Can J Anesth/J Can Anesth (2022) 69:885–897
https://doi.org/10.1007/s12630-022-02257-6

REVIEW ARTICLE/BRIEF REVIEW

Effect of intravenous acetaminophen on postoperative outcomes in hip fracture patients: a systematic review and narrative synthesis

Effet de l'acétaminophène par voie intraveineuse sur les devenirs postopératoires chez les patients atteints d'une fracture de la hanche: une revue systématique et synthèse narrative

Jenny Sue Hyun Cho, BSc · Kristian McCarthy, BMSc · Simone Schiavo, MSc, MD · Binu Jacob, MSc, PhD · Marina Engelsakis, HBA, MLIS · Michael Zywiel, MD, MSc, FRCSC · Keyvan Karkouti, MD, FRCPC · Stuart McCluskey, MD, PhD, FRCPC · Hance Clarke, MD, PhD, FRCPC · Jean Wong, MD, FRCPC

Received: 12 October 2021 / Revised: 3 February 2022 / Accepted: 23 February 2022 / Published online: 10 May 2022

Abstract

Purpose *Hip fractures are debilitating in older adults because of their impact on quality of life. Opioids are associated with adverse effects in this population, so oral acetaminophen is commonly prescribed to minimize opioid use. Intravenous (iv) acetaminophen has been reported to have superior efficacy and bioavailability than oral acetaminophen. Nevertheless, its effect on postoperative outcomes in emergency hip fractures is unclear. This systematic review assessed the effect of iv acetaminophen on postoperative outcomes in older hip fracture patients.*

Source *We searched multiple databases from inception to June 2021 for studies on adults > 50 yr of age undergoing emergency hip fracture surgery who received iv acetaminophen (or paracetamol) and that reported postoperative outcomes. Relevant titles, abstracts, and full texts were screened based on the eligibility criteria.*

Jenny Sue Hyun Cho and Kristian McCarthy have contributed equally to this work.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s12630-022-02257-6.

J. S. H. Cho, BSc · K. McCarthy, BMSc
Temerty Faculty of Medicine, University of Toronto, Toronto, ON, Canada

S. Schiavo, MSc, MD
Department of Anesthesiology and Pain Management, University Health Network, University of Toronto, Toronto, ON, Canada

Department of Anesthesiology and Pain Medicine, Women's College Hospital, Toronto, ON, Canada

B. Jacob, MSc, PhD
Department of Anesthesiology and Pain Management, University Health Network, University of Toronto, Toronto, ON, Canada

M. Engelsakis, HBA, MLIS
General Surgery, Anesthesia & Perioperative Care Education Investigator, The Institute of Education Research Library & Information Services, University Health Network, Toronto, ON, Canada

M. Zywiel, MD, MSc, FRCSC
Division of Orthopedic Surgery, Toronto Western Hospital, University Health Network, University of Toronto, Toronto, ON, Canada

Institute of Health Policy, Management and Evaluation, Dalla Lana School of Public Health, University of Toronto, Toronto, ON, Canada

K. Karkouti, MD, FRCPC
Department of Anesthesiology and Pain Management, University Health Network, University of Toronto, Toronto, ON, Canada

Department of Anesthesiology and Pain Medicine, Sinai Health System, Toronto, ON, Canada

The Newcastle-Ottawa scale was used to assess the quality of the selected papers.

Principal findings *Of 3,510 initial studies, four met the inclusion criteria. One was a prospective cohort study and three were retrospective cohort studies. All four studies used historical control groups. Three studies reported a significantly lower mean opioid dose with iv acetaminophen than with oral acetaminophen. Three studies also reported a significantly shorter hospital stay. One study each reported a significant decrease in the number of missed physical therapy sessions, the need for one-to-one supervision, and episodes of delirium.*

Conclusion *There is very limited low-level evidence that iv acetaminophen improves preoperative and postoperative analgesia and shortens hospital stay in older hip fracture patients. Nevertheless, our results should be interpreted with caution since there are no prospective randomized trials investigating whether iv acetaminophen improves postoperative outcomes in this patient population.*

Study registration *PROSPERO (CRD42021198174); registered 15 August 2021.*

Résumé

Objectif *Les fractures de la hanche sont débilitantes chez les personnes âgées en raison de leur impact sur leur qualité de vie. Les opioïdes sont associés à des effets indésirables chez cette population, de sorte que l'acétaminophène par voie orale est couramment prescrit pour minimiser la consommation d'opioïdes. L'acétaminophène par voie intraveineuse (IV) a une efficacité et une biodisponibilité supérieures à celles de l'acétaminophène par voie orale. Néanmoins, son effet sur les devenirs postopératoires dans les fractures d'urgence de la hanche n'est pas clair. Cette revue systématique a évalué l'effet de l'acétaminophène IV sur les devenirs postopératoires chez les patients âgés avec une fracture de la hanche.*

Sources *Nous avons effectué des recherches dans plusieurs bases de données de leur création à juin 2021 pour en tirer les études portant sur des adultes > 50 ans bénéficiant d'une chirurgie d'urgence pour une fracture de la hanche et ayant reçu de l'acétaminophène IV (ou paracétamol), et qui rapportait les devenirs postopératoires. Les titres, résumés et textes intégraux pertinents ont été sélectionnés en fonction des critères d'admissibilité. L'échelle de Newcastle-Ottawa a été utilisée pour évaluer la qualité des articles sélectionnés.*

Constatations principales *Sur les 3510 études initiales, quatre ont répondu aux critères d'inclusion. L'une était une étude de cohorte prospective et trois étaient des études de cohorte rétrospectives. Les quatre études ont utilisé des groupes témoins historiques. Trois études ont rapporté une dose moyenne d'opioïdes significativement plus faible avec l'acétaminophène IV qu'avec de l'acétaminophène par voie orale. Trois études ont également rapporté un séjour à l'hôpital significativement plus court. Une diminution significative du nombre de séances de physiothérapie manquées a été rapporté dans une étude, une autre a rapporté une diminution significative de la nécessité de supervision individuelle, et une troisième une réduction des épisodes d'état confusionnel aigu.*

Conclusion *: Il n'existe que très peu de données probantes qui sont de faible qualité et selon lesquelles l'acétaminophène IV améliore l'analgésie préopératoire et postopératoire et réduit la durée de séjour à l'hôpital chez les patients âgés atteints d'une fracture de hanche. Néanmoins, nos résultats doivent être interprétés avec prudence car il n'existe pas d'étude randomisée prospective évaluant si l'acétaminophène IV améliore les issues postopératoires dans cette population de patients.*

Enregistrement de l'étude *PROSPERO (CRD420211 98174); enregistrée le 15 août 2021.*

Keywords acetaminophen · elderly · hip fracture · pain · postoperative

Department of Anesthesiology and Pain Medicine, Women's College Hospital, Toronto, ON, Canada

Department of Anesthesiology and Pain Medicine, University of Toronto, University Health Network, University of Toronto, MCL 2-405, 399 Bathurst St, Toronto, ON M5T 2S8, Canada

S. McCluskey, MD, PhD, FRCPC · H. Clarke, MD, PhD, FRCPC
Department of Anesthesiology and Pain Management, University Health Network, University of Toronto, Toronto, ON, Canada

Department of Anesthesiology and Pain Medicine, University of Toronto, University Health Network, University of Toronto, MCL 2-405, 399 Bathurst St, Toronto, ON M5T 2S8, Canada

J. Wong, MD, FRCPC (✉)
Department of Anesthesiology and Pain Management, University Health Network, University of Toronto, Toronto, ON, Canada
e-mail: jean.wong@uhn.ca

Department of Anesthesiology and Pain Medicine, Women's College Hospital, Toronto, ON, Canada

Department of Anesthesiology and Pain Medicine, University of Toronto, University Health Network, University of Toronto, MCL 2-405, 399 Bathurst St, Toronto, ON M5T 2S8, Canada

Hip fractures are a global public health issue. In Canada, over 30,000 hip fractures occur annually, and approximately two million people suffer a hip fracture

each year worldwide.[1] The term *hip fracture* refers to fractures spanning from the femoral head–neck junction to 5 cm below the lesser trochanter. This injury occurs commonly among the elderly population, and its incidence is increasing as the proportion of elderly individuals rises.[2] This is concerning because hip fractures have an extensive morbidity profile that substantially affects the functional status and post-injury independence of patients.[3] Elderly hip fracture patients are also at a higher risk of developing postoperative complications including delirium, chronic pain, ambulation difficulties, and death.[3] Effective analgesia is critical for patients to participate in the postoperative rehabilitation needed to prevent disability. Although opioids are irrefutably effective analgesics, their use in the frail geriatric population is potentially hazardous because of severe adverse effects, including nausea, vomiting, constipation, delirium, and respiratory depression.[4] To help address this issue, multimodal analgesia has been recommended with various nonopioid pharmacologic treatments to manage pain optimally.[5]

Acetaminophen (also known internationally as *paracetamol*) is an effective adjunct to opioids because of its well-established analgesic effects and safety profile.[6] This medication is critical in the geriatric population, who have a high incidence of comorbidities. Acetaminophen is a cornerstone of multimodal postoperative analgesia, and its scheduled oral formulation is widely used. Nevertheless, oral acetaminophen has limited bioavailability. The systemic concentration of an oral formulation is reduced by up to 40% by first-pass hepatic metabolism.[7] If the patient is also receiving concomitant opioids, absorption can be limited further.[8] Acetaminophen has a central site of action, so its systemic concentration is critical for uptake across the blood–brain barrier. As such, as an intravenous (*iv*) formulation, acetaminophen has a higher and more reliable bioavailability.[8] In addition, different studies have analyzed the pharmacokinetics of *iv* acetaminophen and showed that its maximum observed concentration (C_{max}) and area under the curve were significantly higher than oral acetaminophen.[8–12] Nevertheless, a drawback of the *iv* formulation is that it is more expensive than the oral formulation. At the time of article submission, the current cost in Canada of a 1-g dose of *iv* acetaminophen ranged from CAD 10 to CAD 19. This is compared against the average cost of oral acetaminophen at CAD 0.03 for a 1-g dose.[13]

The efficacy of *iv* acetaminophen, compared with oral acetaminophen for postoperative analgesia, is contentious. Recent studies in patients undergoing elective hip and knee arthroplasties and colorectal surgery (both elective and emergent) have shown no significant improvement in postoperative analgesia when comparing *iv* acetaminophen to oral acetaminophen.[6,14–17] Previous studies have not reported adverse effects with the use of *iv* acetaminophen.[6,14–18] As emergency hip fracture patients are vulnerable to adverse effects of opioids, it is critical to determine whether this formulation improves analgesia and other outcomes, justifying the higher cost. In this systematic review, we sought to assess the efficacy and safety of *iv* acetaminophen in elderly hip fracture patients in reducing pain or preventing postoperative complications. Our research question was, "In older hip fracture patients, does the use of perioperative intravenous acetaminophen, compared against oral acetaminophen, affect postoperative outcomes?"

Methods

Inclusion and exclusion criteria

The inclusion criteria were as follows: 1) general human population ≥ 50 yr of age with no geographic restrictions; 2) known diagnosis of a hip fracture undergoing emergency surgical repair/replacement of the hip; 3) *iv* acetaminophen used as an intervention; 4) randomized controlled trials, prospective and retrospective cohort studies, or case–control and nested case–control studies; 5) studies in English or French; and 6) studies reporting any of the following assessments and outcome measures: pain, opioid use, delirium, cognitive impairment, ambulatory ability, length of stay, discharge location, readmission, quality of life, depression, overall health, costs, all-cause morbidity, or all-cause mortality.

The exclusion criteria were as follows: 1) pathologic hip fractures secondary to a malignancy or metastasis; 2) elective arthroplasty; 3) qualitative studies; 4) nonhuman studies (*in vivo, in vitro*, other); and 5) case reports.

Search strategy

This systematic review protocol was registered in the International Prospective Register of Systematic Reviews (PROSPERO) (registration number: CRD42021198174; registered 15 August 2021). The following databases were searched from inception via the Ovid search interface: Medline, Medline ePubs/In-Process (daily), Embase, Cochrane Central Register of Controlled Trials, and the Cochrane Database of Systematic Reviews. The Web of Science (Clarivate™; London, UK), Scopus (Elsevier; Amsterdam, The Netherlands), and the Cumulative Index to Nursing and Allied Health (EbscoHost, 1982–present) databases were also searched from inception. ClinicalTrials.gov and the World Health Organization's International Clinical Trials Registry Platform (ICTRP) were also searched. All databases and trial registries were searched on 21 September 2021.

The search process followed the Cochrane Handbook[19] and the Cochrane Methodological Expectations of Cochrane Intervention Reviews[20] for conducting the search, the PRISMA 2020 guideline[21] for reporting the search, and the Peer Review of Electronic Search Strategies (PRESS) guidelines,[22] drawing on its 2015 Guideline Evidence-Based Checklist to avoid potential search errors.

Preliminary searches were conducted and full-text literature was mined for potential keywords and appropriate controlled vocabulary terms (such as Medical Subject Headings [MeSH] for Medline and Emtree descriptors for Embase) using the databases, target articles, and the Yale MeSH Analyzer.[23] The search strategy used the following terms: "Acetaminophen" AND "Hip Fractures OR Hip Surgery," with each component being fleshed out with controlled vocabularies, text word terms, and synonyms.

To supplement the search, references and citations were searched on the Web of Science (Clarivate) for one target citation: *Tsang KS, Page J, Mackenney P. Can intravenous paracetamol reduce opioid use in preoperative hip fracture patients? Orthopedics. 2013 Feb;36(2 Suppl):20–4.* https://doi.org/10.3928/01477447-20130122-53. *PMID: 23379572*. For details, please see the Medline search strategy provided in the Electronic Supplementary Material, eAppendix.

Study selection

Duplicated studies were detected and removed using Covidence (Melbourne, Australia). Next, two reviewers (J. C. and K. M.) independently screened the titles and abstracts according to the eligibility criteria. Disagreements were resolved by consensus or by consulting a third author (J. W. or S. S.).

The approved articles underwent a full-text review by the same two reviewers (J. C. and K. M.) to ensure they met all the eligibility criteria. Reasons for excluding articles at this stage were recorded. The resulting list of included studies for full review was circulated to the entire systematic review team to identify any potentially missing studies.

Data extraction and quality assessment

In duplicate, two authors (J. C. and K. M.) extracted study characteristics from the approved articles. For each included study, the following data were extracted: year, study location, study design, demographics, sample size, intervention, details on the primary outcome, details on the secondary outcome, and follow-up period. All the statistics, except for confidence intervals (CIs) of differences, came from the original four articles. Two authors (J. C. and K. M.) independently rated each article's quality using the Newcastle-Ottawa Quality Assessment Scale.[24] Each study was judged on nine items. These items were the representativeness of the exposed cohort, the selection of the nonexposed cohort, the ascertainment of exposure, the demonstration that the outcome of interest was not present at the start of the study, whether the study controlled for type of hip fractures, whether the study controlled for age and sex, the assessment of the outcome, whether the follow-up was long enough for the outcome to occur, and the adequacy of the follow-up. These nine items were categorized into the following groups: study group selection, study group comparability, and ascertainment of the outcomes of interest and scored accordingly. If disagreements occurred, they were resolved by consensus or by consulting a third author (J. W. or S. S.). We initially planned to complete a meta-analysis; however, this was not possible because study design and outcomes were not consistent between the studies.

Calculation of 95% confidence intervals of differences

To calculate the 95% CIs of the differences in means for studies that did not report these, we used the following formula: $\mu_1 - \mu_2 = (M_1 - M_2) \pm ts_{(M1\ -\ M2)}$, where M_1 and M_2 = sample means; $t = t$ statistic determined by confidence level; and $s_{(M1\ -\ M2)}$ = standard error.[25]

Morphine milligram equivalent conversion

To ensure consistency and accurate comparison, all opioid medications described in the studies were converted to morphine milligram equivalents (MME) as outlined by the 2016 Centers for Disease Control and Prevention guidelines.[26] For intravenous opioids, the values were converted to their oral equivalent using the following ratio: 1 mg of *iv* morphine = 3 mg oral morphine.

Results

Search results

The literature search yielded 3,510 studies, with the search in the Cochrane database yielding 187 articles (Figure 1). After the duplicates were removed, 2,355 studies remained. Once titles and abstracts were screened, 106 articles were deemed eligible for full-text assessment. Of these articles, four studies met the inclusion criteria and were subsequently included in the final review.[3,4,27,28] Additionally, we contacted Hansen *et al.* to obtain the hip fracture-specific data that were acquired during their study.[28]

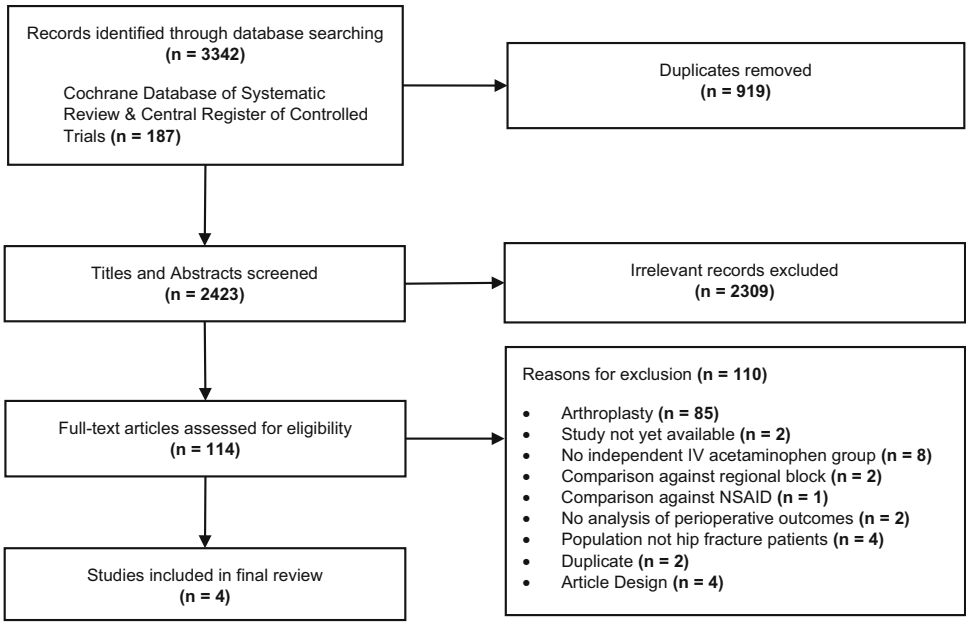

Figure 1 Prisma flow diagram of literature search

Study characteristics

Of the four studies, one study was a prospective cohort study[4] and the rest were retrospective cohort studies (see Table 1).[3,27,28] Study locations included the UK (n = 1)[4] and USA (n = 3).[3,27,28] Three of the four studies, excluding the study conducted by Hansen *et al*., directly compared the control group of oral acetaminophen with the intervention group of *iv* acetaminophen.[3,4,27] These three studies included 255 control patients and 279 intervention patients in total. Hansen *et al*. compared 64,395 control patients prescribed *iv* opioids to 17,928 intervention patients prescribed *iv* acetaminophen.[28] Hansen *et al*. informed us that all patients received standard of care (personal correspondence), so there was no restriction on oral acetaminophen in both the control and intervention groups of this study.[28] Nevertheless, Hansen *et al*. did not describe the dosing regimens of oral acetaminophen. Excluding the study by Hansen *et al*. (age and sex characteristics of fracture patients were not provided), the average age of participants was 81 yr and 29% were male. All studies reported the mean opioid dose used,[3,4,27,28] and three used the visual analogue scale as a subjective measure of pain.[3,4,27] Three studies reported the length of hospital stay[3,27,28] and two studies reported the percentage of patients discharged home.[3,27] Only one study analyzed each of the remaining outcomes: total cost of hospitalization,[28] missed physical therapy sessions,[27] chart-based delirium identification,[3] the need for one-to-one supervision as a surrogate outcome of delirium,[3] and readmission rate.[3]

Study outcomes

Pain

All four studies compared the mean opioid dose administered to the intervention and control groups (Table 2).[3,4,27,28] Three studies reported a significantly lower mean opioid dose with the administration of *iv* acetaminophen.[3,4,27] One of these studies, by Connolly *et al*., reported the dose for postoperative days 0 to 3.[3] Compared against the oral acetaminophen group, the *iv* acetaminophen group required significantly less *iv* opioid administration on postoperative day 1 (7.14 mg *vs* 2.22 mg; P = 0.01). There were no significant differences between the two groups on postoperative day 2 (4.56 mg *vs* 2.22 mg, P = 0.11) and postoperative day 3 (2.7 mg *vs* 1.2 mg, P = 0.16). The study by Hansen *et al*. also compared the opioid doses in the postoperative period from postoperative days 0–2.[28] In this study, the use of *iv* acetaminophen was associated with a difference of 0.6 mg compared with the *iv* opioid group; however, this difference was not significant ($P > 0.01$).

One study by Tsang *et al*.[4] reported the preoperative opioid dose from hospital admission to the anesthetic room. They found that the *iv* acetaminophen group required a significantly lower total opioid dose (mean, 65.4 mg *vs* 19.5 mg $P < 0.005$) and significantly fewer opioids per day (mean 27.0 mg *vs* 11.4 mg, $P < 0.005$). Lastly, Bollinger *et al*. reported the opioid dose from the time of admission to discharge.[27] Comparing oral *vs iv* acetaminophen, Bollinger *et al*. reported a total mean opioid consumption of 41.3 mg *vs* 28.3 mg (95% CI of the difference, -8.195 to

Table 1 Study characteristics

Study	Country	Design	Type of hip fracture repair	Intervention	Sample size (*n*)	Mean age (yr)	Sex (% male)	Remarks
Tsang, 2013[4]	UK	Prospective cohort	Intra- or extracapsular hip fracture repair	Group 1 (control)(preop): • Acetaminophen 1000 mg *po* q6h[a] • Codeine or tramadol *po* (standing) (dose NR)[b] • Morphine *iv* (breakthrough) (dose NR) Group 2 (intervention)(preop): • Acetaminophen 1000 mg *iv* q6h[a] • Codeine or tramadol *po* (breakthrough) (dose NR)[b] • Morphine *iv* (breakthrough) (dose NR)	Acetaminophen *po*: 28 Acetaminophen *iv*: 47 Total: 75	Acetaminophen *po*: 81.9 Acetaminophen *iv*: 79.5	Acetaminophen *po*: 7 Acetaminophen *iv*: 30	Excluded: • Polytrauma • Chronic opioid use • Medically unfit for surgery
Bollinger, 2015[27]	USA	Retrospective cohort	Intertrochanteric or femoral neck fracture repair	Group 1 (control) (pre- and postop): • Acetaminophen 1000 mg *po* q8h[a] • Tramadol 50 mg *po* q6h or oxycodone 5-10 mg *po* q4h PRN[b] • Morphine 2-4 mg *iv* q2h PRN Group 2 (intervention): • Acetaminophen 1000 mg *iv* q8h[c] (for 24 hr preop or until operation) • Acetaminophen 1000 mg *po* q8h[a] (postop) • Tramadol 50 mg *po* q6h or oxycodone 5-10 *po* mg q4h PRN[b] (pre- and postop) • Morphine 2-4 mg *iv* q2h PRN (pre- and postop)	Acetaminophen *po*: 169 Acetaminophen *iv*: 167 Total: 336	Acetaminophen *po*: 83.3 Acetaminophen *iv*: 81.8	Acetaminophen *po*: 27 Acetaminophen *iv*: 28	Excluded: • Subtrochanteric fracture • Pathologic fracture • Periprosthetic • Polytrauma • Perioperative death
Hansen, 2016[28]	USA	Retrospective cohort	Hip fracture repair	Group 1 (control) (postop): • Opioid *iv* (standing) (dose NR)[d] Group 2 (intervention) (postop): • Acetaminophen *iv* (dose NR)[d] • Opioid *iv* (standing) (dose NR)[d]	Opioid monotherapy: 64,395 Acetaminophen *iv*: 17,928 Total: 82,323	Opioid monotherapy: 64.3[f] Acetaminophen *iv*: 63.6[f]	Opioid monotherapy: 42[g] Acetaminophen *iv*: 41[g]	Excluded: • *iv* acetaminophen use beyond postop day 2

Table 1 continued

Study	Country	Design	Type of hip fracture repair	Intervention	Sample size (*n*)	Mean age (yr)	Sex (% male)	Remarks
Connolly, 2020[3]	USA	Retrospective cohort	Intertrochanteric, subtrochanteric or femoral neck fracture repair	Group 1 (control) (postop): • Acetaminophen 1000 mg *po* q8h[a] • Oxycodone 2.5-5 mg *po* q4h PRN[b] • Morphine 2 mg *iv* q2h PRN Group 2 (intervention) (postop): • Acetaminophen 1 000 mg *iv* q8h (for 24 hr postop)[e] • Acetaminophen 1 000 mg *po* q8h (after 24 hr of *iv*) • Oxycodone 2.5-5 mg *po* q4h PRN[b] • Morphine 2 mg *iv* q2h PRN	Acetaminophen *po*: 58 Acetaminophen *iv*: 65 Total: 123	Acetaminophen *po*: 78.9 Acetaminophen *iv*: 81.1	Acetaminophen *po*: 45 Acetaminophen *iv*: 37	Excluded: • Pathologic fracture • Injury > 2 weeks prior to presentation • Previous arthroplasty or surgical fixation of involved hip

[a] Duration of medication NR.

[b] Oral doses converted into morphine *iv* equivalent dose for standardization.

[c] Minimum of 24 hr from the time of admission or until they were taken to surgery if that time exceeded 24 hr.

[d] Provided on postoperative days 0 to 2.

[e] Provided for 24 hr after surgery.

[f] Age provided for all orthopedic surgery patients within this group, not specific for the subanalysis of the hip fracture patients.

[g] Sex distribution for all orthopedic surgery patients within this group, not specific for the subanalysis of hip fracture patient.

iv = intravenous; NR = not reported; *po* = oral; postop = postoperative; PRN = as needed; q2h = every two hours; q4h = every four hours; q6h = every six hours; q8h = every eight hours

Table 2 Study outcomes

Study	Comparison groups	Outcome measures								
		Mean visual analogue scale[a]	Mean opioid dose (MME)	Length of hospital stay (d)	Missed physical therapy sessions (%)	Discharge home (%)	Total cost of hospitalization (USD)	Delirium (%)[b]	Need for one-to-one supervision (%)	Readmission (%)
Tsang, 2013[4]	Acetaminophen *po vs iv*	Preoperative score: 2.1 *vs* 1.8 ($P = 0.30$)	From time of admission to anesthetic room: Total: 65.4 *vs* 19.5 mg ($P < 0.005$) Per day: 27.0 *vs* 11.4 mg ($P < 0.005$)	NR	NR	NR	NR	NR	NR	NR
Bollinger, 2015[27]	Acetaminophen *po vs iv*	Mean (SD) score[c]: 4.2 (2.1) *vs* 2.8 (1.8) ($P < 0.001$)	From time of admission to discharge: Total: 41.3 (135.9) *vs* 28.3 (30.5) ($P < 0.001$) Per day: 9.6 (8.1) *vs* 7.8 (8.7) ($P < 0.05$)	4.4 (3.8) *vs* 3.8 (1.7) days ($P < 0.001$)	During hospital stay: 21.8 (121.1) *vs* 10.4 (17.9) ($P < 0.001$)	7.0 *vs* 19.0 ($P < 0.001$)	NR	NR	NR	NR
Hansen, 2016[28]	Difference between acetaminophen *iv vs* opioids-only	NR	From postop day 0 through 2: - 0.6 mg ($P > 0.01$)	-0.55 days ($P < 0.01$)	NR	NR	-879.60 ($P > 0.01$)	NR	NR	NR
Connolly, 2020[3]	Acetaminophen *po* vs *iv*	Postop day 1: 4.23 *vs* 3.89 ($P = 0.41$) 2: 3.94 *vs* 3.63 ($P = 0.50$) 3: 2.98 *vs* 2.68 ($P = 0.30$)	Postop day 1: 7.14 *vs* 2.22 mg ($P = 0.01$) 2: 4.56 *vs* 2.22 mg ($P = 0.11$) 3: 2.70 *vs* 1.20 mg ($P = 0.16$)[de]	8.47 *vs* 6.37 days ($P = 0.04$)	NR	10.3 *vs* 10.8 ($P = 0.65$)	NR	32.8 *vs* 15.4 ($P = 0.02$)	24.1 *vs* 9.2 ($P = 0.03$)	27.6 *vs* 18.5 ($P = 0.23$)

P indicates statistical significance ≤ 0.05.

[a] Pain intensity from 0 to 10, lowest–highest.

[b] Score of "possible," 40–60% likelihood, was the cut off to be considered delirious.

[c] Reported data are based on the subgroup analysis of the hip fracture patients.

[d] Mean pain score calculated from four time points: the first entry at admission, six hours postop, 24 hr postop, and the last entry before discharge.

[e] Solely including *iv* opioid administration; no standardized oral opioid regimen reported.

d = days; *iv* = intravenous; MME = morphine milligram equivalent; NR = not reported; *po* = oral; postop = postoperative; SD = standard deviation

34.195;[A] $P < 0.001$), and a daily mean opioid consumption of 9.6 mg *vs* 7.8 mg (95% CI of the difference, -0.004 to 3.604;[A] $P = 0.05$).[27]

Three studies used a visual analogue scale (VAS) to assess patients' postoperative pain levels, directly comparing the control oral acetaminophen group to the intervention *iv* acetaminophen group.[3,4,27] Two studies were retrospective cohort studies,[3,27] and the remaining study was a prospective cohort study.[4] These three studies included 255 control patients and 279 intervention patients. With all patients receiving appropriate standardized analgesic medications, with the reduction in MME not at the expense of the patient's pain, only Bollinger *et al*. reported a significant VAS pain score reduction in the *iv* acetaminophen group *vs* the oral acetaminophen group (mean, 2.8 *vs* 4.2; 95% CI of the difference, 0.98 to 1.82;[A] $P < 0.001$).[27]

Physiotherapy sessions

Bollinger *et al*. reported the percentage of missed in-hospital physical therapy (PT) sessions as a surrogate marker for postoperative pain.[27] This study included 169 control patients and 157 intervention patients, and 27.5% were male. Comparing oral to *iv* acetaminophen, the latter group missed 10.4% sessions compared with 21.8% in the control group (95% CI of the difference, -7.232 to 30.032;[A] $P < 0.001$).[27]

Length of stay

Three studies reported the length of hospital stay.[3,27,28] All of these studies reported a significant decrease in the length of stay for patients administered *iv* acetaminophen (Table 2). Bollinger *et al*. and Connolly *et al*. directly compared oral and *iv* acetaminophen, with the length of stay at 4.4 days *vs* 3.8 days (95% CI of the difference, -0.033 to 1.233;[A] $P < 0.001$) and 8.47 days *vs* 6.37 days ($P = 0.04$), respectively.[3,27] Hansen *et al*. reported a mean difference of -0.55 days in the length of stay for the *iv* acetaminophen group ($P < 0.01$).[28]

Discharge home

Two studies comparing 227 control patients with 232 intervention patients reported the percentage of patients discharged home.[3,27] During hospitalization, patients who experienced adverse outcomes were discharged to a secondary care facility, such as an acute rehabilitation facility or a nursing institution.[27] Only Bollinger *et al*. described a significant difference between the two groups. They noted that 19% of patients were discharged home in the *iv* acetaminophen group compared with 7% in the oral acetaminophen group ($P < 0.001$).[27]

Readmission rate

In one study, Connolly *et al*. reported the readmission rate, comparing 58 control patients and 65 intervention patients.[3] The readmission rate was 18.5% in the *iv* acetaminophen group *vs* 27.6% in the control group; nevertheless, the difference was not statistically significant ($P = 0.23$).

Costs

One study by Hansen *et al*. compared the total cost of hospitalizations (USD); the authors compared 64,395 control patients on *iv* opioids with 17,928 intervention patients on *iv* acetaminophen. Calculating the systems-level cost of hospitalizations among 14 different departments, the authors reported a decrease of USD 879.60 for hip fracture patients administered *iv* acetaminophen *vs* those who received *iv* opioids. Nevertheless, this decrease was not statistically significant ($P > 0.01$).[28] The authors of this study predominantly attributed the decrease in hospital costs to the difference in length of stay between the groups.[28]

Delirium

Only one study (by Connolly *et al*.) reported delirium incidence by reviewing medical records, including various healthcare professionals' notes and the administered treatments.[3] Using a Chart-based Delirium Identification Instrument (CHART-DEL), the authors selected a "possible" level of delirium as a cutoff for a positive diagnosis.[29] Significantly fewer patients developed delirium when managed with *iv* acetaminophen (15.4%) than patients managed with oral acetaminophen (32.8%; $P = 0.02$).[3]

The same study also included the need for one-to-one supervision as a secondary outcome measure. The need for one-to-one supervision was lower in the *iv* acetaminophen group than in the oral acetaminophen group (9.2% *vs* 24.1%; $P = 0.03$).[3]

Safety/adverse effects

None of the studies reported adverse effects of *iv* acetaminophen compared with oral acetaminophen.

[A] The 95% CIs were computed post hoc based on aggregated data.

Table 3 Quality assessment: Newcastle-Ottawa Scale

	Selection				Comparability		Outcome			Overall quality score (max., 9)
	Representativeness of exposed cohort?	Selection of the nonexposed cohort?	Ascertainment of exposure?	Demonstration that outcome of interest was not present at start of study?	Study controls for type of hip fractures?	Study controls for age and sex?	Assessment of outcome?	Was follow-up long enough for outcome to occur?	Adequacy of follow-up of cohorts?	
Tsang, 2013[4]	*	*	*	*	-	-	*	-	-	5
Bollinger, 2015[27]	*	*	*	*	*	*	*	*	-	8
Hansen, 2016[28]	-	*	*	*	-	-	*	*	-	5
Connolly, 2020[3]	*	*	*	*	*	*	*	*	-	8

Quality assessment

Table 3 shows the quality scores of the studies. Two studies scored 8 out of 9,[3,27] while the other two studies scored 5 out of 9.[4,28] The main concerns with the latter studies were the lack of standardization regarding sex distribution between groups and the inadequacy of follow-up of the cohorts. Neither article by Tsang *et al*. nor Hansen *et al*. mentioned the exclusion criteria of pathologic fractures secondary to malignancy or metastasis. These studies also failed to match patients for age and sex in the two groups. Lastly, the study by Hansen *et al*. solely used billing codes to define analgesic exposures but provided little reference assessing the accuracy of this surrogate marker.

Discussion

Although the evidence is very limited, our results suggest that *iv* acetaminophen may improve analgesia, both pre- and postoperatively, as shown by the reduction of opioid medications consumed. Interestingly, despite the significant reduction in opioid consumption with *iv* acetaminophen, the VAS pain scores were similar or lower, suggesting that *iv* acetaminophen may provide sufficient analgesia to maintain the patients' pain relief. Additionally, the length of hospital stay was reduced when patients used *iv* acetaminophen. Nevertheless, the effect of *iv* acetaminophen on hospital discharge is unclear since the two studies reporting this outcome had conflicting results. In addition, the number of PT sessions missed, readmission rates, delirium, and costs were only reported in one study each.

The effects of *iv* acetaminophen on opioid reduction in other types of surgery, such as general surgery, have also been mixed.[17] Studies have found that the *iv* formulation is not more effective than oral acetaminophen in these patient populations. In elective joint arthroplasties, Studner *et al*. showed that oral acetaminophen produced more consistent results in opioid reduction, along with fewer reported opioid-related adverse effects than *iv* acetaminophen did.[14] The discrepancy in results between elective arthroplasties and nonelective fracture repair may arise for multiple reasons.[30] The most notable factor is the older patient population that undergoes hip fracture repair surgeries compared with elective arthroplasty. The average age of the patients included in our studies was 81.1 yr. As such, these patients have a higher burden of perioperative comorbidities and frailty. For instance, an elderly patient may have renal impairment, which prevents the use of nonopioid analgesic medications, such as nonsteroidal anti-inflammatory drugs. This patient population also has a

much higher risk of postoperative morbidity and mortality than elective joint arthroplasty patients.[31]

Of the two studies reporting the percentage of patients discharged home, only Bollinger *et al.* showed a significant increase with *iv* acetaminophen.[3,27] The correlation between analgesia and subsequent functional outcomes has been studied in other settings, including elective hip arthroplasty. For instance, Erlenwein *et al*. reported that maximal preoperative pain intensity independently influenced daily function six months after surgery.[31] The authors indicated that those patients with more persistent hip pain intensity had more limitations in daily activities.[31] One study in our review reported that patients using *iv* acetaminophen missed fewer PT sessions than those using oral acetaminophen did.[27] They concluded that postoperative pain, associated with prolonged bed rest, could disrupt PT sessions. This result may be clinically significant as increased participation in PT sessions suggests improvements in pain, potentially leading to the earlier recovery of their functional status. Further investigation on whether better analgesia improves subsequent functional outcomes, specifically in elderly hip fracture patients, is warranted. Thus, future studies investigating medication-induced side effects should also include clinical outcomes, such as the patients' ability to complete activities of daily living independently following orthopedic surgery.

Although the acquisition cost of both *iv* and oral acetaminophen is relatively low, widespread use of *iv* acetaminophen can lead to substantially higher costs. The price for *iv* acetaminophen varies depending on the country, region, and institution. Nevertheless, this cost may be mitigated if the *iv* formulation provides better analgesia, enabling quicker rehabilitation and reducing adverse outcomes, such as delirium, which may reduce the overall length of hospital stay.[32] Furthermore, one study showed that *iv* acetaminophen reduces postoperative delirium and the subsequent need for one-to-one supervision, but this study did not compare the costs associated with hospitalization.[3] In a study at our institution, delirium was correlated with a mean incremental episode-of-care cost of CAD 8,286 compared with patients who experienced no delirium.[33] A recent study from the USA reported that the cumulative healthcare costs attributable to delirium after major elective surgery were USD 44,291 per patient per year.[34] Thus, *iv* acetaminophen may reduce overall hospital costs when compared with the oral formulation.

Elderly hip fracture patients are at very high risk for delirium. Connolly *et al*. reported that delirium was reduced in hip fracture patients who received *iv* acetaminophen.[3] Although there are no randomized trials on *iv* acetaminophen in hip fracture patients, the effect of *iv* acetaminophen on reducing delirium was recently examined in cardiac surgery patients.[35] Cardiac surgery has a high incidence of postoperative delirium and postoperative neurocognitive disorders. A pilot randomized study (DEXACET) and the subsequent multicentre protocol proposal (PANDORA) explored the mitigating effect of *iv* acetaminophen on delirium in the cardiac surgical population.[35,36] The DEXACET study was the first randomized controlled trial to analyze the effects of *iv* acetaminophen on delirium outcomes. With a sample size of 120 patients, the authors showed that the use of *iv* acetaminophen significantly reduced the incidence of postoperative delirium (-18%; $P = 0.01$).[35] Although these results are encouraging, one of the major weaknesses of the DEXACET study's methodology is the use of a placebo rather than an active comparator such as oral acetaminophen.[37]

Thus, the study by Connolly *et al*. on hip fracture patients showing "significant reduction of delirium and hospital length of stay" provides preliminary evidence supporting the use of *iv* acetaminophen in reducing postoperative delirium.[3] Nevertheless, as the authors acknowledged, the retrospective methodology, the lack of follow-up, the "chart-based" diagnosis of delirium, and its "likelihood," instead of an actual diagnosis based on validated clinical tools, along with the use of a "before and after" study design with historical cohorts, limit the quality of this study. These factors could undermine the finding that delirium is reduced.

Limitations

The present systematic review has several limitations. First, our literature search yielded only four articles and lacked high-level evidence publications, such as prospective randomized controlled trials, which emphasizes the gap in the literature on this subject. Second, the analysis of many postoperative outcomes, such as delirium, was reported by only one study. Third, we could not conduct a meta-analysis because of heterogeneity, variable outcome definitions, inconsistencies between comparison groups, and different timelines for administration of *iv* acetaminophen (before *vs* after surgery). Fourth, the sample sizes of the studies included in our review were small, with only one study including more than 350 people. None of the studies reported 95% CIs for the pairwise difference in outcomes. Only one study provided aggregate data for us to calculate a 95% CI; however, the distribution assumption used when calculating the 95% CI from aggregate data may not match the actual distribution of the data very well and the calculated CI may be more conservative than the actual CI. In addition, none of the studies included pharmacokinetic/

pharmacodynamic analyses. Finally, one study received funding from the company that manufactures *iv* acetaminophen.[27]

Conclusion

There is some very limited low-level evidence that *iv* acetaminophen may decrease the use of preoperative and postoperative opioids and shorten the length of hospital stay. Nevertheless, there were few studies in this patient population, and all of the studies used historical controls. As such, our results should be interpreted with caution. Our review highlights a prominent gap in the literature regarding the efficacy of *iv* acetaminophen and its impact on postoperative outcomes. With the aging population and increasing numbers of hip fracture patients, improving the perioperative care of these vulnerable patients is essential. Therefore, adequately powered randomized controlled trials are needed to determine *iv* acetaminophen's efficacy in improving mortality, pain, activities of daily living, mobility, and health-related quality of life in elderly hip fracture patients.

Acknowledgements The authors would like to thank Drs. Hansen and Tsang for providing us with additional information.

Author contributions *Jenny Cho* and *Kristian McCarthy* performed title/abstract and full-text screening, data extraction, and data interpretation, created Tables and Figures, and wrote the manuscript. *Simone Schiavo* and *Binu Jacob* helped conceptualize the review and helped write and edit the manuscript. *Marina Engelsakis* conducted the literature search. *Michael Zywiel*, *Keyvan Karkouti*, *Stuart McCluskey*, and *Hance Clarke* edited the manuscript. *Jean Wong* conceptualized the review, helped with data interpretation, helped with study selection, and helped write and edit the manuscript.

Funding Department of Anesthesiology and Pain Medicine, Toronto Western Hospital, University Health Network, Toronto, ON, Canada.

Disclosures Hance Clarke and Keyvan Karkouti are supported by a Merit Research award from the University of Toronto, Department of Anesthesiology and Pain Medicine. Jean Wong reports grants from the Ontario Ministry of Health and Long-Term Care, and Merck Inc. outside of the submitted work. She is supported by a Merit Research award from the University of Toronto, Department of Anesthesiology and Pain Medicine. The remaining authors have no disclosures to report.

Editorial responsibility This submission was handled by Dr. Stephan K. W. Schwarz, Editor-in-Chief, *Canadian Journal of Anesthesia/Journal canadien d'anesthésie.*

References

1. *Johansen A, Golding D, Brent L, et al.* Using national hip fracture registries and audit databases to develop an international perspective. Injury 2017; 48: 2174–9.
2. *Dhanwal DK, Dennison EM, Harvey NC, Cooper C.* Epidemiology of hip fracture: worldwide geographic variation. Indian J Orthop 2011; 45: 15–22.
3. *Connolly KP, Kleinman RS, Stevenson KL, Neuman MD, Mehta SN.* Delirium reduced with intravenous acetaminophen in geriatric hip fracture patients. J Am Acad Orthop Surg 2020; 28: 325–31.
4. *Tsang KS, Page J, Mackenney P.* Can intravenous paracetamol reduce opioid use in preoperative hip fracture patients? Orthopedics 2013; 36: 20–4.
5. *Griffiths R, Babu S, Dixon P, et al.* Guideline for the management of hip fractures 2020: guideline by the Association of Anaesthetists. Anaesthesia 2020; 76: 225–37.
6. *Fillingham YA, Hannon CP, Erens GA, AAHKS Anesthesia & Analgesia Clinical practice Guideline Workgroup, Hamilton WG, Della Valle CJ.* Acetaminophen in total joint arthroplasty: the clinical practice guidelines of the American Association of Hip and Knee Surgeons, American Society of Regional Anesthesia and Pain Medicine, American Academy of Orthopaedic Surgeons, Hip Society, and Knee Society. J Arthroplasty 2020; 35: 2697–9.
7. *Oscier C, Bosley N, Milner Q.* Paracetamol: a review of three routes of administration. Update Anaesth 2007; 23: 112–4.
8. *Raffa RB, Pawasauskas J, Pergolizzi Jr JV, et al.* Pharmacokinetics of oral and intravenous paracetamol (acetaminophen) when co-administered with intravenous morphine in healthy adult subjects. Clin Drug Investig 2018; 38: 259–68.
9. *Singla NK, Parulan C, Samson R, et al.* Plasma and cerebrospinal fluid pharmacokinetic parameters after single-dose administration of intravenous, oral, or rectal acetaminophen. Pain Pract 2012; 12: 523–32.
10. *Owens KH, Murphy PG, Medlicott NJ, et al.* Population pharmacokinetics of intravenous acetaminophen and its metabolites in major surgical patients. J Pharmacokinetic Pharmacodyn 2014; 41: 211–21.
11. *Liukas A, Kuusniemi K, Aantaa R, et al.* Pharmacokinetics of intravenous paracetamol in elderly patients. Clin Pharmacokinet 2011; 50: 121–9.
12. *Atkinson H, Stanescu I, Frampton C, Salem I, Beasley C, Robson R.* Pharmacokinetics and bioavailability of a fixed-dose combination of ibuprofen and paracetamol after intravenous and oral administration. Clin Drug Investig 2015; 35: 625–32.
13. *AVIR Pharma Inc.* Acetaminophen injection product monograph. Available from URL: https://www.avirpharma.com/pdf/Product-Monograph-AcetaInj.pdf (accessed February 2022).
14. *Stundner O, Poeran J, Ladenhauf HN, et al.* Effectiveness of intravenous acetaminophen for postoperative pain management in hip and knee arthroplasties: a population-based study. Reg Anesth Pain Med 2019; 44: 565–72.
15. *O'Neal J, Freiberg A, Yelle M, et al.* Intravenous vs oral acetaminophen as an adjunct to multimodal analgesia after total knee arthroplasty: a prospective, randomized, double-blind clinical trial. J Arthroplasty 2017; 32: 3029–33.
16. *Sun L, Zhu X, Zou J, Li Y, Han W.* Comparison of intravenous and oral acetaminophen for pain control after total knee and hip arthroplasty: a systematic review and meta-analysis. Medicine (Baltimore) 2018; https://doi.org/10.1097/md.0000000000009751.

17. *Wasserman I, Poeran J, Zubizarreta N, et al.* Impact of intravenous acetaminophen on perioperative opioid utilization and outcomes in open colectomies: a claims database analysis. Anesthesiology 2018; 129: 77–88.
18. *Needleman SM*. Safety of rapid intravenous infusion of acetaminophen. Proc (Bayl Univ Med Cent) 2013; 26: 235–8.
19. *Higgins JP, Thomas J, Chandler J, et al*. Cochrane handbook for systematic reviews of interventions, 2nd ed. Chichester: John Wiley & Sons; 2021.
20. *Higgins JP, Lasserson T, Chandler J, et al*. Methodological expectations of cochrane intervention reviews (MECIR) 2022. Available from URL: https://community.cochrane.org/mecir-manual (accessed February 2022).
21. *Page MJ, McKenzie JE, Bossuyt PM, et al*. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. PLOS Med 2021. DOI: https://doi.org/10.1371/journal.pmed.1003583.
22. *McGowan J, Sampson M, Salzwedel DM, Cogo E, Foerster V, Lefebvre C*. PRESS peer review of electronic search strategies: 2015 guideline statement. J Clin Epidemiol 2016; 75: 40–6.
23. *Grossetta Nardini HK, Wang L.* The Yale MeSH Analyzer [Internet]. New Haven, CT: Cushing/Whitney Medical Library; 2021. Available from URL: https://mesh.med.yale.edu/help#how-to-cite (accessed March 2022).
24. *Wells GA, Shea B, O'Connell D, et al.* The Newcastle-Ottawa scale (NOS) for assessing the quality of nonrandomised studies in meta-analysis. Available from URL: http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp (accessed February 2022).
25. *Social Science Statistics*. Independent samples confidence interval calculator. Available from URL: https://www.socscistatistics.com/confidenceinterval/default4.aspx (accessed February 2022).
26. *Dowell D, Haegerich TM, Chou R*. CDC guideline for prescribing opioids for chronic pain—United States, 2016. JAMA 2016; 315: 1624–45.
27. *Bollinger AJ, Butler PD, Nies MS, Sietsema DL, Jones CB, Endres TJ*. Is scheduled intravenous acetaminophen effective in the pain management protocol of geriatric hip fractures? Geriatr Orthop Surg Rehabil 2015; 6: 202–8.
28. *Hansen RN, Pham A, Strassels SA, Balaban S, Wan GJ*. Comparative analysis of length of stay and inpatient costs for orthopedic surgery patients treated with *iv* acetaminophen and *iv* opioids vs. *iv* opioids alone for postoperative pain. Adv Ther 2016; 33: 1635–45.
29. *Xu G, Fong TG, Yee J, Inouye SK*. Delirium identification: a training guide to a chart-based delirium instrument 2011. Available from URL: http://www.hospitalelderlifeprogram.org/uploads/disclaimers/CHART-DEL_Manual_03-27-2015.pdf (accessed February 2022).
30. *Fillingham YA, Hannon CP, Erens GA, et al.* The efficacy and safety of acetaminophen in total joint arthroplasty: systematic review and direct meta-analysis. J Arthroplasty 2020; 35: 2715–29.
31. *Erlenwein J, Müller M, Falla D*, et al. Clinical relevance of persistent postoperative pain after total hip replacement; a prospective observational cohort study. J Pain Res 2017; 10: 2183–93.
32. *Yeh YC, Reddy P.* Clinical and economic evidence for intravenous acetaminophen. Pharmacotherapy 2012; 32: 559–79.
33. *Zywiel MG, Hurley RT, Perruccio AV, Hancock-Howard RL, Coyte PC, Rampersaud YR.* Health economic implications of perioperative delirium in older patients after surgery for a fragility hip fracture. J Bone Joint Surg Am 2015; 97: 829–36.
34. *Gou RY, Hshieh TT, Marcantonio ER, et al.* One-year medicare costs associated with delirium in older patients undergoing major elective surgery. JAMA Surg 2021; 156: 430–42.
35. *Subramaniam B, Shankar P, Shaefi S, et al.* Effect of intravenous acetaminophen vs placebo combined with propofol or dexmedetomidine on postoperative delirium among older patients following cardiac surgery. JAMA 2019; 321: 686–96.
36. *Khera T, Mathur PA, Banner-Goodspeed VM, et al.* Scheduled prophylactic 6-hourly *iv* acetaminophen to prevent postoperative delirium in older cardiac surgical patients (PANDORA): protocol for a multicentre randomised controlled trial. BMJ Open 2021; https://doi.org/10.1136/bmjopen-2020-044346.
37. *Subramaniam B, Shankar P, Mueller A.* Intravenous acetaminophen for postoperative delirium—reply. JAMA 2019; https://doi.org/10.1001/jama.2019.6134.