Randomized clinical trial comparing the efficacy and safety of ketamine and fentanyl for analgesia in pediatric orthopedic procedures

Ensaio clínico randomizado comparando a eficácia e a segurança da cetamina e do fentanil para analgesia em procedimentos ortopédicos pediátricos

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ABSTRACT

BACKGROUND AND OBJECTIVES: Bone fractures constitute a frequent cause of emergency care in the pediatric population. Opioid drugs are routinely used for analgesia during the hospitalization of children victims of trauma. Few studies have evaluated the importance of a multimodal approach to analgesia in this context. The aim of this study was to compare the analgesic effect and possible side effects of fentanyl compared to those of ketamine.

METHODS: The study analyzed 50 children and adolescents, aged between 24 and 192 months, submitted to surgical treatment of upper limb fractures in a tertiary trauma care hospital. The participants were randomized into two groups: one that received Ketamine and the other Fentanyl. In the post-anesthetic recovery room (PARR), pain intensity and the occurrence of delirium were measured for a period of 30 minutes. The incidence of respiratory depression, nausea, vomiting and other side effects during the surgical procedure were assessed.

RESULTS: The sample consisted mostly of male individuals (76.0%). The mean age of the participants was 90.1 months. The use of a low-flow oxygen cannula was necessary in 30.0% of the participants. The incidence of vomiting and laryngospasm was 2.0% among the participants, and 6.0% presented increased salivary secretion. The occurrence of pain, delirium and respiratory depression was not different between the two assessed groups, as well as the occurrence of nausea and laryngospasm.

CONCLUSION: Ketamine is not an effective and safe option to opioids for analgesia in children undergoing surgical procedures to treat upper limb fractures.

Keywords: Child, Delirium, Fracture fixation, Ketamine, Pain.

RESUMO

JUSTIFICATIVA E OBJETIVOS: As fraturas ósseas constituem causa frequente de atendimento de emergência na população pediátrica. Fármacos opioides são rotineiramente utilizados para analgesia durante a hospitalização de crianças vítimas de trauma. Poucos estudos avaliaram a importância de uma abordagem multimodal para analgesia nesse contexto. O objetivo deste estudo foi comparar o efeito analgésico e possíveis efeitos adversos do fentanil em relação aos da cetamina.

MÉTODOS: Foram analisadas 50 crianças e adolescentes, com idade entre 24 e 192 meses, submetidos ao tratamento cirúrgico das fraturas de membros superiores em um hospital terciário de atendimento ao trauma. Os participantes foram aleatorizados em dois grupos: um recebeu cetamina e outro fentanil. Na sala de recuperação pós-anestésica (SRPA), a intensidade da dor e a ocorrência de *delirium* foram mensuradas por um período de 30 minutos. A incidência de depressão respiratória, náuseas, vômitos e outros efeitos adversos durante o procedimento cirúrgico foram avaliados.

RESULTADOS: A amostra foi composta, em sua maioria, por indivíduos do sexo masculino (76,0%). A média de idade dos participantes foi de 90,1 meses. O uso de cânula de oxigênio de baixo fluxo foi necessário em 30,0% dos participantes. A incidência de vômitos e laringoespasmo foi de 2,0% entre os participantes, sendo que 6,0% apresentaram aumento da secreção salivar. A ocorrência de dor, *delirium* e depressão respiratória não foi diferente entre os dois grupos avaliados, assim como a ocorrência de náuseas e laringoespasmo.

CONCLUSÃO: A cetamina não se mostrou uma opção eficaz e segura aos opioides para analgesia em crianças submetidas a procedimentos cirúrgicos para tratamento de fraturas de membros superiores.

Descritores: Cetamina, Criança, Delírio, Dor, Fixação de fraturas.

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HIGHLIGHTS

- Pediatric trauma is one of the main causes of care in pediatric emergency units.
- Adequate pain control is essential in the humanized care of the pediatric population.
- The drugs used are associated with a series of adverse effects.

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INTRODUCTION

In the pediatric population, bone fractures are a major public health problem and a frequent cause of emergency care. In the United States of America in 2010, 14.7% of pediatric emergency department visits were due to orthopedic emergencies. Trauma in the forearm was the most common type, accounting for 17.8% of all occurrences[1].

Opioid drugs are routinely used for analgesia during the hospitalization of these patients, especially during surgical procedures. In this context, therapeutic procedures for upper limb fractures in children constitute a favorable environment for the over-prescription of drugs belonging to this class[2,3].

In pediatric trauma surgical care, the combination of non-opioid analgesics and anesthetic blocks can reduce the risks associated with the use of opium derivatives. Ketamine is widely used in the care of these patients in emergencies. For decades, this drug was most often used as a sedative, but it also has an analgesic action, which occurs by blocking the excitatory N-methyl D-Aspartate (NMDA) receptor[4,5].

A previously published clinical trial[6] compared the analgesic effect of intranasal ketamine versus fentanyl in children undergoing surgical procedures for extremity injuries. This study showed a significant decrease in pain scores after the use of analgesic drugs, with no difference in pain perception between the groups studied. Adverse effects were higher in the group of participants who received ketamine.

A systematic review[7] compiled five clinical trials which compared the analgesic effect of fentanyl to that of ketamine in pediatric emergency patients. Of these five studies, only one reported the intravenous application of the drugs and none of the studies used the associated technique of regional anesthesia. Despite the strengths of this systematic review, the limitation of including only 5 studies demonstrates the gap and the need for new clinical trials with a larger sample of participants.

When evaluating the current literature, it became clear that studies comparing the analgesic effect and possible complications of ketamine in children undergoing orthopedic procedures are quite limited, especially under regional anesthesia. Therefore, the present study's objective was to compare the analgesic and adverse effects of using ketamine and fentanyl in pediatric patients undergoing orthopedic procedures.

METHODS

The present study is a randomized double-blind clinical trial. The study was carried out at the *Instituto Doutor José Frota* (IJF), a tertiary trauma care hospital located in the city of Fortaleza, Ceará, Brazil. It was approved by the institution's Research Ethics Committee (CEP) on 12/18/2020, under CAAE number 39285820.6.0000.5047 and by the Brazilian Registry of Clinical Trials (ReBEC) on 11/05/2021, under number 11787.

The study population consisted of children and adolescents who underwent surgery to treat upper limb fractures in a surgical setting between January and July 2021. Both closed manipulations with plaster cast placement and open surgical procedures were included in the study. All procedures were performed in a surgical environment.

The inclusion criteria consisted of participants with ASA (American Society of Anesthesiologists) physical status classification scores I to II, aged between 24 and 192 months, undergoing surgical repair of upper limb fractures at the IJF. The surgeries lasted less than two hours. The ASA classification is based on a scoring system for assessing patients' health and comorbidities before a surgical procedure[8]. Patients with a score of I have no comorbidities and a score of II have controlled comorbidities.

Exclusion criteria were participants with no venous access upon arrival at the operating room, undergoing general anesthesia, patients with proven pharmacological allergy to any of the drugs in the study, patients with chronic use of sedatives or analgesics, or with previous neurological or motor disabilities. Participants with a history of alcohol or illicit drug use were also excluded.

The primary outcome analyzed was the analgesic effect of ketamine compared to fentanyl. Therefore, the sample calculation was based on the difference in the means of the results observed in the study[6]. Due to the scarcity of studies on the subject, the present study served as the basis for calculating the sample size, despite the obvious methodological differences. Considering a type I error limit of 0.05 and 0.20 for type II, the calculations determined a minimum sample size of 42 participants in order to produce reliable results.

Fifty participants were selected, anticipating possible losses during the study. All the participants and their legal guardians agreed to take part in the study. All guardians signed the Free and Informed Consent Term and participants over the age of 84 months signed the Term of Agreement to take part in the study. All the recruited children completed the study. The sociodemographic data analyzed were: age in months, weight and gender.

Participants were randomized into two groups using the Randomizer for Clinical Trial application. The control group (group F) received fentanyl as a pre-anesthetic drug. The intervention group (group K) received ketamine. There was no division of patients in relation to the scheduled surgical procedure. The study's pharmacological solutions (ketamine or fentanyl solution, as determined by the application) were prepared in coded and labeled syringes by a specialist physician who did not participate in the procedure or the evaluation of the participant patient's sedation.

Participants were submitted to a fasting for two-hours for liquids without residue, four hours for liquids with residue and six hours for all other foods before the intervention, in accordance with the institution's protocol. No sedative drugs were administered prior to arrival at the operating room.

On admission to the operating room, the patients were administered an intravenous dose of midazolam (IV) of 0.10 to 0.15 mg/kg, before separating the patients from their parents/guardians, according to an assessment by the doctor responsible for the procedure. Midazolam was administered at least 10 minutes before the infusion of drugs present in the study.

Upon entering the operating room, group F received a fentanyl dose of 1 μg/kg in a syringe with 5 mL of solution and group K received a ketamine dose of 1 mg/kg in a 5 mL syringe. In

addition, the participants received either continuous controlled targeted sedation with propofol, using an infusion pump with a pharmacokinetic model suitable for the pediatric population, or inhaled sedation with sevoflurane using their own ventilation system. After non-invasive blood pressure, oximeter and electrocardiographic monitoring, sedation was adjusted to achieve a score of 4 or 5 on the Ramsay sedation scale[9].

The anesthesiologist responsible for the procedure monitored and administered sedation to the participant and was aware of which group the participant belonged to. In addition, this same professional was responsible for choosing the drugs used to sedate the patients (sevoflurane or propofol) according to availability in the hospital pharmacy.

A resident doctor took notes on the parameters assessed and was unaware of which group the intervention participants were allocated to. The questionnaire assessed the participants' sociodemographic and anthropometric data. In addition, blood pressure (BP), heart rate (HR) and peripheral oxygen saturation (SpO_2) were measured every five minutes in the operating room.

During each procedure, the manifestation of adverse effects was recorded, such as respiratory depression (apnea for more than 15 seconds), decrease in SpO_2 < 90%, myoclonus, convulsions, skin rash, distorted emergency phenomena (agitation, hallucinations), vomiting, increased salivary secretion, visual disturbances and changes in BP and HR above 20% of the pre-anesthetic level. Length of stay in the post-anesthetic recovery room (PARR) was not a variable assessed.

On the recommendation of the anesthesiologist in charge of the procedure, the participants underwent brachial plexus block via the supraclavicular or axillary route with the aid of an ultrasound device, immediately after the start of the participant's sedation. For the anesthetic block, 0.25% bupivacaine at a dose of 2 mg/kg was used. Participants with an ineffective block were submitted to general anesthesia and consequently excluded from the study. After the end of the surgical procedure, continuous sedation was suspended and the participants were transferred to the PARR. In addition, the surgical procedure time was measured in minutes.

In the postoperative period, the presence of pain and delirium was evaluated every 10 minutes for 30 minutes. Pain was measured using the Hanallah scale. The occurrence of postoperative delirium (POD) was assessed using the Pediatric Anesthesia Emergence Delirium (PAED) scale[10,11].

The PAED scale is made up of five criteria which assess whether the child makes eye contact with the caregiver, whether their actions are intentional, whether they are aware of their surroundings, whether they are restless or inconsolable. Each criterion is scored using a five-point scale. The scores for each criterion are added together to form a total score. The maximum score achievable is 20. A score greater than 10 has a sensitivity of 64% and specificity of 86% for the diagnosis of emergency delirium (ED). A score greater than 12 has a sensitivity of 100% and specificity of 94.5% for the diagnosis of ED[11].

The Hannallah scale was developed in 1987 based on a study on analgesia for orchidopexy procedures in children aged between 18 months and 12 years[10]. It is an instrument widely used in pediatric studies to assess the level of pain using an objective scale based on physiological parameters, especially after surgical procedures. As this study analyzed participants aged between 2 and 16 years, this classification was chosen[12].

Statistical analysis

Data collected was initially stored in an electronic spreadsheet using the IBM SPSS Statistics software for MAC OSX, version 26.0 (IBM, USA). Statistical analyses were carried out using the JAMOVI statistical software and Microsoft Excel 2016. Numerical variables were presented as mean and standard deviation, median and percentiles, while categorical variables were presented as frequency and prevalence, with the objective of investigating associations between risk factors and disease.

The Mann-Whitney U-test was used to analyze the characteristics of the participants. Checking of non adherence of data to the Gaussian distribution was done through the Shapiro-Wilk test. Pearson's chi-square and Fisher's exact tests were used to investigate the association between categorical variables. A value of $p<0.05$ was considered significant for all tests.

RESULTS

The evaluated population consisted of fifty participants aged between 24 and 192 months, the majority of whom were male (76.0%). Of the participants, 94.0% were classified as ASA I and 6.0% as ASA II. There were no demographic differences between the groups (Table 1). The average surgical procedure time

Table 1. Comparative analysis of demographic variables between groups (n=50).

Variables	Total	Ketamine	Fentanyl	p-value
Age (months)	90.1 ± 43.4 80.5 (52.0 – 120.0)	83.6 ± 38.6 72.0 (51.0 – 98.0)	96.5 ± 47.6 94.0 (60.0 – 120.0)	0.352[a]
Female gender	12 (24.0%)	5 (20.0%)	7 (28.0%)	0.508[b]
Male gender	38 (76.0%)	20 (80.0%)	18 (72.0%)	
Weight (kg)	27.5 ± 11.2 25.0 (19.0 – 37.0)	25.0 ± 8.9 22.0 (19.0 – 34.0)	30.0 ± 12.8 27.0 (21.0 – 38.0)	0.145[a]
ASA				
I	47 (94.0%)	24 (96.0%)	23 (92.0%)	>0.999[c]
II	3 (6.0%)	1 (4.0%)	2 (8.0%)	

[a] = Mann-Whitney test; [b]: Pearson's Chi-square test; [c] = Fisher's Exact test. Data expressed as Mean±Standard Deviation, Median (25^{th} percentile - 75^{th} percentile).

in group F was 60 minutes and in group K it was 57 minutes, with no significant difference between the groups in this respect. The average pain values according to the Hannallah scale and the comparison between the groups are shown in table 2. The pain values in the first 30 minutes after surgery were not different between the study groups.

The incidence of respiratory depression among the participants was 28.0%, 24.0% in group K and 32.0% in group F. A total of 34.0% of the procedures presented an episode of peripheral oxygen saturation below 90.0%, with an incidence of 36.0% in group K and 32.0% in group F. The nasal oxygen catheter was used by 30% of the participants to maintain oxygenation above 90%. There were no differences between the groups in terms of the occurrence of respiratory depression, use of supplementary oxygen and drop in oxygen saturation (Table 3). This result covers the time from the use of the drugs under study until discharge from the PARR.

The mean values of the PAED[11] scale and the comparison between the groups are shown in table 4. The incidence of delirium in the first 30 minutes after surgery was not different between the groups. The intraoperative adverse effects for participants in group K were nausea and vomiting (n=1), laryngospasm (n=1), increased salivary secretion (n=2), versus one case of increased salivary secretion in the group F participants (Table 5).

Table 2. Comparison between the average pain values of the two groups according to the Hannallah scale (n=50).

Variables	Total	Ketamine	Fentanyl	p-value
Pain 10 minutes	1.0 ± 2.2 0.0 (0.0 – 1.0)	1.4 ± 2.7 0.0 (0.0 – 1.0)	0.6 ± 1.5 0.0 (0.0 – 0.0)	0.302[a]
Pain 20 minutes	1.0 ± 2.2 0.0 (0.0 – 1.0)	1.0 ± 2.0 0.0 (0.0 – 1.0)	0.5 ± 1.7 0.0 (0.0 – 0.0)	0.111[a]
Pain 30 minutes	1.1 ± 2.2 0.0 (0.0 – 1.0)	0.9 ± 2.0 0.0 (0.0 – 1.0)	0.6 ± 1.8 0.0 (0.0 – 0.0)	0.117[a]

[a] = Mann-Whitney test. Data expressed as Mean±Standard Deviation, Median (25th percentile - 75th percentile).

Table 3. Analysis of respiratory depression occurrence between the groups (n=50).

Variables		Total	Ketamine	Fentanyl	p-value
Presence of ventilatory depression	Absent	36 (72.0%)	19 (76.0%)	17 (68.0%)	0.529[b]
	Present	14 (28.0%)	6 (24.0%)	8 (32.0%)	
$SpO_2 < 90$ Episode	Present	17 (34.0%)	9 (36.0%)	8 (32.0%)	0.765[b]
	Absent	33 (66.0%)	16 (64.0%)	17 (68.0%)	
Use of O_2 cannula	Yes	15 (30.0%)	7 (28.0%)	8 (32.0%)	0.758[b]
	No	35 (70.0%)	18 (72.0%)	17 (68.0%)	

[b] = Pearson's Chi-square test. Data expressed as Mean±Standard Deviation, Median (25th percentile - 75th percentile).

Table 4. Analysis of the incidence of delirium in the groups (n=50).

Variables	Total	Ketamine	Fentanyl	p-value
PAED 10 minutes	3.8 ± 5.3 0.0 (0.0 – 8.0)	4.0 ± 4.9 0.0 (0.0 – 8.0)	3.5 ± 5.8 0.0 (0.0 – 4.0)	0.653[a]
PAED 20 minutes	3.8 ± 5.1 0.0 (0.0 – 8.0)	4.0 ± 4.6 2.0 (0.0 – 8.0)	3.5 ± 5.7 0.0 (0.0 – 8.0)	0.381[a]
PAED 30 minutes	3.1 ± 4.6 0.0 (0.0 – 6.0)	3.2 ± 3.8 2.0 (0.0 – 6.0)	3 ± 5.4 0.0 (0.0 – 3.0)	0.319[a]

PAED = Pediatric Anesthesia Emergence Delirium; [a] = Mann-Whitney test. Data expressed as Mean ± Standard Deviation, Median (25th percentile - 75th percentile).

Table 5. Analysis of the incidence of complications in the groups (n=50).

Variables	Total	Ketamine	Fentanyl	p-value
Vomit				
Yes	1 (2.0%)	1 (4.0%)	0 (0.0%)	>0.999[c]
No	49 (98.0%)	24 (96.0%)	25 (100.0%)	
Laryngospasm				
Yes	1 (2.0%)	1 (4.0%)	0 (0.0%)	>0.999[c]
No	49 (98.0%)	24 (96.0%)	25 (100.0%)	
Increased salivary secretion				
Yes	3 (6.0%)	2 (8.0%)	1 (4.0%)	>0.999[c]
No	47 (94.0%)	23 (92.0%)	24 (96.0%)	

[c] = Fisher's Exact Test. Data expressed as Mean ± Standard Deviation, Median (25th percentile - 75th percentile).

DISCUSSION

The present study is a randomized, double-blind clinical trial that evaluated the analgesic effects and adverse reactions of two classes of drugs frequently used in the pediatric population. Differently from previous studies carried out, upper limb orthopedic procedures in children and adolescents undergoing anesthetic blocks with the aid of ultrasound were analyzed.

When comparing the analgesic and adverse effects of using ketamine and fentanyl in pediatric patients undergoing orthopedic procedures, it was found that there was no difference between the two drugs regarding the two outcomes analyzed. Analgesia and the incidence of adverse effects were not significantly different between the groups studied. Clinically, there was a higher incidence of intraoperative complications in the group K.

Due to its effect on the NMDA receptor, ketamine is used in dissociative anesthesia in children undergoing invasive procedures. In addition, it is widely used in environments with limited resources, as it is a safe, easy-to-use and low-cost option[13,14]. Because it provides good hemodynamic stability and preserves airway protection reflexes, it is mainly prescribed in emergency procedures. Another advantage in this scenario is the possibility of intramuscular administration, since it can be difficult to obtain venous access in pediatric patients[13].

The pain variable was analyzed using the Hanallah scale and the difference between the groups was analyzed by the difference in averages. The mean values for this variable did not exceed the diagnostic threshold in any of the groups studied.

Moreover, when comparing the study groups, there was no statistical difference in relation to the pain score analyzed in the first thirty minutes postoperatively (Table 2). The authors[6] carried out a recent clinical trial and compared the analgesic effect between two groups using fentanyl or ketamine in children with extremity injuries. In this study, the authors used the Visual Analog Pain Scale to measure the analgesic state, which showed a reduction in pain scores with no difference between the groups studied. This analgesic equivalence between the two drugs in the treatment of pediatric patients has also been reported in other studies[6,15,16].

For ethical reasons, the present study did not use a placebo group for pain control. Although the groups evaluated did not differ in this respect, it was clear from the results that both drugs were effective in controlling immediate pain in the perioperative period. All participants who failed the anesthetic block were submitted to general anesthesia and consequently excluded from the study.

Regarding the incidence of ventilatory depression, there was no difference between the evaluated groups. The authors[17] carried out a systematic review which analyzed the occurrence of respiratory distress in the context of sedation in pediatric patients in the emergency setting. This review showed an incidence of hypoxia of 1.5% in the studies analyzed. The combination of ketamine and propofol or the use of propofol alone was associated with more cases of hypoxia.

The present study showed an incidence of 30% of participants requiring oxygen support to maintain SpO_2 above 90% after receiving the sedatives in the protocol. Although a significant number of participants required oxygen support, there were no cases of complications related to respiratory depression. All cases were resolved with the use of a low-flow oxygen cannula. As in the present study, several recent studies have not associated the use of ketamine with a higher incidence of hypoxia when compared to fentanyl[6,16].

The group of participants who used ketamine did not have a higher incidence of delirium in the immediate postoperative period. This finding corroborates data from a systematic review published by the authors[18]. Previously, another group of researchers had shown that both fentanyl and ketamine were effective in preventing agitation on awakening in children. Recent publications that associated a higher incidence of agitation and psychomimetic effects with the use of ketamine, such as the study[20], excluded pediatric studies, associating these effects with the use of high doses to control severe pain. Therefore, the finding of a similar incidence of delirium during awakening, related to the drugs analyzed in the study, reinforces the evidence already found in the literature[18-20].

In the present study, there were no differences in the occurrence of nausea, vomiting, laryngospasm or increased salivary secretion between the studied groups. The authors[17] observed that the main side effects associated with sedation in pediatric emergency procedures included agitation and vomiting. In their study, the incidence of vomiting was not associated with the use of ketamine, but the incidence of laryngospasm was. Recent studies have associated the use of ketamine with a higher incidence of minor events such as nausea and vomiting. On the other hand, the results found in this study did not associate an increase in adverse effects with the specific use of both drugs in the study, probably due to the single administration protocol and low doses[6,17].

Limitations of the study

This study had several limitations. The great variation in age among its participants was the main one. An analysis with participants from more specific age groups could result in data with more scientific evidence, since the findings for children in early childhood may be different from those found for adolescents.

Another important limitation was the sample size. Possibly, the lack of difference between the groups in relation to the outcomes studied is due exclusively to the small number of participants in each.

The use of inhaled and intravenous sedation may have generated a confounding factor in the data analysis. In addition, not all participants underwent regional anesthesia, which can be considered another important bias in the analysis.

Another limitation was that the post-operative follow-up lasted only 30 minutes. A follow-up period of at least 60 minutes, such as that carried out by previous studies[6,20], would probably allow for a better comparison with the evidence already found in the literature. Measuring the time taken to discharge from the PARR would be a valuable piece of data that has not yet been evaluated.

CONCLUSION

Based on the analysis of the data, it was not possible to state whether ketamine can be an effective and safe option to opioids for analgesia in children undergoing surgical procedures to treat upper limb fractures. Further studies with a larger sample are needed to confirm this hypothesis.

AUTHORS' CONTRIBUTIONS

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Statistical analysis, Funding acquisition, Data Collection, Conceptualization, Resource Management, Project Management, Research, Methodology, Writing - Preparation of the original, Writing - Review and Editing, Software, Supervision, Visualization
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