RESEARCH ARTICLE

pharmadvances

Volume **4**, issue **3**, **2022: 179-88**

FASTER ABSORPTION OF IBUPROFEN LYSINATE THAN STANDARD IBUPROFEN ACID IN PEDIATRIC POST-SURGICAL PAIN

V. Fabiano[1,2], V. Calcaterra[1,3], A. Mari[1], G. Pelizzo[4,2], F. Destro[4], E. Clementi[2], G. V. Zuccotti[1,2], D. Cattaneo[5]

[1] Department of Pediatrics, Vittore Buzzi Children's Hospital, Milan, Italy
[2] Department of Biomedical and Clinical Sciences, University of Milan, Milan, Italy
[3] Department of Internal Medicine and Therapeutics, University of Pavia, Pavia, Italy
[4] Department of Pediatric Surgery, Vittore Buzzi Children's Hospital, Milan, Italy
[5] Luigi Sacco University Hospital, Milan, Italy

E-mail: valentina.fabiano@unimi.it. **ORCID:** 0000-0001-6449-1724

Doi: 10.36118/pharmadvances.2022.36

SUMMARY

Surgery represents one of the most painful events that a child may experience. Advanced pharmaceutical formulations, including salts of ibuprofen, were developed to provide faster drug absorption and rapid onset of analgesic effects. The aim of this pilot study was to evaluate the rate of early drug absorption of ibuprofen lysinate (Algidrin® Pediatrico, FARDI S.A., Barcelona, Spain) compared to standard ibuprofen (MomentKid®, Aziende Chimiche Riunite Angelini Francesco, Rome, Italy) in children receiving the drug for the treatment of post-surgical pain.

Twenty-one children (4-16 years) were enrolled in a randomized, open-label, controlled, pilot study. Patients were randomly assigned to the experimental-group (LYS-group, n = 10, treated with the lysinate formulation after surgery) or the standard-group (STAND-group, n = 11 treated with standard ibuprofen formulation). Four blood samples (immediately before and 5, 15 and 20 minutes after the oral administration) were collected 24-hours after starting ibuprofen; pain (faces pain scale) and vital parameters (heart rate, blood pressure, oxygen saturation) were also considered.

Patients from the LYS-group had significantly higher ibuprofen concentrations at 5 minutes after drug intake compared with those from the STAND-group (11.9 ± 8.6 *versus* 3.6 ± 3.6 mg/L, p = 0.010), with the same trend for all other pharmacokinetic parameters. Remarkably, ibuprofen basal concentrations, were more than doubled in the LYS- *versus* STAND-group (5.7 ± 7.8 *versus* 2.1 ± 1.0 mg/L, p = 0.141). The LYS-group was also associated with a trend for reduced inter-individual variability in the drug exposure compared with the STAND-group (coefficient of variation of the AUC0-20 min: 52% *versus* 84%. Pain control was also obtained.

The use of ibuprofen lysinate was associated with an early fast absorption and reduced pharmacokinetic variability compared to the traditional ibuprofen acid formulation, supporting fast action and an improved clinical response to mild-moderate post-surgical pain in children.

Key words
Ibuprofen lysinate; Ibuprofen; children; post-surgical pain; pharmacokinetic.

Impact statement
Ibuprofen lysinate presents faster absorption and reduced pharmacokinetic variability compared to standard ibuprofen in children.

INTRODUCTION

According to the revised definition provided by Williams and Craig in 2016, pain is a "distressing experience associated with actual or potential tissue damage with sensory, emotional, cognitive and social components" (1). Pain, among all the symptoms, undermines physical and psychological integrity of the subject who is experiencing it, affecting, at the same time, also family and caregivers. This applies especially to pediatric population, in which pain is a frequent finding. In fact, up to 80% of hospital admissions into pediatric departments are due to pathologies which involve pain as a symptom.

Despite the tremendous advantages in knowledge about pain reached in the last decades, this condition is still frequently under-recognized and thus inadequately treated in children. It is now widely known that there is no age limit to perception of pain, as the development of anatomic substrates required for pain transmission occurs mainly during fetal life (2, 3).

The Italian Health Ministry in 1995 issued a document about correct pediatric pain management, in which is stated that "pain should always be assessed and treated whenever there are signs and symptoms of its presence, even if the child does not verbally express his discomfort, and when possible, with a prophylactic approach" (4).

In particular, in case of predictable onset of pain, such as in the postoperative period, it must be prevented with adequate prophylaxis. Children who underwent surgery may not feel pain immediately after awakening from anesthesia, but this should not discourage clinicians from starting a pharmacological pain prophylaxis. In fact, analgesic therapy should be administered "by the clock" and not on demand (5).

In pediatric age, paracetamol and ibuprofen are the first-choice drugs to treat acute mild to moderate pain.

Ibuprofen, (±)-(R,S)-2-(4-isobutylphenyl)-propionic acid, is a chiral 2-arylpropionic acid derivative nonsteroidal anti-inflammatory drug (NSAID) widely used in the management of mild to moderate pain, fever and inflammation since early seventies acting as is a non-selective inhibitor of cycloxygenase-1 and -2 derived prostaglandin biosynthesis (6).

Ibuprofen free acid is a lipophilic compound with limited aqueous solubility. As dissolution is a key factor in the process of drug permeation through the cellular membranes, poor water solubility may limit drug absorption, ultimately delaying systemic bioavailability and in some cases restraining it. Therefore, one common way pursued to improve aqueous solubility and dissolution rate of a drug without changing its chemical structure and biological properties is by the formation of salts with the conjugate acids. This concept well applies to ibuprofen, due to its carboxylic acid moiety. Indeed, although the free acid formulation is still largely used and prescribed worldwide, different salts of ibuprofen have been introduced on the market in the past few years as gastrointestinal absorption enhancers, with the goal to improve ibuprofen absorption in terms either of higher peak of drug levels (C_{max}) and faster time to reach maximum concentration (T_{max}) compared with the conventional formulation (7). Testing alternative ibuprofen formulations, with rapid absorption and improved oral bioavailability may, therefore, be useful to obtain a more efficient acute pain control.

Limited data is available on the lysinate formulation of ibuprofen. In 2015 Ferrero-Cafiero et al evaluated the bioavailability of pediatric suspension of lysinate ibuprofen compared to pediatric suspension of standard ibuprofen, in healthy, adult volunteers and found that the rate of absorption of the ibuprofen lysinate suspension is quicker and less variable than that of the ibuprofen base reference suspension and it exhibits a shorter T_{max}, which is of particular interest for achieving a rapid and homogeneous analgesic and antipyretic effect (8). However, to our knowledge, no comparative pharmacokinetic study comparing the early absorption of lysinate ibuprofen and stan-

dard ibuprofen in the pediatric population has been carried out so far.
The aim of the present pilot study was to evaluate the rate of early drug absorption of ibuprofen lysinate compared to standard ibuprofen in children receiving the drug for the treatment of post-surgery pain. The secondary outcome was to evaluate the analgesic efficacy to control post-operative pain of the two ibuprofen formulations.

MATERIALS AND METHODS

Patients

Twenty-one pediatric patients (both genders), aged 4 to 16 years, undergoing surgical procedures at the Pediatric Surgery Unit, Vittore Buzzi Children's Hospital, Milan, were sequentially enrolled in this study. Inclusion criteria included: abdominal or thoracic surgery, operative time < 3 hours, mild (FPS-R: 2-4) or moderate (FPS-R: 4-6) self-reported postoperative pain according to Faces pain scale–revised (FPS-R) (9), no complications of surgery. Exclusion criteria included: chronic illness (including heart failure, kidney disease, inflammatory bowel diseases), history of NSAIDs' related gastrointestinal bleeding, use of any analgesic medication before surgery, hypersensitivity or allergy to ibuprofen or excipients, language barrier.
Participants were recruited between June 1, 2021 and November 30, 2021.
This pilot study was performed in accordance with the Helsinki Declaration of 1975, as revised in 2008. The institutional Ethics Committee approved the study (2020/EM/210). Written informed consent was obtained from subjects' parents or guardians; the assent was also recorded in children and adolescents from 8 to 16 years of age.

Study protocol

This was a randomized, open-label, controlled, pilot study. The two arms consisted of an experimental group, treated with an Ibuprofen Lysinate (Algidrin® Pediatrico, FARDI S.A., Barcelona, Spain, 20 mg/ml oral suspension) formulation (LYS-group) after a surgical procedure and a control group, treated with a standard ibuprofen (MomentKid®, Aziende Chimiche Riunite Angelini Francesco, Rome, Italy, 100 mg/5ml oral suspension) formulation (STAND-group) after surgery; doses administered according to weight as reported in the summary of product characteristics (or in the patient leaflet) of the medicinal product. The flow chart of the progress through the phases of our pilot study is showed in **figure 1**.
The study variables were determined in each patient independently of the assigned group, before and after the experimental intervention.

Procedures and data collection

At admission, a complete clinical examination including weight measurement and detections of the vital signs, including heart rate (HR), blood pressure (BP), oxygen saturation (SpO2) was performed in all enrolled children. All subjects were in good physical condition. Pre-surgery, enrolled children were randomly assigned to the experimental-group, where the lysinate formulation was adopted (LYS-group), or the standard-group (STAND-group) where they received standard ibuprofen formulation as analgesic medication for pain control after surgery. A simple randomization based on a single sequence of random assignments was carried out. In all children, surgery was performed between 8.30 am and 12 am under general anesthesia.
After surgery, all patients were transferred from the operating theater to the recovery room. After a complete awakening from anesthesia, the children received the first weight-calculated dose of one of the two ibuprofen formulations, as an analgesic, according to the randomization list. Administration of the assigned ibuprofen formulation was then continued on an 8-hours interval until 48 ± 6 hours after surgery.
Vital signs, including HR, BP, SpO2 and measure the child's self-reported pain, according

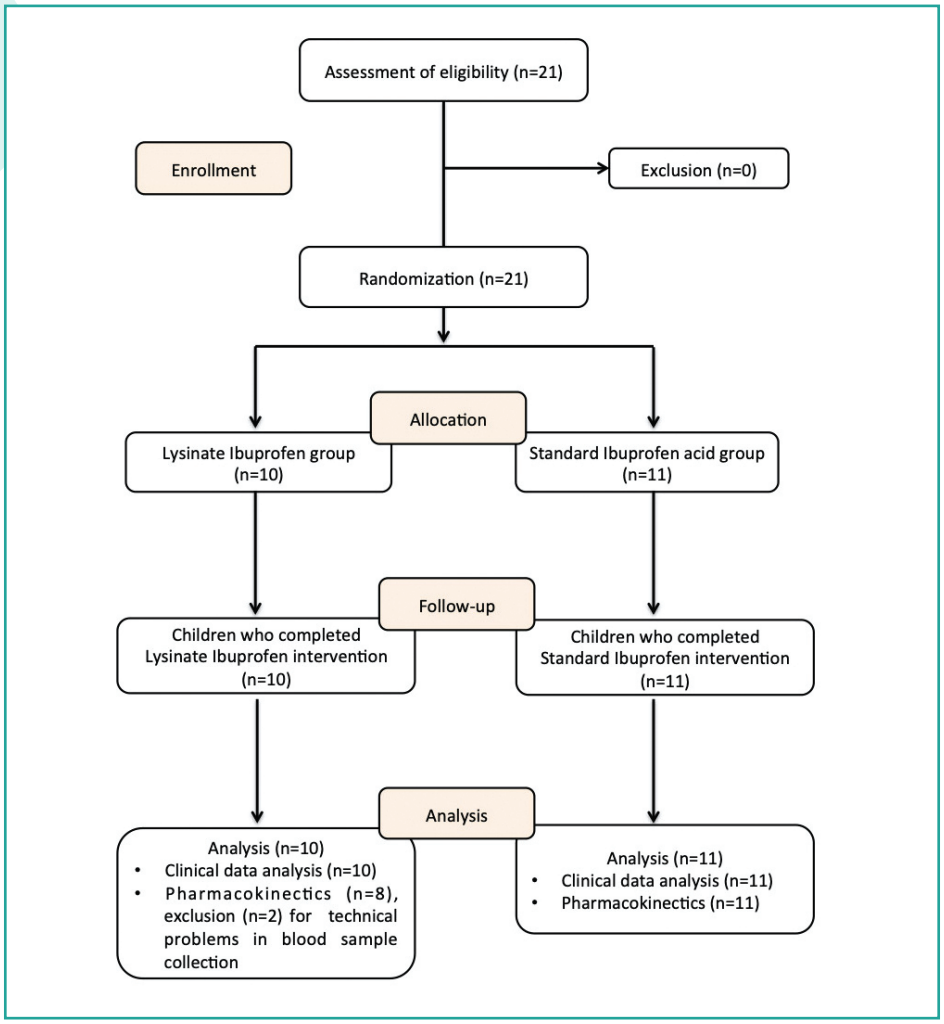

Figure 1. Flow chart of the phases of the randomized pilot study of two groups (lysinate ibuprofen and standard ibuprofen after surgery).

to Faces pain scale – revised (FPS-R) (9) (**figure 2**), were monitored before the first administration of one of the two ibuprofen formulations on day 1 post-surgery, 20 minutes after, and 48 hours after surgery.

Estimation of early ibuprofen absorption

Based on early pharmacokinetic assessments in adult healthy volunteers (8) and with the goal to limit discomforts for the pediatric patients, we decided to focus on the rate of ibuprofen absorption in the first 20 minutes after oral drug intake. In particular, after 24 hours (to ensure steady state conditions) of the three times a day oral administration of one of the 2 ibuprofen formulations, we collected 4 blood samples at 0 (immediately before the administration of the fourth dose) and 5, 15 and 20 minutes after the oral administration for a maximum total volume collected for each individual equal to 8 mL (2 mL for pharmacokinetic evaluation).

Ibuprofen concentrations were quantified by a validated liquid-chromatography tandem mass spectrometry method. The lower limit of quantification was set at 0,5 mg/L. Inaccuracy and imprecisions, tested during each analytical run by internal quality control samples, were in every instance less than 15%.

As the main ibuprofen pharmacokinetic parameters, we considered the basal (trough) drug concentrations, drug concentrations at 5, 10

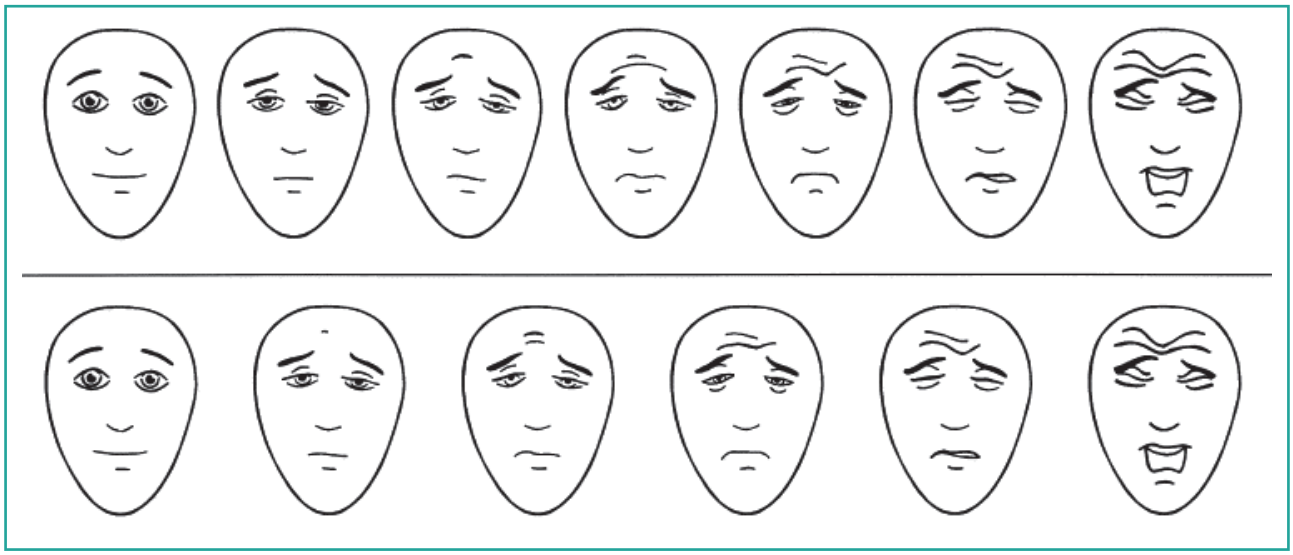

Figure 2. Faces pain scale-revised. Adapted from: Young KD. Assessment of Acute Pain in Children. Clin Pediatr Emerg Med. 2017;18:235-41.

and 20 min after drug intake and the $AUC_{0\text{-}20min}$ estimated using the trapezoidal rule.

Statistical analysis

Continuous variables were described as the mean and standard deviation (SD) or median and quartiles, and categorical variables as counts and percentages. The statistical significance of the continuous variable comparisons was assessed using the unpaired Student's t-test; the comparison of categorical variables was conducted using the chi square test or Fisher's Exact test if there was a small (< 5) expected cell size. A p-value below 0.05 was considered statistically significant. No multiple test correction was applied given the exploratory nature of the pilot study. The data analysis was performed with the STATA statistical package (release 15.1, 2017, Stata Corporation, College Station, Texas, USA).

RESULTS

Clinical data at the enrollment and follow-up

21 children (12 M and 9 F; mean age 10.46 ± 3.51 years; range 6.9-16.7 years), were randomly assigned to one of the two groups: the LYS-group (n = 10) and STAND-group (n = 11). In LYS-group, 9 patients were submitted to abdominal surgery (laparoscopic appendectomy) and one to thoracic surgery (breast abscess surgery); all STAND-patients were submitted to abdominal surgery (laparoscopic appendectomy).
Pre-experimental intervention clinical, demographics and vital signs in the two groups are reported in **table I**; no significant differences for age, gender and vital signs were noted ($p > 0.05$ for all parameters).
Twenty minutes after ibuprofen administration, pain control (FPS 0-2) was obtained in 19/21 (90.4%). At 48 ± 6 hours after surgery, pain control was reached in all but one patient in the lysinate group (with FPS = 4).
As reported in **figure 3**, vital signs remained stable during monitoring, without significant differences between groups ($p > 0.05$). No adverse effects were recorded.

Ibuprofen absorption

Data on ibuprofen pharmacokinetics during the absorption phase were available in 11 patients in the STAND-group and 8 patients in the LYS-group (blood samples collection was not performed in 2 LYS-children due to technical problems).

Features	LYS-group (n = 10)	STAND-group (n = 11)	p-value
Age (years)	11.61 ± 3.3	10.18 ± 1.7	0.223
Gender (M/F)	5/5	7/4	0.397
Weight (kg)	43.6 ± 16.5	38.9 ± 17.6	0.545
Heart rate (bpm)	67.8 ± 7.1	66.7 ± 12.7	0.828
Systolic blood pressure (mmHg)	107.7 ± 12.0	107.0 ± 11.1	0.882
Diastolic blood pressure (mmHg)	60.5 ± 16.6	59.8 ± 12.2	0.910
Oxygen saturation (%)	99.8 ± 0.4	99.5 ± 0.5	0.304
Face pain scale - < 4 - ≥ 4	 7 3	 9 2	0.403

Table I. Clinical and demographic features pre-experimental intervention in Lysinate Ibuprofen group (LYS-group) and Standard Ibuprofen acid (STAND-group).

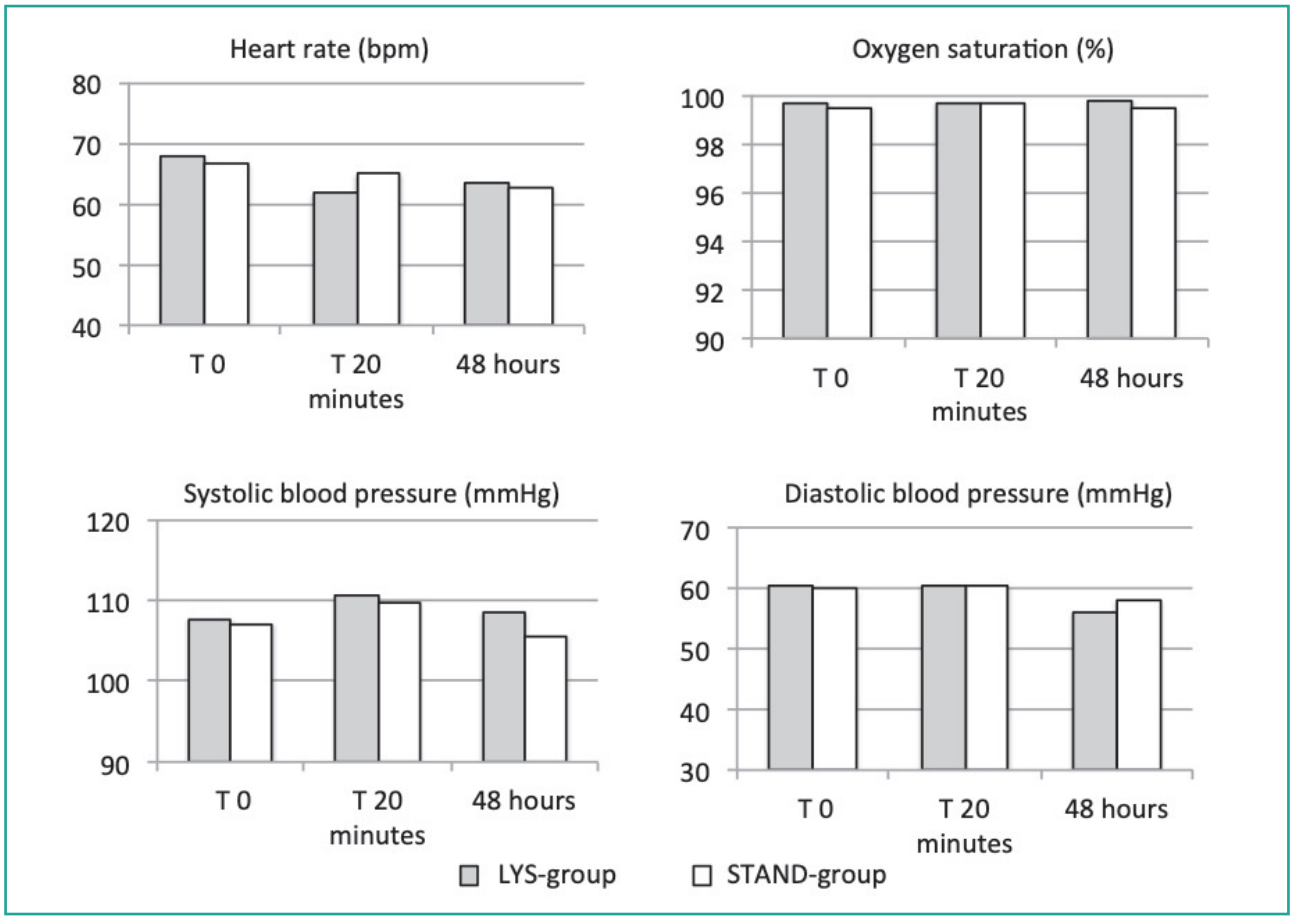

Figure 3. Average values of the vital signs during monitoring in Lysinate Ibuprofen group (LYS-group) and Standard Ibuprofen acid (STAND-group).

As shown in **table II**, pediatric patients from the LYS-group had significantly higher ibuprofen concentrations at 5 minutes after drug intake compared with those from the STAND-group (11.9 ± 8.6 *versus* 3.6 ± 3.6 mg/L, p = 0.010). Although not reaching statistical significance,

Main pharmacokinetic parameters	Ibuprofen lysinate	Ibuprofen acid	P-value
Patients, n	8	11	------
Ibuprofen basal, mg/L	5.7 ± 7.8	2.1 ± 1.0	0.141
Ibuprofen 5 min after intake, mg/L	11.9 ± 8.6	3.6 ± 3.6	0.010
Ibuprofen 10 min after intake, mg/L	17.3 ± 9.0	10.6 ± 10.2	0.153
Ibuprofen 20 min after intake, mg/L	23.0 ± 12.4	20.7 ± 18.0	0.762
Ibuprofen $AUC_{0\text{-}20\ min}$, mg/L*min	318 ± 168	206 ± 173	0.176
Min: minutes; AUC: area under the curve			

Table II. Main ibuprofen pharmacokinetic parameters in pediatric patients treated with ibuprofen lysine *versus* standard ibuprofen base.

the same trend was confirmed also for all the other pharmacokinetic parameters. Remarkably, ibuprofen basal concentrations, that represent the minimum measurable drug concentrations between two consecutive drug doses, were more than doubled in the LYS- versus STAND-group (5.7 ± 7.8 *versus* 2.1 ± 1.0 mg/L, p = 0.141). The LYS-group was also associated with a trend for reduced inter-individual variability in the drug exposure compared with the STAND-group (coefficient of variation of the $AUC_{0\text{-}20min}$: 52% *versus* 84%).

DISCUSSION

Surgery represents one of the most painful events that a child may experience (10). Inadequate pain treatment may lead to short-term consequences, such as prolongation of hospitalization and clinical worsening, but also to long term-consequences, as impairment of pain threshold and increased risk of chronic pain (11). Post-surgical pain is usually managed with multiple analgesics. The appropriate type, delivery and dose of medications depend on the type of surgery and the age of patients. In pediatrics, paracetamol and ibuprofen have been thoroughly described and are widely used in children to treat mild-moderate pain (12, 13). To obtain a correct management of pain, advanced pharmaceutical formulations, including salts of ibuprofen, were developed to provide faster-acting analgesics (14).

In the present observational, pilot study we have evaluated the rate of early drug absorption of two formulations of ibuprofen in pediatric patients requiring analgesic treatment for post-surgery pain and we have documented that the use of the lysinate salt of ibuprofen was associated with a fast absorption in the first 20 minutes after drug intake compared with the traditional ibuprofen acid formulation, confirming previous results in adult healthy volunteers (8). Moreover, our study extends previous findings by showing that the rate of absorption of the ibuprofen lysinate suspension is quicker and less variable than that of the ibuprofen acid reference in a population of pediatric patients at steady state conditions (that is 24-hours after starting ibuprofen treatment). More specifically, we have documented that, once given at the same molar drug doses, patients in the LYS-group at 5 minutes post-dosing had ibuprofen concentrations nearly 3-fold higher that those measured in the STAND-group. Remarkably, this trend was confirmed up to 20 minutes after drug intake.

The main issue with pain management is often the difficulty in evaluating it, especially in younger children. Many different tools and pain scales have been developed to help clinicians to identify pain in pediatric population, either based on observation of the child or on self-assessment, depending on the child's age. Faces pain scale has firstly been developed in

1990 and then revised in 2001 and it is widely used. As used in our study, FPS-R is made up of 6 faces resembling different severity of pain, starting from the first face on the left, corresponding to "absence of pain" and finishing with the last face on the right, corresponding to "the worst pain ever". The scale has been validated in children and has some advantages respect to other self-reported pain scales, as the absence of smiles and tears, that may be associated with misinterpretation of severity of pain with the related emotions. Moreover, the use of this scale has been recommended in clinical trials involving pediatric patients reporting their pain (15). With the aid of these tools, together with clinical information such as vitals and physical examination, pain can be classified as mild, moderate, or severe, and, for each category, appropriate treatment can be started (5).

Even though in our patients a pain control and vital signs stability were obtained, the study was not powered to test potential differences between the two formulations in terms of clinical efficacy. However, consistent evidence is available showing that a clear relationship exists between the maximum ibuprofen concentrations and the peak of analgesic effect or duration of analgesia (16, 17). Consequently, it can be assumed that the use of ibuprofen lysinate – due to the improved absorption – may result in a fast drug action and improved clinical response, especially when ibuprofen is given with the goal to treat acute pain, such as migraine attacks, dental or ears pain. In the only clinical trial published so far, Kyselovic *et al*. have documented that a single dose of ibuprofen lysinate was non-inferior to ibuprofen acid in terms of analgesic efficacy, onset of action, and tolerability in patients who have recently undergone dental surgery (18). However, as indirect support of this hypothesis, several investigations are available in literature showing that ibuprofen associated with arginine, which also provides fast absorption was significantly more effective than standard ibuprofen at the same dose in patients with osteoarticular pain, postoperative dental pain, periodontitis and primary dysmenorrhea (7).

We acknowledge some study limitations, including the small sample size; thus, further studies with a larger number of patients are mandatory to confirm the results. Secondly, to limit discomforts for the pediatric patients, we decided to focus on the rate of early drug absorption; additional data are useful to define a detailed pharmacokinetic profile of the drug. Finally, in addition to pain scale, endocrinological response on the hypothalamic–pituitary–adrenal axis could be useful to a better evaluation of the adaptive behavioral response to pain and to define the clinical efficacy of the formulation. The safety profile and the tolerability of ibuprofen lysinate have been thoroughly described by previous studies (19, 20). As of today, there is no evidence of increased rate of ADRs in lysinate ibuprofen compared to standard formulations, as both pharmacokinetic studies and efficacy ones, have shown a comparable incidence of ADRs between the two formulations (18, 21, 22). Although we did not include safety profile evaluation as an aim of our study, we did not record any ADRs in both LYS and STAND-groups.

CONCLUSIONS

Despite the acknowledged limitations, this study may be considered a first step suggesting the necessity to test new drug formulations for treating pain in pediatrics.

In conclusion, the use of ibuprofen lysinate in the form of oral suspension was associated with an early fast absorption after drug intake, compared to the traditional ibuprofen acid formulation, supporting fast action and an improved clinical response to mild-moderate postsurgical pain in children.

ETHICS

Fundings

Study design was funded by Dicofarm.

Conflict of interests

The authors declare that they have no conflict of interests.

Authors' contributions

VF, DC, EC, GVZ conceptualized the research; AM, VC, FD, GP collected research data; VF, VC, DC analyzed data; VF, AM, VC, DC, drafted the manuscript, EC, GVZ revised the manuscript, VF, VC, AM, FD, GP, EC, GVZ and DC approved the final version of the manuscript.

Availability of data and materials

The data underlying this article cannot be shared publicly due to privacy of research participants. The data can be shared just before a reasonable request to the corresponding author.

Ethical approval

Authors intend to respect the autonomy of individuals involved in the research by supplying the research's participants with sufficient and clear information to make an informed decision as to participate (informed consent to participate); ensuring that participants are not subject to coercion to participate or penalty for not participating; assuring that all the participants are free to withdraw from the research at any time without giving a reason and without any form of prejudice; respecting and defending the personal data made available by the participants following rigorous and recommended procedures to take in account both the confidentiality and anonymisation.

REFERENCES

1. Williams AC de C, Craig KD. Updating the definition of pain. Pain. 2016;157(11):2420-3. doi:10.1097/j.pain.0000000000000613.
2. Anand KJ, Carr DB. The neuroanatomy, neurophysiology, and neurochemistry of pain, stress, and analgesia in newborns and children. Pediatr Clin North Am. 1989;36(4):795-822. doi:10.1016/s0031-3955(16)36722-0.
3. Fitzgerald M. The development of nociceptive circuits. Nat Rev Neurosci. 2005;6(7):507-20. doi:10.1038/nrn1701.
4. Benini F. Il Dolore Nel Bambino. Riv Ital di Pediatr. 1995;21(4):510-3.
5. Organization WH. Cancer pain relief and palliative care in children. Published online 1998: Companion volume to: Cancer pain relief : with a g. Available from: https://apps.who.int/iris/handle/10665/42001?locale-attribute=en. Accessed: May 24, 2022.
6. Rainsford KD. Ibuprofen: pharmacology, efficacy and safety. Inflammopharmacology. 2009;17(6):275-342. doi:10.1007/s10787-009-0016-x.
7. Cattaneo D, Clementi E. Clinical pharmacokinetics of ibuprofen arginine. Curr Clin Pharmacol. 2010;5(4):239-45. doi:10.2174/157488410793352012.
8. Ferrero-Cafiero JM, Gich I, Puntes M, Martínez J, Ballester MR, Coimbra J , et al. Ibuprofen lysinate, quicker and less variable: relative bioavailability compared to ibuprofen base in a pediatric suspension dosage form. Int J Clin Pharmacol Ther. 2015;53(11):972-9. doi:10.5414/CP202368.
9. Hicks CL, von Baeyer CL, Spafford PA, van Korlaar I, Goodenough B. The Faces Pain Scale-Revised: toward a common metric in pediatric pain measurement. Pain. 2001;93(2):173-83. doi:10.1016/S0304-3959(01)00314-1.
10. Calcaterra V, Veggiotti P, Palestrini C, De Giorgis V, Raschetti R, Tumminelli M, et al. Post-operative benefits of animal-assisted therapy in pediatric surgery: a randomised study. PLoS One. 2015;10(6):e0125813. doi:10.1371/journal.pone.0125813.
11. Mitchell A, Boss BJ. Adverse effects of pain on the nervous systems of newborns and young children: a review of the literature. J Neurosci Nurs J Am Assoc Neurosci Nurses. 2002;34(5):228-36. doi:10.1097/01376517-200210000-00002.
12. Cooper TE, Fisher E, Anderson B, Wilkinson NM, Williams DG, Eccleston C. Paracetamol (acetaminophen) for chronic non-cancer

pain in children and adolescents. Cochrane database Syst Rev. 2017;8(8):CD012539. doi:10.1002/14651858.CD012539.pub2.
13. Eccleston C, Cooper TE, Fisher E, Anderson B, Wilkinson NM. Non-steroidal anti-inflammatory drugs (NSAIDs) for chronic non-cancer pain in children and adolescents. Cochrane database Syst Rev. 2017;8(8):CD012537. doi:10.1002/14651858.CD012537.pub2.
14. Rabbitts JA, Aaron R V, Fisher E, Lang EA, Bridgwater C, Tai GG, Palermo TM. Long-Term Pain and Recovery After Major Pediatric Surgery: A Qualitative Study With Teens, Parents, and Perioperative Care Providers. J pain. 2017;18(7):778-86. doi:10.1016/j.jpain.2017.02.423.
15. Tomlinson D, von Baeyer CL, Stinson JN, Sung L. A systematic review of faces scales for the self-report of pain intensity in children. Pediatrics. 2010;126(5):e1168-98. doi:10.1542/peds.2010-1609.
16. Schou S, Nielsen H, Nattestad A, et al. Analgesic dose-response relationship of ibuprofen 50, 100, 200, and 400 mg after surgical removal of third molars: a single-dose, randomized, placebo-controlled, and double-blind study of 304 patients. J Clin Pharmacol. 1998;38(5):447-54. doi:10.1002/j.1552-4604.1998.tb04452.x.
17. Laska EM, Sunshine A, Marrero I, Olson N, Siegel C, McCormick N. The correlation between blood levels of ibuprofen and clinical analgesic response. Clin Pharmacol Ther. 1986;40(1):1-7. doi:10.1038/clpt.1986.129.
18. Kyselovič J, Koscova E, Lampert A, Weiser T. A Randomized, Double-Blind, Placebo-Controlled Trial of Ibuprofen Lysinate in Comparison to Ibuprofen Acid for Acute Postoperative Dental Pain. Pain Ther. 2020;9(1):249-59. doi:10.1007/s40122-019-00148-1.
19. Schleier P, Prochnau A, Schmidt-Westhausen AM, Peters H, Becker J, Latz T, Jackowski J, et al. Ibuprofen sodium dihydrate, an ibuprofen formulation with improved absorption characteristics, provides faster and greater pain relief than ibuprofen acid. Int J Clin Pharmacol Ther. 2007;45(2):89-97. doi:10.5414/cpp45089.
20. Sörgel F, Fuhr U, Minic M, Siegmund M, Maares J, Jetter A, et al. Pharmacokinetics of ibuprofen sodium dihydrate and gastrointestinal tolerability of short-term treatment with a novel, rapidly absorbed formulation. Int J Clin Pharmacol Ther. 2005;43(3):140-9. doi:10.5414/cpp43140.
21. Miles L, Hall J, Jenner B, Addis R, Hutchings S. Predicting rapid analgesic onset of ibuprofen salts compared with ibuprofen acid: Tlag, Tlow, Tmed, and a novel parameter, TCmaxRef. Curr Med Res Opin. 2018;34(8):1483-90. doi:10.1080/03007995.2018.1466697.
22. Weiser T, Schepers C, Mück T, Lange R. Pharmacokinetic Properties of Ibuprofen (IBU) From the Fixed-Dose Combination IBU/Caffeine (400/100 mg; FDC) in Comparison With 400 mg IBU as Acid or Lysinate Under Fasted and Fed Conditions - Data From 2 Single-Center, Single-Dose, Randomized Crossover Studies in Healthy Volunteers. Clin Pharmacol Drug Dev. 2019;8(6):742-53. doi:10.1002/cpdd.672.