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CADTH RAPID RESPONSE REPORT: SUMMARY OF ABSTRACTS

Nonsteroidal Anti-Inflammatory Drugs and Acute Kidney Injury: Safety

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Research Question

What is the evidence associated with the development of acute kidney injury upon the use of nonsteroidal anti-inflammatory drugs to treat acute pain?

Key Findings

Four systematic reviews, one meta-analysis, one randomized controlled trial, and five non-randomized studies were identified regarding the evidence associated with the development of acute kidney injury upon the use of nonsteroidal anti-inflammatory drugs to treat acute pain.

Methods

A limited literature search was conducted on key resources including PubMed, the Cochrane Library, University of York Centre for Reviews and Dissemination (CRD) Medline via OVID, Canadian and major international health technology agencies, as well as a focused Internet search. Methodological filters were applied to limit retrieval to safety data. Where possible, retrieval was limited to the human population. The search was also limited to English language documents published between January 1, 2013 and January 7, 2019. Internet links were provided, where available.

Selection Criteria

One reviewer screened citations and selected studies based on the inclusion criteria presented in Table 1.

Table 1: Selection Criteria

Population	Adult and pediatric patients (with or without co-morbidities) in any setting (e.g., hospital, clinic, community, long-term care facilities) with acute pain
Intervention	Nonsteroidal anti-inflammatory drugs (NSAIDs) (traditional/non-selective NSAIDs [e.g., diclofenac, naproxen, and ibuprofen] and Cox-2 inhibitors [e.g., celecoxib])
Comparators	• Any NSAID (alone or in combination with a diuretic and an angiotensin-converting-enzyme inhibitor [ACE] or Angiotensin II receptor blockers [ARB]) • Opioids • Placebo • No treatment • No comparator
Outcomes	Safety (acute kidney injury, e.g. increased creatinine clearance, or anything indicative of acute kidney injury)
Study Designs	Health technology assessments, systematic reviews, meta-analyses, randomized controlled trials, and non-randomized studies

Results

Rapid Response reports are organized so that the higher quality evidence is presented first. Therefore, health technology assessment reports, systematic reviews, and meta-analyses are presented first. These are followed by randomized controlled trials and non-randomized studies.

Four systematic reviews, one meta-analysis, one randomized controlled trial, and five non-randomized studies were identified regarding the evidence associated with the development of acute kidney injury upon the use of nonsteroidal anti-inflammatory drugs to treat acute pain. No relevant health technology assessments were identified.

Additional references of potential interest are provided in the appendix.

Overall Summary of Findings

Four systematic reviews[1-5] (one with meta-analysis),[4] one randomized controlled trial,[6] and five non-randomized studies[7-11] were identified regarding the evidence associated with the development of acute kidney injury (AKI) upon the use of nonsteroidal anti-inflammatory drugs (NSAIDs) to treat acute pain. Detailed study characteristics are provided in Table 2.

No reliable conclusion could be drawn from the first systematic review, where authors were uncertain of the effect of NSAIDs at or around the time of surgery on the risk of AKI, renal replacement therapy, death, and on increasing the length of hospital stay.[1] Still in the presence of low certainty, the authors concluded that NSAIDs may slightly increase serum creatinine (SCr).[1] This uncertainty of effect is echoed by the authors of two additional systematic reviews,[2,3] who were unable to support or reject the use of NSAIDs, citing insufficient information to assess whether their respective NSAID had a different rate of renal dysfunction[2] or AEs in general[3] versus their respective comparators. The authors of a fourth systematic review found that major adverse effects are not reported in the literature for the use of NSAIDs in the treatment of renal colic.[5] Furthermore, the authors of a meta-analysis on the risk of AKI in the general population and those with chronic kidney disease concluded that baseline risk, and therefore the absolute risk, of NSAID exposure is likely to be higher in people with CKD and older people.[4]

The authors of a randomized controlled trial saw nine cases of elevated creatinine levels resulting in acute renal injury following ibuprofen and lansoprazole administration for postoperative pain-management.[6] The oxycodone group did not see the same increase in creatinine levels.[6]

One non-randomized study found no significant differences in the incidence of renal failure between participants who received celecoxib and those who did not, for postoperative analgesia.[7] Similarly, another study found that ketorolac was well tolerated for use when administered selectively after cardiac surgery.[10]

This contrasts with the results of another non-randomized study, where authors found that AKI can result even in young adults who have undergone a short course of ketorolac.[8] Similarly, another study found that incorporating NSAIDs postoperatively resulted in a 4.8% rate of AKI.[9] Lastly, authors of a third study found that the concomitant use of aspirin with ketorolac is associated increased renal morbidity in young post-cardiac surgical infants.[11]

Additionally, the reader will find several references in the appendix classified as "outcomes not sufficiently described". These were appended during the citation screening since the type of adverse events measured is unclear and the relevance to acute kidney injury is undetermined. Further information may be gained from referring to their integral text.

Table 2: Summary of Included Studies

Author, Year	Study Characteristics; Intervention; Comparator	Outcomes	Results	Author Conclusions
Systematic Reviews and Meta-Analyses				
Bell, 2018[1]	N = 26 studies (8,835 participants); NSAIDs; Placebo	Post-operative kidney function.	Uncertain effects on AKI, urine output, RRT, death, LOS. May slightly increase SCr.	"The available data therefore does not confirm the safety of NSAIDs in patients undergoing surgery"[1]
McNicol, 2018[2]	N = 8 studies (1,756 participants); IV diclofenac; Placebo or an active comparator	Secondary outcome: AEs, serious AEs, NSAID-related AEs	AE rates were similar between IV diclofenac and placebo, as well as IV diclofenac and another NSAID. Serious and specific AEs were rare.	"[AEs] appear to occur at a similar rate to other NSAIDs. Insufficient information is available to assess whether [IV] diclofenac has a different rate of bleeding, renal dysfunction, or cardiovascular events versus other NSAIDs."[2]
McNicol, 2018[3]	N = 13 studies (920 participants); Ketorolac; Placebo or an active comparator	Secondary outcome: safety of Ketorolac	Insufficient data to analyse overall AEs or serious AEs.	"Due to the lack of data for our primary outcomes, and the very low-quality evidence for secondary outcomes, the efficacy and safety of ketorolac in treating postoperative pain in children were both uncertain. The evidence was insufficient to support or reject its use."[3]
Zhang, 2017[4]	N = 10 studies; NSAIDs; None	Risk of AKI in community-dwelling adults and those with pre-existing CKD.	The pooled odds ratio of AKI in NSAID exposed general population was 1.73 (2.51 in older people), whereas it was 1.63 in people with CKD.	"No study reported baseline risk of AKI in different populations meaning absolute risks could not be estimated, but baseline risk and therefore the absolute risk of NSAID exposure is likely to be higher in people with CKD and older people"[4]

Author, Year	Study Characteristics; Intervention; Comparator	Outcomes	Results	Author Conclusions
Afhar, 2015[5]	N = 50 studies (5,734 participants); NSAIDs; Non-narcotic drugs or placebo	Secondary: any adverse effects (minor or major)	Side effects were presented inconsistently, but no major events were reported.	"Major adverse effects are not reported in the literature for the use of NSAIDs for treatment of renal colic"[5]
Randomized Controlled Trial				
Qazi, 2015[6]	N = 182 participants; Ibuprofen combined with lansoprazole; Oxycodone	Secondary: renal failure	Median follow-up period was 25 months. Creatinine increased by 100% in nine ibuprofen patients, resulting in acute renal injury. Levels were not found to increase by the same magnitude in the oxycodone group.	"Renal function should, however, be closely monitored and in the event of any decrease in renal function ibuprofen must be discontinued."[6]
Non-Randomized Studies				
Hokuto, 2017[7]	N = 453 participants; Celecoxib; No celecoxib	Safety (major complications, serum bilirubin, creatinine, indocyanine green retention rate)	No significant differences in the incidences of acute renal failure.	"The use of celecoxib for postoperative analgesia in the early period after liver resection is safe"[7]
Mariano, 2017[8]	N = 1,397 participants; Ketorolac; No comparator	Postoperative readmission due to AKI	Four patients were readmitted, presenting with oliguric AKI and frank proteinuria.	"AKI can ensue even in young adults who have undergone a short course of ketorolac, when they suffered from relative dehydration, abdominal disturbances, flank pain and oliguria after discharge. Urine findings were characterized by a marked nonselective glomerular proteinuria disappearing in 2-3 weeks."[8]

Author, Year	Study Characteristics; Intervention; Comparator	Outcomes	Results	Author Conclusions
Warth, 2016[9]	N = 903 participants; Scheduled celecoxib and ketorolac when necessary. No comparator	Rates of AKI	Postoperative AKI was in 43 participants (4.8%).	"With a protocol incorporating NSAIDs in patients without evidence of preoperative renal impairment, there is a 4.8% rate of AKI, which is 2.7 times higher than the reported literature."[9]
Olivieri, 2014[10]	N = 1,309 participants; Ketorolac NA	Safety (including renal failure required dialysis)	Treatment with ketorolac was not a predictor for adverse outcome, adjusted multivariate model.	"Ketorolac appears to be well-tolerated for use when administered selectively after cardiac surgery."[10]
Moffett, 2013[11]	N = NA Ketorolac; No comparator	Risk factors for AKI, patients with a 50% or greater increase in SCr	"Significant differences in primary surgical procedure, baseline serum creatinine, and concomitant aspirin use were noted."[11]	"We conclude that the concomitant use of aspirin with ketorolac is associated with increased renal morbidity in young post-cardiac surgical infants."[11]

AEs = adverse events; AKI = acute kidney injury; CKD = chronic kidney disease; IV = intravenous; LOS = length of stay; NA = not available; NSAIDs = non-steroidal anti-inflammatory drugs; RRT = renal replacement therapy; SCr = serum creatinine.

References Summarized

Health Technology Assessments

No literature identified.

Systematic Reviews and Meta-analyses

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Randomized Controlled Trials

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Non-Randomized Studies

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PubMed: PM26377377

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PubMed: PM24231193

11. Moffett BS, Cabrera A. Ketorolac-associated renal morbidity: risk factors in cardiac surgical infants. *Cardiol Young*. 2013;23(5):752-754.
PubMed: PM23088994

Appendix — Further Information

Previous CADTH Reports

12. Perioperative use of nsaids: safety and guidelines. *(CADTH Rapid response report: summary with critical appraisal)*. Ottawa (ON): CADTH; 2018; https://www.cadth.ca/perioperative-use-nsaids-safety-and-guidelines. Accessed 2019 Jan 21.

Systematic Reviews and Meta-analyses

Outcome Insufficiently Described

13. Moore PA, Ziegler KM, Lipman RD, Aminoshariae A, Carrasco-Labra A, Mariotti A. Benefits and harms associated with analgesic medications used in the management of acute dental pain: an overview of systematic reviews. *J Am Dent Assoc*. 2018;149(4):256-265.e3.
PubMed: PM29599019

14. Derry S, Wiffen PJ, Kalso EA, et al. Topical analgesics for acute and chronic pain in adults - an overview of Cochrane reviews. *Cochrane Database of Systematic Reviews*. 2017;5:CD008609.
PubMed: PM28497473

15. Hartling L, Ali S, Dryden DM, et al. How safe are common analgesics for the treatment of acute pain for children? A systematic review. *Pain Res Manag*. 2016;2016:5346819.
PubMed: PM28077923

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PubMed: PM26461263

18. van den Bekerom MPJ, Sjer A, Somford MP, Bulstra GH, Struijs PAA, Kerkhoffs G. Non-steroidal anti-inflammatory drugs (NSAIDs) for treating acute ankle sprains in adults: benefits outweigh adverse events. *Knee Surg Sports Traumatol Arthrosc*. 2015;23(8):2390-2399.
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20. van Durme CMPG, Wechalekar MD, Buchbinder R, Schlesinger N, van der Heijde D, Landewé RBM. Non-steroidal anti-inflammatory drugs for acute gout. *Cochrane Database of Systematic Reviews.* 2014;9: CD010120.
PubMed: PM25225849

21. Derry S, Moore RA. Single dose oral celecoxib for acute postoperative pain in adults. *Cochrane Database of Systematic Reviews.* 2013;10: CD004233.
PubMed: PM24150982

Randomized Controlled Trials

Alternative Intervention – Prophylaxis

22. Fabricio de Souza R, Gama de Matos D, Pires Ferreira AR, et al. The effect of ibuprofen on muscle, hematological and renal function, hydric balance, pain, and performance during intense long-distance running. *J Strength Cond Res*. 2018;14:14.
PubMed: PM29461420

Outcome Insufficiently Described

23. Predel HG, Giannetti B, Connolly MP, Lewis F, Bhatt A. Efficacy and tolerability of a new ibuprofen 200mg plaster in patients with acute sports-related traumatic blunt soft tissue injury/contusion. *Postgrad Med*. 2018;130(1):24-31.
PubMed: PM29110567

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PubMed: PM29049211

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PubMed: PM25886424

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PubMed: PM25526232

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PubMed: PM23964752

Non-Randomized Studies

Alternative Intervention - Combination Drug

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PubMed: PM29382434

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PubMed: PM24445686

Outcome Insufficiently Described

31. Raja Rajeswari S, Gowda T, Kumar T, Mehta DS, Arya K. Analgesic efficacy and safety of transdermal and oral diclofenac in postoperative pain management following dental implant placement. *Gen Dent*. 2017;65(4):69-74.
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Review Articles

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Consensus statement

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Evidence Summary

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