Multimodal Perioperative Pharmacological Protocol in Pediatric Spine Surgery

Lucas Piantoni, Carlos A. Tello, Rodrigo G. Remondino, Eduardo Galaretto, Mariano A. Noel
Department of Spinal Pathology, Hospital de Pediatría Prof. Dr. Juan P. Garrahan. Buenos Aires, Argentina

ABSTRACT

Introduction: Spine surgery has one of the highest morbimortality rates in the pediatric population. Pain management has not been standardized on said population. Multimodal analgesia (MMA) was developed to resolve that problem. **Objective:** To develop, based on a systematic review, a detailed and original pain management multimodal pharmacology protocol for pre and post-operative (intra and extra-hospital) periods for the pediatric population undergoing spine surgery. **Materials and Methods:** We conducted a systematic review of full texts in English and Spanish from PubMed, Embase, Cochrane Library, and LiLacs Database from 2000 to 2021. We used the PRISMA flow diagram. **Results:** From a total of 756 papers, 38 were included in the final evaluation. Considering the bioethical difficulties to develop a manuscript from clinical trials with drugs and drug combinations in the pediatric population, we developed an original and detailed pain management protocol for pre and post-operative (intra and extra-hospital) periods for the pediatric population undergoing spine surgery. **Conclusion:** Based on a systematic review, we succeeded in developing a simple and easily reproducible perioperative multimodal pain management protocol (intra and extra-hospital), intending to expedite the patient's functional recovery and reduce global socioeconomic costs.

Level de Evidence: II

Keywords: spine surgery; pediatrics; post-operative pain; multimodal analgesia

Protocolo multimodal farmacológico perioperatorio en cirugía de columna pediátrica

RESUMEN

Introducción: La cirugía de columna es uno de los procedimientos con mayor morbimortalidad dentro de la población pediátrica; el manejo farmacológico del dolor en dicha población aún no se encuentra estandarizado. La analgesia multimodal (MMA) trata de responder a esta problemática. **Objetivo:** Desarrollar, basados en una revisión sistemática de la literatura, un detallado protocolo multimodal farmacológico para el manejo del dolor pre- y posoperatorio intra/extrahospitalario en cirugía de columna pediátrica. **Materiales y Métodos:** Se realizó una revisión sistemática de textos completos en inglés o español en PubMed, Embase, Cochrane Library y LILACS Database publicados entre 2000 y 2021; se aplicó el diagrama de flujo PRISMA. **Resultados:** De 756 artículos preseleccionados, 38 fueron incluidos en la evaluación final. Dada la dificultad bioética de desarrollar trabajos en formato de ensayos clínicos con fármacos y combinaciones de ellos en la población pediátrica, desarrollamos un protocolo detallado de manejo de dolor pre- y posoperatorio EV/VO, intra- y extrahospitalario, para aplicar en niños llevados a cirugía de columna. **Conclusión:** Logramos desarrollar un detallado protocolo multimodal farmacológico para el perioperatorio intra- y extrahospitalario de cirugía de columna en niños, sencillo y reproducible, tendiente a acelerar la recuperación funcional del paciente y disminuir los costos socioeconómicos globales.

Palabras clave: cirugía de columna, pediatría, dolor posoperatorio, analgesia multimodal

Nivel de Evidencia: II

Received on May 1th, 2022. Accepted after evaluation on July 20th, 2022 • Dr. LUCAS PIANTONI • lucaspiantoni@gmail.com https://orcid.org/0000-0002-6616-9314

How to cite this article: Piantoni L, Tello CA, Remondino RG, Galaretto E, Noel MA. Multimodal Perioperative Pharmacological Protocol in Pediatric Spine Surgery. *Rev Asoc Argent Ortop Traumatol* 2022;87(6):825-837. https://doi.org/10.15417/issn.1852-7434.2022.87.6.1490

INTRODUCTION

Scoliosis is a three-dimensional deformity of the spine, which generates a pathological angulation. Treatment may eventually require surgery, its objective is to prevent the progression of the deformity and to correct and obtain a solid arthrodesis. This surgery is recognized as one of the most invasive orthopedic procedures performed on pediatric patients.[1-4]

Spinal surgery in the pediatric population is associated with considerable postoperative pain, which frequently requires the parenteral use of opioids. The counterpart is the usual adverse effects, such as nausea, vomiting, pruritus, urinary retention and respiratory depression. At the same time, states of moderate sedation could delay the patient's functional recovery and discharge.[1,4-32]

The other pharmacological group usually associated with opioids and used in pediatric surgery are NSAIDs (non-steroidal anti-inflammatory drugs). These are considered analgesic, anti-inflammatory, antipyretic and antiplatelet agents for the most part. They have a peripheral and central mechanism of action, less analgesic efficacy than opioids, with a ceiling effect of toxicity. The adverse effects to take into account are gastrotoxicity, hepatotoxicity, neurotoxicity, cardiotoxicity, anaphylaxis and inhibition of platelet aggregation, among others. [1-12,16-19,22-24,32-41]

In some patients and their families, fear of Post-Op Pain creates stress, and this negatively affects recovery. In turn, the literature describes postoperative pain associated with spinal surgery as one of the most frequent variables for hospital readmission, among others.[42]

Pain management after spinal surgery in the pediatric population can be approached in different ways. To our knowledge, this topic does not appear clearly standardized in the literature, so there are innumerable references to multiple drugs, routes of administration, and possible combinations associated with pre-, intra-, and postoperative pain management. [1-15,32-39,43-45] Among them, we can mention the use of opioid derivatives, administered by health personnel or through a patient-controlled analgesia (PCA) device. Continuous epidural infusion (CEI) of opioids or intrathecal injection (IDD) of morphine in a single dose (pre- or intraoperative) are also indicated. These regimens, added to the use of adjuvants, have been used intravenously (IV) and orally (PO) during the postoperative period during hospitalization and after discharge.[1-21,23-39,46,47]

Multimodal analgesia (MMA), first described in 1993 by Kehlet and Dahlj, arises in response to this problem. It is based on the combination of different analgesic and anti-inflammatory drugs, taking into account the different underlying pathophysiological mechanisms. This approach proposes to achieve a more adequate control of pain using lower doses of drugs, thus reducing their adverse effects. [1-21,23-39,47]

The pharmacological management of postoperative pain after pediatric spine surgery, which includes MMA, is not clearly standardized in the international literature. It is possible to find various papers that propose alternative, not completely defined algorithms for pre-, intra- and postoperative medication, for intra- or extra-hospital use. We understand that the development and subsequent implementation of such a protocol, with an adequate detail of the complete dosage, frequency, and days, both in the in-hospital and out-of-hospital context (within the availability of each means), would improve the quality of life of the patient and accelerate their functional recovery while decreasing the socioeconomic costs of the family group and the health system. [1-21,23-39,47]

The objective of this research was to develop, through a systematic review of the literature, a detailed and original multimodal pharmacological protocol for the management of pre- and postoperative pain, intra- and extra-hospital, in spinal surgery in the pediatric population.

MATERIALS AND METHODS

We conducted a literature search of full texts in English or Spanish published between 2000 and 2021 in the PubMed, Embase, Cochrane Library and LILACS Databases. For the literature search, the following combination of MeSH (Medical Subject Headings) terms was used: "spine surgery", "postoperative pain" and "pediatrics". Additionally, a manual search was performed. The extracted information was ordered by main author, year of publication, department in charge, study design, drugs used and recommended doses, conclusions, and recommendations.

A total of 756 articles were found, of which 38 were included in the final evaluation. Inclusion criteria were patients aged 10-18 years who had undergone primary instrumented spinal surgery and had received a multimodal management protocol for postoperative pain.

As this is a systematic review, approval by an ethics committee or institutional review board (IRB) was deemed unnecessary. The flowchart standard known as PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) was followed, as summarized in Figure 1.

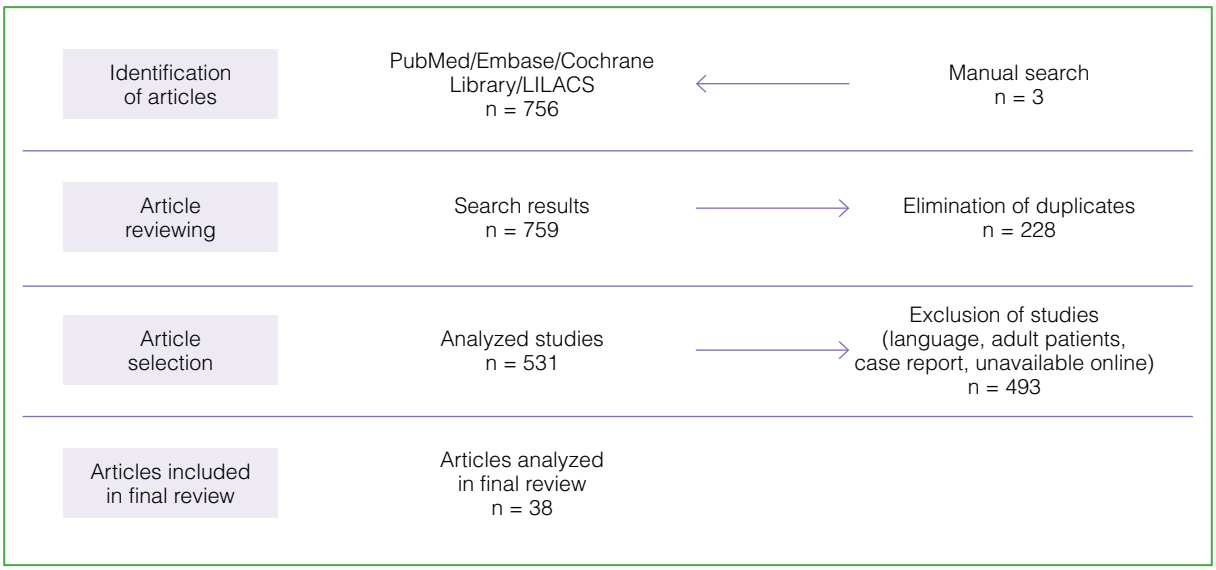

Figure. 1. Flowchart (PRISMA)

RESULTS

756 articles were found, of which 718 were excluded because they had not met the inclusion criteria, because they were duplicated, because they were not available online, or because they were case reports. In short, the final analysis included 38 studies and significant heterogeneity was detected among them in terms of methodology, population evaluated, and arbitrary comparisons between drugs and doses.

Most of the 38 papers considered had a multidisciplinary approach; 14 papers were in charge of anesthesiologists, 13 were authored by trauma surgeons, 7 responded to clinical medicine, 3 to the specialty of palliative care, and 2 were approached by neurosurgeons. Within the methodologies followed, we registered 14 systematic reviews, 11 case series, 5 were not clearly specified, and 3 were expert recommendations.

The vast majority of these works described the need to introduce a multimodal analgesia scheme, be it preoperative, intraoperative (in its various routes of administration) or postoperative, or their combinations. Some of them were inconclusive and made little reference to intra- and extra-hospital postoperative pain management.

The work of Lee et al. is worth noting, a systematic review in which they developed an intraoperative and postoperative pain MMA scheme (admission and discharge), where opioids were used with PCA. In this work, no reference was made to preoperative medication, and extensive reference was made to the difference between intraoperative and epidural opioids versus intrathecal opioids.[32]

On the other hand, Frizzell et al., included general orthopedic patients, with a methodology not fully specified, where various tools were listed for the management of postoperative pain, with drugs and possible doses not clearly defined, and they developed an intra- and extra-hospital protocol with opioids (with PCA).[39]

In a case series with 57 patients who underwent spinal surgery, Anderson et al. described a protocol with opioids and PCA. The doses of the different drugs were not detailed and regarding the frequency, it was indicated "as needed". They did not describe it according to days of postoperative pain nor with respect to the out-of-hospital period.[30]

Yoo et al. comprehensively described the physiopathogenesis of pain; the methodology of work is not completely clear. An MMA pain management protocol was described on postoperative days 1 and 2 only, and no reference was made to management at hospital discharge.[23] In a retrospective study of 29 patients with Post-Op Pain of the pectus in pediatrics, Man et al. described an interesting and rich MMA pain management protocol during the postoperative period and after discharge, but did not clarify the dose or relationship with Post-Op Pain days.[37]

Rao et al. referred to the importance of pain management in a MMA format within an ERAS (Enhanced Recovery After Surgery) protocol, and supported the use of opioids with PCA. They did not detail the doses of the Post-Op Pain drugs and the study lacked an analgesic plan at discharge.[25] Table 1 summarizes the information collected from the works finally evaluated.

Table 1. Main characteristics of the selected works

#	Authors/ Year	Department/s in charge of research	Study design	Pediatric population included	Described MMA pain scheme (drugs/dose)	Drugs/doses described	Strengths and/or limitations of the work
1	Wong et al./2017	Orthopedics/ Rehabilitation/Physical Therapy	Systematic review	Yes	No	NSAIDs, paracetamol	Promoted patient and family education
2	Rawal et al./2016	Anesthesia	Not specified	Not specified	No	NSAIDs, ketamine, gabapentinoids, opioids	Promoted communication between palliative care specialists, nurses, and surgeons
3	Joshi et al./2019	General Surgery	Not specified	Not specified	No	NSAIDs, ketamine, gabapentinoids, opioids	Collaborated with ERAS
4	Kaye et al./2020	Anesthesia	Systematic review	Not specified	No	Dexmedetomidine	Promoted use of dexmedetomidine
5	Borgeat et al./2008	Anesthesia	Systematic review	Yes	No	NSAIDs, acetaminophen, gabapentin, opioids, corticosteroids, and muscle relaxants	Promoted use of epidural analgesia
6	Chou et al./2018	Orthopedics / Neurology / Epidemiology	Systematic review	Not specified	No	NSAIDs, acetaminophen, antidepressants, gabapentinoids	No corticosteroids/BZD, adaptation of analgesia to low-resource countries. Patient education
7	Oliveira et al./2018	Clinical / Physical Therapy	Systematic review	Not specified	No	NSAIDs, acetaminophen, opioids, antidepressants	Promoted practical pain treatment guidelines
8	Hsu et al./2019	Orthopedics / Palliative care	Expert recommendation	Not specified	No	NSAIDs, acetaminophen, gabapentin, opioids	Promoted MMA treatment/ physical and cognitive therapy
9	Zielinski et al./2020	Head and neck surgery	Systematic review	Yes	No	NSAIDs, opioids, paracetamol	Promoted practical pain treatment guidelines
10	Koes et al./2010	Clinic	Systematic review	Not specified	No	NSAIDs, acetaminophen, antidepressants, corticosteroids, gabapentinoids	Using how-to guides are challenging
11	Aubrun et al./2019	Clinic / Palliative	Expert recommendation	Not specified	No	NSAIDs, ketamine, gabapentin, opioids	Addition of opioids, dexamethasone, NSAIDs

12	Apfelbaum et al./2012	Anesthesia	Case series	Not specified	Partially	Paracetamol, fentanyl, opioids, NSAIDs, ketamine.	Promoted MMA treatment, did not describe it with doses/days
13	Yousefifard et al./2019	Anesthesia / Emergencies / Physiology	Systematic review	Adult and pediatric	No	Paracetamol, fentanyl, opioids, NSAIDs, ketamine.	Did not recommend unimodal use of opioids
14	Joshi et al./2017	Anesthesia	Expert recommendation	Not specified	No	Paracetamol, fentanyl, opioids, NSAIDs, ketamine.	Review methodology to develop pain guidelines
15	Creary et al./2020	Anesthesia / Clinic / Palliative	Retrospective study (n= 1505)	Yes	No	NSAIDs, opioids	Stimulating work with opioids in pediatric guidelines
16	Dabbagh et al./2020	Emergency	Not specified	Yes	No	No	Adding non-pharmacological therapies
17	Frizzell et al./2017	Orthopedics	Not specified	Yes	Partially	Acetaminophen, NSAIDs, opioids, gabapentinoids, BZDs.	Methodology not specified; did not dose all drugs; opioids with PCA; orthopedic surgery; High MMA without dose.
18	Young/2017	Emergency	Systematic review	Yes	No	No	Promoted rapid diagnosis and treatment of pain, adding non-pharmacological therapies
19	Lee et al./2020	Anesthesia	Systematic review	Yes	Yes, w/ PCA	Opioids, ketamine, gabapentin, BZD.	Systematic review; opioid differences EPI vs. ITM; no pre-OP drugs; opioids with PCA; MMA day/day with dose
20	Jones et al./2014	Anesthesia	Retrospective study (n= 163)	Yes	No	Dexmedetomidine, opioids	No differences between groups with or without dexmedetomidine
21	Hong et al./2017	Anesthesia	Retrospective study (n= 40)	Yes	No	Fentanyl, oxycodone, ketorolac, paracetamol, diazepam	Promoted MMA treatment
22	Mc Nicol et al./2018	Anesthesia	Systematic review	Yes	No	Opioids, ketorolac	Insufficient data to support use of ketorolac
23	Aoki et al./2021	Anesthesia	Retrospective study (n= 142)	Yes	No	Dexmedetomidine, opioids, NSAIDs, acetaminophen	MMA and fentanyl use need to be better studied
24	Sheffer et al./2017	Orthopedics	Non-systematic review	Yes	No	NSAIDs, ketamine, gabapentinoids, opioids	Promoted MMA treatment
25	Shah et al./2020	Orthopedics / Clinic	Systematic review	Yes	No	NSAIDs, acetaminophen, gabapentin, opioids	Promoted MMA treatment
26	Johnson et al./2021	Orthopedics	Systematic review	Yes	No	NSAIDs, opioids, gabapentinoids, corticosteroids	Reduction of pain to improve recovery

27	Anderson et al./2020	Orthopedics	Case series (n= 57)	Yes	Partially	NSAIDs, gabapentin, opioids, acetaminophen	prospective; idiopathic PIA; opioids with PCA; Post-Op Pain drugs without doses; drugs "according to pain"; high MMA without dose
28	Yoo et al./2019	Orthopedics / Anesthesia	Non-systematic review	Yes	Partially	NSAIDs, acetaminophen, gabapentin, opioids, corticosteroids, and muscle relaxants	Methodology not specified; detailed pain pathophysiology; Post-Op Pain day 1-2 only; no discharge MMA protocol
29	Rajpal et al./2010	Orthopedics / Neurosurgery	Case series	Not specified	No	NSAIDs, acetaminophen, gabapentin, opioids	Promoted MMA treatment
30	Devin et al./2015	Orthopedics / Neurosurgery	Systematic review	Not specified	No	NSAIDs, acetaminophen, gabapentin, opioids	Promoted MMA treatment
31	Man et al./2017	Anesthesia / Clinic	Case series (n= 29)	Yes	Partially	NSAIDs, acetaminophen, gabapentin, opioids and muscle relaxants, ketamine, corticosteroids	Retrospective; Post-Op Pain pectus; did not give Post-Op Pain dose; discharge MMA without dose
32	Rao et al./2021	Orthopedics	Case series (n= 117)	Yes	Partially	NSAIDs, acetaminophen, gabapentin, opioids	Retrospective; did not give dosage; opioids with PCA; no discharge MMA protocol
33	Song et al./2014	Orthopedics / Anesthesia	Case series (n= 155)	Yes	No	NSAIDs, acetaminophen, gabapentin, opioids, and muscle relaxants	Promoted ERAS in Post-Op Pain and MMA
34	YaDeau et al./2019	Orthopedics / Anesthesia	Case series (n= 154)	No	Partially	Acetaminophen, NSAIDs, opioids	Shoulder arthroplasty, MMA for Post-Op Pain without doses/days, no discharge MMA protocol
35	Pagnotto et al./2012	Not specified	Technique description	No	Partially	Acetaminophen, NSAIDs, opioids	Knee arthroplasty; includes pre-OP MMA, no post-OP MMA doses/days, no discharge MMA protocol
36	Bean et al./2018	Orthopedics	Case series (n= 61)	No	Partially	Acetaminophen, NSAIDs, opioids, gabapentinoids, antipsychotics	knee arthroplasty Post-Op Pain; uses trade names of drugs; MMA Post-Op Pain protocol without clear dosage and without days
37	Li et al./2021	Orthopedics	Case series (n= 216)	No	Yes, Post-Op Pain knee arthroplasty	Acetaminophen, NSAIDs, opioids, gabapentinoids	Post-Op Pain knee arthroplasty; uses trade names of drugs; MMA Post-Op Pain protocol without days/dosage
38	Karam et al./2021	Orthopedics	Non-systematic review	No	Partially	Acetaminophen, NSAIDs, opioids, gabapentinoids, corticosteroids	MMA Post-Op Pain hip/knee arthroplasty; no regulated opioids, no dosage/days

MMA, multimodal analgesia; NSAIDs, non-steroidal anti-inflammatory drugs; ERAS, Enhanced Recovery After Surgery; BZD, benzodiazepines; PCA, patient-controlled analgesia; EPI, epidural morphine; ITM; intrathecal morphine; PIA, posterior instrumented arthrodesis; n, number of patients.

DISCUSSION

Spinal surgery is one of the procedures with the highest morbidity and mortality among surgeries performed in the pediatric population.[1-3,20,32,33,37,42-45] postoperative pain is frequently severe and requires advanced pharmacological management in the pre-, intra- and postoperative period through intrathecal, intravenous and oral administration and a combination of other methods. [1-21,25-38] In regimens used as the main or only drug, systemic opioids are associated with numerous adverse effects such as nausea, constipation, pruritus, urinary retention, sedation, respiratory depression, deep vein thrombosis, pulmonary embolism, depression and insomnia, and greater probabilities of developing chronic pain, prolonged hospitalization, hospital readmissions, possibility of addiction and effects on the hypothalamus-pituitary axis.[1-3,21,32,33,37,43-45]

Within the other group of drugs commonly used in schemes for the management of perioperative pain, NSAIDs, their gastrotoxicity, hepatotoxicity, neurotoxicity, cardiotoxicity, anaphylaxis and inhibition of platelet aggregation, among others, must be taken into account. [1-12,16-19,22-24,32-38,40] The prevention and effective multimodal management of acute pain could improve clinical outcomes and the quality of life of the patient and their family, avoiding complications and reducing family and health system costs.[1-19,21-47]

It is vitally important to contextualize, within the possibilities of each demographic region and availability of the health group, the variables of each patient, such as weight, age, comorbidities and contraindications for the appropriate use of opioids, NSAIDs and multiple other pharmacological options detailed in this work. Our objective was to propose a rational and balanced multimodal pharmacological scheme for pain, which implies lower doses and a more reduced profile of expected adverse effects, in a context suitable for the patient, as a unique individual, which is a difficult task.

In a prospective study whose objective was to evaluate the concerns in the perioperative period of both the patients and their relatives, Chan et al. found that the greatest concern was postoperative pain, at 55%.[48] For their part, Landaman et al. concluded that postoperative pain management success has been measured by radiographic images, classifications, and magnitudes of correction; however, the system has consistently failed to report pre- and postoperative pain.[49]

Members of the American Society of Anesthesiology (ASA) strongly recommend the evaluation of pediatric patients who are about to undergo surgical procedures for timely perioperative management. Analgesic therapy will depend on age, weight, comorbidities and contraindications, within an important multidisciplinary work. postoperative pain management has to be aggressive and proactive in bringing to fruition a generally undertreated problem.[13]

It is not possible to achieve optimal management of postoperative pain with a single drug or a single method without significant adverse effects.[1-5,32,34,37,39,43-45] Piantoni et al. reported that 80% of the pediatric population reported a poor experience in post-surgery pain management, and only half of these patients resolved their pain satisfactorily in the following days.[4] Wong et al. found that 7-10% of adolescent patients reported back pain more than 12 months after surgery.[50]

During pediatric spinal surgery, several anesthetic techniques involve high doses of opioids, but with short durations of action, such as remifentanil, to facilitate neurophysiological monitoring.[51] PCA, described in all postoperative pain protocols in the international literature, has the loss of control during the night as its first disadvantage; regardless of this, it is not available in all media. Other articles refer to the use of morphine EPI in scoliosis surgery, the difficulty of which is placement and maintenance of the catheter in the epidural space. The application of an MMA regimen in the pediatric population has been delayed due to the lack of literature focused on this age group. The current concern about the adverse effects of drugs in children is, today, the basis of countless investigations, and the published studies focus on finding ways to reduce opioid use and its adverse effects.[1-4,6,7,9,10,13-15,23-31,34,35,39,38,45,52]

There are new trends to reinforce the idea of this modality, for example, the addition of NSAIDs and antineuritics.[1-20,22-40,42-45,47] It has been shown that the administration of postoperative pain NSAIDs would reduce the probability of prolonged use of opioids, their adverse effects and hospital stay.[2-15,37-37,43-45] Muhly et al. recently examined a way to rapidly recover and decrease postoperative pain after spinal instrumentation using preoperative gabapentin and acetaminophen, and postoperative intravenous acetaminophen, opioid PCA, gabapentin, and ketorolac.[31]

Milbrant et al. reported that a simple IT morphine infusion would produce fewer adverse effects compared to EPI and PCA, which can range from pruritus or transient neurological changes to respiratory depression.[1] In a system-

atic review, Zielinski et al . promoted the use of MMA in the pediatric population,[21] like Hsu et al.[7] and Oliveira et al.[6] Along the same lines, Sha et al.[9] and Sheffer et al.[10] referred to the need to promote an MMA scheme. PCA involves, on the one hand, a problem of equipment availability, and, on the other, an organizational and patient monitoring inconvenience. The epidural catheter, in addition to being expensive and technically complex, is not the choice for surgery in our setting, because one of the primary objectives is the rapid mobilization of the patient, and this would hinder said functional recovery.

Chou et al. concluded that the use of NSAIDs, acetaminophen and antidepressants is convenient.[33] In turn, Aubrun et al. recommended the use of NSAIDs, ketamine, opioids, and gabapentin.[8] Yousefifard et al. recommended the use of paracetamol, fentanyl and opioids, and did not advise the isolated use of opioids, both in the adult and pediatric population.[5]

The use of muscle relaxants and benzodiazepines was widely developed as an important adjunctive tool within MMA regimens in the works of Walker et al.,[2] Lee et al.,[32] Oliveira et al., [6] Parrish et al., [34] Frizzell et al., [39] Hong et al., [35] Koes et al., [36] Borgeat et al., [12] Man et al., [37] Yoo et al., [23] and Song et al., [47] among others. In turn, there is an extensive description of the incorporation of glucocorticoids in MMA schemes, for example, in Cozowicz et al.,[3] Chou et al., [33] Parrish et al., [34] Johnson et al., [11] Koes et al., [36] Borgeat et al., [12] Man et al., [37] Ntalouka et al., [43] Mathiensen et al., [44] Momon et al., [45] and Yoo et al., [23] among others.

Being aware of the bioethical difficulty of conducting research in the form of clinical trials with drugs and their combinations in the pediatric population and considering the scant international literature on physiopathogenesis and pharmacodynamics in this population, in this report we propose a basic perioperative pain management protocol— IV/PO, intra- and extra-hospital—to be applied in the pediatric population subjected to spinal surgery. This protocol is supported by treatment guidelines such as Cochrane, ASA "American Society of Anesthesiology" and others, and published case series (see Table 1). This protocol includes drugs and devices available in our setting (not PCA) and is described by agent, dose, route, and day.

The drugs and their doses were adjusted to the availability and regulations of the hospital handbook, after the consensus of the Sociedad Argentina de Pediatría.[53] During the postoperative period, pain assessment was performed daily according to the Numerical Assessment Scale, with a diet rich in fiber and supervision by the palliative care team (referral). Hospital discharge: same pharmacological scheme for 7 days and outpatient control by the palliative care team, taking into account that the aim is a short-term pharmacological intervention.

Special considerations with respect to the original pharmacological protocol

Regarding the adjustment of the morphine dose as rescue, this will be done as needed; which will be evaluated with the FLACC pain scale, VAS/VNS, Wong & Baker, every 6 h. Depending on the value it returns, different measures will be taken, namely:

a) 4-5 (moderate pain): administer rescue doses and reassess after 10 minutes, wait for a decrease or control of pain.

b) 6-8 (intense pain): administer rescue doses and increase the infusion rate of the analgesic plan by 15%. Reassess after 10 minutes, wait for a decrease or control of pain.

c) 9-10 (maximum pain): administer rescue doses and increase analgesic plan by 30%. Reassess after 10 minutes, wait for a decrease or control of pain.

Balance dose/adverse effects at all times, check co-analgesics and adjuvants, rule out complications. Oral reassessment could be considered every 60 minutes.

In the event of adverse effects:

-*Nausea and vomiting*: adjust ondansetron 0.1 mg/kg/dose IV up to 3 times/day, without exceeding 4 mg/dose. If the episodes continue, add metoclopramide 0.15 mg/kg/dose IV infused over 20 minutes, every 8 h.

-*Pruritus (more common in subcutaneous administration)*: naloxone 1 mcg/kg/ IV dose in 20 minutes, with the possibility of repeating the infusion every 4 h.

-*Urinary retention*: if there is a bladder balloon, perform a bladder catheter, gradually evacuating its contents. Naloxone 1 mcg/kg/ IV dose will then be administered over 20 minutes, with the possibility of repeating the infusion every 4 hours (the same if there is urinary retention without a bladder balloon).

-*Respiratory depression*: assess the respiratory rate (RR) according to age (<1 year: 30 to 60 rpm, 1-4 years: 24-40 rpm, 4-5 years: 22 to 34 rpm, 6-12 years: 18 to 30 rpm and 13-18 years: 12 to 16 rpm).

Table 2. Perioperative pain management protocol in pediatric spine surgery

Preoperative period
Single dose gabapentin (10 mg/kg) PO
Single dose paracetamol (20 mg/kg) PO

Postoperative day 0 (POp-D0 - from the operating room)
Morphine 0.4 mg/kg/day IV (continuous infusion/CI)
Rescue with morphine 0.04 mg/kg/IV dose (administer max. every 4 h)
Paracetamol 12.5 mg/kg/dose IV every 6 h (CI)
Ibuprofen 5 mg/kg/ IV dose every 6 h (CI)
Ketamine (0.2 mg/kg/h) (CI)
Dexmedetomidine (0.3 mcg/kg/h) (CI)
Ondasentron 0.15 mg/kg/dose IV every 8 h IV (CI)
Omeprazole 1 mg/kg/dose IV every 24 h (CI)

Postoperative day 1 (POp-D1)
Morphine 0.3 mg/kg/day IV (continuous infusion)
Rescues with morphine 0.03 mg/kg/IV dose (administer max. every 4 h)
Paracetamol same dose/frequency PO
Ibuprofen same dose/frequency PO
Dexamethasone same dose/frequency PO
Ketamine (0.2 mg/kg/h) (CI)
Dexmedetomidine (0.3 mcg/kg/h) (CI)
Ondasentron same dose/frequency VO
Omeprazole same dose/frequency PO
Gabapentin 100 mg/dose PO every 8 h PO
PKT (physiokinesiotherapy) - exercises (GMFCSI-V); sitting and standing on the edge of the bed (GMFCS I-II-III)-

Postoperative day 2 (POp-D2)
Morphine 0.6 mg/kg/day PO
Rescues with morphine 0.06 mg/kg/dose PO (administer max. every 4 h)
Paracetamol same dose/frequency PO
Ibuprofen same dose/frequency PO
Dexamethasone same dose/frequency PO
Ondasentron same dose/frequency PO
Omeprazole same dose/frequency PO
Gabapentin 300 mg/dose every 8 h PO
PKT - exercises (GMFCSI-V); free ambulation (GMFCS I-II-III)-

Postoperative day 3 (POp-D3) and subsequent days…
Tramadol 1.5 mg/kg/dose every 8 h PO
Rescues with morphine 0.05 mg/kg/dose PO (administer max. every 4 h)
Paracetamol same dose/frequency PO
Ibuprofen same dose/frequency PO
Ondasentron same dose/frequency VO
Omeprazole same dose/frequency PO
Gabapentin same dose/frequency PO
PKT (same)

Out-of-hospital protocol (see palliative/medication reduction plan)
Tramadol 1.5 mg/kg/dose every 8 h PO
Rescues with PO morphine (10% of the oral morphine dose)
Paracetamol same dose/frequency PO
Ibuprofen same dose/frequency PO
Ondasentron same dose/frequency PO (optional)
Omeprazole same dose/frequency PO
Gabapentin same dose/frequency PO

POp-D0-1-2-3, postoperative day 0-1-2-3; IV, intravenous; PO, orally; GMFCS: gross motor function classification system; CI, continuous infusion.

If there is a 30% decrease in the minimum value established according to age, the treating physician in charge will be notified and the use of naloxone will be evaluated. If the patient is sedated and there is a RR <50% of expected, put on an oxygen mask, stop the opioid infusion, and administer naloxone 1 mcg/kg until the RR returns to normal values for the age group. Due to its half-life, the glucocorticoid will be administered during the intraoperative period, without repeating it regularly during the postoperative period. Bear in mind that its half-life is much shorter than that of morphine, if it is used to reverse respiratory depression.

During the first 48 hours, pain will be managed with morphine associated with NSAIDs and adjuvants (ketamine/dexmedetomidine, see options), in continuous infusion according to the rules established in the treating center. After this period, tramadol will be rotated for 24 to 48 h in continuous infusion. The intention of continuous infusion is to avoid periods of low effective drug concentration, with subsequent onset of pain. Given the need for rescue, this would be performed with IV morphine and after the IV catheter is removed, it is changed to PO. In order to avoid the appearance of tolerance in patients in whom it is difficult to gradually decrease the dose of morphine, it is recommended to associate methadone to the plan, although it is difficult to develop tolerance to the opioid in 48/96 h.

Patients should be assessed daily for catharsis and fed high-fiber diets, with plenty of hydration, during the time opioids are being administered. The goal is to reduce the appearance of constipation. If this appears, the recommended laxatives are osmotic. The first choice of treatment in children of any age is polyethylene glycol 3350 due to its safety, effectiveness and tolerance. Its dose varies between 0.25 to 1.5 g/kg. In our country, peripheral μ-receptor inhibitors are not yet available.

With this report we begin the definition of a multidisciplinary protocol for pain management in pediatric spinal surgery, which ranges from the preoperative period and covers the intra- and extra-hospital postoperative period. Its purpose is to improve the quality of care and hospital stay, and reduce the appearance of adverse effects, for which the multidisciplinary approach is essential.

As limitations, it should be noted that we limited the systematic review to the English and Spanish languages, that we limited the search for articles to those published between 2000 and 2021, and that we found significant heterogeneity in the materials and methods described in the papers.

CONCLUSION

This systematic review evidences, on the one hand, the profound problems regarding standardized postoperative pain management, and, in turn, highlights the need to develop a detailed, simple and easily reproducible multimodal pharmacological protocol for the intra- and extra-hospital perioperative period of spinal surgery in the pediatric population. We believe we have achieved it. New research will be required to optimize postoperative analgesia protocols in this group of patients, due to their various pathologies.

Acknowledgments

Dr. Luciano H.R. Ronconi and Dr. Merlina A Conti, from the Anesthesia Department of “Hospital de Pediatría “Prof. Dr. Juan P. Garrahan”.

Conflict of interest: The authors declare no conflicts of interest.

Carlos A Tello ORCID ID: https://orcid.org/0000-0002-1733-1004
Rodrigo G Remondino ORCID ID: https://orcid.org/0000-0002-8388-298X
Eduardo Galaretto ORCID ID: https://orcid.org/0000-0003-4121-8228
Mariano A Noel ORCID ID: https://orcid.org/0000-0002-6668-1342

REFERENCES

1. Milbrandt TA, Singhal M, Minter C, McClung A, Talwalkar VR, Iwinski HJ, et al. A comparison of three methods of pain control for posterior spinal fusions in adolescent idiopathic scoliosis. *Spine (Phila Pa 1976)* 2009;34(14):1499-503. https://doi.org/10.1097/BRS.0b013e3181a90ceb
2. Walker CT, Gullotti DM, Prendergast V, Radosevich J, Grimm D, Cole TS, et al. Implementation of standardized multimodal postoperative analgesia protocol improves pain control, reduces opioid consumption, and shortens length of hospital stay after posterior lumbar spinal fusion. *Neurosurgery* 2020;87(1):130-6. https://doi.org/10.1093/neuros/nyz312
3. Cozowicz C, Bekeris J, Poeran J, Zubizarreta N, Schwenk E, Girardi F, et al. Multimodal pain management and postoperative outcomes in lumbar spine fusion surgery: A population-based cohort study. *Spine (Phila Pa 1976)* 2020;45(9):580-9. https://doi.org/10.1097/BRS.0000000000003320
4. Piantoni L, Tello CA, Francheri Wilson IA, Remondino R, Galaretto E, et al. Manejo del dolor posoperatorio por cirugía de columna en la población pediátrica. Resultados preliminares. *Rev Asoc Argent Ortop Traumatol* 2019;84(3):224-35. https//doi.org/10.15417/issn.1852-7434.2019.84.3.9314
5. Yousefifard M, Askarian-Amiri S, Madani Neishaboori A, Sadeghi M, Saberian P, Baratloo A. Pre-hospital pain management; a systematic review of proposed guidelines. *Arch Acad Emerg Med* 2019;7(1):e55. PMID: 31875209
6. Oliveira CB, Maher CG, Pinto RZ, Traeger AC, Lin CWC, Chenot JF, et al. Clinical practice guidelines for the management of non-specific low back pain in primary care: an updated overview. *Eur Spine J* 2018;27(11):2791-803. https://doi.org/10.1007/s00586-018-5673-2
7. Hsu JR, Mir H, Wally MK, Seymour RB. Orthopaedic Trauma Association Musculoskeletal Pain Task Force. Clinical practice guidelines for pain management in acute musculoskeletal injury. *J Orthop Trauma* 2019;33(5):e158-e182. https://doi.org/10.1097/BOT.0000000000001430
8. Aubrun F, Nouette-Gaulain K, Fletcher D, Belbachir A, Beloeil H, Carles M, et al. Revision of expert panel's guidelines on postoperative pain management. *Anaesth Crit Care Pain Med* 2019;38(4):405-11. https://doi.org/10.1016/j.accpm.2019.02.011
9. Shah SA, Guidry R, Kumar A, White T, King A, Heffernan MJ. Current trends in pediatric spine deformity surgery: multimodal pain management and rapid recovery. *Global Spine J* 2020;10(3):346-52. https://doi.org/10.1177/2192568219858308
10. Sheffer BW, Kelly DM, Rhodes LN, Sawyer JR. Perioperative pain management in pediatric spine surgery. *Orthop Clin North Am* 2017;48(4):481-6. https://doi.org/10.1016/j.ocl.2017.06.004
11. Johnson MA, Andras LM, Andras LE, Ellington MD, Upasani VV, Shah AS. What's new in pain management for pediatric orthopaedic surgery. *J Pediatr Orthop* 2021;41(10):e923-3928. https://doi.org/10.1097/BPO.0000000000001956
12. Borgeat A, Blumenthal S. Postoperative pain management following scoliosis surgery. *Curr Opin Anaesthesiol* 2008;21(3):313-6. https://doi.org/10.1097/ACO.0b013e3282f82baa
13. Practice Guidelines for Acute Pain Management in the Perioperative Setting: An Updated Report by the American Society of Anesthesiologists Task Force on Acute Pain Management. *Anesthesiology* 2012;116:248–273. https://doi.org/10.1097/ALN.0b013e31823c1030
14. Aoki Y, Iwata H, Akinaga C, Shiko Y, Kawasaki Y, Kobayashi K, et al. Intraoperative remifentanil dosage in surgery for adolescent idiopathic scoliosis does not increase postoperative opioid consumption when combined with epidural analgesia: A retrospective cohort study. *Cureus* 2021;13(8):e17361. https://doi.org/10.7759/cureus.17361
15. Bean BA, Connor PM, Schiffern SC, Hamid N. Outpatient shoulder arthroplasty at an ambulatory surgery center using a multimodal pain management approach *J Am Acad Orthop Surg Glob Res Rev* 2018;2:e064. https://doi.org/10.5435/JAAOSGlobal-D-18-00064
16. Creary SE, Chisolm DJ, Wrona SK, Cooper JN. Opioid prescription filling trends among children with sickle cell disease after the release of state-issued guidelines on pain management. *Pain Med* 2020;21(10):2583-92. https://doi.org/10.1093/pm/pnaa002
17. Joshi GP, Kehlet H. Postoperative pain management in the era of ERAS: An overview. *Best Pract Res Clin Anaesthesiol* 2019;33(3):259-67. https://doi.org/10.1016/j.bpa.2019.07.016
18. Joshi GP, Kehlet H; PROSPECT Working Group. Guidelines for perioperative pain management: need for re-evaluation. *Br J Anaesth* 2017;119(4):703-6. https://doi.org/10.1093/bja/aex304

19. Jones JS, Cotugno RE, Singhal NR, Soares N, Semenova J, Nebar S, et al. Evaluation of dexmedetomidine and postoperative pain management in patients with adolescent idiopathic scoliosis: conclusions based on a retrospective study at a tertiary pediatric hospital. *Pediatr Crit Care Med* 2014;15(6):e247-52. https://doi.org/10.1097/PCC.0000000000000119
20. Rawal N. Current issues in postoperative pain management. *Eur J Anaesthesiol* 2016;33(3):160-71. https://doi.org/10.1097/EJA.0000000000000366
21. Zieliński J, Morawska-Kochman M, Zatoński T. Pain assessment and management in children in the postoperative period: A review of the most commonly used postoperative pain assessment tools, new diagnostic methods and the latest guidelines for postoperative pain therapy in children. *Adv Clin Exp Med* 2020;29(3):365-74. https://doi.org/10.17219/acem/112600
22. McNicol ED, Rowe E, Cooper TE. Ketorolac for postoperative pain in children. *Cochrane Database Syst Rev* 2018;7(7):CD012294. https://doi.org/10.1002/14651858.CD012294.pub2
23. Yoo JS, Ahn J, Buvanendran A, Singh K. Multimodal analgesia in pain management after spine surgery. *J Spine Surg* 2019;5(2):S154-9. https://doi.org/10.21037/jss.2019.05.04
24. Rajpal S, Gordon DB, Pellino TA, Strayer AL, Brost D, Trost GR, et al. Comparison of perioperative oral multimodal analgesia versus IV PCA for spine surgery. *J Spinal Disord Tech* 2010;23(2):139-45. https://doi.org/10.1097/BSD.0b013e3181cf07ee
25. Rao KE, Krodel D, Toaz EE, Fanelli J, Hajduk J, Kato K, et al. Introduction of an enhanced recovery pathway results in decreased length of stay in patients with adolescent idiopathic scoliosis undergoing posterior spinal fusion: A description of implementation strategies and retrospective before-and-after study of outcomes. *J Clin Anesth* 2021;75:110493. https://doi.org/10.1016/j.jclinane.2021.110493
26. YaDeau JT, Dines DM, Liu SS, Gordon MA, Goytizolo EA, Lin Y, et al. What pain levels do TSA patients experience when given a long-acting nerve block and multimodal analgesia? *Clin Orthop Relat Res* 2019;477:622-32. https://doi.org/10.1097/CORR.0000000000000597
27. Pagnotto MR, Pagnano MW. Multimodal pain management with peripheral nerve blocks for total knee arthroplasty. *Instr Course Lect* 2012;61:389-95. PMID: 22301247
28. Li WT, Bell KL, Yayac M, Barmann JA, Star AM, Austin MS. A postdischarge multimodal pain management cocktail following total knee arthroplasty reduces opioid consumption in the 30-day postoperative period: A group-randomized trial. *J Arthroplasty* 2021;(36) 164e172. https://doi.org/10.1016/j.arth.2020.07.060
29. Karam JA, Schwenk ES, Parvizi J. An update on multimodal pain management after total joint arthroplasty. *J Bone Joint Surg Am* 2021;103:1652-62. https://doi.org/10.2106/JBJS.19.01423
30. Anderson DE, Duletzke NT, Pedigo EB, Halsey MF. Multimodal pain control in adolescent posterior spinal fusion patients: a double-blind, randomized controlled trial to validate the effect of gabapentin on postoperative pain control, opioid use, and patient satisfaction. *Spine Deform* 2020;8(2):177-85. https://doi.org/ 10.1007/s43390-020-00038-z
31. Muhly WT, Beltran RJ, Bielsky A, Bryskin RB, Chinn C, Choudhry DK, et al. Perioperative management and in-hospital outcomes after minimally invasive repair of pectus excavatum: a multicenter registry report from the society for pediatric anesthesia improvement network. *Anesth Analg* 2019;128(2):315-27. https://doi.org/10.1213/ANE.0000000000003829
32. Lee CS, Merchant S, Chidambaran V. Postoperative pain management in pediatric spinal fusion surgery for idiopathic scoliosis. *Paediatr Drugs* 2020;22(6):575-601. https://doi.org/10.1007/s40272-020-00423-1
33. Chou R, Côté P, Randhawa, Torres P, Yu H, Nordin M, et al. The Global Spine Care Initiative: applying evidence-based guidelines on the non-invasive management of back and neck pain to low- and middle-income communities. *Eur Spine J* 2018;27(6):851-60. https://doi.org/10.1007/s00586-017-5433-8
34. Parrish JM, Jenkins NW, Brundage TS, Hrynewycz NM, Podnar J, Buvanendran A, et al. Outpatient minimally invasive lumbar fusion using multimodal analgesic management in the ambulatory surgery setting. *Int J Spine Surg* 2020;14(6):970-81. https://doi.org/10.14444/7146
35. Hong RA, Gibbons KM, Li GY, Holman A, Voepel-Lewis T. A retrospective comparison of intrathecal morphine and epidural hydromorphone for analgesia following posterior spinal fusion in adolescents with idiopathic scoliosis. *Paediatr Anaesth* 2017;27(1):91-7. https://doi.org/ 10.1111/pan.13037
36. Koes BW, van Tulder M, Lin CW, Macedo LC, McAuley J, Maher C. An updated overview of clinical guidelines for the management of non-specific low back pain in primary care. *Eur Spine J* 2010;19(12):2075-94. https://doi.org/10.1007/s00586-010-1502-y

37. Man JY, Gurnaney HG, Dubow SR, DiMaggio TJ, Kroeplin GR, Adzick S, et al. A retrospective comparison of thoracic epidural infusion and multimodal analgesia protocol for pain management following the minimally invasive repair of pectus excavatum. *Paediatr Anaesth* 2017;27(12):1227-34. https://doi.org/10.1111/pan.13264
38. Devin CJ, McGirt MJ. Best evidence in multimodal pain management in spine surgery and means of assessing postoperative pain and functional outcomes. *J Clin* Neurosci 2015;22(6):930-8. https://doi.org/10.1016/j.jocn.2015.01.003
39. Frizzell KH, Cavanaugh PK, Herman MJ. Pediatric perioperative pain management. *Orthop Clin North Am* 2017;48(4):467-80. https://doi.org/10.1016/j.ocl.2017.06.007
40. Wong JJ, Côté P, Sutton DA, Randhawa K, Yu H, Varatharajan S, et al. Clinical practice guidelines for the noninvasive management of low back pain: A systematic review by the Ontario Protocol for Traffic Injury Management (OPTIMa) Collaboration. *Eur J Pain* 2017;21(2):201-16. https://doi.org/ 10.1002/ejp.931
41. Young VB. Effective management of pain and anxiety for the pediatric patient in the emergency department. *Crit Care Nurs Clin North Am* 2017;29(2):205-16. https://doi.org/10.1016/j.cnc.2017.01.007
42. Bull J, Grogan S. Children having spinal surgery to correct scoliosis: A qualitative study of parents' experiences. *J Health Psychol* 2010;15(2):299-309. https://doi.org/10.1177/1359105309351607
43. Ntalouka MP, Brotis AG, Bareka MV, Stertsou ES, Fountas KN, Arnaoutoglou EM. Multimodal analgesia in spine surgery: An umbrella review. *World Neurosurg* 2021;149:129-39. https://doi.org/10.1016/j.wneu.2021.02.040
44. Mathiesen O, Dahl B, Thomsen BA, Kitter B, Sonne N, Dahl JB, et al. A comprehensive multimodal pain treatment reduces opioid consumption after multilevel spine surgery. *Eur Spine J* 2013;22(9):2089-96. https://doi.org/10.1007/s00586-013-2826-1
45. Momon A, Verdier B, Dolomie JO, Gardette M, Pereira B, Curt I, et al. A Single preoperative administration of dexamethasone, low-dose pregabalin, or a combination of the 2, in spinal surgery, does not provide a better analgesia than a multimodal analgesic protocol alone. *Clin J Pain* 2019;35(7):594-601. https://doi.org/10.1097/AJP.0000000000000719
46. Kaye AD, Chernobylsky DJ, Thakur P, Siddaiah H, Kaye RJ, Eng LK, et al. Dexmedetomidine in Enhanced Recovery After Surgery (ERAS) Protocols for postoperative pain. *Curr Pain Headache Rep* 2020;24(5):21. https://doi.org/10.1007/s11916-020-00853-z
47. Song K, Melroy MJ, Whipple OC. Optimizing multimodal analgesia with intravenous acetaminophen and opioids in postoperative bariatric patients. *Pharmacotherapy* 2014;34(Suppl 1):14-21S. https://doi.org/10.1002/phar.1517
48. Chan P, Skaggs DL, Sanders AE, Villamor GA, Choi PD, Tolo VT, et al. Pain is the greatest preoperative concern for patients and parents before posterior spinal fusion for adolescent idiopathic scoliosis. *Spine (Phila Pa 1976)* 2017;42(21):E1245-50. https://doi.org/10.1097/BRS.0000000000002147
49. Landman Z, Oswald T, Sanders J, Diab M. Spinal Deformity Study Group. Prevalence and predictors of pain in surgical treatment of adolescent idiopathic scoliosis. *Spine (Phila Pa 1976)* 2011;36(10):825-9. https://doi.org/10.1097/BRS.0b013e3181de8c2b
50. Wong GT, Yuen VM, Chow BF, Irwin MG. Persistent pain in patients following scoliosis surgery. *Eur Spine J* 2007;16(10):1551-6. https://doi.org/10.1007/s00586-007-0361-7
51. Pestieau SR, Finkel JC, Junqueira MM, Cheng Y, Lovejoy JF, Wang J, et al. Prolonged perioperative infusion of low-dose ketamine does not alter opioid use after pediatric scoliosis surgery. *Paediatr Anaesth* 2014;24(6):582-90. https://doi.org/10.1111/pan.12417
52. Hwang SW, Pendleton C, Samdani AF, Bastrom TP, Keeny H, Lonner BS, et al. Preoperative SRS pain score is the primary predictor of postoperative pain after surgery for adolescent idiopathic scoliosis: an observational retrospective study of pain outcomes from a registry of 1744 patients with a mean follow-up of 3.4 years. *Eur Spine J* 2020;29, 754–760. https://doi.org/10.1007/s00586-020-06293-y
53. Vademecum Intranet. Hospital Nacional de Pediatría Prof. Dr. Juan P. Garrahan. Sitio web. 2021. Available at: https://farmacia.garrahan.gov.ar/Vademecum/Busqueda