Acute pain control by Pethidine versus intravenous acetaminophen in maxillofacial surgeries: a double blind randomized-controlled trial

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Abstract: Background and aim: In a double-blind randomized-controlled trial we wanted to assess the efficacy of intravenous acetaminophen in controlling early postoperative pain in maxillofacial inpatient operations compared to routinely administered opioids. Materials and methods: We studied 52 consecutive patients. All patients had an operation on their mandible. The patients were randomly divided into two groups by simple randomization. Postoperative pain was measured by visual analogue score (VAS) 1, 2, 4, 8, 12 and 24 hours after the operation. The first group (26 patients) received postoperative Pethidine 1 mg per kg every 4 hours while the second group (26 patients) received postoperative acetaminophen 15 mg per kg every 6 hours. Results: There was not any significant difference between age and sex ratio in two study groups ($p > 0.05$). There was not any significant difference between pain scores of two groups at postoperative time intervals ($p > 0.05$). Repeated-measure ANOVA test revealed that the decline of pain was observed in both groups and the trend of decline had no significant difference between two groups ($p > 0.05$). Conclusion: In conclusion, we found that intravenous acetaminophen is equal to routine opioid administration in controlling acute pain after maxillofacial surgeries.
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1. Introduction

Pain control and relief is one of the main conflicts after maxillofacial surgeries. Head and face fractures are the leading causes of maxillofacial fractures and necessitate potential pain control and postoperative care (Kehlet and Dahl, 2003). Pain control of inpatient maxillofacial surgery is of potential clinical interest and a thorough understanding of analgesic strategies is essential (Coulthard, 2000).

During recent decades, novel improvements have been made in maxillofacial surgery and oral medicine and anesthetic techniques have lead surgeons to conduct necessary procedures without pain (Desjardins, 2000). The routine approach to pain control in dental and maxillofacial surgeries is general anesthesia followed by postoperative pharmacological pain control (Zuniga, 2000). Research into the basic mechanisms of pain and anxiety in oral and maxillofacial surgery has led to a number of new strategies that have yield more precise and controlled forms of analgesia.

Benzodiazepines, high-potency synthetic opioids, and other agents such as propofol that are all useful in outpatient settings are among the most frequently used druds. Similarly, new classes of analgesic drugs (such as nonsteroidal anti-inflammatory drugs [NSAIDs], cyclooxygenase-II [COX-II] inhibitors, and opioid agonist-antagonists) have also been developed, and these are playing increasingly important roles in managing pain of oral and maxillofacial surgeries(Desjardins, 2000; Buvanenderan, 2007).

Besides the availability of novel pharmacologic agents, the goal of pain control has remained the same and patient comfort and preference are the most important factors (Joshi, 2000). Furthermore, inpatient control of postoperative pain is often more complex and necessitates intravenous analgesic administration (Zuniga, 2000; Joshi, 2000; Haas, 2002). The most frequently used analgesic agents in these settings are opioids. Opioid analgesics have their potential drawbacks and may lead to respiratory depression and tolerance when used continuously in high doses

(Coulthard, 2000; Desjardins, 2000 Joshi, 2000). It has been proposed that combination of opioids with novel analgesics such as NSAIDs may diminish the need for opioids and may significantly decrease their side effects (Coulthard, 2000).

In the present study we wanted to assess the efficacy of intravenous acetaminophen in controlling early postoperative pain in maxillofacial inpatient operations compared to routinely administered opioids.

2. Material and Methods

We wanted to compare the efficacy of intravenous acetaminophen in controlling postoperative pain in oral and maxillofacial surgeries with opioids. We studied 52 consecutive patients. All patients had an operation on their mandible. The inclusion criteria were being candidate of mandible surgery and being 18 to 50 years of age. However, exclusion criteria were having a systemic illness, history of previous surgery, history of alcohol abuse, history of opioid use, pain syndromes, mental disorders, using opioid drugs during anesthesia, history of monoamine oxidase (MAO) inhibitors use and history of mental disorders. The patients were randomly divided into two groups by simple randomization. We used the website www.randomizer.org to allocate the patients to acetaminophen and opioid groups. Figure 1 illustrates the follow diagram of the study patients.

All patients received 8 mg Dexamethasone intravenously (IV) together with prophylactic cefazolin (1 mg IV) preoperatively. For induction of general anesthesia, atracurium besilate (6 mg per kg) and propofol (2 mg per kg) were used. The maintenance was done by mixture of isoflurane 2%, nitrous oxide 50% and oxygen 50%. Before the initiation of the surgery, 5 ml of mixture of lidocaine 2% plus epinephrine 1/100000 was injected to the incision site to improve the homeostasis.

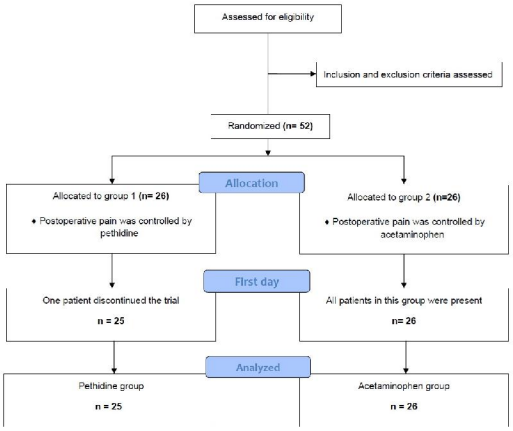

Figure 1: Follow diagram of the study patients.

The patients were divided into two groups. In the first group, postoperative pain control was conducted by administration of intravenous Pethidine 50 mg in 1 ml while the second group received intravenous acetaminophen (Apotel 1000 mg). Pethidine was administered 1 mg per kg every 4 hours and acetaminophen was administered 15 mg per kg every 6 hours. The first dose of analgesic either Pethidine or acetaminophen was administered after transferring the patient to the recovery room. In the cases who had pain despite the administered doses of Pethidine and acetaminophen, extra doses of Pethidine was planned to be used in both groups.

Postoperative pain was measured by visual analogue score 1, 2, 4, 8, 12 and 24 hours after the operation. The scores were from 0 to 10. 0 was feeling no pain while 10 was indicative of the most severe pain the patient have ever experienced or would ever experience in the future. Blood pressure measurements were also conducted at the same time intervals. Patients were evaluated for nausea, vomiting, headache, vertigo and respiratory depression during their postoperative admission. All pain assessments and blood pressure measurements were done by one person. This person and the surgeon were not aware of the type of analgesics which were administered to the patients. The patients were also not aware whether they are receiving Pethidine or acetaminophen. Thus, the present clinical trial was a double-blind randomized controlled trial.

Demographic variables of the study consisted of age, sex, weight and duration of operation. These variables were measured by descriptive statistics. They were compared between two groups by independent sample t-test and chi-square test. Pain measurements were by visual analogue score (VAS) and they were considered quantitative scale for pain. The measurements of pain in time intervals were compared between two groups by t-test. In addition, confidence intervals for 95% statistical significance were measured and were shown by error bars. The analysis for measurement of the trend of pain 1, 2, 4, 8, 12 and 24 hours after the operation was done by repeated-measure ANOVA test. Systolic and diastolic blood pressures were described as mean ± standard deviation (SD) and the comparison between two groups was done by independent sample t-test. Postoperative nausea, vomiting, headache, vertigo and respiratory depression were also described by frequency and percent and compared between two groups by chi-square test. All statistical analyses were done by SPSS 18.0 software.

The protocol of this study was approved by the ethical committee and vice chancellor office of

Tabriz University of Medical Sciences, Tabriz, Iran under number 5.4.655 (ID: 928). Informed consent was obtained from all patients prior to their enrollment to the study. The patients were aware that they will receive analgesics for their postoperative pain but the type of drug would be unknown.

3. Results

We studied 52 patients who had operations on their mandible. The patients were divided randomly into two groups. The first group (26 patients) received postoperative Pethidine while the second group (26 patients) received postoperative acetaminophen. The mean age of patients in Pethidine group was 25.6 ± 4.3 years of age while it was 26.9 ± 9.2 years of age in acetaminophen group. In Pethidine groups, 19 patients (76.0%) were male and 6 patients (24.0%) were female. In acetaminophen group, 19 patients (73.1%) were male and 7 patients (26.9%) were female. There was not any significant difference between age and sex ratio in two study groups ($p > 0.05$). Mean weight was 71.7 ± 13.0 kg and 70.9 ± 13.5 kg in Pethidine and acetaminophen groups respectively. Mean duration of operation was 97.0 ± 19.4 and 88.7 ± 23.2 minutes in Pethidine and acetaminophen groups respectively. The differences between weight and duration of operation were also not statistically significant between two groups ($p > 0.05$).

Pain measurements were based on visual analogue scores (VAS). Table 1 illustrates pain measurements by VAS 1, 2, 4, 8, 12 and 24 hours after the operation. Confidence intervals have also been presented. Data revealed that there was not any significant difference between pain scores of two groups 1, 2, 4, 8, 12 and 24 hours postoperatively. Thus, acetaminophen and Pethidine could equally control pain on first postoperative day. Figure 2 illustrates box plots of pain scores in two groups 1, 2, 4, 8, 12 and 24 hours postoperatively.

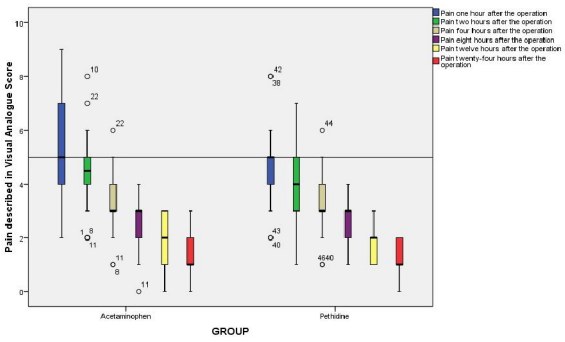

Figure 2: Box plots of visual analogue pain scores 1, 2, 4, 8, 12 and 24 hours after the operations in Pethidine and acetaminophen groups.

The trend of reduction in pain during the first postoperative day was also measured. Repeated-measure ANOVA test revealed that the decline of pain was observed in both groups and the trend of decline had no significant difference between two groups ($p > 0.05$). Figure 3 demonstrates estimated marginal means of pain scores on repeated measurements in two groups.

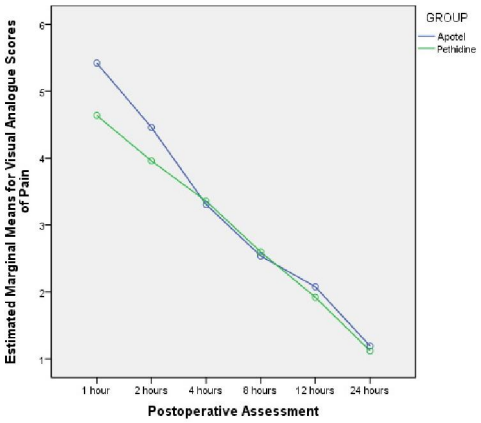

Figure 3: Estimated marginal means of visual analogue scores of pain in Pethidine and acetaminophen groups.

Systolic and diastolic blood pressure measurements were compared between two groups by independent sample t-test. Table 2 illustrates mean systolic and diastolic blood pressure 1, 2, 4, 8, 12 and 24 hours after operations. As it is evident, systolic blood pressure was statistically higher in acetaminophen group than the Pethidine group at 4, 12 and 24 hours postoperative measurements ($p < 0.05$). Other systolic blood pressures and all diastolic blood pressures did not have any significant difference between two groups ($p > 0.05$).

Table 1: Pain measurement by visual analogue score (VAS) on first postoperative day in Pethidine and acetaminophen groups

Hours	Pethidine group		Acetaminophen group		p-value
	Mean ± SD*	95% CI**	Mean ± SD*	95% CI**	
One	4.6 ± 1.5	4.0-5.3	5.4 ± 1.8	4.7-6.2	0.102
Two	4.0 ± 1.5	3.4-4.6	4.5 ± 1.5	3.9-5.1	0.228
Four	3.4 ± 1.2	2.9-3.9	3.3 ± 1.2	2.8-3.8	0.878
Eight	2.6 ± 1.0	2.2-3.0	2.5 ± 1.0	2.1-3.0	0.833
Twelve	1.9 ± 0.8	1.6-2.2	2.1 ± 0.9	1.7-2.5	0.515
Twenty-four	1.1 ± 0.7	0.9-1.4	1.2 ± 0.7	1.0-1.5	0.706

*SD, Standard Deviation; **CI, Confidence Interval

Vertigo and respiratory depression was seen in none of the patients of Pethidine and acetaminophen groups. However, a number of patients had nausea, vomiting and headache on first postoperative day (Table 3). The presence of these

complications was not statistically different between two groups ($p > 0.05$).

Table 2: Systolic and diastolic blood pressures of patients in pethidine and acetaminophen groups on first postoperative day

Hours	Systolic blood pressure* (Mean ± SD**)			Diastolic blood pressure* (Mean ± SD**)		
	Pethidine	Acetaminophen	p-value	Pethidine	Acetaminophen	p-value
One	121.2 ± 8.8	125.7 ± 7.7	0.090	71.0 ± 7.8	72.9 ± 5.5	0.321
Two	119.6 ± 9.1	124.2 ± 7.4	0.052	68.4 ± 6.7	70.0 ± 5.3	0.349
Four	115.4 ± 10.1	120.6 ± 6.7	0.035	66.0 ± 6.0	66.4 ± 4.6	0.817
Eight	112.4 ± 6.8	115.0 ± 21.0	0.558	63.8 ± 6.0	65.2 ± 3.6	0.318
Twelve	112.2 ± 5.8	116.6 ± 4.6	0.005	61.6 ± 4.7	63.7 ± 3.6	0.087
Twenty-four	111.4 ± 5.9	116.2 ± 4.6	0.002	62.8 ± 4.6	64.4 ± 5.1	0.247

*Measurements are in mmHg; SD, Standard Deviation

Table 3: Postoperative drug side effects in pethidine and acetaminophen groups

Group	Nausea	Headache	Vertigo
Pethidine	3 (12.0%)	7 (28.0%)	0 (0.0%)
Acetaminophen	6 (23.1%)	3 (11.5%)	1 (3.8%)
p-value	0.465	0.130	0.510

4. Discussions

In the present study, we found that intravenous acetaminophen is equal to routine opioid administration in controlling acute pain after maxillofacial surgeries. Visual analogue scoring of the pain illustrated that intravenous acetaminophen (Apotel) may replace opioid use in inpatient maxillofacial procedures. Systolic blood pressure was significantly higher in acetaminophen group compared to Pethidine group. However, the observed differences in blood pressure are not clinically important and none of the patients had postoperative hypertension.

Acute pain control after oral and maxillofacial surgery is of potential surgical interest and clinical importance. A number of studies have evaluated the quality of pain control 24 to 48 hours after the surgery (Coulthard, 2000; Nehra, 1995) but acute pain control the first day following the operation needs to be outlined more in detail. In the present study, we found that pethidine and intravenous acetaminophen both can control pain on the fist postoperative day. Pain severity had a decreasing trend in both study groups (Figure 3). It is supposed that patients feel comfort 24 hours after their operation. Thus, intravenous acetaminophen could potentially control acute pain after maxillofacial operations.

According to Coulthard et al. patients expectations from pain control is low and adequate information should be available for them to allow them to request effective pain control (Coulthard, 2000). They found that 93% of patients who underwent maxillofacial operations experience postoperative pain to some extent among them, 34% experience severe pain.

We believe than pain control strategies should be explained to all patients who are candidates of maxillofacial operations. Regarding side effects of opioid use, intravenous acetaminophen would be of potential interest during postoperative acute pain episodes.

Zackova et al assessed the effectiveness of Ketorolac vs Tramadol or their combinations to control acute pain after maxillofacial surgeries (Zackova, 2001).

They assessed their patients during the first postoperative days. They found that Ketorolac, Tramadol and combination of Ketorolac and Tramadol could effectively control acute postoperative pain in maxillofacial operations. They observed that only a few patients required additional opioid analgesics. Likewise, according to Akural et al. the combination of ketoprofen 100 mg + acetaminophen 1000 mg provide a significantly more rapid onset of analgesia and could potentially control postoperative pain after oral surgery (Akural, 2009). We also found that non-opioid strategies could successfully control acute postoperative pain.

Pain control after routine dento-alveolar day surgery is also of potential clinical concern. Oral medication such as acetaminophen, ibuprofen and codeine may be used to alleviate postoperative pain in these settings (Jiménez-Martínez, 2004; Korn,

2004; Zuniga, 2004; Chang, 2002). It has been showed that combination of acetaminophen with oral opioid agents such as oxycodone could potentially lessen the need for oral opioids and also may act superior to opioid-only regimens (Gammaitoni, 2003). These regimens are also effective in controlling postoperative acute pains in outpatient surgeries in areas other than maxillofacial region (Mitchell, 2008; Gimbel, 2001). However, acute pain control in inpatient settings necessitates IV administration of analgesics and adequate pain control is essential.

In addition to postoperative oral and IV pain control, premedication with oral NSAIDs and acetaminophen has been shown to reduce postoperative pain and increase patient satisfaction (Issioui, 2002; Watcha, 2003). Issioui et al. believe that acetaminophen alone could not potentially decrease postoperative pain in this setting and it sjould be combined by an oral NSAID such as celecoxib (Issioui, 2002). However, Watcha et al. revealed that although premedication with acetaminophen can potentially decrease postoperative pain, but premedication with oral NSAIDs have more postoperative analgesic effects (Watcha, 2003). In the present study, we did not use any preoperative analgesics to precisely measure the effects of postoperative pethidine and acetaminophen. Both studies of Issioui et al. and Watcha et al. have been conducted on patients undergoing otolaryngologic operations (Issioui, 2002;Watcha, 2003).

Pain perception is a physical sensation and is influenced by a great number of interacting factors. Patients' view from pain may be significantly different from what physicians or surgeons understand. Clinicians are constantly required to combine subjective and objective information to determine optimal treatment of pain (Bagheri, 2008). Indeed, knowledge of pain treatment and communication between surgeons, anesthesiologists, nurses and patients must be improved to make postsurgical pain relief adequate (Juhl, 1993). We believe that adequate postoperative pain control is essential in maxillofacial operations to achieve optimal postsurgical care and patients' satisfaction.

In conclusion, we found that intravenous acetaminophen could potentially control acute postoperative pain after maxillofacial surgeries. Less adverse effects compared to pethidine and similar analgesic effects make acetaminophen a favorable pharmaceutical to control postoperative pain. Blood pressure and drug side effects did not differ significantly by the use of acetaminophen. Thus, intravenous acetaminophen is recommended for pain control after maxillofacial operations.

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