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Review Article

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Pediatric Gabapentin Use in Postoperative Pain following Craniotomy: A Scoping Review

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Abstract

Management of postoperative pain following craniotomy can be dealt with in several forms. Treatment options range from conventional protocols involving opioid narcotics, NSAIDS, non-opioid pain management, and non-pharmacological management. Due to the massively publicized opioid crisis in the United States and in other countries there is a call for alternative methods for pain management. Of the alternative pain management techniques, gabapentin has been used in acute postoperative settings due to its anticonvulsant properties and pain management capabilities. This drug has been extensively used in the adult population, but its use in the pediatric population is uncommon. This scoping review aims to identify the lack of documented postoperative use in the pediatric population, specifically following craniotomy. It will aim to emphasize the need for further exploration of the use of gabapentin in a postoperative setting and accentuate gabapentin's theoretical benefit as an alternative medication for pain management. This article will also discuss the potential of Gabapentin as either an opioid alternative or in combination with non-opioid analgesics for postoperative pain management in pediatric populations. Execution of this through the use of multiple scholarly databases yielded 229 articles. Of these 229 articles 227 were excluded, two articles met inclusion criteria, unfortunately these did not directly utilize Gabapentin for pain relief, leaving the research regarding this topic to be non-existent.

Keywords: Gabapentin, Craniotomy, Decompressive Craniotomy, NSAIDS, Narcotics, Craniectomy

1. Introduction

A scoping review utilizes a systematic approach to identify and gather existing literature on specific topics with the aim of determining if there are gaps in evidence. In this study, a scoping review was conducted to determine the availability, or lack thereof, of research regarding the use of gabapentin in a pediatric postoperative setting, specifically post-craniotomy. During data collection from January 2022 through August 2022, the reviewers sought to determine the possibility of Gabapentin being used in the pediatric population following neurological surgery, specifically craniotomies. The reviewers seek to emphasize the importance of the need for further research regarding the postoperative use of gabapentin in a pediatric setting by presenting the topic of gabapentin being an alternative to opioids. This topic is supplemented by what is seen in the current literature regarding pediatric pain management.

Postoperative pain following craniotomy is managed in several ways and can be based on the attending physician's discretion. Treatment options utilized can be either conventional or unconventional methods of pain management, some of which include the use of non-opioid-associated narcotics, narcotic medications, NSAIDs, as well as other management options. Gabapentin is one of the options that has been extensively used in acute postoperative settings due to its properties, such as its anticonvulsant effects and the ability to alleviate acute and chronic pain [1]. This is due to the increasing opioid crisis in the United States, as well as across the globe. The use case for moving towards a non-opioid medical management direction by using other options will be a way to have a hopeful impact on this crisis. In contrast, gabapentin utilization in the pediatric population has been rarely used despite having shown to be an effective alternative alone or in combination with narcotics as a strong analgesic option for post-operative pain [2].

While it has been well established in the adult population, the pediatric population seems to have increased benefits of stepping away from the opioid option and using alternative and effective pain management techniques. [LE1]. Furthermore, the reviewers observed the contribution of gabapentin in the pediatric population for postoperative nausea and vomiting [3]. Gabapentin is used in pediatric patients to manage postoperative pain after a variety of surgeries such as spinal fusion and corrective scoliosis surgeries (unfortunately, the literature did not provide instances where Gabapentin was used for post-operative pain in brain surgeries) [4]. It effectively reduces postoperative pain and opioid consumption in pediatric patients, is well-tolerated, and has a low incidence of adverse effects in the pediatric population [4].

Postoperative pain management is a vital aspect of care for pediatric patients undergoing craniotomy. (The procedure is highly invasive as it involves removing a portion of the skull to access the brain) Despite continued advancements in medicine and pain management, the pain experienced by pediatric patients can be both acute and chronic following this procedure. Both forms of pain can negatively affect the recovery and quality of life of patients [5]. Pain management in pediatric patients who have undergone craniotomy remains a challenge; the use of opioids for pain management is common. With alternative options to opioids and the implementation of effective pain management strategies, there can be better options to improve the quality of life of pediatric patients. Understanding the importance of reducing postoperative opioid usage while using an alternative effective pain management medication without opioid-related complications is imperative in the progression of pain management, especially in children.

2. Methods

During data collection from January 2022 through August 2022, the reviewers searched the literature for examples of Gabapentin used in pediatric populations following neurological surgery, specifically craniotomies. For this scoping review, the pediatric population age range is defined as zero days to 18 years old. Over eight months, reviewers characterized specific topics related to gabapentin in the pediatric population and observed the occurrence of its use for postoperative pain management following craniotomy. The databases utilized included Embase and PubMed. Search terms include: “Gabapentin,” “craniotomy,” “Decompressive Craniectomy,” and “Craniectomy.” (craniectomy is utilized as a search term to broaden the literature search. Researchers are not examining postoperative craniectomy pain control, only craniotomy). Inclusion criteria included any article where gabapentin was utilized in patients aged 18 years and under who were to undergo or had undergone a craniotomy. The initial results yielded 33 publications organized using a Google Excel sheet. Medical Subject Headings (MeSH) terms were created to be used in the PubMed search and specific terms were selected for Embase (Table 1).

Database	Search Terms
PubMed	("Gabapentin" [MeSH Terms] OR "Gabapentin" [All Fields] OR "gabapentin" [All Fields] OR "gabapentins" [All Fields] OR "Gabapentin" [MeSH Terms]) AND ("Craniotomy" [MeSH Terms] OR "Decompressive Craniectomy" [MeSH Terms] OR "craniotomy* "[All Fields])
Embase	('gabapentin'/exp OR 'gabapentin') AND ('craniotomy'/exp OR 'craniotomy' OR 'craniectomy'/exp OR 'craniectomy')

Table 1: Search Terms for Each Database

Data retrieval used an approach that incorporated a three-stage method:

- **Stage 1:** Perform a limited search of relevant databases such as PubMed and Embase utilizing phrases such as “Gabapentin for postoperative craniotomy pain”, “Post-Operative Craniotomy Pain Management”, “Gabapentin and craniotomy neurosurgery”, “Alternative pain management in craniotomy”, and “Gabapentin and craniotomy”, “Decompressive Craniectomy”, and “craniectomy”. This examination prompted several questions. (A) What is currently used for postoperative pain management during craniotomy? B) Why is gabapentin an effective pain medication C) What are the reasons why gabapentin is used in the adult population but not in the pediatric population?
- **Stage 2:** Identify keywords and index terms that we wanted to utilize in the data collection and perform a detailed investigation of the databases listed above.
- **Stage 3:** Compile all the identified publications that met the following inclusion criteria: focus on pediatric patients, including references to gabapentin usage, postoperative pain management, and craniotomy. (Note: Articles were excluded if they focused on the adult population or did not include gabapentin, or craniotomy).

Reviewers conducted the search strategy using several keywords related to the research question, "Why is Gabapentin not used in a pediatric setting for Postoperative pain of craniotomy.” A search was performed using Embase and MEDLINE databases. Search terms were created to select publications that depicted a relationship with the topic. The full process synopsis is outlined in the PRISMA flowsheet. (Figure) Reviewers synthesized the objectives and findings from two articles (Table 2) Researchers did not feel there were limitations affecting the data yielded with respect to the search strategy implemented. This included, but was not limited to, restrictions associated with language or database function.

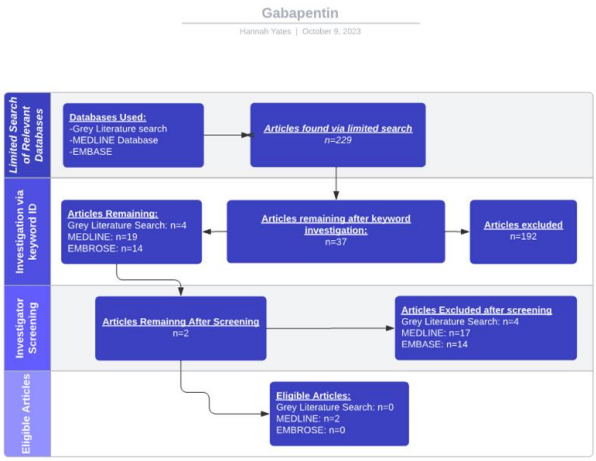

Figure: PRISMA Flow Diagram. PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses

Title	Database	Alternative medications used	Included
Gabapentin for Postoperative Vomiting in Children Requiring Posterior Fossa Tumor Resection [6]	PubMed	Gabapentin	Included
Gabapentin premedication decreases the hemodynamic response to skull pin insertion in patients undergoing craniotomy [7]	PubMed	Gabapentin	Included

Table 2: Articles Included After Complete Text Review

3. Results

Reviewers found a total of 229 articles for potential use. After further investigation, 37 remained. Of those 37 articles, 4 consisted of grey literature, which included materials beyond Embase and PubMed, such as Google Scholar. 14 consisted of Embase data, and of these results none met the inclusion criteria which included: any article gabapentin was utilized in patients under the age of 18 who were to undergo or had undergone a craniotomy. The remaining 19 articles from MEDLINE yielded only 2 articles which initially fit the inclusion criteria. These articles were as follows.

3.1. Article 1

Tsai et al, completed a study Gabapentin for Postoperative Vomiting in Children Requiring Posterior Fossa tumour resection [8].

• **Study Characteristics:** The study examined two cases of gabapentin use in pediatric patients for treatment in post-craniotomy vomiting of patients with posterior fossa tumors.

• **Participant Demographics:** An 11-year-old girl who underwent near-total excision of a medulloblastoma tumor in the fourth ventricle and a 4-year-old boy with near-total excision of a medulloblastoma tumor in the fourth ventricle.

• **Main Findings:** It found that the utilization of gabapentin was successful as an alternative antiemetic agent for recurrent vomiting that was refractory to antiemetic agents.

• **Research Gaps Identified:** The study's gaps include a small sample size, a lack of understanding of gabapentin's mechanism of action for its antiemetic effects, and no comparison with other treatment options. Additionally, for the purposes of our scoping review found no discussion on pain management and gabapentin's effects in these cases were identified or present.

3.2. Article 2

Misra et al, completed a study Gabapentin Premedication Decreases the Hemodynamic Response to Skull Pin insertion in Patients Undergoing Craniotomy [9].

• **Participant Demographics:** 47 patients ranging from 18 to 60 years old were included in this study.

• **Study Characteristics:** This article conducted a comparative analysis of techniques used to attenuate stress responses during skull pin insertion in craniotomies in a group of patients undergoing intracranial tumor surgery. Three treatment groups were utilized: one with placebo and 2% lidocaine, another with gabapentin and normal saline, and the third with gabapentin and 2% lidocaine at pin insertion sites. Hemodynamic responses were evaluated to determine the effectiveness of each treatment in mitigating stress responses during the procedure.

• **Main Findings:** Gabapentin with 2% lidocaine was successful as a premedication to blunt the hemodynamic response of skull pin insertion, reducing the need for additional analgesia.

• **Research Gaps Identified:** The study's gaps included a small sample size, without a head to head comparison of other aesthetic approaches. There is indication for more research to better understand mechanism of action from an analgesic and hemodynamic standpoint. For the purposes of our scoping review, the population tested was older than 18 even though they had undergone craniotomy, gabapentin was used in conjunction with another analgesic and was not used as the lone therapy for pain relief.

Unfortunately, neither article directly utilized Gabapentin for pain relief and were later excluded. This demonstrates the lack of research regarding the use of this medication in the use of pain management.

4. Discussion

This scoping review demonstrates that Gabapentin and opioids are frequently used in managing postoperative pain, but their use in treating pain following craniotomy in children is poorly documented. Supporting the potential use of Gabapentin, the researchers also compare this medication to other more mainstream medications that are widely used for postoperative craniotomy pain management. Gabapentin is found to be used 83% of the time for off-label use [10]. This drug's conventional use is for epilepsy management, partial seizures, as well as post-herpetic neuralgia. However, gabapentin's use goes beyond that; it can be used for bipolar disorder, neuropathic pain, diabetic neuropathy, complex regional pain syndrome, attention effect disorder, restless leg syndrome, trigeminal neuralgia, periodic limb movement disorder of sleep, migraine and drug and alcohol withdrawal seizures [11]. Gabapentin is a medication that features synergistic properties when combined with other drugs that exhibit CNS depression by inhibition of central voltage-gated Calcium channels, lead to a reduction in levels of excitatory neurotransmitters such as glutamate, norepinephrine, and other contraceptive and neuroinflammatory neurotransmitters [12-14]. The varying pharmacological attributes and versatile properties of gabapentin contribute to its efficacy across a large therapeutic domain. Its intricate interactions in synergetic pharmacotherapy and its ability to feature such a spectrum and clinical practice and therapeutic modalities give it a unique characteristic that makes it so widely used.

Another modality for pain control is the Enhanced Recovery After Surgery (ERAS) pathways which are tailored for a multitude of different surgical procedures that incorporate evidence-based practices that are aimed to improve patient outcomes, reduction of opioid consumption, lower occurrences of post-operative nausea and vomiting (PONV), and a decrease in hospital length of stay, across a range of surgical interventions [15]. A study that looked at ERAS and gabapentin usage for patients after autologous breast reconstruction found that postoperative pain with gabapentin that was associated with a decrease in milligram morphine equivalent, found to reduce stress and return patients to homeostasis after surgery, reduction in postoperative opioid use, self-reported pain, and PONV [16]. While not pertaining to a neurological procedure, this study provides further importance to ERAS protocol that can integrate a successful modality, leading to enhancing patient outcomes, and a notable reduction in postoperative opioid usage and most importantly the reduction of pain.

A key aspect in the management of pain is addressing what type of pain it is as well as its relation to trauma, surgery, progressive injury, and so forth. Depending on the mechanism attributed to the pain, pain management differs. Management can vary from nonpharmacological techniques such as rest, ice, compression, and elevation to pharmacologic agents differing in strength, starting with basic analgesics like NSAIDS and increasing to more potent agents such as Opioids [17]. Non-pharmacologic management of pain includes components of the RICE acronym. Resting after surgery helps with pain by promoting healing, reducing strain, inflammation, edema, and complications. Ice has less use in the immediate postoperative period; however, a cold towel applied to the area may have anti-inflammatory properties. However, caution is urged when utilized in the immediate postoperative period. Compression and elevation are not typically recommended in post-craniotomy patients due to complications from pressure placed onto unhealed sutures and a lack of adequate healing. The discretion of using these non-pharmacologic treatments should be left to the surgeon's discretion [18].

Nonsteroidal anti-inflammatory drugs (NSAIDs) consist of a wide variety of medications that act through the inhibition of cyclooxygenase enzymes COX-1 and COX-2. COX-1 and COX-2 produce lipid molecules (prostaglandins) that are important in the perception of pain and inflammatory response. When these enzymes are inhibited, the number of prostaglandins produced is decreased, which results in a decrease in inflammation as well as pain. Examples of lower tier NSAIDs include over-the-counter medications Ibuprofen, Naproxen, Ketoprofen, and Diclofenac. Some of the more potent NSAIDs include Celecoxib, Meloxicam, prescription strength Ibuprofen/Diclofenac, Etodolac, and Toradol [19].

Gabapentin and opioids share multiple similarities in terms of their mechanism of action and capability of managing pain. There are also significant differences that must be addressed when considering gabapentin for postoperative pain management. Both the use of gabapentin and opioid-class pain medications modulate the transmission of pain in the central nervous system. One mechanism of gabapentin is the ability to bind the alpha-2-delta subunit of voltage-gated calcium channels in the central nervous system. This decreases the influx of calcium ions into neurons, which reduces the release of excitatory neurotransmitters, such as glutamate and substance P. Through decreased release of these neurotransmitters, gabapentin can help decrease the perception of pain. Gabapentin can also increase the production of GABA, which also causes an inhibitory effect on the nervous system, leading to decreased excitability and further potentiates the decreased release of neurotransmitters, decreasing pain [8]. The main mechanism of action of opioids is their ability to bind to and activate mu, delta, and kappa, which are opioid receptors in the brain and spinal cord. Once activated, they can inhibit the transmission of pain signals to the brain, leading to decreased pain and pain relief. Opioids can also activate opioid receptors in other parts of the body, which can cause other effects, such as sedation, respiratory depression, and constipation [9].

Both methods of pain control could contribute to the production of analgesia and are effective in reducing pain. Still, opioids are favoured to be more potent with regard to pain relief. The natural higher potency of opioids leads to a higher risk of side effects. Some of these are the risk factors for addiction, respiratory depression, constipation, nausea, and dizziness. Side effects of Gabapentin vary wildly depending on dosing and can range from rare serious side effects such as suicidality, depression, Steven-Johnson syndrome, angioedema, erythema multiforme, rhabdomyolysis, to more common side effects such as fever, fatigue, diarrhea, constipation, weight gain, dizziness, drowsiness,

and confusion [20]. The main benefit of choosing gabapentin over opioid postoperative treatment is the decreased risk of addiction potential in comparison, complications, and delayed postoperative recovery associated with opioids [21]. Gabapentin has also been shown to decrease the need for postoperative opioids and contribute to a positive effect on recovery [2]. The cumulative benefits of utilizing gabapentin in the recovery period of postoperative surgery, as listed above, are grounds for exploration regarding the use of gabapentin in the pediatric population who undergo craniotomies.

In a study of patients who underwent lumbar laminectomy at Yavapai Regional Medical Centre, it was found that gabapentin effectively reduces postoperative pain and opioid consumption, is well tolerated, and appears to have a low incidence of adverse effects in the general population [2]. In contrast, a similar study found no significant difference in postoperative pain following craniotomies [22]. Further research specific to pain management in the acute postoperative patient would be useful in confirming which of these conclusions are more accurate. The limited data available underscores the significant gap in research on gabapentin use in pediatric postoperative pain management following craniotomies. This lack of data highlights an urgent need for well-designed clinical trials as well as observational studies focusing specifically on this patient population. Given the current opioid crisis and the potential benefits of gabapentin, investigating the efficacy and safety in pediatric neurosurgery could lead to improved pain management strategies which minimize opioid use and its associated risks. Future research should aim to develop standardized protocols for including gabapentin administration in pediatric postoperative care, determine optimal dosing regimens, and evaluate long-term outcomes to ensure both efficacy and safety. Addressing these gaps are crucial in advancing pediatric pain management and enhancing the quality of care for young patients undergoing major surgical procedures like craniotomy.

4.1. Summary - Accelerating Translation

This scoping review outlines and demonstrates the lack of research and need to further evaluate the use of gabapentin in neurosurgical patients, particularly in pediatric patients who have undergone craniotomy for pain management. This review is aimed at emphasizing the importance of the need for further research regarding the postoperative use of gabapentin in a pediatric setting by presenting an alternative use of gabapentin to the traditional opioids.

However, the use of gabapentin for treating pain following craniotomy in children is poorly documented. Our scoping review addressed the lack of research on this unconventional method for postoperative pain management. An initial review of data collected through MEDLINE revealed 19 articles, including the use of gabapentin in some capacity; however, further review excluded 17 of these articles and included 2. An initial review of data collected through Embase revealed 14 articles that included the use of gabapentin in some capacity; however, 0 of these articles were included due to exclusion criteria. Thus, this review demonstrates the need for further research on gabapentin use in the pediatric population following craniotomy. A potential prospective study that included Gabapentin in the post-operative management of pain in pediatric craniotomy patients may be able to evaluate the necessity for standard pain management versus optimization of decreased opioids in those who were also given gabapentin. Further research is needed prior to any definitive conclusions are able to be drawn [23].

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