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Intravenous acetaminophen (paracetamol) for post craniotomy pain: systematic review

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ABSTRACT

Background: Up to 80% of people who have craniotomies may have moderate to severe pain that lasts for many days after the procedure. Acetaminophen administered intravenously has been developed to manage pain in acute situations.

Aim: The purpose of the current research was to ascertain how intravenous paracetamol treatment affected individuals having elective craniotomies in terms of pain after the procedure.

Patients and methods: This systematic review included blinded or unblinded RCT either with parallel or cross-over design, human RCTs with patients undergoing craniotomy, the intervention group received IV paracetamol/acetaminophen, whereas 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, craniotomy patients".

Results: The present study demonstrated that IV acetaminophen helps patients undergoing craniotomies have far less discomfort after surgery. The usage of opioids was not significantly reduced when IV acetaminophen was added to treat postoperative craniotomy pain. Within the first 24 hours after surgery, both groups had comparable timeframes to get rescue drugs, volumes of rescue medications, durations of stay in the ICU and hospital, numbers of successful neurological examinations, delirium, sedation, satisfaction ratings, VAS pain scores, and temperatures.

Conclusion: For patients having an elective craniotomy, intravenous paracetamol is a safe and effective way to manage postoperative pain; nevertheless, there are no advantages in terms of hospital stay, opioid need, or patient satisfaction.

Key words: Intravenous acetaminophen, post craniotomy pain, patient-controlled analgesia (PCA), Opioids.

INTRODUCTION

Following craniotomies, patients often feel somatic postoperative discomfort that is superficial to the site of the incision. Some have described it as throbbing or pulsing, similar to tension headaches. Untreated or inadequately managed persistent pain may lead to severe anxiety, hypertension, chills, and vomiting, which might further escalate intracranial pressure and result in hemorrhage. **(1).**

Furthermore, the nature of acute pain may herald the development of central sensitization and chronic pain. For this reason, proper pain management during craniotomy treatments may help patients feel more comfortable while also minimizing some of the unfavorable side effects of ongoing pain. **(2).**

Depending on the kind of treatment done, pain may range from mild to severe in up to 80% of craniotomy patients and last for many days after the procedure. For neurosurgical patients, opioids are the main analgesic used to manage pain after surgery. Patient-controlled analgesia (PCA) devices or nursing personnel may sporadically deliver these analgesics. Nevertheless, there are serious adverse effects linked to opioids, such as respiratory depression, nausea, vomiting, and distortion of the neurological evaluation. **(3, 4).**

The effectiveness and safety of opioid-based PCA after cranial surgery have been shown, despite these possible adverse effects. When used in conjunction with other analgesics like nonsteroidal anti-inflammatory drugs (NSAIDs), opioids may decrease systemic opioid levels and, therefore, the likelihood of side effects. **(5, 6).** The intravenous formulation of acetaminophen has been developed in the last ten years for the purpose of controlling pain in acute settings. It has been shown to be linked to the least amount of problems and side effects as well as adequate pain management. **(7).** The medication, which is non-opioid and has a long half-life, good bioavailability, and few adverse effects, is accessible worldwide and may be used to treat postoperative pain in a variety of contexts. **(8).**

Intraoperative intravenous (IV) acetaminophen administration has been shown to improve postoperative pain management and decrease opioid use, particularly in procedures involving the abdomen, pelvis, and joints. **(9, 10).**

Its effectiveness or usefulness in patients after craniotomy, however, has not been well studied; the few randomized clinical studies (RCTs) that have been conducted on the subject have produced inconsistent findings. The current research sought to ascertain the effects of intravenous paracetamol administration on post-craniotomy pain in patients having elective craniotomy, given the significance of effective post-craniotomy pain treatment using acceptable medications.

PATIENTS AND METHODS

Study selection criteria for this review:

Search strategy: Two authors independently looked 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, craniotomy patients". 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 with patients undergoing craniotomy, 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, type of study, study location, sample size in intervention and comparison groups, dose of supplement, type of placebo and outcomes.

RESULTS

Table 1 Baseline Characteristics of the included studies:

Study ID	Year	Sample size (control/ intervention)	Country	Type of study	Surgical Procedure	Age (y) (control, intervention)
Verchère et al., (11)	2002	29/27	France	Prospective randomized, blinded, controlled study	Supratentorial craniotomies	48.8 ± 15, 45 ± 18 years
Dilmen et al.,(12)	2016	18/20	Turkey	Prospective, randomized, double blinded, placebo-controlled study	Supratentorial craniotomy	41.90 ±15.47, 49.27 ± 13.86 years
Sivakumar et al., (13)	2018	102/102	Canada	Randomized, double-blinded, placebo-controlled, prospective, single-center study	Supratentorial craniotomy	50.6, 50.3 years
Greenberg et al., (14)	2018	65/66	USA	Randomized controlled clinical trial.	Craniotomy	59±13, 56±15 years
Artime et al., (15)	2018	41/45	USA	Randomized, double-blind, placebo-controlled prospective clinical investigation	Craniotomy	50.0±16.3, 51.5±14.4 years

Table 2 The main findings of the included studies:

Study ID	Treatments	Outcomes
Verchère et al., (11)	30 mg/kg Intravenous paracetamol plus 0.15 mg/kg nalbuphine	In the P group, postoperative analgesia did not work. With the exception of hour 1, when nalbuphine was more effective, the two remaining groups' VAS values were equal, indicating that postoperative analgesia was effective. However, obtaining this outcome required a much higher tramadol dosage than nalbuphine (P <.05. Although there

		were more occurrences of nausea and vomiting in the PT group, there was no discernible difference. After supratentorial neurosurgery, pain management is important, and the patient will not get better with paracetamol by itself. It seems that adding either tramadol or nalbuphine to paracetamol will provide sufficient analgesia.
Dilmen et al.,(12)	1000 mg Intravenous paracetamol-every 6 h	According to their study's findings, patients having supratentorial craniotomy who received morphine-based patient-controlled analgesia (PCA) were able to avoid moderate to severe postoperative pain without experiencing any potentially fatal side effects as long as they were well monitored during the first 24 hours after surgery. Additional metamizole, paracetamol, and dexketoprofen usage had no discernible impact on pain severity. Despite the fact that dexketoptofen and metamizole both showed lower morphine consumption than the control group at every time point, a statistical demonstration was not possible.
Sivakumar et al., (13)	1000 mg Intravenous Acetaminophen-Each 8 hours until 48 h after surgery	The usage of opioids was not significantly reduced when IV acetaminophen was added to treat postoperative craniotomy pain. Secondary measures such as time to ambulation, time to discharge, cranial imaging events, and nausea episodes did not show any significant differences. There was evidence of an improvement in overall pain management. The use of intravenous acetaminophen to relieve postoperative craniotomy pain is only partially supported by these findings. Considering the significance of minimizing opioid usage while maximizing pain management in individuals who have had craniotomies.
Greenberg et al., (14)	1000 mg Intravenous Acetaminophen-Each 6 hours until 18 h after surgery	They showed that, in comparison to the placebo group, a greater proportion of patients in the IV acetaminophen group (15.2% vs. 6.2%) did not need opioids within the first 24 hours postoperatively, but this difference was not statistically significant. Within the first 24 hours after surgery, both groups had comparable timeframes to get rescue drugs, volumes of rescue medications, durations of stay in the ICU and hospital, numbers of successful neurological examinations, delirium, sedation, satisfaction ratings, VAS pain scores, and temperatures.
Artime et al., (15)	1000 mg Intravenous Acetaminophen-Each 6 hours until 24 h after surgery	The IV acetaminophen group and the placebo group did not vary in the amount of morphine equivalents consumed in the 24 hours after surgery. Between the two therapy groups, there was no statistically substantial change in the pain scores on the visual analog scale. On a scale of 1 to 10, the IV acetaminophen group's patient satisfaction with overall

		postoperative treatment of pain was considerably greater than that of the placebo group. Secondary outcomes, including as the frequency of opioid-related side effects, did not significantly vary. They came to the conclusion that while IV acetaminophen did not exhibit an opioid-sparing effect in patients over the 24 hours after craniotomy operations, it was linked to increased patient satisfaction with reference to overall pain management.

DISCUSSION

Paracetamol is currently considered a safe and feasible agent for pain control, either in acute setting or for postoperative care. Effective post-craniotomy pain treatment is essential for lowering complications, improving patient comfort, improving results, and shortening hospital stays. **(16, 17).**

Although the efficiency of IV paracetamol in postoperative pain management has been vastly investigated, its efficacy and safety in neurosurgical patients undergoing craniotomy is yet to be identified. Up to now, 5 standard RCTs has addressed the issue with conflicting results which does not lead to a standard level of evidence **(11-15).** Thus, the goal of the current systematic review to determine the efficacy and safety of intravenous paracetamol in patients undergoing elective craniotomy.

A systemic review and meta-analysis done by **Ghaffarpasand et al.,** suggested that preoperative administration of intravenous paracetamol was significantly associated with reduced rescue dose, total dosage of rescue, ICU length of stay, visual analogue scale and increased satisfaction and comfort in patients undergoing elective craniotomy. However, they have found that the paracetamol administration did not affect the time to rescue and hospital length of stay **(18).**

Intravenous opioids have long been utilized as first-line medication for postoperative pain control in those experiencing moderate to severe pain. however, their use in NCC units and neurosurgical patients is limited by its side effects of neurological status deterioration and miosis which makes the patients clinical evaluation unreliable and hard **(19).**

In addition, inappropriate post-craniotomy pain control will result in patients' discomfort, secondary intracranial hematoma formations and raised length of ICU and hospitalization. Paracetamol, has gained a great popularity during the previous decade for acute pain control especially in operation room setting being associated with appropriate pain control, least side effects and wide toxic window **(20, 21).**

Previously, **Smyth et al.,** demonstrated that early postoperative oral acetaminophen in children undergoing Chari malformation decompression was associated with reduced postoperative pain and length of hospitalization. However, as most patients undergoing craniotomy have postoperative nausea and vomiting, administration of oral acetaminophen is limited and mostly unpractical **(22)**.

Also, **Sivakumar et al.,** reported that little evidence to support the use of intravenous acetaminophen to decrease pain during craniotomy surgery. Considering how crucial it is to minimize narcotic use while maximizing pain management for individuals who have had craniotomies **(13).** Similarly, patients in the IV acetaminophen group had substantially lower VAS pain levels compared to the placebo group, according to a meta-analysis of five RCTs with a total of 493 patients done by **Ebada et al.** (SMD=-0.28, 95% CI: -0.46 to -0.10). Nonetheless, there

were no statistical substantial variations between the two groups in regards to the need for opioids, length of hospital stay, or patient satisfaction. **(23).**

CONCLUSION

The present study demonstrated that in patients undergoing craniotomies, intravenous acetaminophen has a remarkable safety record when it comes to reducing postoperative pain. We came to the conclusion that intravenous paracetamol is a safe and effective therapy for postoperative pain in patients having elective craniotomies, but there are no advantages in terms of length of hospital stay, need for opioids, or patient satisfaction.

REFERENCES

1. Haldar R, Kaushal A, Gupta D, Srivastava S, Singh PK. Pain following craniotomy: reassessment of the available options. Biomed Res Int. 2015;2015.
2. Flexman AM, Ng JL, Gelb AW. Acute and chronic pain following craniotomy. Curr Opin Anesthesiol. 2010;23(5):551–7.
3. Vadivelu N, Kai AM, Tran D, Kodumudi G, Legler A, Ayrian E. Options for perioperative pain management in neurosurgery. J Pain Res. 2016;37–47.
4. Vacas S, Van de Wiele B. Designing a pain management protocol for craniotomy: A narrative review and consideration of promising practices. Surg Neurol Int. 2017;8.
5. Chou R, Gordon DB, de Leon-Casasola OA, Rosenberg JM, Bickler S, Brennan T, et al. Management of Postoperative Pain: a clinical practice guideline from the American pain society, the American Society of Regional Anesthesia and Pain Medicine, and the American Society of Anesthesiologists' committee on regional anesthesia, executive committee, and administrative council. J pain. 2016;17(2):131–57.
6. Albert-Vartanian A, Boyd MR, Hall AL, Morgado SJ, Nguyen E, Nguyen VPH, et al. Will peripherally restricted kappa-opioid receptor agonists (pKORA s) relieve pain with less opioid adverse effects and abuse potential? J Clin Pharm Ther. 2016;41(4):371–82.
7. 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.
8. Koh W, Nguyen KP, Jahr JS. Intravenous non-opioid analgesia for peri-and postoperative pain management: a scientific review of intravenous acetaminophen and ibuprofen. Korean J Anesthesiol. 2015;68(1):3.
9. Bhatia A, Buvanendran A. Anesthesia and postoperative pain control—multimodal anesthesia protocol. J Spine Surg. 2019;5(Suppl 2):S160.
10. Turan A, Essber H, Saasouh W, Hovsepyan K, Makarova N, Ayad S, et al. Effect of intravenous acetaminophen on postoperative hypoxemia after abdominal surgery: the FACTOR randomized clinical trial. Jama. 2020;324(4):350–8.
11. Verchére E, Grenier B, Mesli A, Siao D, Sesay M, Maurette P. Postoperative pain management after supratentorial craniotomy. J Neurosurg Anesthesiol. 2002;14(2):96–101.
12. Dilmen OK, Akcil EF, Tunali Y, Karabulut ES, Bahar M, Altindas F, et al. Postoperative analgesia for supratentorial craniotomy. Clin Neurol Neurosurg. 2016;146:90–5.
13. Sivakumar W, Jensen M, Martinez J, Tanana M, Duncan N, Hoesch R, et al. Intravenous acetaminophen for postoperative supratentorial craniotomy pain: a prospective, randomized, double-blinded, placebo-controlled trial. J Neurosurg. 2018;130(3):722–66.
14. Greenberg S, Murphy GS, Avram MJ, Shear T, Benson J, Parikh KN, et al. Postoperative

intravenous acetaminophen for craniotomy patients: a randomized controlled trial. World Neurosurg. 2018;109:e554–62.
15. Artime CA, Aijazi H, Zhang H, Syed T, Cai C, Gumbert SD, et al. Scheduled intravenous acetaminophen improves patient satisfaction with postcraniotomy pain management: a prospective, randomized, placebo-controlled, double-blind study. J Neurosurg Anesthesiol. 2018;30(3):231–6.
16. 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).
17. 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.
18. Ghaffarpasand F, Dadgostar E, Ilami G, Shoaee F, Niakan A, Aghabaklou S, et al. Intravenous acetaminophen (paracetamol) for postcraniotomy pain: systematic review and meta-analysis of randomized controlled trials. World Neurosurg. 2020;134:569–76.
19. Fischer M, Jackson M, Abd-Elsayed A. Pain in the neurocritical care unit. Textb Neuroanesthesia Neurocritical Care Vol II-Neurocritical Care. 2019;319–31.
20. Dunn LK, Naik BI, Nemergut EC, Durieux ME. Post-craniotomy pain management: beyond opioids. Curr Neurol Neurosci Rep. 2016;16:1–10.
21. Vijayan R, San LP. Postoperative pain management after craniotomy. Challenging Top Neuroanesthesia Neurocritical Care. 2017;139–45.
22. Smith HS. Perioperative intravenous acetaminophen and NSAIDs. Pain Med. 2011;12(6):961–81.
23. Ebada MA, Ali AS, Elshakankiry A, Essa T, Khater AG, Hossam M, et al. Should intravenous acetaminophen be considered for post craniotomy pain management? A meta-analysis of randomized controlled trials. J Neurosurg Sci. 2021;66(5):413–9.