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Fentanyl-sparing Effect of Acetaminophen as a Mixture of Fentanyl in Intravenous Parent-/Nurse-controlled Analgesia after Pediatric Ureteroneocystostomy

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ABSTRACT

Background: Although acetaminophen has been used widely and is well tolerated in children, its efficacy and safety have not been clarified when combined with an opioid in intravenous parent-/nurse-controlled postoperative analgesia.

Methods: Sixty-three children (aged 6–24 months) who had undergone elective ureteroneocystostomies were enrolled in this prospective, randomized, double-blinded study. After the surgery, an analgesic pump was programmed to deliver fentanyl at a basal infusion rate of 0.25 $\mu g \cdot kg^{-1} \cdot h^{-1}$ and 0.25 μg/kg bolus after a loading dose of 0.5 μg/kg. In the fentanyl–acetaminophen group, acetaminophen was coadministered as a solution mixture at a basal infusion rate of 1.5 $mg \cdot kg^{-1} \cdot h^{-1}$ and 1.5 mg/kg bolus after a loading dose of 15 mg/kg, whereas saline was administered to the fentanyl group.

Results: Postoperative pain scores were similar between the two groups. The total dose (micrograms per kilogram per day, mean ± SD) of fentanyl at postoperative days 1 (8.3 ± 3.7 *vs.* 18.1 ± 4.6, $P = 0.021$) and 2 (7.0 ± 2.4 *vs.* 16.6, $P = 0.042$) was significantly less in the fentanyl–acetaminophen group compared with that in the fentanyl group. The incidences of vomiting (16.1 *vs.* 56.3%, $P = 0.011$) and sedation (9.7 *vs.* 46.9%, $P = 0.019$) were significantly lower in the fentanyl–acetaminophen group than those in the fentanyl group.

Conclusions: Acetaminophen has significant fentanyl-sparing effects and reduces side effects when combined with fentanyl in intravenous parent-/nurse-controlled analgesia for postoperative pediatric pain management.

What We Already Know about This Topic

- Acetaminophen is a useful adjunct for postoperative analgesia, but its application by parent-/nurse-controlled intravenous analgesia with fentanyl in infants has not been examined

What This Article Tells Us That Is New

- In 63 infants (6–24 months old), addition of acetaminophen to intravenous fentanyl parent-/nurse-controlled analgesia after ureteroneocystostomy reduced fentanyl dose, vomiting, and sedation by more than 50%

PAIN after surgical procedures in children has received deserved attention, especially in children undergoing ureteral reimplantation who have suffered from moderate to severe pain due to postoperative bladder spasms. Although the precise mechanism of postoperative bladder spasms is not known, there is evidence that suggests that prostaglandins may play an important role.[1,2]

A ready-to-use injectable acetaminophen (Perfalgan 10 mg/ml; Bristol-Myers-Squibb GmbH, Munich, Germany) works by inhibiting the cyclooxygenase enzyme in the central nervous system while sparing peripheral prostaglandin production. Intravenous acetaminophen has been shown to provide effective postoperative analgesia and is well tolerated in children,[3,4] but currently there has been no information regarding its continuous administration with opioids in pediatric pain management. The effective use of acetaminophen could contribute to keeping the postoperative opioid requirement and the potential for opioid-related adverse effects[5] to a minimum, particularly in infants and small children.

We designed a prospective, randomized, double-blinded study to evaluate the effects of acetaminophen combined with fentanyl as an intravenous parent-/nurse-controlled analgesia (PNCA)[6] on postoperative analgesic efficacy and to

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examine the adverse effects it has in infants and small children undergoing elective ureteroneocystostomy.

Materials and Methods

This study was approved by the Institutional Review Board (Yonsei University Health System Clinical Trial Center in Seoul, Republic of Korea), and informed consent was obtained from the parents of the patients. On the day of the preanesthetic visit, parents were taught the principles of PNCA and were explained their role in the study. Every participating parent should be at the child's bedside continuously for PNCA during the study period because the parent should activate the PNCA device (AutoMed3200; AceMedical, Seoul, Republic of Korea) when necessary. Written instructions for the parents as the "primary pain manager" were provided. The instructions included the process of PNCA, pediatric pain assessment, and how to monitor the adverse effects of PNCA and then notify the anesthesiologist in the ward as needed.

We enrolled 63 full-term infants and small children (physical status I or II according to the American Society of Anesthesiology) who were between 6 and 24 months of age and scheduled for elective ureteroneocystostomies. Patients were excluded if they had a known allergy to acetaminophen, kidney or liver dysfunction, or received other analgesics or sedatives before the surgery.

Before the induction of anesthesia, patients were randomly separated into two groups using a computer-generated randomization table. Premedication was not administered. Anesthesia was induced with 5 mg/kg thiopental sodium, and 0.6 mg/kg rocuronium was given for tracheal intubation while under standard monitoring. Then, mechanically controlled ventilation was used to maintain end-tidal carbon dioxide at 35 ± 5 mmHg during the surgery. Anesthesia was maintained with 1.0–4.0 vol% end-tidal sevoflurane in an air–oxygen mixture (fraction of inspired oxygen = 0.5). The concentration of end-tidal sevoflurane was adjusted according to the clinical parameters (blood pressure or heart rate within 20% of the baseline). All patients received 1 μg/kg intravenous fentanyl before the surgical incisions. The peripheral oxygen saturation, heart rate, and noninvasive blood pressure were monitored and recorded throughout the surgery. The same urologist performed all surgical procedures to maintain a uniform application of surgical stimulus.

At the peritoneal closure, the children in the fentanyl–acetaminophen (F–P) group received an intravenous bolus dose of 0.5 μg/kg fentanyl and 15 mg/kg acetaminophen, whereas the patients in the fentanyl group received 0.5 μg/kg fentanyl and saline. One nurse prepared all of the initial boluses and PNCA drugs, and this nurse was not involved in the surgical procedure or postoperative care. The anesthesiologist who administered the injections was unaware of their content. After emerging from anesthesia, a PNCA pump was attached to an intravenous catheter by an anesthesiologist blinded to the drug mixture. The intravenous infusion tubing contained a one-way, back-check valve to prevent backflow and inadvertent dosing of the drug by gravity. The duration of postoperative pain management using the PNCA pump was limited to 72 h.

In the F–P group, the syringe contained 1.5 μg/ml fentanyl and 9 mg/ml acetaminophen. In the fentanyl group, the syringe contained only 1.5 μg/ml fentanyl. In both groups, the basal infusion was set at 0.166 ml $\cdot$ kg^{-1} $\cdot$ h^{-1}. Patients in the F–P group thus received a postoperative basal infusion of 0.25 μg $\cdot$ kg^{-1} $\cdot$ h^{-1} fentanyl and 1.5 mg $\cdot$ kg^{-1} $\cdot$ h $\cdot$ $^{-1}$ acetaminophen, whereas patients in the fentanyl group received only 0.25 μg $\cdot$ kg^{-1} $\cdot$ h^{-1} fentanyl. For breakthrough pain despite the basal infusion, patients received 0.166 ml/kg bolus doses (0.25 μg/kg fentanyl and 1.5 mg/kg acetaminophen), with lock-out intervals of 30 min and a 6-h limit of four bolus doses (giving a 6-h maximum total dose of fentanyl and acetaminophen of 2.5 μg/kg and 15 mg/kg, respectively). If the patient seemed to be consistently uncomfortable with these initial settings despite the repeated bolus doses for 1 h, the fentanyl dose of the mixture was doubled by the anesthesiologist blinded to the drug mixture. Similarly, if a child seemed to be overly sedated or desaturated, the dose was reduced by half.

Both the nurse, who was blinded to the group allocation and stationed in the recovery room, and the educated parent in the ward were allowed to administer bolus doses to the child when they seemed to be in pain ($\geq$4 on the Children's Hospital of Eastern Ontario Pain Scale).[7] Throughout the PNCA use, the patient's vital signs and adverse effects were monitored by the nurse or parent. If the child had any adverse effects, the infusion was temporarily stopped, and a blinded anesthesiologist was immediately notified for appropriate management.

Postoperative sedation was evaluated using the eight-point modified Ramsay Sedation Scale,[8] and oversedation was defined as more than 4. Postoperative desaturation was defined as a decreasing peripheral oxygen saturation of less than 90%. Continuous pulse oximetry was performed for all children during the first 24 h of PNCA use and whenever the bolus doses were increased. Supplemental oxygen was provided for oxygen saturations less than 95%. Supplemental oxygen and naloxone were prepared on an as-needed basis for all patients in the case of desaturation. A total of 0.1 mg/kg ondansetron was administered if patients vomited even once. One milligram per kilogram pheniramine maleate was given when patients showed pruritus.

The postoperative total doses of fentanyl (as a primary outcome), pain scores measured by the parent, and adverse effects (as a secondary outcome), including vomiting, sedation, pruritus, desaturation, and poor oral feeding at 1, 6, 12, 24, 36, 48, 60, and 72 h after surgery were recorded. A liver function test (serum glutamic-oxaloacetic transaminase and glutamic pyruvictransferase) and urine analysis (pH, specific gravity, glucose, protein, and bilirubin content) were performed on the first and third postoperative days. After completion of the study, a questionnaire was distributed to assess

Table 1. Demographic Data and Intraoperative Characteristics

	Fentanyl Group (n = 32)	F–P Group (n = 31)
Age, mo	17.8 ± 10.4 (6–22)	16.9 ± 8.3 (6–24)
Weight, kg	11.4 ± 2.5 (7–20)	10.6 ± 2.4 (8–17)
Height, cm	80.0 ± 10.6 (69–98)	80.9 ± 11.1 (63–99)
Duration of surgery, min	94.5 ± 18.4 (65–120)	97.7 ± 23.0 (70–135)
Fluid administered, ml	181 ± 92 (90–255)	184 ± 68 (100–240)

Data are given as mean ± SD (ranges). There was no difference in variables between the groups.
F–P group = fentanyl–acetaminophen group.

the satisfaction level of the parents on a four-point scale (excellent = 1, good = 2, fair = 3, and poor = 4).

The sample size was taken from data previously published by Choi *et al.*,[9] who found that the total dose of fentanyl during the first postoperative day in similarly aged children at a basal infusion rate of 0.5 $\mu g \cdot kg^{-1} \cdot h^{-1}$ was 13.5 ± 0.5. Thirty patients in each group allowed for an alpha of 0.05 and a power of 0.9 for a 30% difference in the reference value. All data were expressed as the mean ± SD or the number (%) of patients. Statistical analyses were performed using SPSS 12.0 (SPSS Inc., Chicago, IL). The differences between the two groups were analyzed using the two-tailed Student *t* test, Mann-Whitney rank sum test, chi-square test, and Fisher exact test when appropriate. A normality test was performed using the Kolmogorov-Smirov and Shapiro-Wilk tests. A repeated-measured ANOVA with Bonferroni correction was performed to test for intergroup difference in terms of the total fentanyl doses and pain scores measured at the designated time points from 1 to 72 h. $P < 0.05$ was considered significant.

Results

A total of 63 patients were enrolled, and no patient was excluded or dropped out, leaving 32 patients in the fentanyl group and 31 patients in the F–P group. The two groups were comparable in terms of age, weight, height, duration of surgery, and intraoperative fluid administration (table 1). PNCA was successfully administered to all patients in the recovery room and the wards. All parents stayed with their children at their bedside, and they did not reject administering analgesics to their children during the study. No technical problems related to the use of the PNCA pumps were found during the study.

The total dose of fentanyl at postoperative days 1 and 2 was significantly lesser by half in the F–P group compared with that in the fentanyl group, as summarized in table 2. The cumulative dose of fentanyl for the 3 days after surgery was also significantly lower in the F–P group than that in the fentanyl group (fig. 1). In the fentanyl group, 14 children (43.8%) were given "double fentanyl" 1–2 times each on postoperative day 1 and another four (12.5%) on postoperative day 2 because of inadequate analgesia. No patient in the F–P group needed a higher fentanyl concentration. The dosing strategy was never decreased because neither of the two groups showed oversedation or desaturation during the study.

Postoperative pain scores between the two groups recorded at 1, 6, 12, 24, 36, 48, 60, and 72 h after the surgery were not significantly different (fig. 2).

Table 3 compares the incidences of side effects of the groups 3 days after the surgery. The fentanyl group had a significantly greater number of patients who vomited and had Ramsay scores higher than 4 compared with the F–P group. However, the patients who vomited postoperatively were well controlled by a single dose of ondansetron. Pruritus was spontaneously resolved in one child in the F–P group, and it was treated with pheniramine in three children in the fentanyl group and one child in the F–P group. There was no postoperative desaturation in either group.

The liver function test and urine analysis at postoperative days 1 and 3 did not show significant intergroup differences. The majority of patients (84.4% of the fentanyl group and

Table 2. Total Doses of Fentanyl and Acetaminophen during the Postoperative Period

	Fentanyl Group (n = 32)	F–P Group (n = 31)	*P* Value
Day 1			
Fentanyl, $\mu g \cdot kg^{-1} \cdot d^{-1}$	18.1 ± 4.6	8.3 ± 3.7	0.021
Acetaminophen, $mg \cdot kg^{-1} \cdot d^{-1}$	—	49.8 ± 3.8	
Day 2			
Fentanyl, $\mu g \cdot kg^{-1} \cdot d^{-1}$	16.6 ± 5.5	7.0 ± 2.4	0.042
Acetaminophen, $mg \cdot kg^{-1} \cdot d^{-1}$	—	42.2 ± 3.6	
Day 3			
Fentanyl, $\mu g \cdot kg^{-1} \cdot d^{-1}$	12.5 ± 5.8	6.4 ± 3.0	0.357
Acetaminophen, $mg \cdot kg^{-1} \cdot d^{-1}$	—	39.5 ± 4.2	

Data are given as mean ± SD. Fentanyl dose at postoperative days 1, 2, and 3 was significantly lower in the fentanyl–acetaminophen group (F–P group) compared with the fentanyl group.

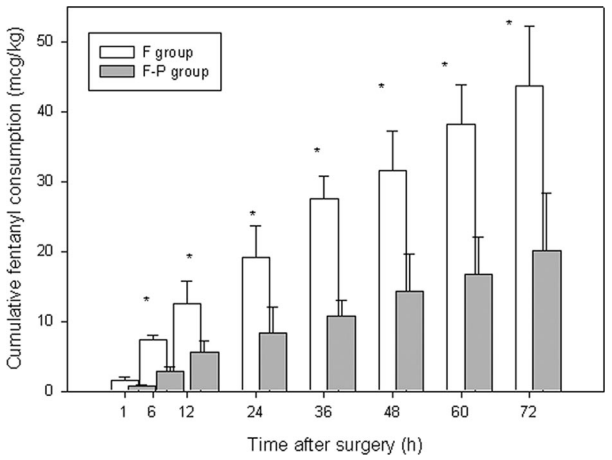

Fig. 1. The cumulative fentanyl dose (μg/kg) for 3 days after surgery. F group = fentanyl group; F–P group = fentanyl–acetaminophen group. The cumulative dose of fentanyl at 1, 6, 12, 24, 36, 48, 60, and 72 h after surgery was significantly lower in the F–P group than in the fentanyl group. * $P < 0.05$ compared with the F–P group.

100% of the F–P group) were satisfied (excellent or good) with the PNCA modality (table 4). Patients in the F–P group were more satisfied with the PNCA than those in the fentanyl group according to the chi-square test ($P = 0.020$).

Discussion

Our data confirm for the first time that PNCA, which was administered as a mixture of fentanyl and acetaminophen, was efficacious for postoperative pain control after pediatric ureteroneocystostomy. The results also indicate that continuous intravenous acetaminophen has significant fentanyl-sparing effects and is associated with fewer side effects compared with fentanyl alone.

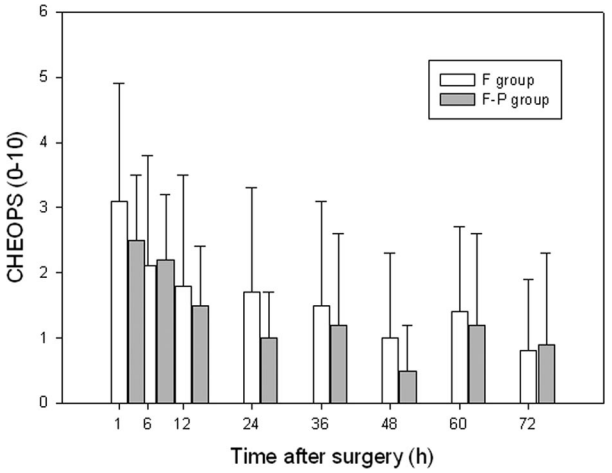

Fig. 2. Postoperative pain scores based on the Children's Hospital of Eastern Ontario Pain Scale (CHEOPS, 0–10). F group = fentanyl group; F–P group = fentanyl–acetaminophen group. Pain scores recorded at 1, 6, 12, 24, 36, 48, 60, and 72 h after surgery did not show statistically significant differences between the two groups.

Table 3. Incidence of Side Effects for the 3 Days after the Surgery

	Fentanyl Group (n = 32)	F–P Group (n = 31)	*P* Value
Vomiting	18 (56.3)	5 (16.1)	0.011
Sedation	15 (46.9)	3 (9.74)	0.019
Pruritus	3 (9.4)	2 (6.5)	0.515
Poor oral feeding	4 (12.5)	0 (0)	0.060
Desaturation	0 (—)	0 (—)	—

Data are given as the number (%) of patients. Sedation: modified Ramsay Sedation Scale >4. Desaturation: pulse oximeter values <90%. There was no respiratory depression in either group.
F–P group = fentanyl–acetaminophen group.

In this study, the average fentanyl dose used for the fentanyl group was approximately 0.75 $\mu g \cdot kg^{-1} \cdot h^{-1}$, which is close to the median dose (0.86 $\mu g \cdot kg^{-1} \cdot h^{-1}$ with a range of 0.6–1.17) as reported by Monitto *et al.*[6] in their fentanyl group using PNCA. The analgesic effect of intravenous acetaminophen is directly related to its plasma concentration. For postoperative pain, plasma acetaminophen levels of 10–20 mg/l are considered therapeutic for analgesia in children with peak therapeutic effects after about 1 h of postpeak plasma levels for all routes of administration.[10,11] Although we did not measure acetaminophen concentrations, we can expect that the plasma concentrations of acetaminophen in our patients were lower than those in previous reports[4,12] because we administered smaller doses of acetaminophen than the recommended total daily dose in the United Kingdom and Australia (60 $mg \cdot kg^{-1} \cdot day^{-1}$).[13,14] It is interesting that the analgesic effects might be attributable in part to continuous administration of acetaminophen because the bolus doses of acetaminophen were infrequently administered. Therefore, further pharmacologic studies regarding the concentration of acetaminophen when using continuous infusion are needed.

Our results suggest a possible synergic interaction between fentanyl and acetaminophen, although this study did not address this issue. There are some previous animal studies about the interactions between these two drugs. Gaitan *et al.*[15] demonstrated that a subanalgesic dose of nitroparacetamol strongly potentiated fentanyl antinociception in rats. The development of acute tolerance of fentanyl is also prevented by the combined administration of these drugs,[15] but

Table 4. Parent Satisfaction with Postoperative PNCA

	Fentanyl Group (n = 32)	F–P Group (n = 31)
Excellent	10 (31.3)	18 (58.1)
Good	17 (53.1)	13 (41.9)
Fair	5 (15.6)	0 (0)
Poor	0 (0)	0 (0)

Data are given as the number (%) of patients. Patients in the fentanyl–acetaminophen group (F–P group) were more satisfied with parent-/nurse-controlled analgesia (PNCA) than those in the fentanyl group according to the chi-square test ($P = 0.020$). .

the mechanism remains unclear. Further experimental studies are required to elucidate the underlying mechanisms, but it seems that they do not involve direct opioid receptor activation. Otherwise, acetaminophen could inhibit fentanyl metabolism. In an *in vitro* study by Feierman,[16] acetaminophen inhibited the oxidation of fentanyl to norfentanyl in a concentration-dependent manner. According to the kinetic analysis,[16] 10–20 mg/l acetaminophen inhibited the fentanyl metabolism in a normocompetitive fashion. Further clinical investigation in humans is needed to determine whether acetaminophen affects the bioavailability of fentanyl.

PNCA is considered a safe and efficacious modality for postoperative pain control in infants and small children.[17,18] Although PNCA has become common practice in our institution and no patient showed PNCA-related respiratory compromises in our study, there are still some concerns regarding the risk of overdosage and the potential of respiratory compromise. It is unclear whether PNCA causes fewer or more respiratory complications than routine p.r.n. dosing of opioids in children because few data are available for comparison.[6,9,19] Particular attention, of course, must be paid to each child's coexisting medical problems and the use of additional sedatives, both of which may decrease the safety margin of the technique. In addition, we advocate that PNCA could be used only in settings in which adequate resources are available to minimize the risk of serious complications and to intervene rapidly and effectively if complications do occur. Our teaching hospital includes a Hospital Pain Service Center with 24-h, extensive, and careful monitoring with nursing protocols and parent education.

Although the incidence of respiratory complications associated with patient-controlled analgesia using opioids has been found to be small, previous studies have shown that many patients who received intravenous patient-controlled analgesia experienced opioid-related side effects. For example, nausea and vomiting have been reported in 30–50% of children receiving patient-controlled analgesia,[20,21] and pruritus has been reported in up to 20% of patients.[21] We observed similar incidences of these side effects in our patients receiving PNCA using only fentanyl.

However, PNCA with the F–P mixture required significantly less fentanyl than those receiving fentanyl alone. Consequently, we found that acetaminophen combined with fentanyl in a PNCA regimen significantly decreased the incidence of fentanyl-related side effects as we had expected. Several studies have revealed significant morphine-sparing effects of acetaminophen in adults and children (24–36%),[22–24] but the benefits of a drug combination in terms of side effects was documented in only one study.[25] Remy *et al.*[25] suggested in their meta-analysis of randomized controlled trials that acetaminophen using patient-controlled analgesia had a significant morphine-sparing effect (20%) but did not change the incidence of morphine-related adverse effects, including nausea, vomiting, and sedation, during the postoperative period. However, it is difficult to understand the failure of acetaminophen to decrease these side effects despite the decrease in morphine requirement. These could be explained by the limitation of their review. In their study, not all morphine side effects were reported. Furthermore, the study was performed on too few numbers of patients.

Despite the clinical effects of this study, special caution is required in general application. Recently, low to moderate grade reflux is less often treated with ureteral implantation but rather with endoscopic collagen injections.[26] In addition, many anesthesiologists might prefer regional techniques for the control of lower abdominal pain after reimplantation. However, the benefit-to-risk ratio of regional techniques should be reconsidered in some children.[27] Therefore, PNCA with opioids and acetaminophen could be offered as an important alternative to regional blocks, such as for children with neurologic disorders or spinal anomalies, and older and/or obese children in whom caudal blocks are often difficult to perform successfully. When this technique is used in critically ill patients, more sensitive monitors will be needed because of the risks of apnea and desaturation.[6]

In conclusion, we demonstrated that acetaminophen has a significant fentanyl-sparing effect and could reduce the side effects of opioids when combined with fentanyl-based intravenous PNCA for postoperative analgesia in children who have undergone ureteroneocystostomies.

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