Comparison of the effects of preemptive intravenous and rectal acetaminophen on pain management after inguinal herniorrhaphy in children: a placebo-controlled study

Gholam Reza Khalili*, Amir Shafa** and Ramin Yousefi***

Background: Postoperative pain management is a critical concern in pediatric surgery. Acetaminophen is the safest and most widely used analgesic in children. The present study compared the analgesic efficacy of intravenous (IV) and rectal acetaminophen versus placebo in children undergoing inguinal herniorrhaphy.

Methods: A total of 120 children, who were candidate for elective surgical repair of unilateral inguinal hernia, were enrolled and randomly allocated to four groups of 30 patients each to receive IV acetaminophen, acetaminophen suppository, IV placebo, and placebo suppository during surgery. Postoperative pain scores, measured on the Face, Legs, Activity, Cry, and Consolability (FLACC) scale, were recorded and compared.

Results: The four groups had no significant differences in the mean age, weight, length of stay in the recovery room, and duration of operation. The frequency of postoperative vomiting was significantly lower in the IV and rectal acetaminophen groups compared to the two placebo groups (P = 0.04). The mean pain scores of the two acetaminophen groups were similar during the first two hours after surgery. These scores were significantly lower than the scores of the placebo groups. However, the four groups were not significantly different in terms of pain scores at the fourth, sixth, and 12th postoperative hours. During the first hour after surgery, IV acetaminophen had the largest analgesic effect. Moreover, among all four groups, the IV acetaminophen group had the highest sedation level in the recovery room.

Conclusion: Both IV and rectal acetaminophen were more effective than placebo in pain relief after inguinal hernia repair in children. They were also associated with lower frequencies of postoperative vomiting. The greatest analgesic efficacy of both forms was observed during the first two hours after surgery.

Keywords: acetaminophen, suppositories, placebos, herniorrhaphy, groin, analgesia, pediatrics.

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Introduction

Postoperative pain and its complications have long been a concern to surgeons and anesthesiologists. Various methods of perioperative pain management can facilitate patient recovery. Optimal perioperative pain management can consequently reduce postoperative complications, enhance recovery after surgery, and shorten the length of hospital stay. The mechanism of postoperative pain and its related complications necessitates the administration of appropriate pain management strategies by anesthesiologists. Meanwhile, due to the physiological, pharmacological, developmental, and emotional differences between adults and children, pain management in children is usually challenging. According to available literature, 80% of children experience pain during the first day after a surgical operation. Moreover, the intensity of pain after discharge depends on the requested amount of opioids in the hospital. While pain is a major cause of post-operative agitation, children's inability to express their feelings generally prevents them from receiving adequate doses of analgesics. In addition to its physiological effects on different body organs, pain can alter the physical and mental states of young children (< five years).

Considering the significance of pain management, preemptive analgesia, first introduced by Crile in the beginning of the 20th century, has received increasing attention. Numerous clinical and experimental studies have confirmed this approach as an efficient pain management strategy with both short- and long-term benefits during the recovery period. A variety of medications, including opioids, non-steroidal anti-inflammatory drugs (NSAIDs), and acetaminophen, have been recommended for preemptive analgesia. However, opioids should be strictly avoided since even a single dose of them can increase postoperative vomiting and cause sedation, nausea, and respiratory depression. NSAIDs, on the other hand, may lead to gastrointestinal bleeding and trigger severe asthmatic attacks. Acetaminophen has thus gained growing popularity as a safe analgesic, especially in children.

Acetaminophen is administered in different forms and routes. Several studies have evaluated the effects of acetaminophen rectal suppositories. Razavi et al. compared the effects of acetaminophen suppository and caudal anesthesia on postoperative pain relief in children. Despite similar baseline pain intensity scores of the two groups during the first two hours after surgery, they reported that the acetaminophen suppository group had higher scores over the next hours. In another study, acetaminophen suppository failed to effectively reduce pain after major pediatric surgeries and morphine had to be administered for all patients. The changing and unpredictable bioavailability of rectally administered acetaminophen, ranging between 6.5% and 92.2% in different patients, has been suggested as the reason for the unfavorable analgesic effect of acetaminophen suppositories in postoperative pain relief.

The analgesic effects of intravenous (IV) acetaminophen (paracetamol) has also been widely examined. Murat et al. concluded that propacetamol and Perfaligan injections (two forms of paracetamol) had identical analgesic effects 15 minutes and six hours after herniorrhaphy in children. It is undoubtedly essential to find a cost-effective analgesic with adequate pain-reducing efficacy. While intravenous and rectally administered acetaminophen have different bioavailability, no research has compared the analgesic effects of these two forms of the medicine. Moreover, previous studies on acetaminophen suppositories have yielded inconclusive results. The aim of the current study is to compare the effects of IV and rectally administered acetaminophen and placebo on postoperative pain in children.

Methods

Upon the approval of the study protocol by the Ethics Committee of Isfahan University of Medical Sciences (Isfahan, Iran), this randomized, double-blind, prospective clinical trial was conducted in Alzahra Hospital and Imam Hossein Pediatric Hospital (Isfahan, Iran) during 2013-14. A total of 120 children who were candidates for elective surgical repair of unilateral inguinal hernia were enrolled. The children were included if they aged six months to 6 years, had no history of allergy to acetaminophen, and were not receiving antiepileptic or sedative drugs. Participants who had perioperative bleeding, underwent prolonged...
surgery, and required blood transfusion were excluded. Also, children were also excluded if their inguinal canal was explored.

All patients underwent general anesthesia. While being NPO (nil per os) time, the children received standard maintenance fluids, according to their body weight. In all patients, general anesthesia was induced by the administration of fentanyl 1 - 2 µg/kg, atropine 0.02 mg/kg, atracurium 0.6 mg/kg, and sodium thiopental 5-7 mg/kg. A mixture of 50% oxygen, 50% nitrous oxide, 1.2 minimum alveolar concentration (MAC) isoflurane, and morphine 0.15 mg/kg was also used during anesthesia.

The children were randomly allocated to four groups of 30 patients each. In Groups A and C, general anesthesia was induced and the patients were infused with IV paracetamol (15 mg/kg) and normal saline (15 mg/kg) respectively over 15 minutes before the incision was made. Acetaminophen and placebo suppositories were administered in Groups B and D, respectively. All procedures were performed by an anesthesiologist not involved in patient assessment.

After the surgery, the patients were transferred to the recovery room and the tracheal tube was removed when the children opened their eyes to command and felt uncomfortable with the tube. The first pain measurement, based on the Face, Legs, Activity, Cry, and Consolability (FLACC) scale, was made immediately after extubation. Pain scores were also recorded 30 minutes and one, two, four, six, and 12 hours after extubation. Modified Aldrete Score was used to decide when the children could be transferred from the recovery room.

The sedation levels of the patients were also determined based on their scores on the Richmond Agitation-Sedation Scale (RASS) and the frequency of receiving additional analgesic medicine (acetaminophen suppository) over the 12-hour period of pain measurement. A trained staff member who was unaware of the administered medicines recorded pain scores, sedation levels, frequency of vomiting, length of stay in the recovery room, and duration of operation in a questionnaire. The questionnaire also contained the patients’ file number, age, gender, and weight.

The collected data were entered into SPSS 20.0 (SPSS Inc., Chicago, IL, USA) and analyzed with chi-square tests and one-way analysis of variance (ANOVA) with repeated measures. P-values less than 0.05 were considered significant.

Results

Patients’ characteristics are presented in Table. There are no statistically significance difference among the four groups.

The four groups had a significant difference in the mean frequency of vomiting during the 12-hour postoperative period (P = 0.04). The two placebo groups (Groups C and D) had the highest frequency of vomiting. However, the slight difference between the frequency of vomiting in Groups A and B was not significant.

Significant differences were observed between the groups’ mean scores of pain immediately after the incision. The sedation levels of the patients were also determined based on their scores on the Richmond Agitation-Sedation Scale (RASS) and the frequency of receiving additional analgesic medicine (acetaminophen suppository) over the 12-hour period of pain measurement. A trained staff member who was unaware of the administered medicines recorded pain scores, sedation levels, frequency of vomiting, length of stay in the recovery room, and duration of operation in a questionnaire. The questionnaire also contained the patients’ file number, age, gender, and weight.

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30 minutes and one and two hours after extubation (P < 0.001) (Table 2). However, no such significant differences were observed at four, six, and 12 hours after extubation (P = 0.43, 0.57, and 0.22, respectively). Patients who received IV paracetamol, followed by those who had acetaminophen suppository, had the lowest pain scores during the first hour after surgery. The two mentioned groups had no significant differences in pain scores over the first two hours after surgery. The two placebo groups had the highest pain scores during these two hours. Their scores, however, were not significantly different (Table 2).

A significant difference in the mean frequency of receiving additional analgesics was seen among the four groups (P = 0.02). The pain scores in the IV paracetamol and acetaminophen suppository groups were similar during the 12-hour period of the study. The values in the two placebo groups were also very not different.

There were significant differences in the mean sedation levels of the four groups. The mean sedation levels in the IV paracetamol, acetaminophen suppository, and the two placebo groups were zero, one, and two, respectively (P = 0.02).

Discussion

The present placebo-controlled study examined the effects of preemptive use of IV and rectal acetaminophen on postoperative pain relief in children. The results confirmed both forms of the medicine to have significantly higher analgesic effects compared to placebo. While the greatest analgesic effect during the first hour after surgery was observed in the IV paracetamol group, both forms of acetaminophen had similar and acceptable efficacy in pain relief two hours after surgery. Moreover, the two forms of acetaminophen were as effective in reducing the need for additional analgesics to significantly lower levels compared to the placebo groups. Likewise, vomiting was less frequent in groups receiving acetaminophen than in the two placebo groups. Assessments in the recovery room suggested IV paracetamol to have greater sedative effects in comparison with placebo and acetaminophen suppository.

In one study, Razavi et al. found acetaminophen suppository and caudal anesthesia to have similar efficacy in relieving postoperative pain during the first two hours after surgery. After this period, however, pain scores significantly increased in the acetaminophen suppository group. Heshmati et al. also compared the analgesic efficacy of acetaminophen suppository and pethidine in postoperative pain management in children. While both groups had favorable pain scores (< three) during the first two hours after surgery, the medicines failed to maintain their analgesic effects until the fourth postoperative hour. Consequently, four hours after surgery, pain scores of both groups increased to over three and the patients required additional pain

<table>
<thead>
<tr>
<th>Time after decannulization</th>
<th>IV paracetamol (n=30)</th>
<th>Acetaminophen suppository (n=30)</th>
<th>IV placebo (n=30)</th>
<th>Placebo suppository (n=30)</th>
<th>P value</th>
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<tr>
<td>Immediately after</td>
<td>0.6 ± 0.2</td>
<td>1.1 ± 0.2</td>
<td>2.2 ± 0.3</td>
<td>2.3 ± 0.3</td>
<td>&lt; 0.001</td>
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<tr>
<td>30 minutes</td>
<td>1.2 ± 0.2</td>
<td>2.0 ± 0.3</td>
<td>2.8 ± 0.4</td>
<td>3.0 ± 0.3</td>
<td>&lt; 0.001</td>
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<tr>
<td>One hour</td>
<td>2.0 ± 0.2</td>
<td>2.4 ± 0.2</td>
<td>3.5 ± 0.2</td>
<td>3.6 ± 0.2</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Two hours</td>
<td>2.5 ± 0.2</td>
<td>2.8 ± 0.3</td>
<td>3.3 ± 0.2</td>
<td>3.3 ± 0.2</td>
<td>0.01</td>
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<tr>
<td>Four hours</td>
<td>1.9 ± 0.2</td>
<td>2.1 ± 0.3</td>
<td>2.2 ± 0.2</td>
<td>2.1 ± 0.2</td>
<td>0.43</td>
</tr>
<tr>
<td>Six hours</td>
<td>1.1 ± 0.2</td>
<td>1.3 ± 0.2</td>
<td>1.4 ± 0.3</td>
<td>1.3 ± 0.2</td>
<td>0.57</td>
</tr>
<tr>
<td>12 hours</td>
<td>0.6 ± 0.1</td>
<td>0.8 ± 0.2</td>
<td>1.0 ± 0.1</td>
<td>1.0 ± 0.2</td>
<td>0.22</td>
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Values are mean (SD).
A study in Turkey compared the effects of penile block, caudal block, and IV paracetamol on pain management after circumcision. At the first postoperative hour, pain scores in the penile and caudal block groups were equally lower than that in the paracetamol group. However, no differences were observed between the pain scores of the three groups at 1.5 and 2 hours after the surgery. A systematic review and meta-analysis by McNicol et al. revealed that 37% of patients receiving IV paracetamol experienced a 50% reduction in pain intensity over four hours (vs. 16% in placebo recipients). Furthermore, the administration of IV paracetamol was associated with a lower need for additional analgesics. Capici et al. concluded that both IV and rectal acetaminophen had good analgesic effects during the first six hours after surgery. Meanwhile, acetaminophen suppository caused a longer duration of analgesia compared to IV acetaminophen.

Consistent with previous research, the present study showed acetaminophen to have greater analgesic efficacy compared to placebo. Maximum effects of both IV and rectal forms of the medicine were observed during the first two hours after surgery. This finding can be justified by the half-life (four hours) and the peak effect (one-three hours) of acetaminophen. Despite the effectiveness of both forms of acetaminophen, patients receiving the IV form had higher sedation levels in the recovery room and lower pain scores during the first postoperative hour. This finding is acceptable since acetaminophen suppository has an unpredictable bioavailability (6.5%-92%) and may not be able to increase the plasma levels of the medicine to the required levels. Based on available literature, the IV form of acetaminophen achieves its maximum plasma concentrations and penetrates into the central nervous system at an earlier time compared to the other forms of the medicine. Owing to such properties, IV acetaminophen can be regarded as a faster-acting analgesic in comparison to the other two forms of the medicine.

Heshmati et al. reported postoperative vomiting in 16% of patients who received acetaminophen suppositories. The rates varied between 6% and 19% following the administration of IV acetaminophen. Similar frequencies of vomiting were also observed in the present study (10% and 13% in the IV and rectal acetaminophen groups, respectively).

We administered the recommended doses of acetaminophen and did not measure the serum concentrations of the medicine in the two groups. However, monitoring of serum levels and other pharmacokinetic properties of the medicine can not only clarify the mechanisms involved in different analgesic effects of IV and rectal acetaminophen at different times, but also determine the optimal doses and times of administration.

In conclusion, considering the favorable analgesic efficacy and limited half-life of IV and rectal acetaminophen, maintenance doses of the medicine are recommended for effective postoperative pain management in children undergoing inguinal herniorrhaphy.
References


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† Train-of-four
‡ Post-tetanic count
§ Second twitch

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