Health Sciences Division, Medical Research Institute, University of Dundee, Dundee, UK

Contact address: Samira Bell, Renal Unit, NHS Tayside, Ninewells Hospital, Dundee, DD1 9SY, UK. samira.bell@nhs.net.

Editorial group: Cochrane Kidney and Transplant Group.
Publication status and date: New, published in Issue 8, 2014.

Citation: Bell S, Marwick CA, Rennie T, Davey P. Effects of peri-operative nonsteroidal anti-inflammatory drugs on postoperative kidney function for adults with normal kidney function. *Cochrane Database of Systematic Reviews* 2014, Issue 8. Art. No.: CD011274. DOI: 10.1002/14651858.CD011274.

ABSTRACT

This is the protocol for a review and there is no abstract. The objectives are as follows:

This review aims to look at the effect of NSAIDs used in the peri-operative period on post-operative kidney function in patients with normal kidney function.

BACKGROUND

Description of the condition

There is increasing evidence that acute kidney injury (AKI) is associated with both short- and long-term adverse consequences. These include increased length of hospital stay, mortality and future development of chronic kidney disease (CKD) even with small transient rises in serum creatinine (Bucaloiu 2012; Chertow 2005; Coca 2012; Lassnigg 2004). Surgery is a leading cause of AKI in hospitalised patients (Carmichael 2003).

Effective management of post-operative pain is extremely important. It facilitates early mobilisation thereby reducing hospital costs through shortened duration of hospital in-patient stay, reduces pulmonary and cardiovascular complications and risk of deep vein thrombosis. In addition, it impacts on quality of patient care by relieving suffering and distress and improving satisfaction. The major aim of post-operative pain management is providing adequate pain relief using the minimal possible dose thereby minimising adverse effects. Clinical guidelines for managing perioperative pain were updated in 2012 by the American Society of Anesthesiologists Task Force on Acute Pain Management. It recommends a multimodal approach to post-operative pain including the use of both nonselective nonsteroidal anti-inflammatory drugs; (NSAIDs) as well as selective NSAIDs (Cox-2 inhibitors) (ASA Practice Guideline 2012). NSAIDs can affect the kidneys in a number of ways. This includes haemodynamically mediated AKI, electrolyte and acid-base disorders and acute interstitial nephritis. These adverse effects are thought to occur in 1% to 5% of all patients using NSAIDs (Whelton 1999).

Description of the intervention

NSAIDs inhibit prostaglandin synthesis by inhibiting cyclooxygenase-1 (Cox-1) and cyclooxygenase -2 (Cox-2). Cox-1 is expressed in most tissues regulating normal cellular processes such as gastric cytoprotection, vascular homeostasis, platelet aggregation and kidney function. Cox-2 is expressed in brain, kidney and bone. Most traditional NSAIDs are non-selective inhibitors of both Cox-1 and Cox-2. Selective Cox-2 inhibitors include celecoxib, rofecoxib and valdecoxib.

Cyclooxgenases are produced at multiple sites within the kidney including glomerular and vascular endothelium, medullary and cortical collecting tubules and medullary interstitial cells. Cox-1 is expressed in most tissues and Cox-2 is expressed at low levels increasing with stimulation such as inflammation. Renal prostaglandins are primarily vasodilators in the kidneys. Under normal circumstances, renal prostaglandins do not contribute to regulation of kidney perfusion but in the setting of hypotension and reduced kidney perfusion from vasoconstriction prostaglandin synthesis is increased to maintain kidney perfusion and minimize ischaemia. Other kidney effects of prostaglandins include increased renin secretion, antagonism of anti-diuretic hormone effects and increased sodium excretion.

How the intervention might work

The use of both non-selective and selective NSAIDs for post-operative pain has been evaluated in a number of Cochrane reviews. A single dose of ibuprofen lead to at least 50% pain relief in approximately half of patients with moderate to severe postoperative pain. Adverse effects were similar to placebo (Derry 2009). Aspirin was found to confer a 50% or greater reduction in pain in 39% of those with moderate to severe pain, compared with 15% of those in the placebo group. Adverse events were similar for those taking a lower dose aspirin (600 mg or 650 mg). However, higher dose aspirin (900 mg to 1000 mg) experienced adverse events at more than twice the rate of patients receiving placebo (26% versus 12%) (Derry 2012a) . The use of a single dose of the Cox-2 inhibitor celecoxib in the treatment of acute post-operative pain showed that 33% of patients receiving celecoxib 200 mg, and 44% receiving 400 mg, experienced at least 50% pain relief, compared with between 1% and 11% of patients receiving placebo. Adverse events were similar in the celecoxib and placebo groups (Derry 2012b).

Furthermore, there is evidence supporting the efficacy of NSAIDs for post-operative pain with studies demonstrating opioid sparing effects (McDaid 2010).

NSAIDs have the potential to adversely affect kidney function in the peri-operative setting. Pre-renal insults such as hypovolaemia or hypotension peri-operatively cause NSAID-induced inhibition of prostaglandin mediated afferent arteriolar dilatation leading to reduced glomerular perfusion. The risk of AKI with NSAIDs has led the Medicines and Healthcare Products Regulatory Agency to issue drug safety advice recommending that NSAIDs be avoided in patients with hypovolaemia (MHRA 2009).

Why it is important to do this review

This will expand on the Cochrane review last published in 2007 (Lee 2007). This review showed that NSAIDs caused a clinically unimportant transient reduction in kidney function in the early post-operative period in patients with normal kidney function. Since its publication, a universal definition for AKI has been developed allowing a better understanding of its epidemiology and clinical significance (KDIGO 2012). Since the advent of the KDIGO definition for AKI, there is increasing evidence of the adverse clinical and economic consequences of AKI. In addition, National Institute for Clinical Excellence (NICE) AKI guidance recommends the avoidance of NSAIDs in the post-operative period (Ftouh 2013).

It is therefore important to re-assess the renal safety of NSAIDs in the peri-operative period.

OBJECTIVES

This review aims to look at the effect of NSAIDs used in the peri-operative period on post-operative kidney function in patients with normal kidney function.

METHODS

Criteria for considering studies for this review

Types of studies

All randomised controlled trials (RCTs) and quasi-RCTs (RCTs in which allocation to treatment was obtained by alternation, use of alternate medical records, date of birth or other predictable methods) looking at the use of NSAIDS versus placebo for the treatment of post-operative pain in patients with normal kidney function will be included. As we are looking at an adverse event, we will also examine cohort studies which report on the risk of AKI associated with NSAIDs use in the peri-operative period. However, results from cohort studies will be analysed separately from RCTs.

Types of participants

People of at least 18 years of age undergoing surgical procedures who were treated with NSAIDs or Cox-2 inhibitors with normal kidney function will be included. Normal kidney function is defined as estimated glomerular filtration rate (eGFR) greater than 60 mL/min/1.73 mm^2 without other evidence of kidney disease (proteinuria, haematuria, genetic kidney disease or structural kidney abnormalities).

Types of interventions

All interventions comparing NSAID treatments including Cox-2 inhibitors versus placebo will be considered. Variable doses and all routes of administration will be considered.

Types of outcome measures

Primary outcomes

The primary outcome will be AKI as defined by KDIGO which is based on serum creatinine or urine output (KDIGO 2012). Serum creatinine and urine output based AKI criteria will be analysed both separately and together depending on the number of eligible studies.

Secondary outcomes

1. All-cause mortality
2. Length of hospital stay
3. Need for renal replacement therapy (RRT).

Search methods for identification of studies

Electronic searches

We will search the Cochrane Renal Group's Specialised Register through contact with the Trials' Search Co-ordinator using search terms relevant to this review. The Cochrane Renal Group's Specialised Register contains studies identified from the following sources.

1. Monthly searches of the Cochrane Central Register of Controlled Trials (CENTRAL)
2. Weekly searches of MEDLINE OVID SP
3. Handsearching of renal-related journals and the proceedings of major renal conferences
4. Searching of the current year of EMBASE OVID SP
5. Weekly current awareness alerts for selected renal journals
6. Searches of the International Clinical Trials Register (ICTRP) Search Portal and ClinicalTrials.gov.

Studies contained in the Specialised Register are identified through search strategies for CENTRAL, MEDLINE, and EMBASE based on the scope of the Cochrane Renal Group. Details of these strategies, as well as a list of handsearched journals, conference proceedings and current awareness alerts, are available in the Specialised Register section of information about the Cochrane Renal Group. See Appendix 1 for search terms used in strategies for this review.

Searching other resources

1. Reference lists of review articles, relevant studies and clinical practice guidelines.
2. Letters seeking information about unpublished or incomplete studies to investigators known to be involved in previous studies.

Data collection and analysis

Selection of studies

The search strategy described will be used to obtain titles and abstracts of studies that may be relevant to the review. The titles and abstracts will be screened independently by two authors, who will discard studies that are not applicable, however studies and reviews that might include relevant data or information on studies will be retained initially. Two authors will independently assess retrieved abstracts and, if necessary the full text, of these studies to determine which studies satisfy the inclusion criteria.

Data extraction and management

Data extraction will be carried out independently by two authors using standard data extraction forms. Studies reported in non-English language journals will be translated before assessment. Where more than one publication of one study exists, reports will be grouped together and the publication with the most complete data will be used in the analyses. Where relevant outcomes are only published in earlier versions these data will be used. Any discrepancy between published versions will be highlighted.

Assessment of risk of bias in included studies

The following items will be independently assessed by two authors using the risk of bias assessment tool (Higgins 2011) (see Appendix 2).

- Was there adequate sequence generation (selection bias)?
- Was allocation adequately concealed (selection bias)?
- Was knowledge of the allocated interventions adequately prevented during the study (detection bias)?
    - Participants and personnel
    - Outcome assessors

- Were incomplete outcome data adequately addressed (attrition bias)?
- Are reports of the study free of suggestion of selective outcome reporting (reporting bias)?
- Was the study apparently free of other problems that could put it at a risk of bias?

As suggested in the *Cochrane Handbook for Systematic Reviews of Interventions*, (section 13.5, Higgins 2011) the Newcastle-Ottawa scale for assessing risk of bias of non-randomised studies will be used (Wells 2014). Although the score does not classify the studies according to study quality, the most appropriate scale - the Newcastle-Ottawa Scale for Cohort studies (Appendix 3; Appendix 4) identifies issues with three domains. These three domains looking at selection (or representativeness of cohorts), comparability (of cohorts due to design or analysis) and outcomes (assessment and follow up) are further subdivided into eight questions, which will be represented in the review's risk of bias tables in Characteristics of included studies. In the Scale, a high-quality choice is represented by a star. The selection, comparability and outcome domains have 4, 1 and 3 possible stars respectively.
Appropriate selection criteria of cohorts will be considered to be consecutive series of patients with the controls from the same or similar population. When assessing comparability, a star will be given for matching on age and criteria for the follow up domain to receive stars were that the primary outcome of mortality needed to be included, follow-up to be at least one year and greater than 80% of the original cohort followed to be of high quality.
The overall rating that will be given was based on the number of stars attained. A rating of high requires eight stars, moderate level cohort studies requires a score of six to seven stars, low level four or five5 stars and very low level score three stars or less.

Measures of treatment effect

For dichotomous outcomes such as need for RRT, results will be expressed as risk ratio (RR) with 95% confidence intervals (CI). Where continuous scales of measurement are used to assess the effects of treatment such as length of hospital stay, the mean difference (MD) will be used, or the standardised mean difference (SMD) if different scales have been used.

Unit of analysis issues

We do not expect to find relevant cluster-randomised studies so do not anticipate that unit of analysis issues will arise.

Dealing with missing data

Any further information required from the original author will be requested by written correspondence (e.g. emailing the corresponding author/s) and any relevant information obtained in this manner will be included in the review. Evaluation of important numerical data such as screened, randomised patients as well as intention-to-treat, as-treated and per-protocol population will be carefully performed. Attrition rates, for example drop-outs, losses to follow-up and withdrawals will be investigated. Issues of missing data and imputation methods (for example, last-observation-carried-forward) will be critically appraised (Higgins 2011).

Assessment of heterogeneity

Heterogeneity will be analysed using a Chi² test on N-1 degrees of freedom, with an alpha of 0.05 used for statistical significance and with the I² test (Higgins 2003). I² values of 25%, 50% and 75% correspond to low, medium and high levels of heterogeneity.

Assessment of reporting biases

If possible, funnel plots will be used to assess for the potential existence of small study bias (Higgins 2011).

Data synthesis

Data will be pooled using the random-effects model but the fixed-effect model will also be used to ensure robustness of the model chosen and susceptibility to outliers. Data synthesis will be done separately for RCTs and cohort studies.

Subgroup analysis and investigation of heterogeneity

Subgroup analysis will be used to explore possible sources of heterogeneity such as type of surgery. Heterogeneity among participants could be related to age. Heterogeneity in treatments could be related to agent (Cox-1 versus Cox-2 inhibitors), dose and duration of therapy. In addition, exclusion criteria of studies will be examined to assess for heterogeneity in particular risk factors for post-operative AKI according to NICE and KDIGO guidance (Ftouh 2013; KDIGO 2012). These include intraperitoneal surgery, CKD, diabetes mellitus, chronic disease, advanced age, cancer, anaemia or black race. Adverse effects will be tabulated and assessed with descriptive techniques, as they are likely to be different for the various agents used. Where possible, the risk difference with 95% CI will be calculated for each adverse effect, either compared to no treatment or to another agent.

Sensitivity analysis

We will perform sensitivity analyses in order to explore the influence of the following factors on effect size.
- Repeating the analysis excluding unpublished studies
- Repeating the analysis taking account of risk of bias, as specified
- Repeating the analysis excluding any very long or large studies to establish how much they dominate the results

- Repeating the analysis excluding studies using the following filters: diagnostic criteria, language of publication, source of funding (industry versus other), country.

ACKNOWLEDGEMENTS

We would like to thank the referees for their feedback and advice during the preparation of this protocol.

REFERENCES

Additional references

ASA Practice Guideline 2012
American Society of Anesthesiologists Task Force on Acute Pain Management. Practice guidelines for acute pain management in the perioperative setting: an updated report by the American Society of Anesthesiologists Task Force on Acute Pain Management. *Anesthesiology* 2012;**116**(2): 248–73. [MEDLINE: 22227789]

Bucaloiu 2012
Bucaloiu ID, Kirchner HL, Norfolk ER, Hartle JE 2nd, Perkins RM. Increased risk of death and de novo chronic kidney disease following reversible acute kidney injury. *Kidney International* 2012;**81**(5):477–85. [MEDLINE: 22157656]

Carmichael 2003
Carmichael P, Carmichael AR. Acute renal failure in the surgical setting. *ANZ Journal of Surgery* 2003;**73**(3): 144–53. [MEDLINE: 12608979]

Chertow 2005
Chertow GM, Burdick E, Honour M, Bonventre JV, Bates DW. Acute kidney injury, mortality, length of stay, and costs in hospitalized patients. *Journal of the American Society of Nephrology* 2005;**16**(11):3365–70. [MEDLINE: 16177006]

Coca 2012
Coca SG, Singanamala S, Parikh CR. Chronic kidney disease after acute kidney injury: a systematic review and meta-analysis. *Kidney International* 2012;**81**(5):442–8. [MEDLINE: 22113526]

Derry 2009
Derry CJ, Derry S, Moore RA, McQuay HJ. Single dose oral ibuprofen for acute postoperative pain in adults. *Cochrane Database of Systematic Reviews* 2009, Issue 3. [DOI: 10.1002/14651858.CD001548.pub2]

Derry 2012a
Derry S, Moore RA. Single dose oral aspirin for acute postoperative pain in adults. *Cochrane Database of Systematic Reviews* 2012, Issue 4. [DOI: 10.1002/14651858.CD002067.pub2]

Derry 2012b
Derry S, Moore RA. Single dose oral celecoxib for acute postoperative pain in adults. *Cochrane Database of Systematic Reviews* 2012, Issue 3. [DOI: 10.1002/14651858.CD004233.pub3]

Ftouh 2013
Ftouh S, Thomas M, Acute Kidney Injury Guideline Development Group. Acute kidney injury: summary of NICE guidance. *BMJ* 2013;**347**:f4930. [MEDLINE: 23985310]

Higgins 2003
Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *BMJ* 2003;**327** (7414):557–60. [MEDLINE: 12958120]

Higgins 2011
Higgins JP, Green S (editors). Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [updated March 2011]. The Cochrane Collaboration, 2011. Available from www.cochrane-handbook.org.

KDIGO 2012
KDIGO (Kidney Disease: Improving Global Outcomes) Acute Kidney Injury Work Group. KDIGO clinical practice guideline for acute kidney injury. *Kidney International - Supplement* 2012;**2**(1):1–138.

Lassnigg 2004
Lassnigg A, Schmidlin D, Mouhieddine M, Bachmann LM, Druml W, Bauer P, et al. Minimal changes of serum creatinine predict prognosis in patients after cardiothoracic surgery: a prospective cohort study. *Journal of the American Society of Nephrology* 2004;**15**(6):1597–605. [MEDLINE: 15153571]

Lee 2007
Lee A, Cooper MG, Craig JC, Knight JF, Keneally JP. Effects of nonsteroidal anti-inflammatory drugs on postoperative renal function in adults with normal renal function. *Cochrane Database of Systematic Reviews* 2007, Issue 2. [DOI: 10.1002/14651858.CD002765.pub3]

McDaid 2010
McDaid C, Maund E, Rice S, Wright K, Jenkins B, Woolacott N. Paracetamol and selective and non-selective

non-steroidal anti-inflammatory drugs (NSAIDs) for the reduction of morphine-related side effects after major surgery: a systematic review. *Health Technology Assessment (Winchester, England)* 2010;**14**(17):1-153, iii-iv. [MEDLINE: 20346263]

MHRA 2009
Medicines and Healthcare Products Regulatory Agency. Drug Safety Update: Volume 2 Issue 10, May 2009. www.mhra.gov.uk/Publications/Safetyguidance/DrugSafetyUpdate/CON046451 Vol. (accessed 17 August 2014).

Wells 2014
Wells GA, Shea B, O'Connell D, Peterson J, Welch V, Losos M, et al. The Newcastle-Ottawa Scale (NOS) for assessing the quality of non-randomised studies in meta-analyses. http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp (accessed 17 August 2014).

Whelton 1999
Whelton A. Nephrotoxicity of nonsteroidal anti-inflammatory drugs: physiologic foundations and clinical implications. *American Journal of Medicine* 1999;**106**(5B): 13S–24S. [MEDLINE: 10390124]

* *Indicates the major publication for the study*

APPENDICES

Appendix 1. Electronic search strategies

Database	Search terms
CENTRAL	1. MeSH descriptor: [Anti-Inflammatory Agents, Non-Steroidal] explode all trees 2. ((non-steroidal next anti-inflammatory) next (agent* or drug*)):ti,ab,kw 3. ((nonsteroidal next anti-inflammatory) next (agent* or drug*)):ti,ab,kw 4. ((non-steroidal next antiinflammatory) next (agent* or drug*)):ti,ab,kw 5. ((nonsteroidal next antiinflammatory) next (agent* or drug*)):ti,ab,kw 6. NSAID*:ti,ab,kw 7. ((cox 2 inhibitor*) or (cox-2 inhibitor*)):ti,ab,kw 8. (cyclooxygenase near/2 Inhibitor*):ti,ab,kw 9. apazone:ti,ab,kw 10. aspirin:ti,ab,kw 11. clonixin:ti,ab,kw 12. diclofenac:ti,ab,kw 13. diflunisal:ti,ab,kw 14. epirizole:ti,ab,kw 15. fenoprofen:ti,ab,kw 16. feprazone:ti,ab,kw 17. flurbiprofen:ti,ab,kw 18. ibuprofen:ti,ab,kw 19. indomethacin:ti,ab,kw 20. ketoprofen:ti,ab,kw 21. ketorolac:ti,ab,kw 22. meclofenamic acid:ti,ab,kw 23. mefenamic acid:ti,ab,kw 24. naproxen:ti,ab,kw 25. niflumic acid:ti,ab,kw 26. phenylbutazone:ti,ab,kw

(*Continued*)

	27. piroxicam:ti,ab,kw 28. salicylates:ti,ab,kw 29. sulindac:ti,ab,kw 30. tolmetin:ti,ab,kw 31. celecoxib:ti,ab,kw 32. etodolac:ti,ab,kw 33. meloxicam:ti,ab,kw 34. parecoxib:ti,ab,kw 35. rofecoxib:ti,ab,kw 36. tenoxicam:ti,ab,kw 37. valdecoxib:ti,ab,kw 38. {or #1-#37} 39. analgesi*:ti,ab,kw 40. an*esthesia:ti,ab,kw 41. pain:ti,ab,kw 42. (peri-operativ* or perioperativ*):ti,ab,kw 43. (postoperativ* or post-operativ*):ti,ab,kw 44. (preoperativ* or pre-operativ*):ti,ab,kw 45. {or #39-#44} 46. kidney:ti,ab,kw 47. renal:ti,ab,kw 48. creatinine:ti,ab,kw 49. nephrotoxi*:ti,ab,kw 50. azot*emia:ti,ab,kw 51. dialysis:ti,ab,kw 52. (hemodia* or haemodia* or hemofiltr* or haemofiltr*):ti,ab,kw 53. ("glomerular filtration rate" or "glomerulus filtration rate"):ti,ab,kw 54. (gfr or egfr):ti,ab,kw 55. (urin* near/2 (volume or output)):ti,ab,kw 56. {or #46-#55} 57. {and #38, #45, #56} 58. MeSH descriptor: [Anti-Inflammatory Agents, Non-Steroidal] explode all trees and with qualifier(s): [Adverse effects - AE] 59. {and #45, #58} 60. {or #57, #59}
MEDLINE	1. exp Anti-Inflammatory Agents, Non-Steroidal/ 2. (non-steroidal anti-inflammatory adj (agent* or drug*)).tw. 3. (nonsteroidal anti-inflammatory adj (agent* or drug*)).tw. 4. (non-steroidal antiinflammatory adj (agent* or drug*)).tw. 5. (nonsteroidal antiinflammatory adj (agent* or drug*)).tw. 6. NSAID*.tw. 7. cox 2 inhibitor*.tw. 8. (cyclooxygenase adj2 Inhibitor*).tw. 9. apazone.tw. 10. aspirin.tw. 11. clonixin.tw. 12. diclofenac.tw. 13. diflunisal.tw.

(*Continued*)

	14. epirizole.tw. 15. fenoprofen.tw. 16. feprazone.tw. 17. flurbiprofen.tw. 18. ibuprofen.tw. 19. indomethacin.tw. 20. ketoprofen.tw. 21. ketorolac.tw. 22. meclofenamic acid.tw. 23. mefenamic acid.tw. 24. naproxen.tw. 25. niflumic acid.tw. 26. phenylbutazone.tw. 27. piroxicam.tw. 28. salicylates.tw. 29. sulindac.tw. 30. tolmetin.tw. 31. celecoxib.tw. 32. etodolac.tw. 33. tenoxicam.tw. 34. parecoxib.tw. 35. rofecoxib.tw. 36. meloxicam.tw. 37. valdecoxib.tw. 38. or/1-37 39. exp Analgesia/ 40. analgesi*.tw. 41. an?esthesia.tw. 42. Pain/ 43. Acute Pain/ 44. Pain, Postoperative/ 45. Pain Management/ 46. Perioperative Period/ 47. Postoperative Period/ 48. (peri-operative or perioperative).tw. 49. (postoperative or post-operative).tw. 50. Preoperative Period/ 51. (preoperative or pre-operative).tw. 52. Postoperative Complications/ 53. pain.tw. 54. /39-53 55. and/38,54 56. Kidney/ 57. Kidney Diseases/ 58. Renal Insufficiency/ 59. exp Acute Kidney Injury/ 60. Creatinine/ 61. Kidney Function Tests/

(*Continued*)

	62. (kidney* or renal).tw. 63. creatinine.tw. 64. (nephrotox*).tw. 65. azot?emia.tw. 66. Renal Replacement Therapy/ 67. exp Renal Dialysis/ 68. dialysis.tw. 69. (hemodia* or haemodia* or hemofiltr* or haemofiltr*).tw. 70. glomerular filtration rate.tw. 71. (gfr or egfr).tw. 72. (urin* adj2 (volume or output)).tw. 73. or/56-72 74. and/55,73 75. exp Anti-Inflammatory Agents, Non-Steroidal/ae 76. and/54,75 77. or/74,76
EMBASE	1. exp nonsteroid antiinflammatory agent/ 2. (non-steroidal anti-inflammatory adj (agent* or drug*)).tw. 3. (nonsteroidal anti-inflammatory adj (agent* or drug*)).tw. 4. (non-steroidal antiinflammatory adj (agent* or drug*)).tw. 5. (nonsteroidal antiinflammatory adj (agent* or drug*)).tw. 6. NSAID*.tw. 7. exp Cyclooxygenase 2 Inhibitor/ 8. cox 2 inhibitor*.tw. 9. (cyclooxygenase adj2 Inhibitor*).tw. 10. apazone.tw. 11. aspirin.tw. 12. clonixin.tw. 13. diclofenac.tw. 14. diflunisal.tw. 15. epirizole.tw. 16. fenoprofen.tw. 17. feprazone.tw. 18. flurbiprofen.tw. 19. ibuprofen.tw. 20. indomethacin.tw. 21. ketoprofen.tw. 22. ketorolac.tw. 23. meclofenamic acid.tw. 24. mefenamic acid.tw. 25. naproxen.tw. 26. niflumic acid.tw. 27. phenylbutazone.tw. 28. piroxicam.tw. 29. salicylates.tw. 30. sulindac.tw. 31. tolmetin.tw. 32. celecoxib.tw.

(*Continued*)

	33. etodolac.tw. 34. tenoxicam.tw. 35. parecoxib.tw. 36. rofecoxib.tw. 37. meloxicam.tw. 38. valdecoxib.tw. 39. or/1-38 40. exp Analgesia/ 41. analgesi*.tw. 42. an?esthesia.tw. 43. Pain/ 44. Postoperative Pain/ 45. Postoperative Period/ 46. Postoperative Analgesia/ 47. Perioperative Period/ 48. Preoperative Period/ 49. Postoperative Complication/ 50. (postoperative or post-operative).tw. 51. (peri-operative or perioperative).tw. 52. (preoperative or pre-operative).tw. 53. pain.tw. 54. or/40-53 55. and/39,54 56. Kidney/ 57. Kidney Disease/ 58. Kidney Failure/ 59. Acute Kidney Failure/ 60. Creatinine/ 61. Kidney Function/ 62. Kidney Function Test/ 63. (kidney or renal).tw. 64. creatinine.tw. 65. (nephrotox*).tw. 66. azot?emia.tw. 67. exp Renal Replacement Therapy/ 68. dialysis.tw. 69. (hemodia* or haemodia* or hemofiltr* or haemofiltr*).tw. 70. Glomerulus Filtration Rate/ 71. glomerular filtration rate.tw. 72. (gfr or egfr).tw. 73. Urine Volume/ 74. ((urin* adj2 volume) or output).tw. 75. or/56-74 76. and/55,75 77. exp nonsteroid antiinflammatory agent/ae 78. and/54,77 79. or/76,78

Appendix 2. Risk of bias assessment tool

Potential source of bias	Assessment criteria
Random sequence generation Selection bias (biased allocation to interventions) due to inadequate generation of a randomised sequence	*Low risk of bias:* Random number table; computer random number generator; coin tossing; shuffling cards or envelopes; throwing dice; drawing of lots; minimization (minimization may be implemented without a random element, and this is considered to be equivalent to being random)
	High risk of bias: Sequence generated by odd or even date of birth; date (or day) of admission; sequence generated by hospital or clinic record number; allocation by judgement of the clinician; by preference of the participant; based on the results of a laboratory test or a series of tests; by availability of the intervention
	Unclear: Insufficient information about the sequence generation process to permit judgement
Allocation concealment Selection bias (biased allocation to interventions) due to inadequate concealment of allocations prior to assignment	*Low risk of bias:* Randomisation method described that would not allow investigator/participant to know or influence intervention group before eligible participant entered in the study (e.g. central allocation, including telephone, web-based, and pharmacy-controlled, randomisation; sequentially numbered drug containers of identical appearance; sequentially numbered, opaque, sealed envelopes)
	High risk of bias: Using an open random allocation schedule (e.g. a list of random numbers); assignment envelopes were used without appropriate safeguards (e.g. if envelopes were unsealed or non-opaque or not sequentially numbered); alternation or rotation; date of birth; case record number; any other explicitly unconcealed procedure
	Unclear: Randomisation stated but no information on method used is available
Blinding of participants and personnel Performance bias due to knowledge of the allocated interventions by participants and personnel during the study	*Low risk of bias*: No blinding or incomplete blinding, but the review authors judge that the outcome is not likely to be influenced by lack of blinding; blinding of participants and key study personnel ensured, and unlikely that the blinding could have been broken
	High risk of bias: No blinding or incomplete blinding, and the outcome is likely to be influenced by lack of blinding; blinding of key study participants and personnel attempted, but likely that the blinding could have been broken, and the outcome is likely to be influenced by lack of blinding
	Unclear: Insufficient information to permit judgement

(*Continued*)

Blinding of outcome assessment Detection bias due to knowledge of the allocated interventions by outcome assessors	*Low risk of bias:* No blinding of outcome assessment, but the review authors judge that the outcome measurement is not likely to be influenced by lack of blinding; blinding of outcome assessment ensured, and unlikely that the blinding could have been broken
	High risk of bias: No blinding of outcome assessment, and the outcome measurement is likely to be influenced by lack of blinding; blinding of outcome assessment, but likely that the blinding could have been broken, and the outcome measurement is likely to be influenced by lack of blinding
	Unclear: Insufficient information to permit judgement
Incomplete outcome data Attrition bias due to amount, nature or handling of incomplete outcome data	*Low risk of bias:* No missing outcome data; reasons for missing outcome data unlikely to be related to true outcome (for survival data, censoring unlikely to be introducing bias); missing outcome data balanced in numbers across intervention groups, with similar reasons for missing data across groups; for dichotomous outcome data, the proportion of missing outcomes compared with observed event risk not enough to have a clinically relevant impact on the intervention effect estimate; for continuous outcome data, plausible effect size (difference in means or standardized difference in means) among missing outcomes not enough to have a clinically relevant impact on observed effect size; missing data have been imputed using appropriate methods
	High risk of bias: Reason for missing outcome data likely to be related to true outcome, with either imbalance in numbers or reasons for missing data across intervention groups; for dichotomous outcome data, the proportion of missing outcomes compared with observed event risk enough to induce clinically relevant bias in intervention effect estimate; for continuous outcome data, plausible effect size (difference in means or standardized difference in means) among missing outcomes enough to induce clinically relevant bias in observed effect size; 'as-treated' analysis done with substantial departure of the intervention received from that assigned at randomisation; potentially inappropriate application of simple imputation
	Unclear: Insufficient information to permit judgement
Selective reporting Reporting bias due to selective outcome reporting	*Low risk of bias:* The study protocol is available and all of the study's pre-specified (primary and secondary) outcomes that are of interest in the review have been reported in the pre-specified way; the study protocol is not available but it is clear that the published reports include all expected outcomes, including those that were pre-specified (convincing text of this nature may be uncommon)

(*Continued*)

	High risk of bias: Not all of the study's pre-specified primary outcomes have been reported; one or more primary outcomes is reported using measurements, analysis methods or subsets of the data (e.g. subscales) that were not pre-specified; one or more reported primary outcomes were not pre-specified (unless clear justification for their reporting is provided, such as an unexpected adverse effect); one or more outcomes of interest in the review are reported incompletely so that they cannot be entered in a meta-analysis; the study report fails to include results for a key outcome that would be expected to have been reported for such a study
	Unclear: Insufficient information to permit judgement
Other bias Bias due to problems not covered elsewhere in the table	*Low risk of bias:* The study appears to be free of other sources of bias.
	High risk of bias: Had a potential source of bias related to the specific study design used; stopped early due to some data-dependent process (including a formal-stopping rule); had extreme baseline imbalance; has been claimed to have been fraudulent; had some other problem
	Unclear: Insufficient information to assess whether an important risk of bias exists; insufficient rationale or evidence that an identified problem will introduce bias

Appendix 3. Risk of bias assessment - Newcastle Ottawa Scale Form

Note: A study can be awarded a maximum of one star for each numbered item within the Selection and Outcome categories. A maximum of two stars can be given for comparability.

Selection

1. Representativeness of the exposed cohort
a. truly representative of the average ..... (describe) in the community *
b. somewhat representative of the average ..... in the community *
c. selected group of users (e.g. nurses, volunteers)
d. no description of the derivation of the cohort
2. Selection of the non exposed cohort
a. drawn from the same community as the exposed cohort *
b. drawn from a different source
c. no description of the derivation of the non exposed cohort
3. Ascertainment of exposure
a. secure record (e.g. surgical records) *
b. structured interview *
c. written self report
d. no description
4. Demonstration that outcome of interest was not present at start of study
a. yes *

b. no

Comparability

1. Comparability of cohorts on the basis of the design or analysis
a. study controls for ..... (select the most important factor) *
b. study controls for any additional factor * (This criteria could be modified to indicate specific control for a second important factor.)

Outcome

1. Assessment of outcome
a. independent blind assessment *
b. record linkage *
c. self report
d. no description
2. Was follow-up long enough for outcomes to occur
a. yes (select an adequate follow up period for outcome of interest) *
b. no
3. Adequacy of follow up of cohorts
a. complete follow up - all subjects accounted for *
b. subjects lost to follow-up unlikely to introduce bias - small number lost - <15 % follow-up, or description provided of those lost) *
c. follow-up rate < 85% and no description of those lost
d. no statement

Appendix 4. Risk of bias assessment - Newcastle Ottawa Scale

Coding manual for cohort studies

Selection

1. Representativeness of the exposed cohort

Item is assessing the representativeness of exposed individuals in the community, not the representativeness of the sample of women from some general population. For example, subjects derived from groups likely to contain middle class, better educated, health oriented women are likely to be representative of postmenopausal oestrogen users while they are not representative of all women (e.g. members of a health maintenance organisation (HMO) will be a representative sample of oestrogen users. While the HMO may have an under-representation of ethnic groups, the poor, and poorly educated, these excluded groups are not the predominant users of oestrogen).
Allocation of stars as per rating sheet

2. Selection of the non-exposed cohort

Allocation of stars as per rating sheet.

3. Ascertainment of exposure

Allocation of stars as per rating sheet.

4. Demonstration that outcome of interest was not present at start of study

In the case of mortality studies, outcome of interest is still the presence of a disease/incident, rather than death. That is to say that a statement of no history of disease or incident earns a star.

Comparability

1. Comparability of cohorts on the basis of the design or analysis

A maximum of 2 stars can be allotted in this category. Either exposed and non-exposed individuals must be matched in the design and/or confounders must be adjusted for in the analysis. Statements of no differences between groups or that differences were not statistically significant are not sufficient for establishing comparability. Note: If the relative risk for the exposure of interest is adjusted for the confounders listed, then the groups will be considered to be comparable on each variable used in the adjustment. There may be multiple ratings for this item for different categories of exposure (e.g. ever vs. never, current vs. previous or never) Age = , Other controlled factors =

Outcome

1. Assessment of outcome

For some outcomes (e.g. fractured hip), reference to the medical record is sufficient to satisfy the requirement for confirmation of the fracture. This would not be adequate for vertebral fracture outcomes where reference to x-rays would be required.
Independent or blind assessment stated in the paper, or confirmation of the outcome by reference to secure records (X-rays, medical records, etc.)
Record linkage (e.g. identified through ICD codes on database records)
Self-report (i.e. no reference to original medical records or X-rays to confirm the outcome)
No description.

2. Was follow-up long enough for outcomes to occur

An acceptable length of time should be decided before quality assessment begins (e.g. 5 yrs. for exposure to breast implants)

3. Adequacy of follow-up of cohorts

This item assesses the follow-up of the exposed and non-exposed cohorts to ensure that losses are not related to either the exposure or the outcome.
Allocation of stars as per rating sheet.

CONTRIBUTIONS OF AUTHORS

1. Draft the protocol: SB
2. Study selection: SB, TR
3. Extract data from studies: SB, TR
4. Enter data into RevMan: SB
5. Carry out the analysis: SB, CM, PD
6. Interpret the analysis: SB, CM,PD
7. Draft the final review: SB, TR, CM, PD
8. Disagreement resolution: PD
9. Update the review: SB

DECLARATIONS OF INTEREST

- Samira Bell: none known
- Peter Davey: none known
- Trijntje Rennie: none known
- Charis A Marwick: none known

SOURCES OF SUPPORT

Internal sources

- University of Dundee and National Health Service Tayside, UK.

External sources

- No sources of support supplied