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**Title**

# Administering analgesia sublingually is a suitable option for children with acute abdominal pain in the emergency department

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**ABSTRACT**

**Aim:** Acute abdominal pain is a frequent complaint in children attending emergency departments. The aim of this study was to investigate the pain score reductions when children with acute abdominal pain received medication sublingually.

**Methods:** We carried out a multicentre randomised controlled trial in three children's hospitals in Italy between March 2015 and June 2017. Children from four to 18 years of age with acute abdominal pain were recruited if their self-reported pain was at least six on a scale from 0-10. The children were randomised to receive ketorolac 0.5mg/kg (n=70) or tramadol 2mg/kg (n=70) sublingually or a melt in the mouth powder of 20mg/kg paracetamol (n=70). The main study outcome was the pain scores for the three drugs after two hours.

**Results:** The 210 children (58.6% girls) had a median age of 12 years with an interquartile range of 9-14.3. The median pain scores at two hours were not significantly different between ketorolac 2.0 (IQR 0.0-4.3) and tramadol 3.0 (IQR 1.0-5.0) versus paracetamol 3.0 (IQR 0.8-5.0). The median pain reductions were all 5.0 points.

**Conclusions:** Delivering analgesia sublingually was a suitable option for pain relief in children with acute abdominal pain in the emergency department.

**Keywords:** analgesia, acute abdominal pain, children, emergency department, sublingual

**Abbreviations:** interquartile ranges (IQR), non-steroidal anti-inflammatory drug (NSAID), relative risk (RR)

**Key notes**

- This study compared the pain score reductions when children with acute abdominal pain receive medication sublingually in the emergency department.
- The children were randomised to receive ketorolac 0.5mg/kg (n=70) or tramadol 2mg/kg (n=70) sublingually or a melt in the mouth powder of 20mg/kg paracetamol (n=70).
- After two hours the median pain scores had all reduced by five points, demonstrating that delivering medication sublingually was a feasible option.

## INTRODUCTION

Acute abdominal pain accounts for approximately 9% of childhood visits to primary care and it is a frequent complaint in emergency departments, with a large number of resources spent on its evaluation and management (1,2).

The American Academy of Pediatrics recommends early analgesia in children with acute abdominal pain, to make the physical examination and diagnostic testing more comfortable (3).

The available evidence supports the use of intravenous opioids for analgesia in children with acute abdominal pain and randomised controlled studies have demonstrated that early analgesia does not influence the clinical examination and does not obscure the diagnosis of surgical conditions (4,5). The intravenous route of administration is not the only way to provide early analgesia in paediatric patients with acute pain, as several studies have showed that transmucosal analgesia is effective in this population (6-8).

Ketorolac is a non-steroidal anti-inflammatory drug (NSAID) and tramadol is a synthetic opioid analogue of codeine. Both drugs are effective when administered under the tongue (7) and they could be satisfactorily used in children with acute pain (9,10). To the best of our knowledge, no randomised controlled studies have investigated the effect of ketorolac and tramadol for pain relief in children with acute abdominal pain.

Therefore, the aim of this study was to investigate the pain score reductions achieved with the sublingual administration of ketorolac and tramadol in children with acute abdominal pain, compared to the administration of a melt in the mouth powder of paracetamol. The *a priori* hypothesis was that ketorolac and tramadol could be more effective than paracetamol in inducing pain score reductions.

## METHODS

This study was a multicentre randomised single-blind controlled trial that involved the emergency departments of three urban tertiary-level university teaching children's hospitals in Italy. These were: the Institute for Maternal and Child Health IRCCS Burlo Garofolo, Trieste, the Pausilipon Hospital, AORN Santobono Pausilipon, Naples and the Gemelli Hospital, Catholic University of Sacred Hearth, Rome. Every year, these

emergency departments provide treatment to approximately 23,000, 80,000 and 16,000 paediatric patients, respectively. The study was conducted between March 2015 and June 2017.

We enrolled children from four to 18 years of age who arrived at the emergency department complaining of moderate to severe acute abdominal pain. The children were eligible if they started complaining of abdominal pain started less than 48 hours before the emergency department evaluation and they self-reported their pain as at least six or more on an appropriate rating scale for their age. The exclusion criteria were a known allergy or sensitivity to non-steroidal anti-inflammatory drugs, opioids or paracetamol or the use of analgesic drugs in the eight hours before the medical evaluation. We also excluded children with a history of nephropathy, liver disease, metabolic or neurologic disease, thrombocytopenia or bleeding disorders or if the attending physician suspected during the medical evaluation that their abdominal pain was due to faecal stasis or severe dehydration (11).

After written, informed consent was obtained from a parent or legal guardian, the eligible children were randomly allocated to receive a maximum of 30mg of ketorolac oral drops 0.5mg/kg sublingually, (ABC Farmaceutici SpA, Ivrea, Italy) or a maximum of 100mg of tramadol oral drops 2mg/kg sublingually (Grunenthal Italia Srl, Milan, Italy) or maximum of 1,000mg of a paracetamol 20mg/kg melt in the mouth powder (Angelini SpA, Ancona, Italy).

A randomisation list, stratified by centre, with a fixed block size of 10, was generated using a computer-based method by an independent epidemiologist at the Clinical Epidemiology and Public Health Research Unit at IRCCS Burlo Garofolo. Allocation concealment was guaranteed by the use of sealed, opaque envelopes, which were

consecutively numbered and each contained the allocation group. The emergency department paediatrician opened the envelope marked with the lowest number available and assigned the patient to the corresponding group. The drug was administered by a nurse and the children and their families were blinded to which drug the child received.

After the drug administration, the children were asked to report their pain every 30 minutes.

If no pain control was achieved at two hours, defined as a pain score of at least six point on the 0-10 scale, the patients were given a rescue analgesic, which was chosen by the emergency department paediatrician.

One week after enrolment, the medical records of all children were reviewed to investigate if there was a missed or delayed diagnosis of acute appendicitis or other surgical condition.

The study protocol had received approval from the Independent Bioethic Committee of the Institute for Maternal and Child Health IRCCS Burlo Garofolo. The trial was registered with ClinicalTrial.gov (NCT02465255) before the enrolment of the first participant.

Children from four to seven years of age reported their pain using the Wong-Baker scale (12) and children aged eight or more reported their pain with the Numerical Rating Scale (13). For the statistical analyses, scores from both scales were transformed into a numerical value from zero for no pain to 10 for maximum pain, in accordance with previous studies, which demonstrated that scores reported using these two scales overlapped (14).

The primary study outcome was the child's self-reported pain after 120 minutes.

The secondary outcomes were pain scores at 30 and 60 minutes, the number of complicated cases of appendicitis and the number and types of adverse events.

**Statistical analyses**

This study was designed as a superiority trial. The data available in literature enabled us to estimate that ketorolac and tramadol would be more effective than paracetamol in providing pain relief (15).

We hypothesised that 210 subjects – 70 for each group – would be needed to carry out the study. This was based on a difference in pain score of one point or more using ketorolac or tramadol, with a standard deviation of two alfa of 0.05 and beta of 0.20.

Data were transferred to an electronic database and analysed by the Clinical Epidemiology and Public Health Research Unit of IRCCS Burlo Garofolo. The analyses were carried out according to the intention-to-treat principle. Continuous data were reported as medians and interquartile ranges (IQR) and as median differences and 95% confidence Intervals (95% CI). Categorical data were reported as numbers and percentages and as relative risks (RR) and 95% CIs. To evaluate the differences in pain scores between ketorolac versus paracetamol and tramadol versus paracetamol, we used the non-parametric Mann-Whitney U test, as a non-normal distribution of data was present. Moreover, self-reported pain scores were dichotomised as no pain if the score was one to four out of ten and pain if it was five to 10 and the differences were analysed with the chi-square test or Fisher's exact test, as appropriate. We chose a pain cut-off value of four because, in our practice, it is considered the limit for considerable pain.

Differences in secondary categorical outcomes were analysed with the chi-square test or Fisher's exact test, when appropriate. All p values and estimates of treatment effects were based on separate comparisons, so no adjustments were made for multiple comparisons. Given that tramadol group presented with a higher frequency of appendicitis at diagnosis, multivariate logistic regression analysis was carried out to adjust for this variable, the relationship between tramadol and paracetamol and the main study outcome, which was dichotomised. We considered a p value of $< 0.05$ statistically significant. All the analyses were carried out with SPSS software, version 21.0 (IBM Corp, Armonk, New York, USA).

**RESULTS**

We assessed 649 children for eligibility. Of these 158 decline to participate and 281 were excluded because they did not fulfil the study criteria. The main causes of exclusion were suspected constipation and a previous analgesic treatment. We enrolled 210 children: 70 were randomised to receive ketorolac, 70 to receive tramadol and 70 to receive paracetamol (Figure 1). No violation of the randomisation occurred. Table 1 shows the main characteristics of the study population. There were no relevant differences between the three groups, expect for the number of cases of appendicitis, which was higher in the tramadol group (Table 1).

Table 2 provides continuous data and Table 3 provides categorised data and they show the differences in pain scores between the three groups at the different times considered. No statistically significant differences between ketorolac versus paracetamol and tramadol versus paracetamol were found at any time, and, in particular, at two hours, which was the main study outcome.

When we compared the children who took ketorolac and paracetamol, we found that tramadol had significantly more adverse events, mainly nausea and vomiting. None of the patients experienced an allergic reaction. No statistically significant difference was seen in the number of complicated cases of appendicitis (Table 4).

The multivariate adjustments that took into account the imbalance between the tramadol and paracetamol groups in the number of appendicitis cases at diagnosis did not change the results.

## DISCUSSION

This study showed that sublingual administration was a suitable way to provide prompt and effective analgesia for children with acute abdominal pain in emergency departments.

While evidence is growing about the usefulness of the transmucosal routes of administration to provide analgesia in children with acute pain (6-8,16), no previous experience has focused on children with acute abdominal pain.

Acute abdominal pain is a frequent cause of paediatric emergency department visits and, even though prompt pharmacological analgesia is strongly recommended, children with acute abdominal pain are still often undertreated (17-19). Paediatric studies focusing on analgesia in children with acute abdominal pain have only investigated the usefulness of major opioids such as morphine and oxycodone (4). Even though in clinical practice NSAIDs and paracetamol are frequently prescribed for children with acute abdominal pain (18,19), to the best of our knowledge this was the first trial to investigate the usefulness of an NSAID, paracetamol and an opioid such as tramadol, in this setting. Previous experiences with adult patients showed that intravenous tramadol and paracetamol were equally effective in reducing acute abdominal pain, without influencing examination findings (20,21). Moreover intravenous paracetamol, tramadol

and dexketoprofene were all effective in adults with acute pancreatitis (22) and intravenous ketorolac provided successful pain relief for adults with suspected biliary colic (23). We chose the sublingual route of administration and included tramadol in the study design because previous studies on analgesia for abdominal pain were mainly based on intravenous opiods and we wanted to provide the most efficacious, fast and non invasive route of administration in the study, including an opioid. Tramadol was preferred to fentanyl due to its longer duration of action. The maximum dose of 30mg of ketorolac was chosen in accordance with the maximum intravenous dose. It is notable that a single dose of ketorolac is considered safe even if a patient may undergo surgery (24,25).

In our series ketorolac and tramadol were not superior to paracetamol in managing pain, but children, who took tramadol experienced significantly more adverse events. The data were similar to that of a previous study, which investigated sublingual ketorolac and tramadol in children with acute bone pain (7).

Our study did not focus on the influence of the analgesic treatment on the diagnostic accuracy of a surgical abdominal condition, but in our series the percentage of cases with complicated appendicitis was similar to that reported in children by previous studies (26) and it did not seem to be influenced by the drug regimen.

Sublingual treatment could be more acceptable to children than an intravenous route (16) and a first-line transmucosal treatment could be more convenient for an emergency physician, facilitating prompt and widespread analgesia.

This study had some limitations. First of all, it was not double blinded, but this was not possible because of the different formulations of paracetamol. The route of administration of the drugs cannot be straightforwardly defined as sublingual, in the true sense of the word, since from a chemical perspective the ketorolac and tramadol formulations we used were made for oral absorption and they were not optimised for transmucosal absorption. Furthermore, we could not exclude that the drug effect was due, in part, to the swallowed amount of the drug. Melt in

the mouth paracetamol powder is not available in all countries and this could limit the generalisation of our findings. The trial was carried out before the warning from the American Food and Drug Administration that tramadol should not be used in patients who are younger than 12 years of age (12). Tramadol was still on label for children in many countries at the time of our study, but it had already been reported and was well known that its use should be avoided in children at risk of respiratory depression, such as a history of sleep apnoea, those undergoing a tonsillectomy and obese patients (10). We did not investigate the palatability of the drugs, but sublingual ketorolac and tramadol were very well accepted in a previous study (7). Finally, we found a higher frequency of cases of appendicitis in the tramadol group. This imbalance cannot be attributed to the lack of blindness. An independent epidemiologist carried out the randomisation and the list was adequately concealed using opaque sealed envelopes. Therefore, we believe that the groups were casually imbalanced. However, the multivariate adjustment did not change the results.

The strengths of the study were its multicentre design, the considerable number of patients enrolled and the novel description of the sublingual administration of commonly used medication in children with acute abdominal pain.

## CONCLUSION

This multicentre randomised controlled trial was the first to investigated the sublingual administration of ketorolac and tramadol in children with acute abdominal pain in emergency departments. Both drugs were effective at relieving pain in these children. Our findings suggest that placing these drugs under the tongue may be an alternative route of administration in children presenting with acute abdominal pain in emergency departments.

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**Conflict of interest**

The authors have no conflicts of interest to declare.

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Table 1. Patient's characteristics

| Patient's characteristics | ketorolac (n=70) | tramadol (n=70) | paracetamol (n=70) |
|---|---|---|---|
| Age in years, median (IQR) | 12.0 (9.0-14.0) | 12.0 (9.0-14.0) | 12.0 (9.0-14.3) |
| Male sex, n (%) | 21 (30.0%) | 34 (48.6%) | 32 (45.7%) |
| Pain duration before emergency department evaluation, hours, median (IQR) | 12 (5.8-24) | 10 (5.0-28.5) | 13.5 (7.5-30) |
| Pain intensity at emergency department evaluation, median (IQR) | 7.0 (6.8-8.0) | 8.0 (7.0-8.0) | 8.0 (7.0-8.0) |
| Diagnosis at the medical evaluation: | | | |
| appendicitis | 5 (7.1%) | 15 (21.4%) | 8 (11.4%) |
| gynecological causes | 9 (12.9%) | 4 (5.7%) | 10 (14.3%) |
| urological causes | 3 (4.3%) | 3 (4.3%) | 3 (4.3%) |
| viral infections | 32 (45.7%) | 24 (34.3%) | 29 (41.4%) |
| abdominal colic pain | 16 (22.9%) | 20 (28.6%) | 15 (21.4%) |
| functional pain | 0 (0.0%) | 2 (2.9%) | 2 (2.9%) |
| other | 5 (7.1%) | 2 (2.9%) | 3 (4.3%) |

Table 2. Self-reported pain after 120 (main study outcome), 30 and 60 minutes after drugs administration, continuous variables, comparison between ketorolac and tramadol versus paracetamol

| | ketorolac (n=70) | tramadol (n=70) | paracetamol (n=70) | ketorolac vs paracetamol, median difference (95% CI) | p | tramadol vs paracetamol, median difference (95% CI) | p |
|---|---|---|---|---|---|---|---|
| Pain score at 120 min, median (IQR) | 2.0 (0.0-4.3) | 3.0 (1.0-5.0) | 3.0 (0.8-5.0) | -1.0 (-2.0-0.0) | 0.15 | 0.0 (-1.0-1.0) | 0.97 |
| Pain score at 30 min, median (IQR) | 5.0 (4.0-7.0) | 6.0 (4.0-7.0) | 6.0 (4.0-6.0) | 0.0 (-1.0-0.0) | 0.43 | 0.0 (0.0-1.0) | 0.42 |
| Pain score at 60 min, median (IQR) | 3.5 (2.0-6.0) | 4.0 (2.8-6.0) | 4 (2.0-6.0) | 0.0 (-1.0-1.0) | 0.61 | 0.0 (0.0-1.0) | 0.32 |

Table 3. Self-reported pain after 120 (main study outcome), 30 and 60 minutes after drugs administration, categorical variables, comparison between ketorolac and tramadol versus paracetamol

| | ketorolac (n=70) | tramadol (n=70) | paracetamol (n=70) | ketorolac vs paracetamol, relative risk (95% CI) | p | tramadol vs paracetamol, relative risk (95% CI) | p |
|---|---|---|---|---|---|---|---|
| No or mild pain (score ≤ 4) at 120 min, n (%) | 53 (75.7%) | 49 (70.0%) | 48 (68.6%) | 1.20 (0.81-1.80) | 0.35 | 1.02 (0.82-1.27) | 0.86 |
| No or mild pain (score ≤ 4) at 30 min, n (%) | 28 (40.0%) | 21 (30.0%) | 22 (31.4%) | 1.27 (0.81-2.00) | 0.29 | 0.96 (0.58-1.57) | 0.86 |
| No or mild pain (score ≤ 4) at 60 min | 44 (62.9%) | 37 (52.9%) | 40 (57.1%) | 1.10 (0.84-1.44) | 0.49 | 0.93 (0.69-1.25) | 0.61 |

Table 4. Complicated appendicitis and adverse events, comparison between ketorolac and tramadol versus paracetamol

| | ketorolac (n=70) | tramadol (n=70) | paracetamol (n=70) | ketorolac vs paracetamol, relative risk (95% CI) | p | tramadol vs paracetamol, relative risk (95% CI) | p |
|---|---|---|---|---|---|---|---|
| Complicated appendicitis | 0 | 3 (4.3%) | 1 (1.4%) | - | 1.00* | 3.00 (0.31-28.14) | 0.62* |
| Adverse events, n (%) | 2 (2.9%) | 18 (25.7%) | 2 (2.9%) | 1.00 (0.15-6.90) | 1.00* | 9.00 (2.17-37.34) | <0.001 |
| Types of adverse events | | | | | | | |
| Nausea | 0 | 8 | 1 | | | | |
| Vomit | 1 | 10 | 1 | | | | |
| Dizziness | 0 | 3 | 0 | | | | |
| Epigastric pain | 1 | 0 | 0 | | | | |

* Fisher exact test