Prospective evaluation of the emetogenic profile and analgesic efficacy of intravenous ibuprofen and metamizole in the immediate postoperative period of pediatric acute appendicitis

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Abstract

Background. Literature comparing different alternatives for pain control in the immediate postoperative period of pediatric acute appendicitis (PAA) is scarce.

Materials and methods. We prospectively compared the analgesic and emetogenic profile of intravenous ibuprofen and metamizole in the immediate postoperative period of PAA. For this purpose, we used a sample of patients operated on in 2021 in our center. Participants were recruited on arrival at the Emergency Department and histopathological confirmation of the diagnosis was obtained in all of them. Pain was evaluated every 8 hours after the surgery with validated visual analog scales ranging from 0 to 10 points. Repeated measures ANOVA was used to compare the evolution of pain in the 48 hours after surgery between the two groups.

Results. The sample included 95 patients (65% males) with a mean age of 9.7 years (sd: 3.14). 41 patients were treated with Ibuprofen (group 1) and 54 with metamizole (group 2). No significant differences were found in the level of pain either in the comparisons of point measurements or in its evolution in the 48 hours after surgery (p= 0.58). After adjusting for the received fluid therapy, children in the metamizole group had significantly more emetic episodes and needed significantly more doses of ondansetron.

Conclusions. In our cohort, ibuprofen had a similar analgesic efficacy and a better emetogenic profile than metamizole in the immediate postoperative period of PAA. Future prospective, adequately controlled studies with larger sample sizes are needed to validate these findings.

Key Words: Analgesia; Pediatric acute appendicitis; Non-steroidal anti-inflammatory drugs; Ibuprofen; Metamizole; Dipyrone.

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Evaluación prospectiva del perfil emético y la eficacia analgésica del ibuprofeno y el metamizol intravenosos en el postoperatorio inmediato de la apendicitis aguda pediátrica

Resumen

Introducción. En la literatura existen pocas referencias que comparen las distintas alternativas disponibles para controlar el dolor en el postoperatorio inmediato de la apendicitis aguda pediátrica (AAP).

Material y métodos. Comparación prospectiva del perfil analgésico y emético del ibuprofeno y el metamizol intravenosos en el postoperatorio inmediato de la AAP, para lo cual se recurre a una muestra de pacientes operados en 2021 en nuestro centro. Los participantes fueron reclutados a su llegada a Urgencias, obteniéndose confirmación histopatológica del diagnóstico en todos ellos. La evaluación del dolor se llevó a cabo cada 8 horas tras la cirugía mediante escalas analógicas visuales validadas, con valoraciones entre los 0 y los 10 puntos. Se realizó un ANOVA de las medidas repetidas entre los dos grupos para comparar la evolución del dolor en las 48 horas posteriores a la cirugía.

Resultados. La muestra estaba compuesta por un total de 95 pacientes (65% de ellos varones) con una edad media de 9,7 años (DT: 3,14). 41 pacientes fueron tratados con ibuprofeno (grupo 1) y 54 con metamizol (grupo 2). No se hallaron diferencias significativas en lo que respecta al dolor, ni en las comparaciones de las mediciones puntuales, ni en su evolución en las 48 horas posteriores a la cirugía (p= 0,58). Una vez realizado el ajuste correspondiente a la terapia de fluidos recibida, los niños del grupo metamizol tuvieron significativamente más episodios eméticos y necesitaron significativamente más dosis de ondansetrón.

Conclusiones. En nuestra cohorte, el ibuprofeno tuvo una eficacia analgésica similar y un mejor perfil emético que el metamizol en el postoperatorio inmediato de la AAP. Se hacen necesarios nuevos estudios prospectivos, adecuadamente controlados y con mayor tamaño muestral que validen estos hallazgos.

Palabras Clave: Analgesia; Apendicitis aguda pediátrica; Agentes antiinflamatorios no esteroideos; Ibuprofeno; Metamizol; Dipirona.

INTRODUCTION

Pediatric acute appendicitis (PAA) is the most common urgent surgical abdominal pathology in the world. Classically, most of the research on PAA focused on diagnostic aspects, such as the development of standardized diagnostic pathways or the use of hemogram-derived ratios as diagnostic tools[1,2], but in the last years, a growing interest in surgical and post-surgical aspects has emerged. Recent studies aimed at analyzing fast-track protocols have shown that these are safe and applicable, significantly reducing hospital admissions and the associated economic and healthcare costs[3,4]. Other studies focused on identifying the surgical technique with the most favorable postoperative evolution and faster recovery. In this regard, evidence shows that laparoscopic techniques are preferable to open techniques[5], and the single port transumbilical appendectomy has been demonstrated to be a safe and economical technique with good post-surgical results in the context of PAA[6]. Other working groups have evaluated different strategies, such as the creation of a nurse discharge protocol, aimed to decrease postoperative hospitalization time without an increase in readmissions or associated complications[7].

Concerning pain control in the Emergency Department in the context of PAA, there is evidence that general practitioners tend to provide analgesia earlier than pediatricians[8]. Besides, it has been pointed out that analgesic treatment of PAA in Emergency Departments may present disparities, may be insufficient, and can be optimized[9,10].

Studies that evaluated postoperative pain in PAA are very scarce and are mostly focused on the evaluation of the surgical technique. Evidence on the management of postoperative pain in the context of PAA is mainly focused on the impact of opioid use[11,12] and how to replace them with multimodal analgesia[13], which includes presurgical locoregional blockages under general anesthesia[14]. However, studies are reporting substantial postoperative pain after laparoscopic pediatric appendicectomy, which means that this is a field of relevance for future studies[15]. Although the safety and efficacy of nonsteroidal anti-inflammatory drugs (NSAIDs) has been demonstrated[16], there is a lack of evidence comparing the analgesic profile and associated complications of the most commonly used drugs to manage postoperative pain in the context of PAA. This study aimed to prospectively evaluate the analgesic and emetogenic profile of two NSAIDs (ibuprofen and metamizole) in the immediate postoperative period of PAA.

MATERIALS AND METHODS

This study was approved by our center's clinical research ethics committee on December 18, 2020, under code PI_2020/112. The ethical principles of the Declaration of Helsinki (2013) were applied to the conduct of this research study. The parents or legal representatives of all participants signed an informed consent form before their inclusion in the study.

This study is a sub-analysis of the BIDIAP cohort[17]. The BIDIAP cohort was a single-center prospective study conducted in 2021 in Spain whose primary objective was the evaluation of potential novel diagnostic biomarkers for PAA. This sub-analysis was designed to evaluate the analgesic and emetogenic profile of ibuprofen and metamizole (dipyrone) in the immediate postoperative period of PAA. Inclusion and exclusion criteria are listed in Supplementary File 1. Participants with a clinical diagnosis of PAA were recruited at the Emergency Department of our center between February to December 2021 when a member of the research team was available. Sociodemographic, clinical, radiological, and analytical information was collected at recruitment. Information on the surgical procedure and clinical evolution was extracted from the participant's medical records. Patients were operated on within the 12 first hours after the diagnosis and histological confirmation of the diagnosis was obtained in all of them. The sample was divided into two groups depending on the NSAID used to control postoperative pain: 1) ibuprofen group (n=41) and 2) metamizole (dipyrone) group (n=54). The choice of one or the other drug for pain control was a decision of the surgeon in charge.

At recruitment, we collected information on sociodemographic variables (age, sex, height, weight), clinical variables (hours of pain evolution, axillary temperature, number of diarrheal stools, number of emetic episodes, presence of hyporexia, serum leucocytes, neutrophils, C-reactive protein –CRP– and procalcitonin –PCT–), surgery-related variables (intraoperative findings, surgery duration, category of the surgeon that performed the procedure, surgical technique and need for surgical conversion) and variables related with postoperative evolution in the 24 or 48 hours after the surgery (fluid therapy, postoperative medication, pain intensity, presence of nausea, number of emetic episodes, administered doses of intravenous ondansetron, opioid administration, presence of pain associated with intravenous drugs administration, need for a new venous catheterization, and duration of hospitalization). Body mass index (BMI) was calculated as weight (kg) divided by the height (meters) squared.

Information on pain intensity was collected with validated visual analog scales (VAS) every 8 hours during the first 48 hours after surgery. The Wong-Baker scale was used in children under 8 years of age and the Walco-Howite scale was used in children over 8 years of age. Information on other variables related to the postoperative evolution was extracted from the patient's medical records by the principal investigator.

We calculated that to detect a 1-point difference between groups in the VAS scales with a power of 90%,

Table 1. Sociodemographic characteristics of the study patients.

	Group 1 (Ibuprofen) N = 41	*Group 2 (Metamizole) N = 54*	*Total*	*p-value*
Age (years)	9.77 (3.09)	9.61 (3.21)	9.68 (3.14)	0.80
Sex (Male/Female) (% Male)	27/14 (65.85%)	35/19 (64.84%)	62/33 (65.26%)	0.54
Height (meters)	1.41 (0.2)	1.40 (0.18)	1.40 (0.19)	0.72
Weight (kilograms)	36.13 (11.68)	36.85 (15.25)	36.54 (13.76)	0.94
Body mass index (kg/m^2)	17.22 (1.96)	17.87 (3.70)	17.56 (3)	0.91

Numbers are mean (standard deviation) or absolute number (percentage).

Table 2. Clinical characteristics of the patients included in the study, previous to the admission.

Clinical variables (previous to admission)	*Group 1 (Ibuprofen) (n=41)*	*Group 2 (Metamizole) (n=54)*	*P-value*
Hours of pain evolution	29.5 (20.27)	23.75 (17.08)	0.13
Axillary temperature > 37.8°C (Yes/No/Not reported) (% Yes)	12/28/1 (29.26)	18/36/0 (33.33)	0.82
Number of diarrheal stools	0.25 (0.93)	0.83 (3)	0.32
Complicated appendicitis (Yes/No) (% Yes)	11/30 (26.82%)	18/36 (33.33%)	0.65
Number of emetic episodes	2.52 (2.60)	2.39 (2.39)	0.86
Hyporexia (Yes/No/Not reported) (% Yes)	**4/36/1 (9.75)**	**13/38/3 (25.5)**	**0.05**
Leucocytes (1x10^9/L)	15.51 4.65)	16.42 (4.99)	0.32
Neutrophils (1x10^9/L)	12.40 (4.36)	13.46 (5.11)	0.28
CRP (mg/L)	44.33 (44.73)	43.69 (58.91)	0.33
PCT (ng/mL)	1.92 (7.84)	0.96 (3.48)	0.53

Numbers are mean (standard deviation) or numbers (percentage). CRP: C-Reactive protein; PCT: procalcitonin.

assuming a standard deviation of 1 point and an alpha error of 0.05, 22 participants were needed in each group.

For descriptive purposes, we used mean (standard deviation) for quantitative variables and proportions for categorical ones. Kolmogórov-Smirnov test was used to assess the normality of quantitative variables. Between-group comparisons were performed with the Mann-Whitney U test for quantitative variables and Fisher's exact test for qualitative ones. A repeated measures ANOVA with between-groups comparison was used to compare the evolution of pain control in children treated with ibuprofen and with metamizole in the first 48 hours after surgery. In further analysis we used multivariate adjusted regression to calculate the association between metamizole (compared with ibuprofen), the presence of nausea, and the number of emetic episodes after accounting for the potential confounding effect of fluid therapy.

All p values are two-sided. Statistical significance was settled in a p-value <0.05. Statistical analysis was performed with STATA 17.0 (StataCorp LCC).

RESULTS

This study included 95 patients (65% males) with a mean age of 9.7 years (sd: 3.14) operated on for acute appendicitis between February 2021 and December 2021 in our center. The sample was divided according to the NSAID used to control postoperative pain into 1) ibuprofen group (n=41) and 2) metamizole (dipyrone) group (n=54). No significant differences between groups were observed in participant's sociodemographic characteristics (Table 1). Participants' clinical characteristics by group are shown in Table 2. Children in the metamizole group presented a higher proportion of hyporexia (p=0.05), but no other differences were observed for the rest of the clinical and analytical variables collected at recruitment.

Surgery-related information by group is shown in Table 3. The percentage of patients operated on by a trainee was 65.85% in group 1 and 51.85% in group 2 (p=0.21). Mean surgical time was 43.77 (14.91) minutes in group 1 and

Table 3. Surgical variables of patients included in the study.

Surgical variables	*Group 1 (Ibuprofen) (n=41)*	*Group 2 (Metamizole) (n=54)*	*P-value*
Surgery duration (minutes)	43.77 (14.91)	41.52 (21.85)	0.14
Procedure performed by a trainee (Yes/No) (%Yes)	27/14 (65.85)	28/26 (51.85)	0.21
Single-Port laparoscopic procedure (Yes/No) (% es)	39/2 (95.12)	51/3 (94.44)	0.60
Three-Port Laparoscopic procedure (Yes/No) (%Yes)	1/40 (2.44)	2/52 (3.70)	0.60
Initial laparotomy procedure (Yes/No) (%Yes)	1/40 (2.44)	1/53 (1.85)	0.60
Conversion from 1 or 3 ports laparoscopy to laparotomy (Yes/No) (%Yes)	1/40 (2.44)	2/52 (3.70)	0.60

Numbers are mean (standard deviation) or absolute numbers (percentage)

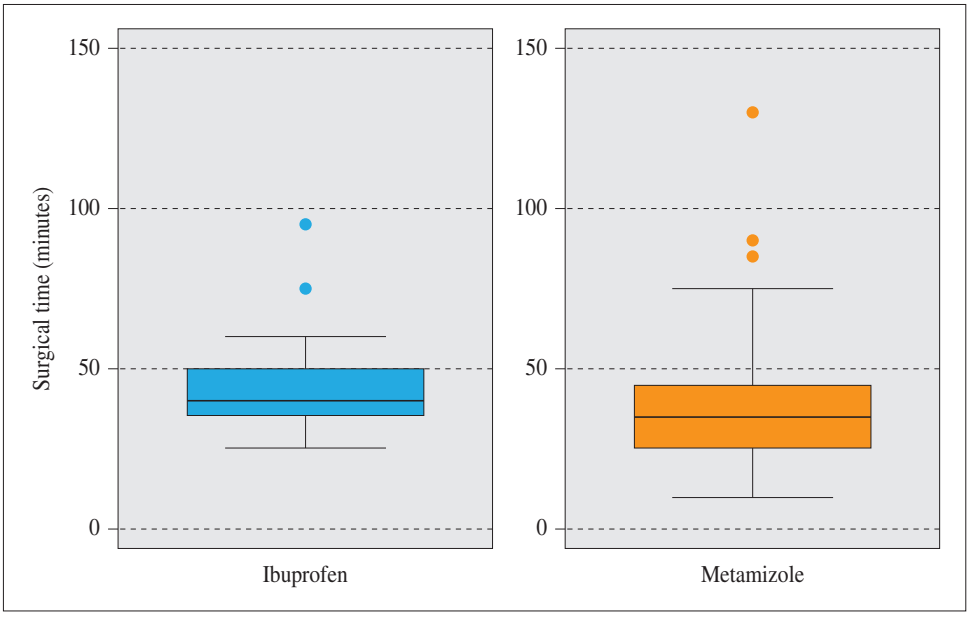

Figure 1. Graphical representation of the surgical time by group.

41.52 (21.85) minutes in group 2 (p=0.14) (Fig. 1). Most of the patients underwent a single-port umbilical laparoscopic appendectomy (TULA), and the conversion to a 3-port laparoscopy appendectomy was performed in 1 patient in group 1 and 2 patients in group 2. The conversion from laparoscopy to laparotomy occurred in 1 patient in group 1 and 2 patients in group 2 as well (p=0.60).

Regarding the anesthetic procedure, a rapid induction sequence (succinylcholine, propofol, and fentanyl, with weight-adjusted doses) was applied in all cases. All patients received a 0.15 mg/kg dose of intravenous dexamethasone at anesthetic induction and an ultrasound-guided anesthetic blockade of the anterior rectus abdominis was performed before the surgery. In cases in which the patient was operated on using a 3-port laparoscopic access, laparotomy, or in those who needed conversion from laparoscopy to laparotomy, all accesses were infiltrated with bupivacaine 0.25% without epinephrine by the surgeon.

Except for the two drugs that define our groups (ibuprofen or metamizole), all patients received the same medication after surgery, which consisted of Paracetamol (15 mg/kg/6 hours), Cefotaxime (33-66 mg/kg/8 hours), Metronidazole (7.5-10 mg/kg/6-8 hours), Meperidine (1 mg/kg/dose, if required), Ondansetron (0.1 mg/kg/6 hours, if required), Omeprazole (1 mg/kg/24 hours) and fluid therapy. As fluid therapy, glucosaline 5% supplemented with 10 mEq potassium chloride every 500 cc. of solution or Plasma-Lyte 148 + 10 grams of glucose every 500 cc. of solution were administered, on the surgeon's discretion). Ibuprofen was prescribed at 10 mg/kg/every 8 hours, and metamizole at 30-40 mg/kg/every 6 hours. Therefore, patients in the ibuprofen group received 7 doses of intravenous analgesia every 24 hours (4 of paracetamol and 3 of ibuprofen) while those in the metamizole group received 8 doses of intravenous analgesia every 24 hours (4 of paracetamol and 4 of metamizole). Information on

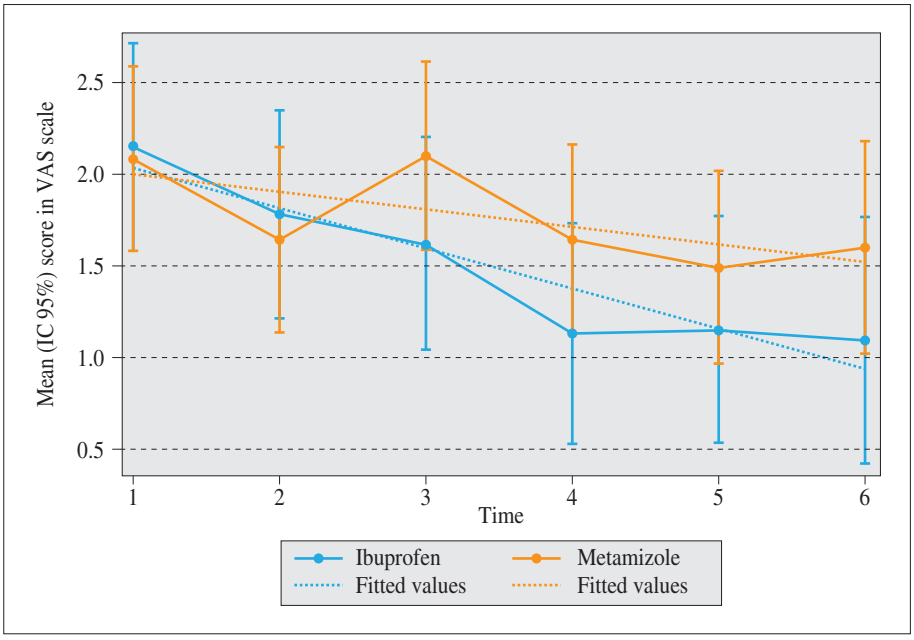

Figure 2. Graphical representation of the level of pain by group. Mean scores and 95% Confidence Intervals on VAS in each of the six determinations by group. The fitted lines represent the evolution of pain over the six measurements.

Table 4. Postoperative analgesic and emetic profiles of the patients included in the study

Variables	*Group 1 (Ibuprofen) (n=41)*	*Group 2 (Metamizole) (n=54)*	*P-value*
Fluid therapy in the first 24 hours*	**102.33 (21.06)**	**90.19 (24.42)**	**0.04**
Nausea in the first 24 hours (Yes/No) (%Yes)	**5/36 (12.19)**	**25/29 (46.29)**	**<0.001**
Number of emetic episodes			
First 24 hours	**0.12 (0.45)**	**0.63 (1.20)**	**0.004**
Second 24 hours	**0.15 (0.43)**	**0.65 (1.19)**	**0.02**
Administered doses of intravenous ondansetron			
First 24 hours	**0.61 (0.99)**	**2.11 (1.13)**	**<0.001**
Second 24 hours	**0.34 (0.80)**	**1.83 (1.26)**	**<0.001**
Postoperative opioid administration (Yes/No/Not reported) (% Yes)	5/36 (12.19)	8/45/1 (15.09)	0.77
Pain associated with intravenous drug administration (Yes/No) (%Yes)	1/40 (2.44)	1/53 (1.85)	0.68
Need for catheterization of new peripheral venous access (Yes/No/Not reported) (% Yes)	1/40 (2.44)	2/51/1 (3.77)	0.59
Mean duration of hospitalization (days)	3.86 (3.88)	3.75 (3.44)	0.99

Numbers are mean (standard deviation) or numbers (percentage).
** % of basal Holliday-Segar requirements*

the number of doses of analgesia not administered due to lack of need was extracted from the patient's medical records.

Mean scores in VAS by group are shown in Figure 2. No significant differences were found between groups in point estimates of the level of pain or pain evolution during the first 48 hours after the surgery, which is represented by the fitted lines over the six measurements (p =0.58).

Information on variables related to clinical evolution in the immediate postoperative period is shown in Table 4. We observed a significantly higher proportion of nausea in children who received metamizole (p<0.001). Along with this, children in group 2 presented a significantly higher number of emetic episodes in the first 24 hours (p=0.004) and the second 24 hours (p= 0.02). These differences explain the need for significantly higher doses of intrave-

nous ondansetron in both the first and the second 24 hours ($p<0.001$). The metamizole group received significantly less fluid therapy than the ibuprofen group, which may have confounded the previous results. After adjusting for fluid therapy, the metamizole remained significantly associated with a higher number of emetic episodes ($p=0.03$), but not with a higher proportion of nausea ($p= 0.38$).

The mean duration of admission was 3.86 (3.88) days in group 1 and 3.75 (3.44) days in group 2 ($p=0.99$). In the first 24 hours after the surgery, 1 patient from each group was discharged because of clinical improvement. In the second 24 hours, the number of patients who were discharged was 15 (37%) in the group 1 and 21 (38%) in the group 2 ($p=0.99$). Therefore, 21 patients (51%) in group 1 and 26 patients (48%) in group 2 required 3 or more days of admission. No differences were observed in the presence of pain associated with intravenous drug administration, the need for opioids, or the need for catheterization between groups.

DISCUSSION

In this prospective observational study with 95 patients, we compared the analgesic efficacy and emetogenic profile of ibuprofen and metamizole, the two NSAIDs most commonly used for the management of postoperative pain in the context of PAA. We observed no differences between groups in the evolution of pain control, but children who received metamizole had significantly more emetic episodes than those who received ibuprofen after adjusting for the received fluid therapy.

To our knowledge, this is the first study that prospectively evaluated the analgesic efficacy and emetogenic profile of two NSAIDs in the immediate postoperative period of PAA. Our results are of great interest considering the high prevalence of pediatric appendicitis and given the economic and health care costs involved. The optimization of pharmacological treatment and the subsequent reduction of the postoperative emetic episodes may help to reduce the duration of hospitalization and, therefore, healthcare costs. We believe that this work lays the groundwork for future studies with larger sample sizes to confirm these findings and investigate the potential pharmacological mechanisms underlying the observed association.

Metamizole is an excellent analgesic drug for the initial control of acute abdominal pain in pediatric emergencies. Its main advantages are its great ability to relax intestinal smooth muscle and its rapid onset of action. Concerning its side effects, dizziness and orthostatic hypotension stand out due to their frequency. Importantly, those side effects seem to be related to the infusion rate and therefore, may be controllable. Agranulocytosis is the most serious potential side effect of metamizole. It is extremely infrequent, with studies reporting 2-15 cases of agranulocytosis per million metamizole administrations, but with a mortality rate reported to be as high as 5%. It is noteworthy that metamizole is banned in multiple countries because of this problem, although several large, industrialized countries continue to prescribe and use metamizole.

Ibuprofen, on the other hand, is an excellent analgesic drug to control postoperative pain as well and lacks the side effects previously mentioned. We have not observed it to be more phlebitic or vesicant than metamizole, and the potential discomfort associated with its administration is reduced with slow administration and the application of non-direct local cold on top of the venous catheterization during it.

Some studies reported that adequate perioperative hydration could help control postoperative emesis[18], although the literature on this subject is scarce. In our initial analysis, we found that children in the metamizole group received a significantly lower volume of fluid therapy adjusted to the Holliday-Segar formula than those in the ibuprofen group, which might explain the higher proportion of nausea and the higher proportion of emetic episodes in that group. However, in the analysis adjusted for the received fluid therapy, the number of emetic episodes remained significantly higher in the metamizole group, suggesting that the observed association was independent of fluid therapy. In any case, our findings reinforce the importance of adequate perioperative hydration in patients with PAA and are consistent with previous literature.

Considering that in our clinical practice no other pediatric pathology routinely treated with metamizole is associated with such a large amount of vomiting, we hypothesize that our results may be explained by the concomitant administration of metamizole and metronidazole. We propose this hypothesis given that our use of metronidazole is almost uniquely circumscribed to PAA. It is important to note that, to date, neither metamizole nor metronidazole have been associated with an increased risk of emesis when used separately. Therefore, further research is needed to contrast this hypothesis and investigate alternative explanations for the observed increased number of emetic episodes in the metamizole group.

Regarding admission time, we think that the lack of significant differences between groups may be, at least partially, explained by the absence of an established fast-track protocol in our center. We believe that the lower number of emetic episodes observed in the ibuprofen group could have resulted in shorter hospitalization times had a fast-track protocol been applied. Given that persistent pain or postoperative emesis are the most common reasons for prolonged postoperative hospitalization, our findings justify the need for studies in the pediatric population to compare the efficacy of the different NSAIDs commonly used in the management of postoperative pain in terms of costs derived from days of hospitalization. New evidence

in this regard will help to improve the existing fast-track protocols and may have a profound impact on the economic and healthcare costs associated with PAA.

We acknowledge some limitations of the study. First, and about emesis, it is known that this is a process of multifactorial etiology, and we are aware that we have not controlled for all the possible related variables. More specifically, 1) we have not applied specific scales for predicting postoperative nausea and vomiting, such as the Eberhart scale. 2) Although in general terms there was homogeneity in the general and locoregional anesthetic procedure, we cannot exclude the presence of inter-anesthesiologist variations that could potentially have had an impact on the results of the study (i.e the use in some cases of nitrogen protoxide, the preoperative vs intraoperative administration of intravenous ondansetron or the administration of opioids in post-anesthesia resuscitation, immediately after the completion of surgery). 3) There may have been an important variability in the presence of postoperative paralytic ileus among the study patients that was not documented in the study 4) although the proportion of complicated and uncomplicated appendicitis by groups did not show significant differences, it should be considered that this pathology constitutes a spectrum and not a rigid categorization. Acute appendicitis itself constitutes per se an acute abdomen and is an emetogenic process. Second, since participants were not randomly assigned to the groups, we cannot deny the possibility of residual confounding by variables that we did not account for. Third, information on the clinical evolution in the second 24 hours after the surgery was not complete in the 38 participants who were discharged due to clinical improvement. Nevertheless, we still had complete information from 57 patients, 35 in the metamizole group and 22 in the ibuprofen group, which is above the required sample size.

Despite those limitations, our study has several strengths. First, our prospective design. Second, the rigorous data extraction, which was performed by the same investigator in all cases. Third, the use of validated VAS to evaluate the level of pain. Fourth, the comparability of the groups in terms of sociodemographic, clinical, surgical, and general anesthetic techniques.

In conclusion, in our cohort ibuprofen had similar analgesic efficacy and a better emetogenic profile than metamizole in the inmediate postoperative period of PAA. It is essential to consider the pharmacological set applied to our patients when interpreting these findings, given that with other antibiotic regimens this postsurgical clinical profile may not be repeated. Considering the high prevalence of PAA and that vomiting is one of the main reasons for delaying the discharge of these patients, prioritizing the use of ibuprofen may result in a reduction of admission time, with the economic repercussions that this implies. Prospective multicenter studies with large sample sizes and adequate control of confounding are needed to confirm these findings.

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