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SCIENTIFIC ARTICLE

Effect of intravenous acetaminophen versus fentanyl on postoperative pain after transurethral lithotripsy☆

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KEYWORDS
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Abstract
Background: Postoperative pain is the most common postoperative complication. This study was conducted to assess the effect of acetaminophen versus fentanyl on postoperative pain relief in patients who underwent urologic surgeries.
Methods: This clinical trial was conducted on patients aged 18–65 years. Patients were randomly assigned to receive either 2000 mg acetaminophen (propacetamol) or 2 mcg.kg^{-1} fentanyl intravenously, 15 min before the end of surgery. The postoperative pain was evaluated every 6 h for 24 h using the Visual Analog Scale. Total morphine dose taken in 24 h and hemodynamic status were evaluated.
Results: Eighty patients were enrolled into the trial. The mean score of pain in 6, 12, 18, and 24 h after surgery was lower in the acetaminophen group than in the fentanyl group but the difference was not statistically significant except in 12 and 18 h after surgery ($p < 0.05$). The amount of administered morphine was higher in the fentanyl group than in the acetaminophen group, but the difference was not statistically significant. The hemodynamic status including systolic and diastolic blood pressure and heart rates were nearly the same in the two groups but the SpO_2 mean was significantly higher in the acetaminophen group than the fentanyl group.
Conclusions: This trial indicated that intravenous acetaminophen is as effective as intravenous fentanyl in pain relief after urologic surgeries (transurethral lithotripsy).

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PALAVRAS-CHAVE
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Dor pós-operatória;
Parâmetros hemodinâmicos;
Litotripsia transuretral

Efeito do acetaminofeno versus fentanil intravenosos na dor pós litotripsia transuretral

Resumo
Justificativa: A dor pós-operatória é a complicação mais comum no período pós-operatório. Este estudo foi realizado para avaliar o efeito de acetaminofeno versus fentanil no alívio da dor pós-operatória em pacientes submetidos a cirurgias urológicas.
Métodos: Este ensaio clínico foi realizado com pacientes cujas idades variou entre 18 e 65 anos. Os pacientes foram randomicamente designados para receber 2.000 mg de acetaminofeno (propacetamol) ou 2 mcg.kg^{-1} de fentanil por via intravenosa 15 min antes do final da cirurgia. A dor pós-operatória foi avaliada a cada 6 horas por 24 horas, utilizando a escala visual analógica. A dose total de morfina administrada em 24 horas e o estado hemodinâmico foram avaliados.
Resultados: Oitenta pacientes foram incluídos no estudo. O escore médio de dor em 6, 12, 18 e 24 horas após a cirurgia foi menor no grupo acetaminofeno que no grupo fentanil, mas a diferença não foi estatisticamente significativa, exceto em 12 e 18 horas após a cirurgia ($p < 0,05$). A quantidade de morfina administrada foi maior no grupo fentanil que no grupo acetaminofeno, mas a diferença não foi estatisticamente significativa. O estado hemodinâmico, incluindo pressão arterial sistólica e diastólica e frequência cardíaca, foi quase o mesmo nos dois grupos, mas a média de SpO_2 foi significativamente maior no grupo acetaminofeno que no grupo fentanil.
Conclusões: Este estudo indicou que acetaminofeno intravenoso é tão eficaz quanto fentanil intravenoso no alívio da dor após cirurgias urológicas (litotripsia transuretral).

Introduction

Pain is always one of the most common postoperative complications that anesthesiologists have to overcome using various medical treatments.[1] Because the pain from surgical incision is somatic in nature, thus conventional opioids are usually used for pain relief. However, opioid drugs are associated with several adverse effects such as apnea, pulmonary problems, cardiovascular complications, nausea and vomiting, gastrointestinal discomfort, pruritus, urinary retention, and probability of drug dependent if they are used for a long time.[1–4]

Physicians are in an effort to use less expensive analgesic drugs with better treatment effect, but with less adverse effects. The conventional perioperative use of opioids used includes fentanyl, sufentanil, alfentanil, and remifentanil. Fentanyl is used more frequently. It is a short-term and rapid-response opioid agent. It is a highly fat-soluble drug, which can attach to the opioid receptors rapidly and result on pain relive efficiently. Fentanyl can be administered either intramuscularly, intravenously or intranasal.[5] It can be used through neuraxial, mucosa, and cutaneous as well. Morphine is another widely used opioid. The effect of morphine on pain reduction is one-tenth of fentanyl. It is less fat-soluble than fentanyl and is used intramuscularly, intravenously, orally, and through neuraxial. Morphine is particularly used in pulmonary edema. All opioids are metabolized in the liver. Therefore, their adverse effects are similar, but with different severity.[1]

Acetaminophen is a non-opiate analgesic. Unlike Non-Steroidal Anti-Inflammatory Drugs (NSAID), which inhibit Prostaglandin (PGD2) production and inflammatory reaction throughout the body,[6] acetaminophen inhibits prostaglandin production only in the brain and spinal cord. Furthermore, it reduces the neurotransmission of the pain through C nerve fiber. Acetaminophen has a direct effect on the hypothalamus, which is the center for regulation of body temperature, and can reduce fever. It has a weak anti-inflammatory effect and is seldom used for treatment of inflammatory disease. Acetaminophen is metabolized in the liver.[7]

Regarding the advantages and disadvantages of fentanyl, which is an opioid drug, and acetaminophen, which is an NSAID, this study was conducted to assess and compare the effect of these two analgesic drugs on postoperative pain relief, total morphine dose taken in 24 h, and the hemodynamic status in patients who underwent urologic surgeries.

Materials and methods

This single-blind randomized clinical trial was conducted in the Shahid Beheshti Hospital, affiliated with Hamadan University of Medical Sciences, in the west of Iran, from March to September 2013. Written informed consent was received from all parents. The Ethics Committee of the university approved the consent procedure, as well as the whole trial.

According to the results of a systematic review conducted by Tzortzopoulou et al.[8] in 2011, the proportion of pain relief within the first four hours after surgery was 50% in patients who received acetaminophen and 16% in those who received placebo. Based on these results, we arrived at a sample size of 39 (rounded to 40) for each group and a total sample size of 80% at 95% significance level and 90% statistical power. Patients were randomly allocated to the acetaminophen and fentanyl groups.

The study population included patients aged 18–65 years with class ASA I or II who were candidates for transurethral lithotripsy. Patients with any of the following

Table 1 Patients characteristics.

Characteristics	Acetaminophen ($n=40$)		Fentanyl ($n=40$)		p-Value
	Number	Percent	Number	Percent	
Education level					0.485
Illiterate	3	7.50	3	7.50	
Primary school	8	20.00	13	32.50	
Secondary school	6	15.00	8	20.00	
High school	14	35.00	12	30.00	
Academic	9	22.50	4	10.00	
Having chronic disease					0.615
No	37	92.50	39	97.50	
Yes	3	7.50	1	2.50	
Drug usage for chronic disease					0.615
No	37	92.50	39	97.50	
Yes	3	7.50	1	2.50	
ASA[a] *class*					0.615
PC-I	37	92.50	39	97.50	
PC-II	3	7.50	1	2.50	

Comparison of the characteristics of the acetaminophen and fentanyl groups using Chi-square test. PC is patient classification.
[a] American Society of Anesthesiologists Classification.

characteristics were excluded from the study: (a) Hypersensitivity to acetaminophen or fentanyl; (b) Known systemic diseases such as liver dysfunction, renal failure, hemorrhagic disorders, or hypertension; (c) Spinal deformity; (d) Using analgesic, alcohol, opioids, or psychotropic substance at the time of enrollment; or (e) Being pregnant. Blood pressure was examined in the sitting position at the time of admission (Table 1).

The eligible patients were randomly assigned to the acetaminophen and fentanyl groups using a systematic random allocation method. For this purpose, the first patient was randomly assigned to one group using tossing coins and then, every other patient was assigned to one group. This action repeated until the sample size was reached. The allocations remained concealed to the patients. Furthermore, the drugs were administered 15 min before the end of surgery; therefore, the patients were unaware of the drugs they received.

Therefore, a noninferiority trial was undertaken to show that the efficacy of the test drug product (acetaminophen) is not clinically inferior to that of the active comparator (fentanyl).

The acetaminophen group received 2000 mg propacetamol (equivalent to 1 g of paracetamol),[9] and the fentanyl group received 2 mcg.kg^{-1} fentanyl intravenously 15 min before the end of surgery. The standard method of spinal anesthesia was the same for all patients. All patients received 10 mL.kg^{-1} serum ringer before surgery, then received 10 mg (2 mL) bupivacaine 0.5% plus 50 mcg fentanyl through a conical needle no. 23. Cardiac monitoring was done during surgery. On request of patients, intravenous morphine (5 mg per dose) was injected intravenously in order to reduce the postoperative pain. Total morphine dose taken in the first 24 h after surgery was recorded for each patient.

The outcomes of interest were: (a) The severity of postoperative pain, which was evaluated every 6 h within the first 24 h after surgery using the Visual Analog Scale (VAS), on a scale of 0–10. Zero denoted no pain, and 10 denoted the most severe pain that the patient had ever experienced (pain plus crying).[10] (b) Total morphine dose taken for pain relief in the first 24 h after surgery. (c) Hemodynamic status including systolic and diastolic blood pressure, heart rate; and arterial hemoglobin oxygen saturation (SpO_2) which was evaluated before surgery and every 6 h within the first 24 h after surgery using cardiac monitoring and pulse oximetry.

The t-test was used for analysis of continuous variables and the Chi-squared test for nominal variables. All statistical analyses were performed at a significance level of 0.05.

Results

Of 210 patients identified, 111 were ineligible and 19 declined to participate. The remaining 80 patients were randomly allocated to the acetaminophen and fentanyl groups, 40 patients were allocated to the acetaminophen group and 40 to the fentanyl group (Fig. 1). No patient was lost to follow-up. Therefore, the analysis was based on data from the 80 patients (72 men and 8 women). The mean (SD) age of the patients in the acetaminophen and fentanyl groups was 38.13 (13.28) and 38.95 (12.50) years, respectively ($p=0.776$).

The effects of intravenous acetaminophen and fentanyl on postoperative pain relief as well as the total morphine dose taken in the first 24 h and the hemodynamic response are given in Table 2. The mean score of postoperative pain in the first hours after transurethral lithotripsy surgery was a bit higher in the acetaminophen group than in the fentanyl group, but it was lower in the 6, 12, 18, and 24 h after same surgery although the differences were not statistically significant except in 12 and 18 h after surgery ($p=0.031$ and $p=0.022$ respectively).

In the first hours after surgery, no patient received any opioid drugs. The frequency of opioids used intravenously in the 6, 12, 18, and 24 h after surgery in the fentanyl group was more frequented than in the acetaminophen group, but the differences were not statistically significant. The mean of

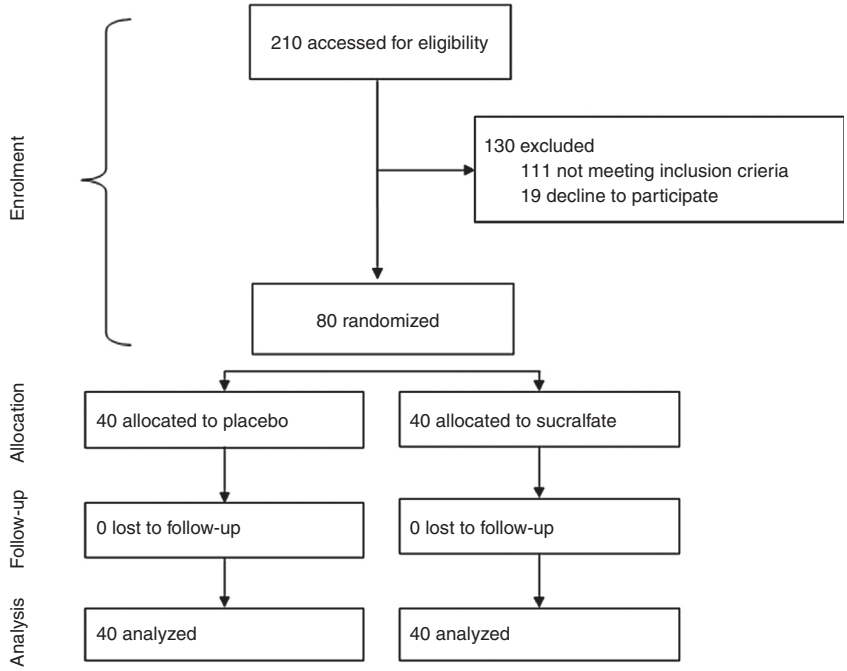

Figure 1 Flow diagram of the progress through the phases of the randomized trial of the two groups.

morphine usage in fentanyl group was higher (4.25 mg) than acetaminophen group (2.5 mg), but the differences were not statistically significant.

The hemodynamic status including systolic and diastolic blood pressure and heart rate in 1, 6, 12, 18, and 24 h after surgery was nearly the same in the two groups. The mean saturation of SpO_2 was significantly higher in the acetaminophen group than in the fentanyl group except in 1 and 12 h after surgery. The mean saturation of SpO_2 in 6 h after surgery in acetaminophen group was 96.85% and in fentanyl group was 95.90%, respectively in 18 h after surgery was 96.95% and 96.2%, in 24 h after surgery was 97.10% and 96.40%. The differences were statistically significant in 6–18–24 h after surgery $p < 0.05$).

Discussion

Opioids are widely used as the first line of palliative therapy for treatment of severe pain. However, they are associated with a number of adverse effects.[11] On the other hand, new generations of the non-opioid drugs, which are now produced by new technologies, have analgesic effect that is comparable with opioid agents. Efficacy of non-opioid medications, such as intravenous acetaminophen (propacetamol), for postoperative pain relief in urologic surgeries (transurethral lithotripsy), was the question that this trial answered. The results of this trial indicated that intravenous acetaminophen could be used successfully instead of fentanyl for pain relief in patients who underwent urologic surgeries.

Our results indicated that SpO_2 was lower in patients who received fentanyl than those who received acetaminophen. This can be attributed to the adverse effects of opioid drugs on pulmonary function by depressing cerebral function and causing hypoventilation and apnea.[12,13]

Acetaminophen is usually used orally as a supplementary analgesic in associated with other analgesic for postoperative pain relief.[14] However, clinical trials, which were conducted recently in the US and Canada, have shown that acetaminophen can be used intravenously for pain relief after surgery.[15,16] Acetaminophen has a mild effect on postoperative pain if it is used orally with a dose of 155–325 mg.[17] But current evidence has shown that the intravenous prescription of acetaminophen has a considerable analgesic effect.[18]

Several studies have been conducted to assess the analgesic effect of acetaminophen on postoperative pain after orthopedic, cardiac, and abdominal surgeries in comparison with other analgesic drugs such as NSAIDS, cyclooxygenase inhibitors, and metamizol.[19–21]

Acetaminophen is cost benefit compared to opioids with several adverse effects such as nausea, vomiting, pulmonary distress, gastrointestinal discomfort, renal dysfunction, and hematologic disorders.[22–24] However, the analgesic effect of non-opioid drugs is directly dependent on the site of surgery. For example, acetaminophen is more effective than metamizol in pain relief after retinal surgery,[25] but less effective after lumbar microdiscectomy.[26]

In 2011, Choudhuri et al.[27] conducted a randomized clinical trial on 80 patients who were candidates for laparoscopic cystectomy. They assessed the analgesic effect of acetaminophen compared to placebo and showed that the mean score of pain relief based on VAS was lower in the acetaminophen group than in the placebo group. In addition, they reported that the total amount of opioid (fentanyl) taken in the intervention group was less than the control group (50 mg vs. 150 mg respectively). Similar studies, which were conducted by Cakan et al.[28] in 2008 and Salihoglu et al.[13] in 2009, assessed the analgesic effect of acetaminophen on pain after cholecystectomy and showed similar results.

In 2011, Tzortzopoulou et al.[8] performed a systematic review, including 36 trials involving 3896 patients and assessed the postoperative analgesic effect of acetaminophen compared to placebo in children and adults.

Table 2 Postoperative characteristics.

Postoperative signs and symptoms (h)	Acetaminophen ($n=40$) Mean ± SD	Fentanyl ($n=40$) Mean ± SD	p-Value
Pain (Visual Analog Scale; 0–10)			
0	0.00 ± 0.00	0.00 ± 0.00	1.000[a]
1	0.05 ± 0.32	0.00 ± 0.00	0.320[a]
6	2.98 ± 3.6	4.04 ± 3.16	0.165[a]
12	2.23 ± 2.93	3.78 ± 3.37	0.031[a]
18	1.25 ± 1.72	2.53 ± 2.98	0.022[a]
24	0.78 ± 1.58	1.00 ± 1.60	0.529[a]
Peripheral oxygen saturation (SpO_2%)			
0	95.90 ± 1.72	95.43 ± 2.04	0.263[a]
1	96.43 ± 2.45	95.98 ± 2.08	0.379[a]
6	96.85 ± 1.63	95.90 ± 1.66	0.012[a]
12	96.63 ± 1.98	96.08 ± 1.82	0.199[a]
18	96.95 ± 1.32	96.20 ± 1.77	0.035[a]
24	97.10 ± 1.17	96.40 ± 1.74	0.038[a]

	Number	Percent	Number	Percent	p-Value
Frequency of morphine use					
0	0	0.00	0	0.00	1.000[b]
1	0	0.00	0	0.00	1.000[b]
6	9	22.50	13	32.50	0.317[b]
12	8	20.00	16	40.00	0.051[b]
18	3	7.50	4	10.00	0.692[b]
24	0	0.00	1	2.50	0.314[b]
Morphine rescue dose (mg)	2.5 ± 3.39		4.25 ± 5	0.071[a]	

Comparison of the clinical signs and symptoms in the acetaminophen and fentanyl groups using t-test[a] and Chi-square test[b] according to the condition.
Data are presented as mean ± standard deviation (SD).

They reported a 50% pain relief in the acetaminophen group compared to 16% in the placebo group. Furthermore, the total amount of opioid taken within the first four hours after surgery in the intervention group was 30% less than in the control group.

This study had a few limitations as follows. It was performed as single-blind trial. Although many measurements conducted in this study have not been influenced by the examiner's judgment such as severity of pain, frequency of opioid use, and SpO_2, however, this issue may raise the possibility of measurement bias. Furthermore, our study sample included patients aged 18–65 years who underwent urologic surgeries. Therefore, the results of this study may not be generalizable to children or patient candidates for other types of surgery. The generalizability of the results to these patients needs further investigations. Despite its limitations, this trial was able to efficiently assess and compare the efficacy of intravenous acetaminophen and fentanyl for postoperative pain in patients who underwent urologic surgery.

Conclusion

The results of this trial indicated that intravenous acetaminophen is a safe drug with no important adverse effects. This drug can efficiently reduce postoperative pain in patients who undergo urologic surgeries. Intravenous acetaminophen and fentanyl have nearly the same analgesic effect but acetaminophen is safer with less adverse effect. However, further investigations are needed to generalize the results of this trial to other types of surgery. Comparison of the effect of acetaminophen to other opioid agents is suggested.

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Conflicts of interest

The authors declare no conflicts of interest.

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