future pharmacology

MDPI

Article

Evaluations of NSAIDs and Opioids as Analgesics in Pediatric Oncology

Eduardo Ladeia Leal [1,2], Paulo Caleb Júnior Lima Santos [1,*], Thuane Sales Gonçalves [1], Mariana Martins Gonzaga do Nascimento [3], Fábio Cardoso Cruz [1], Flávia Borelli Gomes do Nascimento [2] and Carolina Paula Jesus Kasa [2]

[1] Departamet of Pharmacology, Escola Paulista de Medicina, Universidade Federal de São Paulo, 03 de Maio St., 100. INFAR, 4th Floor, Vila Clementino, São Paulo 04044-020, SP, Brazil; eduardo.ladeia@unifesp.br (E.L.L.); thaune.sales@unifesp.br (T.S.G.); f.cruz@unifesp.br (F.C.C.)

[2] Grupo de Apoio ao Adolescente e Criança com Câncer, Universidade Federal de São Paulo, Pedro de Toledo St., 572. Vila Clementino, São Paulo 04039-001, SP, Brazil; flaviaborellinascimento@gmail.com (F.B.G.d.N.); carolinajesus@graacc.org.br (C.P.J.K.)

[3] Departament of Pharmaceutical Products, Faculdade de Farmácia, Universidade Federal de Minas Gerais, Belo Horizonte 31270-901, MG, Brazil; marianamgn@ufmg.br

* Correspondence: paulo.caleb@unifesp.br

Abstract: As one of the leading causes of death in childhood, cancer also causes discomfort to pediatric patients. Even with guidelines for pain management, more than half of hospitalized children have intense and unrelieved pain. The present work aims to describe the intensity of pain and its pharmacological management in a pediatric oncology population. Patients aged 0 to 17 years old, diagnosed with cancer, who were admitted to a children's oncology hospital and had well-documented data on pain management in their medical records were included. A total of 333 patients were included, mostly male (55.8%) with a mean age of 7.9 years. A substantial portion of the patient cohort (51.4%) initially reported experiencing pain of moderate intensity during the first assessment. Subsequently, following the pharmacological intervention, a significant proportion of patients (90.1%) reported complete alleviation of pain. The predominant pharmaceutical agents utilized for pain management encompassed metamizole (76.6%) and morphine (10.2%). All pharmacological interventions used were able to significantly reduce patients' pain. This study underscores the utilization of different pharmacological classes to achieve notable reductions in pain intensity among patients grappling with severe pain.

Keywords: analgesia; oncology pain; analgesic drugs; pediatric oncology

Citation: Leal, E.L.; Santos, P.C.J.L.; Gonçalves, T.S.; Nascimento, M.M.G.d.; Cruz, F.C.; Nascimento, F.B.G.d.; Kasa, C.P.J. Evaluations of NSAIDs and Opioids as Analgesics in Pediatric Oncology. *Future Pharmacol.* **2023**, *3*, 916–925. https://doi.org/10.3390/futurepharmacol3040055

Academic Editor: Gabriel Navarrete-Vázquez

Received: 27 September 2023
Revised: 21 October 2023
Accepted: 1 November 2023
Published: 1 December 2023

1. Introduction

Cancer is one of the leading causes of death in childhood [1,2]. Regardless of the stage, patients with advanced cancer frequently experience significant pain, which negatively affects the quality of life and survival of these patients [1,3]. The most prevalent cancers among children, encompassing those aged 0 to 17 years, include leukemia, brain and nervous system tumors, lymphoma, neuroblastoma, and sarcomas [4].

According to the World Health Organization (WHO) and the International Association for the Study of Pain (IASP), pain is an unpleasant symptom and an emotional experience that impacts an individual's quality of life. It is an individual experience of varying intensity and the pain score referred to is the result of the sum of physical, emotional, social, and spiritual factors experienced at that moment; for this reason, complaints must be verified and treatment instituted as early as possible, whether pharmacological or non-pharmacological [5–7].

In recent years, the WHO has published guidelines about pain, considered one of the main complaints and disabilities worldwide, including in children [7–9]. Highlighting pain as a public health problem, pain control came to be considered the fifth vital sign [10,11].

It is estimated that 70% of children with cancer will experience severe pain during their illness [1,12]. Pain is a distressing experience for anyone, though it is even more problematic in children, as they may have difficulties expressing their sensations and emotions clearly. Cancer treatments often involve painful procedures such as venipuncture, IV catheter insertion, dressing changes, bone marrow aspiration, and lumbar punctures [6,13]. These procedures add more suffering to children who are already facing the disease. The lack of acknowledgment and recognition of pain in children can lead to undertreatment, meaning that pain is not properly managed. This can have negative effects not only on the child's quality of life but also on the treatment process itself [13].

The fear of pain is a primary concern for children with cancer and outweighs other anxieties regarding treatments and the disease [14]. Therefore, it is necessary to incorporate individual characteristics into strategies to modulate drug disposition according to the patient's perception of pain, thus successfully treating pain and achieving safe and adequate analgesic exposure [1].

Pain management should be regarded as a strategic process that necessitates a comprehensive approach, encompassing the thorough evaluation of pain, the implementation of either pharmacological or non-pharmacological interventions, and subsequent reassessment. This multifaceted approach is imperative to verify the effectiveness of interventions or to consider the introduction of novel strategies aimed at enhancing the comfort and well-being of the patient [8,9].

Several instruments have been validated to assist in the assessment of pain in pediatric patients. When self-reporting is not possible, multidimensional scales are recommended that can highlight behaviors or psychological factors indicative of pain. The Neonatal Infant Pain Scale (NIPS) and Face, Legs, Activity, Cry, and Consolability (FLACC) scale are multidimensional instruments used to quantify pain through behaviors and physiological parameters [15–17]. Other tools value self-reporting so that the patient himself can quantify and indicate the intensity of the pain felt through face diagrams or a numerical scale [16–18].

Pain assessment in pediatric patients should consider, in addition to subjective characteristics, the child's developmental stages [19,20]. Likewise, for the WHO, pain management should be individualized for each patient, to assess, intervene, and reassess the individual's pain and cognitive development, the sociocultural context, and the stages of development in which the child is in must be considered [8,19].

Despite the existence of well-structured pain management protocols and pain assessment tools, more than half of hospitalized children experience severe pain without improvement [21]. Similarly, few studies have been performed to evaluate the selection and appropriate dose of analgesics to reach an adequate analgesic effect in pediatric cancer patients [1]. Notwithstanding, other studies indicate that, when there is intervention in pediatric pain, there is a low occurrence of reassessment to demonstrate the effectiveness of its management [19,22].

The main aim of the present study was to evaluate the intensity of pain and its pharmacological management in a pediatric population of a pediatric oncology center.

2. Materials and Methods

This is a descriptive pharmacoepidemiologic study, of the quality of consumption type, referring to the retrospective use of drugs for analgesia in children with cancer treated at the Grupo de Apoio ao Adolescente e Criança com Câncer (GRAACC) Hospital. This is a children's oncology hospital, located in the city of São Paulo, Brazil. Pediatric patients aged 0 to 17 years old, diagnosed with cancer, who were admitted to the hospital during the period spanning from 1 January 2021, to 31 March 2022, and had well-documented data on pain management in their medical records were included.

Pain was evaluated by a nurse by three distinct methods: (1) the FLACC scale [15]; (2) the face scale [18]; and (3) the numerical scale [17]. All nurses received training regarding the choice of assessment tools and how they were used to assess pain. All the pain assessment tools had the intensity standardized to 0 to 10 so that 0 represents no pain

and 10 represents the most intense pain that can be felt. All pain complaints were evaluated prioritizing self-reports. When self-reporting is not possible, a validated instrument that is independent of the patient's report should be applied to measure pain intensity. Subsequently, the intensity from 0 to 10 was recorded in the electronic medical record with indication of pharmacological or non-pharmacological intervention for pain relief. Afterwards, reassessments using the same instrument were carried out to identify pain relief or the need for new intervention.

The choice and dispensation of analgesic agents adhered to the institutional pain management protocol. Accordingly, metamizole and acetaminophen were recommended for mild pain, tramadol for cases of moderate to severe pain, and morphine for severe and unbearable pain. The designated dosage regimen was contingent upon the patient's body weight, and the frequency of administration conformed to established guidelines concerning the medication's serum concentration.

From the patient sample, individuals with meticulously documented pain records in their medical files were considered for inclusion, those who underwent a pain assessment utilizing a scale and obtained a score equal to or greater than 1, and utilized acetaminophen, metamizole, morphine, or tramadol for pain management and subsequently underwent a reassessment by the scale following the pharmacological intervention were included.

Through medical records, data were gathered pertaining to the age, gender, and oncological diagnosis of the enrolled patients. In terms of pain management, the assessment tool and intensity score were documented both before and after the pharmacological intervention, along with the time interval between reassessments. Concerning medications employed, information regarding the drug's name, dosage, and route of administration was recorded. Data on the association of adjuvant analgesic therapy were also collected.

Data about age were described according to age groups of development, considering breastfeeding as being when the patient is from 0 to 1 year old; preschool, from 2 to 4 years old; school, from 5 to 10 years old; and teenagers, from 11 to 19 years old. Data about oncological diagnosis were grouped according to the International Classification of Childhood Cancer (ICCC). The pain intensity score was also grouped into no pain equal to 0, mild pain from 1 to 3, moderate from 4 to 6, severe from 7 to 9, and unbearable equal to 10. Analgesic drugs were described by drug, route of administration, and according to the presence of other analgesic drugs or adjuvants associated with pain treatment. The reassessment score improvement was grouped into total improvement for patients without pain complaints (score = 0); partial for patients with a score lower than the initial; no improvement when the final score was equal to the initial; it is worse when scores are higher than the initial one.

Patient health data, analgesic drugs used, and pain conditions were collected from the medical record and fed into a database in Microsoft® Excel® 2016 MSO 64 bits. The variables were subject to descriptive statistical analyses carried out using the Jamovi®, version 2.3. Statistical analyses for qualitative variables and their absolute and relative frequency were calculated. For quantitative variables, their mean, standard deviation, minimum, and maximum were calculated. The Kolmogorov–Smirnov and Shapiro–Wilk tests were previously applied to evaluate the sample distribution. The W Wilcoxon test was applied to compare pain scores before and after the pharmacological intervention and the Mann–Whitney U test to compare the initial pain scores.

3. Results

3.1. Description of Pediatric Oncology Included Patients

A total of 333 patients were included, mostly male (n = 186; 55.8%) with a mean age of 7.9 $\pm$ 5.1 years (minimum = 0; maximum = 17). Most patients were adolescents (n = 113; 33.9%) and the most frequent oncological diagnosis was leukemia, which is included in group I of the ICCC—leukemias, myeloproliferative, and myelodysplastic diseases (n = 101; 30.1%); central nervous system (SNC) and miscellaneous intracranial and intraspinal neoplasms (n = 76) (Table 1).

Table 1. Demographic and health characteristics of patients included in the study.

Characteristics	*n*	%
Female	147	44.2
Male	186	55.8
Infant	37	11.1
Preschool	72	21.6
School	111	33.3
Adolescent	113	33.9
Leukemias, Myeloproliferative, and Myelodysplastic Diseases	101	30.3
Lymphomas and Reticuloendothelial Neoplasms	21	6.3
CNS and Miscellaneous Intracranial and Intraspinal Neoplasms	75	22.5
Neuroblastoma and Other Peripheral Nervous Cell Tumors	23	6.9
Retinoblastoma	21	6.3
Renal Tumors	25	7.5
Hepatic Tumors	1	0.3
Malignant Bone Tumors	35	10.5
Soft Tissue and Other Extraosseous Sarcomas	20	6.0
Germ Cell Tumors, Trophoblastic Tumors, and Neoplasms of Gonads	1	0.3
Other Malignant Epithelial Neoplasms and Malignant Melanomas	4	1.2
Other and Unspecified Malignant Neoplasms	6	1.8

CNS: Central nervous system.

3.2. Pain Management

A substantial segment of the patient cohort (*n* = 171; 51.4%) initially disclosed the experience of pain characterized as having a moderate intensity during the initial assessment. Subsequent to the pharmacological intervention, a noteworthy majority of patients, precisely 90.1% (*n* = 300), reported complete resolution of their pain, as indicated in Table 2. The average time elapsed between the initial assessment and the final evaluation of pain amounted to 34 min.

Table 2. Absolute and relative frequencies of initial and final pain scores.

Pain Classification	Initial Assessment *n* (%)	Final Assessment *n* (%)
Painless	0 (0)	300 (90.1)
Light	60 (18.0)	16 (4.8)
Moderate	171 (51.4)	11 (3.3)
Intense	83 (24.9)	4 (1.2)
Unbearable	19 (5.7)	2 (0.6)

The predominant pharmaceutical agents utilized for pain management encompassed metamizole (*n* = 255; 76.6%) and morphine (*n* = 34; 10.2%). Taking into consideration the four medications under evaluation, 91.9% (*n* = 306) of them were administered intravenously, while 8.1% (*n* = 27) were delivered via the enteral route. Furthermore, we have identified a notable improvement in pain levels when comparing the scores before and after the pharmacological intervention. All pharmacological interventions used were able to significantly reduce patients' pain (Table 3).

Table 3. Differences between initial and final pain scores, by type of medication used.

Drug	*N* (%)	Initial Score (Mean)	Final Score (Mean)	W Wilcoxon Test	*p*-Value
Morphine	34 (10.2%)	6.174	0.441	561 [b]	<0.001
Tramadol	24 (7.2%)	6.292	0.542	300	<0.001
Metamizole	255 (76.6%)	5.416	0.412	31,109 [a]	<0.001
Acetaminophen	20 (6.0%)	4.950	0.250	190 [b]	<0.001

[a] 6 pair(s) of tied values; [b] 1 pair(s) of tied values.

Our observations suggest that the initial pain assessment score might have exerted a noteworthy influence on the choice of pharmacological intervention. A statistically significant discrepancy emerged when comparing the mean initial pain scores of patients administered non-steroidal anti-inflammatory drugs (NSAIDs) (mean initial score = 5.36) and those receiving opioid medications (mean initial score = 6.20), as determined through the Mann–Whitney U test (U = 10,045.50; $p = 0.004$).

It was observed that the prescribed doses for each analgesic were determined in accordance with the patient's body weight and established reference standards for each medication. In addition to analgesics, adjuvant pharmaceutical agents were administered as warranted to alleviate potential adverse reactions linked to the use of analgesic medications.

Regarding the concomitant prescription of supplementary analgesic medications alongside the administered drug, our observations revealed that 46% of cases involving metamizole, 4% of acetaminophen-related instances, 9% of morphine cases, and 5% of tramadol cases were linked to the simultaneous prescription of another analgesic agent.

4. Discussion

Epidemiological studies indicate that leukemia is the most common cancer among children, representing 25% of cancers that occur before the age of 20. Cases of acute lymphoblastic leukemia (ALL) can occur at any age, but there is a peak incidence between 2 and 6 years of age. Followed by central nervous system tumors (17%) and lymphomas (16%), these three types of cancer are the most common in children [23].

In concordance with epidemiological data pertaining to pediatric oncology, our findings indicate that leukemia constituted the predominant diagnosis among the enrolled patients. Furthermore, the second most prevalent tumor category within this demographic, namely central nervous system tumors, also emerged as the second most frequently diagnosed condition within our sample. Among leukemia patients, the primary pain complaint was correlated with gastrointestinal distress, notably localized to the oral region, and often linked to the presence of mucositis.

Notwithstanding the relatively low incidence of malignant bone tumors in childhood, accounting for approximately 6% [23], our investigation did not reveal any individuals meeting the inclusion criteria harboring such neoplasms. This observation may be correlated with the nature of pain experienced by these patients, which frequently manifests as neuropathic pain, necessitating the utilization of alternative pharmacological modalities for pain mitigation.

This study described analgesic practices in pediatric cancer patients and pain intensity before and after pharmacological intervention. Given that pain in pediatric oncology patients may stem from either the underlying disease or its therapeutic interventions, such as chemotherapy-induced neurotoxicity or invasive medical procedures, our methodology systematically examined any pain-related complaints in pediatric inpatients at the GRAACC facility. The reports of pain ranged from mild pain (score = 1) to unbearable pain (score = 10).

Studies found a 38.7% incidence of pain in children admitted to a pediatric hospital. It is noteworthy that the patients were grouped by diagnostic specialties, and among them, none were related to oncology [19]. Other studies indicated that 30.4% of children hospitalized in the oncology specialty had a pain score available and that for the other 69.4%

of patients, there is no pain score, which may be an underreporting of pain complaints. In their methodology, they also found that 57.14% of the children had intense to unbearable pain that did not improve after drug administration [22].

If the examination is carefully performed and the presence of pain is identified, it is expected that a plan of care will be structured in an agile and cautious manner to meet the needs of the child, with assertive use of both pharmacologic and nonpharmacologic interventions. The American Academy of Pediatrics and WHO recommend linking these interventions so that pain management is more appropriate [8,9,24].

It is worth noting that self-reporting or evaluating qualitative information in pediatric patients is not always possible. Therefore, the presence of tools, such as unidimensional or multidimensional scales, is necessary to standardize information about a patient's pain, especially considering its intensity.

A study conducted with hospitalized children found that in children with pain confirmed by assessment tools, 95.6% were prescribed medication, but only 81.7% were medicated, showing that professionals are still hesitant about medicalizing children [19].

The GRAACC hospital recommends that pain be assessed, prioritizing self-reporting, and that pharmacological or non-pharmacological intervention be recorded after pain identification. Afterward, reassessment must be performed within 30 min. to confirm pain relief. When no significant improvement is identified, a new intervention must be performed and recorded. In addition to the clinical guidelines, the hospital further provides specific dosage recommendations for analgesic and adjuvant medications. After a thorough evaluation, we ascertained that the prescribed doses adhered to the established reference ranges designated for each medication and patient age category, thus ensuring a standardized approach to dosage prescription for each therapeutic agent.

The literature indicates that institutional protocols are positive predictors of changes related to pain assessment [25]. Beyond that, however, improvement of the team responsible for pain management is needed with continuous education based on strategies aimed at making pain important, understandable, visible, and more manageable [17]. The expertise of professionals can be key to best practices, but performing this role requires technical scientific knowledge and daily efforts to maintain consistency in the process [25]. In a U.S. study examining the implementation of strategies to improve teamwork in pain management, continuing education was found to be a positive predictor of teamwork improvement [26].

Studies indicate that morphine and acetaminophen are the most prescribed drugs for children [22,27]. Similarly, other studies verified the difference in the prescription of analgesic drugs in six different pediatric specialties in a hospital where morphine was present in 56.5% and acetaminophen in 73.9% of analgesic prescriptions for pain treatment in the oncology specialty [22].

In hospital admissions, especially for cancer treatment, there is a need for venipuncture to administer medications. When it comes to the administration of chemotherapy drugs, there is a need for large routes for the infusion of drugs and other medications. To avoid the recurrence of peripheral punctures and vascular injuries, long-term access is used. Therefore, the preference for the intravenous route may be related to the fact that all patients are hospitalized. In our study, only acetaminophen was administered enterally.

Considering the use of drugs, our study identified that metamizole was used more than acetaminophen for pain treatment. This fact may be related to the route of administration of acetaminophen being limited in this hospital. A systematic review identified that metamizole at low doses was able to reduce pain in adults with cancer and that high doses were more effective than low doses, but they were equally effective at an oral dose of 60 mg of morphine/day [28].

The management of pharmacological pain in pediatric oncology patients constitutes a multifaceted endeavor necessitating collaborative efforts across various disciplines. The WHO's Guidelines on the Management of Chronic Pain in Children emerge as a pivotal resource, offering evidence-based direction in addressing chronic pain [7]. At the core

of these guidelines is a three-step analgesic ladder, signifying a tiered approach to pain management. This method commences with nonopioid analgesics and adjuvant medications in the initial phase, progresses to incorporating opioids for mild to moderate pain in the subsequent step, and ultimately introduces opioids again at the third stage to address moderate to severe pain [6,7].

The WHO has recommendations for the pediatric population that suggest the use of common analgesics associated with adjuvants for mild pain, and common analgesics combined with adjuvants and strong opioids for moderate to severe pain in patients up to 11 years and 11 months [8]. Differently, for patients aged 12 years and over, there is an addition of an intermediate indication, so strong opioids are now indicated only for severe pain, and for moderate pain, the use of weak opioids is now indicated [9].

Our data may indicate that the institution adheres to the WHO guidelines for pain treatment so that the use of adjuvants is not related to the initial score. Nevertheless, the choice of opioid is related to the intensity of the pain complaint. In this way, all patients had one or more medications prescribed to treat pain, despite this, only the first intervention record was considered.

Similarly to our findings, other studies observed that professionals often opt for drugs from the non-steroidal anti-inflammatory class in the treatment of pain, as seen in this study, even when severe pain is reported [29]. Other studies detected that even in 25.9% of patients who reported severe pain, only 3.7% used morphine, 0.4% codeine, and 0.4% gabapentin [19].

Other studies that evaluated cancer-related mucositis pain relief in pediatric patients indicate that tramadol as a monotherapy provided adequate analgesia with moderate and manageable adverse effects [30]. Tramadol was more associated with the presence of nausea and vomiting according to medical records. This symptom often disappears by increasing the infusion time.

The utilization of opioids offers effective pain relief for pediatric patients; nonetheless, their administration in both acute and chronic pain scenarios necessitates a meticulous equilibrium between potential advantages and risks. It is important to note that the use of opioids can result in the development of tolerance and dependence, which accentuates the significance of vigilance in their application [31,32].

Studies indicate that the lack of evidence in the assessment or reassessment makes it difficult to assess analgesic efficacy in pediatric patients [22]. More recent studies demonstrate that pain management in hospitalized pediatric patients is still ineffective, mainly due to the lack of reassessments. Hence, 40.3% of children with pain underwent reassessment because these records were missing, which suggests that the flow of interventions that would benefit the relief of pain in hospitalized children is interrupted [19]. Our findings indicate that opioid use was related to stronger pain complaints and that approximately 10% of the pain episodes required a new pharmacological intervention in the reassessment. Thus, our data suggest that reassessment is a fundamental step for adequate pain management.

Likewise, a study inferred that reassessment as the most important aspect because it evaluates the effectiveness of the treatment strategies and plan and consequently determines the need for changes to achieve adequate relief [3].

In alignment with the institutional guidelines governing the timing of pain reassessment, our observations indicated that nurses diligently adhered to the stipulated recommendation of reassessing patients within a 30 min timeframe. Furthermore, we noted instances of reassessment within this 30 min window, even while the pharmacological intervention was still in progress. This pattern was particularly evident in cases involving tramadol, which necessitated a protracted infusion duration to mitigate potential adverse effects such as nausea and vomiting. In such instances, a subsequent reassessment took place following the conclusion of the infusion, with both the termination of the infusion and the post-infusion pain score meticulously documented in the patient's medical records. Furthermore, we noted instances of reassessment occurring at intervals shorter than the recommended 30 min. It is noteworthy that these expedited reassessments were consistent

with established protocols and primarily applied to medications with rapid administration routes. However, it is important to highlight that in cases where orally administered medications were involved, frequent reassessments within brief time intervals could potentially influence the drug's onset of action. This consideration is particularly critical as these medications require absorption before manifesting their analgesic effects, and overly frequent reassessments could inadvertently indicate no alleviation of pain or only partial improvement due to insufficient time for the drug to take effect.

The current study possesses certain limitations that should be acknowledged. First, the study relied upon retrospective records encompassing pain complaints, drug preferences, and subsequent assessment. Consequently, patients for whom any of these crucial data were absent could not be included in the evaluation. Secondly, the potential influence of pharmacogenetic variability on drug responsiveness, along with the intricate landscape of drug–drug interactions, could significantly impact treatment outcomes but remained unexplored in this analysis. Furthermore, the investigation into the potential impact of non-pharmacological interventions on pain assessment was not pursued in this study. Lastly, the study lacked the capacity to undertake a comparative assessment of the upper and lower thresholds of analgesic effectiveness for newly reported instances of pain across various selected drugs earmarked for management.

5. Conclusions

Pediatric cancer patients frequently experience severe pain during their hospitalization, and the selection of medications to address these pain complaints has demonstrated efficacy in mitigating pain. Notably, opioids are the preferred choice for managing severe pain.

The implementation of a personalized pain management protocol, wherein therapeutic strategies are tailored to the pain severity in conjunction with the selection of established analgesic agents, demonstrated noteworthy effectiveness in ameliorating pain-related concerns within the studied cohort. In the majority of cases, the selection of analgesics correlated with the pain intensity at the time of assessment; nevertheless, medications designated for mild pain were occasionally administered in response to reports of severe and excruciating pain. Despite this observed variation, subsequent reassessments consistently revealed a notable absence of pain.

Despite the importance, few studies have been conducted in the pediatric population to assess dose, frequency, and analgesic effect. This study underscores the utilization of different pharmacological classes to achieve notable reductions in pain intensity among patients grappling with severe pain.

Author Contributions: Conceptualization, E.L.L., T.S.G., C.P.J.K. and F.C.C.; methodology, E.L.L., T.S.G., M.M.G.d.N. and P.C.J.L.S.; software, T.S.G.; validation, E.L.L., M.M.G.d.N. and P.C.J.L.S.; formal analysis, E.L.L. and P.C.J.L.S.; investigation, E.L.L.; resources, E.L.L. and F.B.G.d.N.; data curation, E.L.L. and T.S.G.; writing—original draft preparation, E.L.L.; writing—review and editing, E.L.L., T.S.G. and P.C.J.L.S.; supervision, M.M.G.d.N.; project administration, P.C.J.L.S. All authors have read and agreed to the published version of the manuscript.

Funding: This research received no external funding.

Institutional Review Board Statement: The study was conducted in accordance with the Declaration of Helsinki, and approved by the Research Ethics Committee of the FEDERAL UNIVERSITY OF SÃO PAULO (64195522.8.0000.5505) and by the scientific committee of the GRAACC HOSPITAL (IOP-007-2020).

Informed Consent Statement: Informed consent was obtained from all subjects involved in the study.

Data Availability Statement: Data are contained within the article.

Conflicts of Interest: The authors declare no conflict of interest.

References

1. Constance, J.E.; Campbell, S.C.; Somani, A.A.; Yellepeddi, V.; Owens, K.H.; Sherwin, C.M.T. Pharmacokinetics, Pharmacodynamics and Pharmacogenetics Associated with Nonsteroidal Anti-Inflammatory Drugs and Opioids in Pediatric Cancer Patients. *Expert Opin. Drug Metab. Toxicol.* **2017**, *13*, 715–724. [CrossRef]
2. Landis, S.H.; Murray, T.; Bolden, S.; Wingo, P.A. Cancer Statistics, 1999. *CA A Cancer J. Clin.* **1999**, *49*, 8–31. [CrossRef]
3. Friedrichsdorf, S.; Postier, A. Management of Breakthrough Pain in Children with Cancer. *J. Pain Res.* **2014**, 117. [CrossRef]
4. Siegel, R.L.; Miller, K.D.; Fuchs, H.E.; Jemal, A. Cancer Statistics, 2021. *CA A Cancer J. Clin.* **2021**, *71*, 7–33. [CrossRef]
5. Raja, S.N.; Carr, D.B.; Cohen, M.; Finnerup, N.B.; Flor, H.; Gibson, S.; Keefe, F.J.; Mogil, J.S.; Ringkamp, M.; Sluka, K.A.; et al. The Revised International Association for the Study of Pain Definition of Pain: Concepts, Challenges, and Compromises. *Pain* **2020**, *161*, 1976–1982. [CrossRef]
6. Treede, R.-D. The International Association for the Study of Pain Definition of Pain: As Valid in 2018 as in 1979, but in Need of Regularly Updated Footnotes. *PAIN Rep.* **2018**, *3*, e643. [CrossRef]
7. World Healt Organization. *Guidelines on the Management of Chronic Pain in Children*; WHO: Geneva, 2020; pp. 1–40.
8. World Health Organization. *Persisting Pain in Children Package: WHO Guidelines on the Pharmacological Treatment of Persisting Pain in Children with Medical Illnesses. Conjunto de doc. Sobre el Dolor Persistente en Niños: Directrices de la OMS Sobre el Trat. Farm. del Dolor Persistente en Niños con Enfermedades Médicas*; WHO: Geneva, Switzerland, 2012.
9. World Healt Organization. *WHO Guidelines for the Pharmacological and Radiotherapeutic Management of Cancer Pain in Adults and Adolescents*; WHO: Geneva, Switzerland, 2018.
10. Peng, N.-H.; Lao, A.H.-C.; Chen, C.-H.; Lee, M.-C.; Chiang, L.-W.; Chang, Y.-C.; Liu, H.-F. Knowledge and Attitudes of Pediatric Clinicians Regarding Pediatric Pain Management. *J. Spec. Pediatr. Nurs.* **2020**, *25*, e12302. [CrossRef]
11. Wuni, A.; Salia, S.M.; Ibrahim, M.M.; Iddriss, I.; Nyarko, B.A.; Seini, S.N.; Tonsagri, I.; Mohammed, J. Evaluating Knowledge, Practices, and Barriers of Paediatric Pain Management among Nurses in a Tertiary Health Facility in the Northern Region of Ghana: A Descriptive Cross-Sectional Study. *Pain Res. Manag.* **2020**, *2020*, 1–11. [CrossRef]
12. Gans, D.; Hadler, M.W.; Chen, X.; Wu, S.-H.; Dimand, R.; Abramson, J.M.; Ferrell, B.; Diamant, A.L.; Kominski, G.F. Cost Analysis and Policy Implications of a Pediatric Palliative Care Program. *J. Pain Symptom Manag.* **2016**, *52*, 329–335. [CrossRef]
13. Taam, B.; Lim, F. Best Practices in Pediatric Oncology Pain Management. *Am. J. Nurs.* **2023**, *123*, 52–58. [CrossRef]
14. Zernikow, B.; Smale, H.; Michel, E.; Hasan, C.; Jorch, N.; Andler, W. Paediatric Cancer Pain Management Using the WHO Analgesic Ladder—Results of a Prospective Analysis from 2265 Treatment Days during a Quality Improvement Study. *Eur. J. Pain* **2006**, *10*, 587. [CrossRef] [PubMed]
15. Bussotti, E.A.; Guinsburg, R.; Pedreira, M. da L.G. Cultural Adaptation to Brazilian Portuguese of the Face, Legs, Activity, Cry, Consolability Revised (FLACCr) Scale of Pain Assessment. *Rev. Lat.-Am. Enferm.* **2015**, *23*, 651–659. [CrossRef]
16. da Silva, F.C.; Thuler, L.C.S. Cross-Cultural Adaptation and Translation of Two Pain Assessment Tools in Children and Adolescents. *J. Pediatr.* **2008**, *84*, 344–349. [CrossRef] [PubMed]
17. Friedrichsdorf, S.J.; Postier, A.; Eull, D.; Weidner, C.; Foster, L.; Gilbert, M.; Campbell, F. Pain Outcomes in a US Children's Hospital: A Prospective Cross-Sectional Survey. *Hosp. Pediatr.* **2015**, *5*, 18–26. [CrossRef]
18. Garra, G.; Singer, A.J.; Taira, B.R.; Chohan, J.; Cardoz, H.; Chisena, E.; Thode, H.C. Validation of the Wong-Baker FACES Pain Rating Scale in Pediatric Emergency Department Patients. *Acad. Emerg. Med.* **2010**, *17*, 50–54. [CrossRef]
19. Carvalho, J.A.; de Souza, D.M.; Domingues, F.; Amatuzzi, E.; Pinto, M.C.M.; Rossato, L.M. Pain Management in Hospitalized Children: A Cross-Sectional Study. *Rev. Esc. Enferm. USP* **2022**, *56*. [CrossRef]
20. Friedrichsdorf, S.J.; Goubert, L. Pädiatrische Schmerztherapie Und -Prävention Bei Hospitalisierten Kindern. *Der Schmerz* **2021**, *35*, 195–210. [CrossRef]
21. Thrane, S.E.; Wanless, S.; Cohen, S.M.; Danford, C.A. The Assessment and Non-Pharmacologic Treatment of Procedural Pain From Infancy to School Age Through a Developmental Lens: A Synthesis of Evidence With Recommendations. *J. Pediatr. Nurs.* **2016**, *31*, e23–e32. [CrossRef]
22. Jacob, E.; Puntillo, K.A. Variability of Analgesic Practices for Hospitalized Children on Different Pediatric Specialty Units. *J. Pain Symptom Manag.* **2000**, *20*, 59–67. [CrossRef]
23. Institute of Medicine (US); National Research Council (US) National Cancer Policy Board. The Epidemiology of Childhood Cancer. In *Childhood Cancer Survivorship: Improving Care and Quality of Life*; Hewitt, M., Weiner, S.L., Simone, J.V., Eds.; National Academies Press: Washington, DC, USA, 2003.
24. Manocha, S.; Taneja, N. Assessment of Paediatric Pain: A Critical Review. *J. Basic Clin. Physiol. Pharmacol.* **2016**, *323-331*, 323–331. [CrossRef]
25. Stevens, B.J.; Yamada, J.; Promislow, S.; Barwick, M.; Pinard, M. Pain Assessment and Management After a Knowledge Translation Booster Intervention. *Pediatrics* **2016**, *138*, e20153468. [CrossRef]
26. Tang, S.P.; Yeo, A.S.H.; Cardosa, M.S. Paediatric Pain Management in Low-Income and Middle-Income Countries. *Lancet Child Adolesc. Health* **2021**, *5*, 5–7. [CrossRef] [PubMed]
27. PhD, J.R. Assessment of Nurses' Judgement for Analgesic Requirements of Postoperative Children. *J. Clin. Pharm. Ther.* **1996**, *21*, 159–163. [CrossRef] [PubMed]

28. Gaertner, J.; Stamer, U.M.; Remi, C.; Voltz, R.; Bausewein, C.; Sabatowski, R.; Wirz, S.; Müller-Mundt, G.; Simon, S.T.; Pralong, A.; et al. Metamizole/Dipyrone for the Relief of Cancer Pain: A Systematic Review and Evidence-Based Recommendations for Clinical Practice. *Palliat. Med.* **2017**, *31*, 26–34. [CrossRef] [PubMed]
29. Miró, J.; Micó, J.A.; Reinoso-Barbero, F. The Management of Pediatric Chronic Pain in Spain: A Web-Based Survey Study. *Curr. Med. Res. Opin.* **2021**, *37*, 303–310. [CrossRef] [PubMed]
30. Ornstein, M.Y.; Stocki, D.; Levin, D.; Dvir, R.; Manisterski, M.; Berger-Achituv, S.; Keidar, H.R.; Peled, Y.; Hazan, S.; Rosenberg, T.; et al. Tramadol Treatment for Chemotherapy-Induced Mucositis Pain in Children. *J. Pediatr. Hematol./Oncol.* **2022**, *44*, e487–e492. [CrossRef]
31. Fortier, M.A.; Yang, S.; Phan, M.T.; Tomaszewski, D.M.; Jenkins, B.N.; Kain, Z.N. Children's Cancer Pain in a World of the Opioid Epidemic: Challenges and Opportunities. *Pediatr. Blood Cancer* **2020**, *67*, e28124. [CrossRef]
32. Yaster, M.; McNaull, P.P.; Davis, P.J. The Opioid Epidemic in Pediatrics: A 2020 Update. *Curr. Opin. Anaesthesiol.* **2020**, *33*, 327–334. [CrossRef]