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Original Article

Role of gabapentin in reducing the need for high-risk medications in patients with stable severe neurological impairment

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الملخص

المقدمة: يعاني الأطفال المصابين باعتلالات عصبية شديدة من نوبات ألم متكررة قد لا يتضح المسبب لها بالضرورة و تعود في الأصل إلى طبيعة الاعتلال العصبي الذي يطلق إشارات الألم بشكل مستمر و متكرر، في هذه الحالات يتم استخدام مستحضرات الجابابنتين كخط أول للعلاج. قد يخضع هؤلاء الأطفال لعلاج أعراض الألم باستخدام مستحضرات أخرى ما يجعلهم عرضة للأخطاء الطبية المتعلقة بالعقاقير و بالتالي فإن تعريضهم لمستحضرات دوائية عالية الخطورة بحاجة إلى مراجعة.

الأهداف: تهدف هذه الدراسة إلى قياس معدل انتشار أعراض الألم في الأطفال المصابين باعتلالات عصبية شديدة و كذلك مدى فاعلية مستحضرات الجابابنتين على في علاج هذا النوع من الألم.

آلية الدراسة: هذه الدراسة عبارة دراسة قبلية و بعدية تم إجراءها في أحد مستشفيات كندا، خضع للدراسة عدد أحد عشر طفلاً مصابين باعتلالات عصبية شديدة تم اختيارهم من خلال مراجعة قاعدة بيانات فريق الرعاية التلطيفية للأطفال و تم خلال الدراسة مراجعة أداء الأطفال من ناحية أعراض الألم المتعلق بالاضطرابات االعصبية قبل و بعد استخدام مستحضر الجابابنتين .

النتائج: قبل البدء باستخدام مستحضر الجابابنتين كانت الأعراض المتعلقة بالألم على النحو التالي: معظم الأطفال المشمولين في الدراسة (ثمانية من أحد عشر) ظهرت عليهم مظاهر التألم كعرض رئيسي للألم، ستة من أطفال الدراسة ظهر عليهم الألم على هيئة خلل في التوتر العضلي.

ثمانية من أطفال الدراسة كانوا يستخدمون مستحضرات البينزوديازيبين لعلاج أعراض الألم، أربعة منهم كانوا يستخدمون المستحضرات الأفيونية، و مريض واحد فقط كان يستخدم المهدئات المنومة.

بعد بدء مستحضر الجابابنتين تحسنت مظاهر الألم لدى عشرة أطفال من أصل أحد عشر، تم تخفيض جرعات الأدوية الأخرى على النحو التالي: البينزوديازيبين في ستة من ثمانية مرضى و المستحضرات الأفيونية في ثلاثة من أربعة مرضى و المنومات المهدئة في المريض الوحيد الذي كان يستخدمها.

بعد وصول الجرعات المناسبة، تم التخلص من الأدوية عالية الخطورة على النحو التالي: خمسة من أصل ثمانية ممن كانوا على مستحضرات البينزوديازيبين، إثنين من أربعة ممن هم على المستحضرات الأفيونية و تم التخلص من المهدئات المنومة في حالة الطفل الوحيد المعتمد عليها لعلاج الألم.

الاستنتاج: نسبة انتشار استخدام العقاقير الطبية التي تعد عالية الخطورة للأطفال من ذوي الاعتلالات العصبية الشديدة من قبل الأطباء تعتبر نسبة عالية في هذه المجموعة المعنية بالدراسة، البدء باستخدام مستحضر الجابابنتين و التدرج فيه حتى الوصول للمستوى المناسب لأعراض الطفل كان مجديا من ناحية السيطرة على أعراض الألم و كذلك من ناحية التخلص من العقاقير عالية الخطورة المستخدمة لهذا الغرض.

الكلمات المفتاحية: الشلل الدماغي؛ الحالات المزمنة و المعقدة؛ الأمراض العصبية؛ الاعتلالات العصبية الشديدة؛ عقار الجابابنتين؛ الألم

Abstract

Objective: The study was aimed at assessing the prevalence of pain behaviors in children with severe neurological impairment (SNI), as well as the use of prescribed pain behavior medications, and the effects of gabapentin initiation on behaviors and use.

Methods: A pre-post study was conducted on data from 11 patients with SNI who received gabapentin at a children's hospital in Canada. Symptoms and the use of high-

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risk pain behavior medications were assessed before and after gabapentin initiation and titration.

Results: Pain was identified as a primary concern in most patients (8/11 [73%]) before gabapentin initiation. Dystonia was the most prevalent pain behavior (6/11 [55%]). Of the 11 patients, eight (73%) were taking benzodiazepines for symptom management, four (36%) were taking opioids, and one was taking a hypnotic sedative. Symptom improvement was observed in 10/11 (91%) patients after gabapentin initiation and titration. The use of benzodiazepine decreased in 6/8 (75%) patients, opioid use decreased in 3/4 patients, and hypnotic sedative use decreased in 1/1 patient. Successful discontinuation occurred for benzodiazepines in 5/8 (62.5%) patients, opioids in 1/4 (25%) patients, and hypnotic sedatives in 1/1 patient.

Conclusions: Prescription medications with substantive risks, including benzodiazepines, opioids, and hypnotic sedatives, were used with high prevalence for pain behaviors in children with SNI. This study revealed an association between gabapentin initiation, and improved symptom burden and decreased use of the three medications.

Keywords: Cerebral palsy; Gabapentin; Medication safety; Pediatric palliative care; Severe neurologic impairment

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Introduction

Severe neurological impairment (SNI) has several definitions in the literature, but the most important considerations are mobility, intellectual disability, and increased healthcare needs.[1] Recurrent pain is a common challenge for children with SNI. Hauer et al. have summarized the assessment and management of pain in children with SNI.[2] Briefly, pain in this population is under-recognized and underestimated; has a broad variety of etiologies; can manifest in various behaviors (e.g., emotional lability, seizures, muscle spasms, irritability, dystonia, and sleep disorders); and requires a special approach to treatment. These "pain behaviors" may be interpreted and treated with various medications, as needed or regularly.[3]

Gabapentinoids are the first-line recommended medications for children with SNI with recurrent pain behaviors without a clear alternative etiology.[2] Gabapentinoids have been demonstrated to improve quality of life, activities of daily living, dystonia, and recurrent pain behaviors in children with SNI.[4–6]

The precise mechanism of action involving gamma-aminobutyric acid (GABA) receptors is unknown; however, researchers have reported that gabapentin crosses the blood–brain barrier and acts on neurotransmitters. Gabapentin's chemical structure includes a cyclohexyl group similar to that of the neurotransmitter GABA. However, it does not bind GABA receptors and does not affect GABA synthesis or uptake, despite having a similar structure. Gabapentin has a high affinity to brain binding sites that correspond to the presence of voltage-gated calcium channels, particularly alpha-2-delta-1, which appear to inhibit the release of excitatory neurotransmitters in the presynaptic area.[7]

To date, no studies have examined the effects of gabapentinoid initiation in this population on the use of other medications prescribed for pain behaviors, particularly those with high-risk profiles (e.g., tolerance, overdose, withdrawal, and misuse by caregivers). This issue is particularly important because children with complex medical considerations are at elevated risk of experiencing medication errors, and pharmacological stewardship is a critical component of their care.[8]

This study explores the effects of gabapentinoid initiation on the use of pain behavior medications in children with SNI.

Materials and Methods

Charts of patients with SNI who received gabapentin initiation at McMaster Children's Hospital, Hamilton, Canada, from November 2015 to June 2017, were retrospectively reviewed. Ethical approval for this study was obtained from the Hamilton Integrated Research Ethics Board (HiREB). Patients were identified by the prescriber on the basis of review of the Quality of Life & Advanced Care database at McMaster Children's Hospital.

The inclusion criteria were as follows: (1) age: no age limit, because the transfer of care to adult services was not intended in this specific population; (2) diagnosis/disease category: SNI of a stable etiology (e.g., cerebral palsy); (3) disability severity: level V of the Gross Motor Function Classification System; physical impairments restricting voluntary control of movement, and the ability to maintain head and neck position against gravity; impairment in all motor function areas; inability to independently sit or stand even with adaptive equipment; and inability to independently walk (powered mobility use was allowed)[9]; and (4) medication history: gabapentin initiation for pain behaviors.

The reviewed patient-specific data included age, sex, weight, gabapentinoid choice, and peak gabapentinoid dose (mg/kg/day). Pain behavior reports were extracted from charts before and after gabapentin initiation and titration, on the basis of the observations of the primary caregivers, who were familiar with using a specific pain assessment tool named the Pediatric Pain Profile, essentially an assessment diary of different pain manifestations and behaviors.[10]

The baseline asseement was conducted by the primary consultant after gabapentin initiation. The response was accordingly graded during follow-up as worsened, no change, improved, or resolved.

Gabapentin initiation and titration occurred as recommended by the 2015 pain and symptom management guidelines for pediatric palliative care.[11]

Over-the-counter medications (e.g., acetaminophen and ibuprofen) were not included in this analysis. The use of prescription medications for pain behaviors was extracted from the charts before and after gabapentinoid initiation and

was graded as increased, no change, decreased, or discontinued.

This study used descriptive statistics to measure the age of participants (mean + standard deviation) and other categorical variables (measured by percentage and frequency count).

Results

The inclusion criteria were met by 11 patients (seven boys and four girls). The mean age of the participants at the initial assessment was 14.3 years (range 7–22). The pain was reported as a primary problem in eight (73.7%) patients, and the pain behaviors included dystonia, irritability, hypersensitivity, sleep disturbance, and emotional lability. Of the three families not reporting a specific pain concern, one child had irritability, sleep disturbance, and hypersensitivity; one child had severe dystonia; and one child had extreme hypersensitivity to external stimuli, thus resulting in frequent seizures.

Of these 11 patients, eight (72%) were receiving benzodiazepines for pain behaviors, four (36%) were receiving opioids, and one (9%) was receiving a scheduled hypnotic sedative. Five (45%) children were taking more than one of these medications before gabapentin initiation (Table 1).

All patients were prescribed gabapentin, which was titrated to a mean dose of 32 mg/kg/day, with a range of 23–57 mg/kg/day.

Pain and pain behavior improvement was identified in most patients after gabapentinoid initiation. Improvement was seen in all children who reported pain, irritability, emotional lability, and disturbed sleep, and 4/6 (66.7%) patients with dystonia. Of eight patients taking benzodiazepines, one (12.5%) had a decreased dose, and five (62.5%) completely discontinued use. Of four patients taking opioids, two (50%) had a decreased dose, and one (25%) completely discontinued opioids. One patient taking a hypnotic sedative was able to have this medication discontinued. No escalation in pain behaviors was reported after the discontinuation of these medications (Table 2).

Table 1: Demographics of the Patient Population.

Characteristics	(N = 11)	
Mean age	14.3 years	
Range	7–22 years	
Sex	***n***	**%**
Male	7	64
Female	4	36
Opioids/benzodiazepines/hypnotic sedatives (pregabapentinoid)	***n***	**%**
Benzodiazepines	8	72
Opioids	4	36
Hypnotic sedatives	1	9
More than one of the above	5	45
Symptoms (pregabapentinoid)	***n***	**%**
Pain	8	72
Pain behaviors	11	100
Dystonia	6	54
Irritability	3	27
Hypersensitivity	3	27
Disturbed sleep	1	9
Emotional lability	1	9

Discussion

Gabapentin is a structural analog of GABA with both antiepileptic and antinociceptive properties. It targets multiple pathways involved in neuropathic pain and inflammation. It has multiple uses, such as in postoperative and visceral pain management, dystonia, and irritability, in children with complex medical and neurological conditions.[12]

Pain behavior management in children with SNI is a major clinical challenge for patients, families, and clinicians. In this study, as in other studies, the addition of a gabapentinoid decreased the symptom burden. Additionally, amelioration of symptoms allowed for weaning and in some cases discontinuation of other medications with high-risk profiles.

Pharmaceutical stewardship is critical in children with medical complexity. As a group, children are at elevated risk of medication errors for the following reasons: (1) off-label use and lack of standardized dosing recommendations; (2) individualized calculated dosing per kg or m^2; (3) frequent need for compounding or subdividing standard dosage forms; and (4) small variations in dose that can lead to significant variations in drug effects because of patient size.[8,13]

Table 2: Patient Status After Gabapentin.

Symptoms	*n*	Worsened (%)	No change (%)	Improved (%)	Resolved (%)
Pain	8	0	0	8 (100%)	0
Pain behaviors					
Dystonia	6	0	2 (33.3%)	4 (66.7%)	0
Irritability	3	0	0	3 (100%)	0
Hypersensitivity	3	0	1 (33.3%)	2 (66.7%)	0
Disturbed sleep	1	0	0	1 (100%)	0
Emotional lability	1	0	0	1 (100%)	0
Medications		**Increased (%)**	**No change (%)**	**Decreased (%)**	**Discontinued g**
Benzodiazepines	8	0	2 (25%)	1 (12.5%)	5 (62.5%)
Opioids	4	1 (25%)	0	2 (50%)	1 (25%)
Hypnotic sedatives	1	0	0	0	1 (100%)

Children with medical complexity are at an even higher risk of experiencing medication errors at home.[8] These children often receive many medications that are prescribed by multiple clinicians, sometimes to various pharmacies, which are administered by family caregivers without mandated breaks or respite, and without independent safety checks. In two studies, Walsh et al. have observed 522 medication administrations in the homes of children with chronic conditions and identified 132 medication errors (25% error rate): thirteen (2.5%) errors caused significant patient harm, and 71 (13%) had potential risk.[14] Medication errors in home settings are multifactorial and may stem from errors at the time of prescription, dispensing errors, or administration errors.[8,15,16] Medication errors may be associated with inadequate counseling, documentation/advice discrepancies, parent health literacy, or overburdened caregivers.[17,18] Systemic improvements in these areas can decrease the risk of medication error, but the best preventive measure is to eliminate medication use.

Benzodiazepines, opioids, and hypnotic sedatives are at high risk of tolerance, withdrawal, overdose, and misuse.[19–21]

The risk is particularly high with concomitant administration. In this study, patients taking opioids were also taking a benzodiazepine and/or chloral hydrate. Gabapentinoids are a comparably safe medication class with low adverse effect rates, which are usually mild to moderate in scope, and have few contraindications with other medications.[22] Gabapentinoids have a relatively low risk of physiologic addiction or withdrawal, particularly under typical use; however, they are increasingly being abused, particularly by individuals with a history of substance use disorder.[23] Additionally, gabapentinoids have limited toxicity in overdose, but they are increasingly being found to have been used alongside other medications in people who have died from intentional overdose; moreover, concomitant gabapentin use has been associated with an elevated risk of opioid-associated death.[24,25] Recently, in the United States, a Food and Drug Administration warning has recognized the risk of gabapentinoid prescription in patients with risk factors, including co-prescription with central nervous system depressants and respiratory diseases.

However, this study suggests that gabapentinoids might have an important role in deprescription of other potentially higher-risk prescription medications and medication combinations for pain behaviors in children with SNI.

This study is limited by its sample size and the absence of objective or standardized measures of symptomatology, or control or placebo comparators, because of its pre–post study design.

Pediatricians and other colleagues may refer children with oncology problems in their end-of-life period to palliative care services. Referring patients with SNI to palliative care is uncommon but critical for quality of life improvement for those patients and their caregivers.

Our study findings indicate the need for a prospective case series with standardized pain behavior measures and detailed medication administration. Additionally, this study complements a study on adverse drug events of benzodiazepines, opioids, hypnotic sedatives, and gabapentin for pain behaviors in children with SNI and medical complexity.

Conclusions

Pain and pain behaviors are common in children with SNI, and these children often receive prescription medications for these symptoms. Children, particularly those with medical complexity in the home setting, are at elevated risk of medication errors. This study revealed that gabapentin ameliorated symptoms and helped decrease the use of benzodiazepines, opioids, and hypnotic sedatives, thus potentially increasing patient safety. However, further studies are needed to confirm these findings.

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Ethical approval

Institutional Review Board Statement: The study was conducted according to the guidelines of the Declaration of Helsinki and was approved by HiREB, Project Number: 3102-C, November 21, 2017.

Consent

All authors gave their consent for publication.

Authors contributions

Conceptualization, K.A.; Data collection, K.A.; Investigation, K.A.; Methodology, D.L. and K.A.; Project administration, D.L. and K.A.; Resources, D.L.; Software, D.L. and K.A.; Supervision, D.L.; Visualization, K.A.; Writing—original draft, K.A. and D. L.; Writing—review and editing, K.A. and D.L. All authors have critically reviewed and approved the final draft and are responsible for the content and similarity index of the manuscript.

Data availability statement

All the data for this study will be made available upon reasonable request.

Conflicts of interest

The authors have no conflict of interest to declare.

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