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Single-Dose Intravenous Paracetamol for Prevention or Treatment of Postoperative Pain: A Systematic Review

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ABSTRACT

Background: One of the main goals of postoperative treatment is providing effective analgesia. Both adult and pediatric patients routinely utilize paracetamol as an analgesic and antipyretic.

Aim and Objectives: to assess the impact of systemic acetaminophen on the results of postoperative pain management when the medication was administered as a prophylactic analgesic.

Methods: This systematic review included studies that was a blinded or unblinded RCT either with parallel or cross-over design, human RCTs, the intervention group received IV paracetamol/acetaminophen, While a placebo or an active comparator was given to the comparison group. Two authors independently searched the online databases including Web of Science, Cochrane Library, Scopus MEDLINE, and EMBASE by combing MeSH and text keywords of "paracetamol and acetaminophen, I.V. intake, postoperative pain".

Conclusion: When taken as a single dosage as part of a preventative program, systemic acetaminophen is a useful strategy to enhance postoperative pain outcomes. Systemic acetaminophen also lessens vomiting and/or nausea after surgery. It is recommended that medical professionals take into account administering a solitary prophylactic dosage of systemic acetaminophen to mitigate discomfort in surgical patients.

Keywords: Paracetamol, postoperative pain, analgesia, Nonsteroidal anti-inflammatory drugs (NSAIDs), systematic review.

INTRODUCTION

One of the main goals of postoperative treatment is providing effective analgesia. Analgesia, whether excessive or insufficient, may worsen myocardial ischemia and raise the risk of myocardial infarction, pulmonary or thromboembolic problems, persistent pain after surgery, a weakened immune system, a worse quality of life, and a delayed hospital release. **(1).**

Early mobility and discharge are the main goals of contemporary postoperative analgesia. The adverse effects of opioid analgesics, such as respiratory depression, nausea/vomiting, gastrointestinal disorder, and urine retention, limit the use of high dosages of these medications. **(2, 3).**

As a result, adjuvant medicine-based balanced or multimodal analgesia has emerged lately. Avoiding excessive opioid dosages and associated negative effects has led to an increased use of neural blockade,

epidural analgesia, wound infiltration with local anesthetics, and non-opioid intravenous (IV) medications alone or in conjunction with opioid analgesics. **(4)**.

Acetaminophen, often known as paracetamol, and nonsteroidal anti-inflammatory medications (NSAIDs) have been used for this purpose. 4 Both adult and pediatric patients routinely utilize paracetamol as an analgesic and antipyretic. Via the cyclooxygenase (COX) pathway, prostaglandin inhibition causes its impact on the central nervous system. IV paracetamol is used for perioperative pain treatment either by itself or in conjunction with opioids. **(5, 6).**

Enhancing the results of postoperative pain management seems to be a key component in improving patients' quality of recovery after surgery. **(7).** Preventative analgesic techniques may help surgery patients with better postoperative pain control. **(8).**

However, when considered as a prophylactic analgesic approach, pharmaceutical therapies that are successful in treating postoperative pain may not be as beneficial. **(9).**

Moreover, a systemic analgesic medication may only be administered once due to unfavorable side effects or the quick hospital release of ambulatory patients. **(10)**.

Although systemic acetaminophen has been around for a while in Europe, it was just recently made accessible in the US. With varied degrees of success, many clinical investigations have looked at the use of systemic acetaminophen in the perioperative context. Furthermore, prior quantitative systematic studies failed to distinguish between the drug's preventative and therapeutic effects. **(11, 12).**

The effectiveness of systemic acetaminophen administered as a single dosage in preventing postsurgical pain is uncertain. This study's primary goal was to assess how systemic acetaminophen affected postoperative pain outcomes when it was used as a preventative analgesic.

PATIENTS AND METHODS

Standards by which research were evaluated for this review:

Search strategy : Two authors independently searched the online databases including Web of Science, Cochrane Library, Scopus MEDLINE, and EMBASE by combing MeSH and text keywords of "paracetamol and acetaminophen, I.V. intake, postoperative pain". Only RCTs done on people and published in English were included in the electronic searches. In order to find further research, we also manually went through the reference lists of the clinical trials that were included and earlier evaluations.

Selection criteria :We selected studies according to the following criteria: the study was a blinded or unblinded RCT either with parallel or cross-over design, human RCTs, the intervention group received IV paracetamol/acetaminophen, whereas a placebo or an active comparator was given to the comparison group, research that provided relevant results data, such as the rescue dosage, time to rescue, total dosage of rescue, patient satisfaction, ICU length of stay (LOS), hospital LOS, and visual analogue scale (VAS) for intervention and comparison groups.

Data extraction: the name of author, year of publication, study location, type of study, sample size in intervention and comparison groups, dose of supplement, type of placebo and outcomes.

RESULTS

Table 1 Baseline features of the studies that are included:

Authors (Ref)	Publication year	Country	Sample size (control/ intervention)	Type of study	Age (y) (control, intervention)
Moon et al., (13)	2011	South Korea	35/36	Double-blind, placebo-controlled, randomised clinical trial	45.5 ± 6.7, 44.5 ± 5.3 years
Olonisakin et al., (14)	2012	Nigeria	28/28	Randomized clinical trial	≥ 18 years
Khalili et al., (15)	2013	Iran	50/25	Randomized, double-blind clinical trial	37.8 ±12.9, 36.8 ±14.8 years
Eftekharian et al., (16)	2014	Iran	40/40	controlled, randomized, parallel-group, single-blind study	29.08 ± 8.77, 29.85 ± 8.07 years

Truelove et al., (17)	2020	USA	11/33	Randomized, double-blind, and placebo-controlled	55, 57, 48, 43 years

Table 2. The main findings of the included studies:

Authors (Ref)	Procedures	Treatments	outcomes
Moon et al., (13)	Hysterectomy	Acetaminophen 2 g before beginning of surgery, placebo (normal saline 200 ml).	At all times, group A's overall hydromorphone intake was much less than group C's. In group A, the overall hydromorphone intake during a 24-hour period was 30% lower. Acetaminophen premedication decreased the amount of hydromorphone used and the adverse effects connected to opioids in patients having abdominal hysterectomy, but it had no discernible impact on pain severity.
Olonisakin et al., (14)	Gynecologic surgery	Following surgery, the placebo group received 1 g of acetaminophen (normal saline).	Iv paracetamol enhanced patient satisfaction and decreased opioid side effects while simultaneously improving analgesia and reducing morphine intake in the early postoperative period.
Khalili et al., (15)	Lower extremity orthopedic surgery	Acetaminophen 15 mg/kg before beginning of surgery or at the end of surgery, placebo (IV normal saline 100 mL)	Six hours after surgery, pain ratings were lower in the acetaminophen preemptive and preventative groups than in the placebo group. The preemptive and preventative acetaminophen groups had a little longer average time to beginning analgesic necessity than the control group. Preventive and preemptive acetaminophen administration may improve analgesia and reduce the need for postoperative analgesics in individuals having lower extremities surgery under spinal anesthesia.
Eftekharian et al., (16)	Maxillofacial surgery	Single dose paracetamol, placebo (normal saline)	For the first six hours after open reduction of mandibular fractures, a single dosage of paracetamol effectively relieves discomfort. The amount of discomfort in both the treatment and control groups is significantly influenced by time. Additionally, in both groups, the length of the operation is positively correlated with the intensity of the pain.
Truelove et al., (17)	Orthopedic Surgery	Placebo (Group 1), IV ketorolac (Group 3), IV acetaminophen (Group 2), or both (Group 4).	The use of intravenous acetaminophen for pain management after endoscopic carpal tunnel release is supported by minor statistically substantial variations in postoperative pain and narcotic intake.

DISCUSSION

Inadequate pain treatment is widespread and may have serious consequences, even though pain is a normal component of the postoperative experience. In order to avoid the altered processing of afferent input that exacerbates postoperative pain, preemptive analgesia involves administering an analgesic prior to a painful stimulus. An effective form of preemptive analgesia should also inhibit the establishment of central sensitization brought on by incisional and inflammatory injuries. **(18).**

Preventive analgesia operates on the premise that total blockage of pain and afferent signals from the surgical site from the moment of incision to the point of ultimate wound healing is the only method to avoid central sensitization. This idea puts more emphasis on the length and severity of the analgesic intervention than on the timing of it. **(19, 20).**

When treating acute pain, the most often given analgesic is paracetamol. Its safe use in individuals with a history of peptic ulcers or asthma, as well as the fact that it does not interfere with platelet function, are its main benefits over non-steroidal anti-inflammatory medicines (NSAIDs). **(21)**. The effectiveness of oral paracetamol for treating acute pain is confirmed by systematic reviews of randomized controlled trials (RCTs). **(22, 23).**

There are three ways to administer paracetamol: orally, rectalally, or intravenously. When compared to the intravenous method, the rectal paracetamol suppository is more costly and has a slower onset and variable absorption. When compared to the oral route at a comparable dosage, intravenous paracetamol has a quicker start of analgesia and more efficiently achieves the plasma analgesic level with a bigger peak plasma level. **(24)**.

Furthermore, there is reduced chance of liver damage and better predictable pharmacodynamics and pharmacokinetics with intravenous paracetamol. The danger associated with intravenous cannulation, which includes the potential for infection and thrombophlebitis, is the drawback of intravenous paracetamol. The recommended dosage for intravenous infusion is 1 g or 15 mg/kg every 6 hours, with a maximum dose of 4,000 mg per day in children over the age of 13 and adults weighing less than 50 kg. Oral paracetamol is easy to use and reasonably priced. Furthermore, the majority of patients tolerate taking oral drugs with ease and are accustomed with them. Oral paracetamol, however, is not recommended for patients recovering from surgery right away. **(25, 26).**

A research by **Eftekharian et al.,** revealed that After surgery for mandibular fractures, pain might be relieved with a single IV dosage of paracetamol. **(16).** According to reports, a single dosage of 1 mg of intravenous paracetamol and 75 mg of intramuscular diclofenac sodium was equally effective in controlling postoperative pain after orthognathic surgery. **(27).** Furthermore, a comprehensive study demonstrated that using NSAIDs and paracetamol together provided superior analgesia for immediate postoperative pain than using either medication alone. **(28).** Comparably, **Sinatra et al.'s** multicenter assessment of IV acetaminophen after hip and knee arthroplasty discovered an important variation in the IV acetaminophen group's real consumption and time to rescue medicine when compared to the placebo group. **(29).** It has been shown that intravenous paracetamol significantly reduces the amount of opioids used after orthognathic surgery and reduces the need for morphine by 33% over the course of 24 hours after major orthopedic surgery. **(30,31).** Furthermore, a single intravenous injection of 1 g paracetamol decreased pain by up to 50% in 37% of patients and reduced the need for opioids by 26% over a 4-hour period when compared to a placebo, according to a Cochrane analysis by **McNicol et al**. **(32).**

CONCLUSION

In conclusion, When taken as a single dosage as part of a preventative program, systemic acetaminophen is a useful strategy to enhance postoperative pain outcomes. Systemic acetaminophen also lessens vomiting and/or nausea after surgery. It is recommended that medical professionals take into account administering a solitary prophylactic dosage of systemic acetaminophen to mitigate discomfort in surgical patients.

REFERENCES

1. Gan TJ. Poorly controlled postoperative pain: prevalence, consequences, and prevention. J Pain Res. 2017;2287–98.
2. Hyland SJ, Brockhaus KK, Vincent WR, Spence NZ, Lucki MM, Howkins MJ, et al. Perioperative pain management and opioid stewardship: a practical guide. In: Healthcare. MDPI; 2021. p. 333.

3. Mitra S, Carlyle D, Kodumudi G, Kodumudi V, Vadivelu N. New advances in acute postoperative pain management. Curr Pain Headache Rep. 2018;22:1–11.
4. Kaye AD, Urman RD, Rappaport Y, Siddaiah H, Cornett EM, Belani K, et al. Multimodal analgesia as an essential part of enhanced recovery protocols in the ambulatory settings. J Anaesthesiol Clin Pharmacol. 2019;35(Suppl 1):S40–5.
5. Ohashi N, Kohno T. Analgesic effect of acetaminophen: a review of known and novel mechanisms of action. Front Pharmacol. 2020;11:580289.
6. Ayoub SS. Paracetamol (acetaminophen): A familiar drug with an unexplained mechanism of action. Temperature. 2021;8(4):351–71.
7. Kim SY, Kim JM, Lee JH, Song BM, Koo BN. Efficacy of intraoperative dexmedetomidine infusion on emergence agitation and quality of recovery after nasal surgery. Br J Anaesth. 2013;111(2):222–8.
8. Barreveld A, Witte J, Chahal H, Durieux ME, Strichartz G. Preventive analgesia by local anesthetics: the reduction of postoperative pain by peripheral nerve blocks and intravenous drugs. Anesth Analg. 2013;116(5):1141–61.
9. De Oliveira Jr GS, Agarwal D, Benzon HT. Perioperative single dose ketorolac to prevent postoperative pain: a meta-analysis of randomized trials. Anesth Analg. 2012;114(2):424–33.
10. Waldron NH, Jones CA, Gan TJ, Allen TK, Habib A. Impact of perioperative dexamethasone on postoperative analgesia and side-effects: systematic review and meta-analysis. Br J Anaesth. 2013;110(2):191–200.
11. Tzortzopoulou A, McNicol ED, Cepeda MS, Francia MBD, Farhat T, Schumann R. Single dose intravenous propacetamol or intravenous paracetamol for postoperative pain. Cochrane Database Syst Rev. 2011;(10).
12. McNicol ED, Tzortzopoulou A, Cepeda MS, Francia MBD, Farhat T, Schumann R. Single-dose intravenous paracetamol or propacetamol for prevention or treatment of postoperative pain: a systematic review and meta-analysis. Br J Anaesth. 2011;106(6):764–75.
13. Moon YE, Lee YK, Lee J, Moon DE. The effects of preoperative intravenous acetaminophen in patients undergoing abdominal hysterectomy. Arch Gynecol Obstet. 2011;284:1455–60.
14. Olonisakin RP. Morphine-sparing effect of intravenous paracetamol for post operative pain management following gynaecological surgery. Afr J Med Med Sci. 2012;41(4):429–36.
15. Khalili G, Janghorbani M, Saryazdi H, Emaminejad A. Effect of preemptive and preventive acetaminophen on postoperative pain score: a randomized, double-blind trial of patients undergoing lower extremity surgery. J Clin Anesth. 2013;25(3):188–92.
16. Eftekharian H, Tabrizi R, Kazemi H, Nili M. Evaluation of a single dose intravenous paracetamol for pain relief after maxillofacial surgery: a randomized clinical trial study. J Maxillofac Oral Surg. 2014;13:478–82.
17. Truelove EC, Urrechaga E, Fernandez C, Fowler JR. Prospective, double-blind evaluation of perioperative intravenous acetaminophen and ketorolac for postoperative pain and opioid consumption after endoscopic carpal tunnel release. HAND. 2021;16(6):785–91.
18. Vadivelu N, Mitra S, Schermer E, Kodumudi V, Kaye AD, Urman RD. Preventive analgesia for postoperative pain control: a broader concept. Local Reg Anesth. 2014;17–22.
19. Dahl JB, Kehlet H. Preventive analgesia. Curr Opin Anesthesiol. 2011;24(3):331–8.
20. Katz J, Clarke H, Seltzer Z. Preventive analgesia: quo vadimus? Anesth Analg. 2011;113(5):1242–53.
21. Bandey S, Singh V. Comparison between IV paracetamol and tramadol for postoperative analgesia in patients undergoing laparoscopic cholecystectomy. J Clin diagnostic Res JCDR. 2016;10(8):UC05.
22. Toms L, McQuay HJ, Derry S, Moore RA. Single dose oral paracetamol (acetaminophen) for postoperative pain in adults. Cochrane database Syst Rev. 2008;(4).
23. Perrott DA, Piira T, Goodenough B, Champion GD. Efficacy and safety of acetaminophen vs ibuprofen for treating children's pain or fever: a meta-analysis. Arch Pediatr Adolesc Med. 2004;158(6):521–6.
24. Mahajan L, Mittal V, Gupta R, Chhabra H, Vidhan J, Kaur A. Study to compare the effect of oral, rectal, and intravenous infusion of paracetamol for postoperative analgesia in women

undergoing cesarean section under spinal anesthesia. Anesth Essays Res. 2017;11(3):594–8.
25. Raffa RB, Pawasauskas J, Pergolizzi J V, Lu L, Chen Y, Wu S, 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.
26. Jibril F, Sharaby S, Mohamed A, Wilby KJ. Intravenous versus oral acetaminophen for pain: systematic review of current evidence to support clinical decision-making. Can J Hosp Pharm. 2015;68(3):238.
27. Öncül AMT, Çimen E, Küçükyavuz Z, Cambazoğlu M. Postoperative analgesia in orthognathic surgery patients: diclofenac sodium or paracetamol? Br J Oral Maxillofac Surg. 2011;49(2):138–41.
28. Ong CKS, Seymour RA, Lirk P, Merry AF. Combining paracetamol (acetaminophen) with nonsteroidal antiinflammatory drugs: a qualitative systematic review of analgesic efficacy for acute postoperative pain. Anesth Analg. 2010;110(4):1170–9.
29. Sinatra RS, Jahr JS, Reynolds L, Groudine SB, Royal MA, Breitmeyer JB, et al. Intravenous acetaminophen for pain after major orthopedic surgery: an expanded analysis. Pain Pract. 2012;12(5):357–65.
30. Phillips SJ, Peck CJ, Pourtaheri N, Reategui A, Carney M, Dinis J, et al. Decreasing inpatient opioid use following orthognathic surgery. J Craniofac Surg. 2021;32(8):2808–11.
31. Sinatra RS, Jahr JS, Reynolds LW, Viscusi ER, Groudine SB, Payen-Champenois C. Efficacy and safety of single and repeated administration of 1 gram intravenous acetaminophen injection (paracetamol) for pain management after major orthopedic surgery. J Am Soc Anesthesiol. 2005;102(4):822–31.
32. McNicol ED, Ferguson MC, Haroutounian S, Carr DB, Schumann R. Single dose intravenous paracetamol or intravenous propacetamol for postoperative pain. Cochrane Database Syst Rev. 2016;(5).