Evaluation of a Single Dose Intravenous Paracetamol for Pain Relief After Maxillofacial Surgery: A Randomized Clinical Trial Study

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Abstract

Objective The aim of this study was to evaluate, using a single dose of intravenous paracetamol, pain relief after maxillofacial surgery.

Materials and Methods This is a controlled, randomized, uni- blind, clinical trial study to evaluate using a single dose of IV paracetamol for pain relief after maxillofacial surgery. The subjects were randomly divided into two groups with 40 subjects in each: group I received paracetamol (Apotel)* as a single dose and group II received placebo. Subjects were randomly allocated according to randomization lists. Paracetamol was used as a single dose (20 mg/kg in 100 cc of normal saline which was infused for 10 min after surgery in recovery room just before discharging). We used a visual analogue scale to investigate pain relief at various times.

Results Analysis of the data, did not show any significant difference for age, sex and weight between the treatment group and the control group. Pain decreased 6 h after paracetamol infusion; then it increased mildly. In the control group, pain severity increased after operation, then it decreased mildly. Results showed a correlation between duration of surgery and pain severity in both the groups.

Conclusion Paracetamol is effective on pain relief after maxillofacial surgeries. Operation time may be an important factor for induction of pain after the surgeries.

Keywords Pain · Paracetamol · VAS ·
Maxillofacial surgery

Introduction

Effective postoperative pain control is essential for the optimal care of surgical patients [1].

Despite improvements in analgesic delivery, including patient controlled analgesia (PCA) and sustained-release opioids, several recent surveys have found that up to 80 % of patients report moderate to severe pain after surgery [2, 3].

The ideal postoperative analgesic treatment should provide rapid and effective pain relief, have a low incidence of adverse effects, and have minimal impact on major organs or no significant interaction with other pharmacologic agents [4]. Systemic opioids are regarded as the gold standard in the relief of severe postoperative pain [1]. However, opioid administration after surgery carries a high risk of side-effects such as nausea, vomiting, pruritus, urinary retention and apnoea [5]. Nonsteroidal antiinflammatory drugs and acetaminophen (paracetamol) are commonly used in the management of moderate to severe pain alone or in combination with opioids [6]. Conventional non-steroidal anti-inflammatory drugs may be associated with serious unwanted effects (such as bleeding or renal impairment) when used perioperatively. Short-term use of acetaminophen at adequate dosages has a well-established safety profile [1]. Paracetamol has major advantages over non-steroidal antiinflammatory drugs (NSAIDs) viz., its lack of interference with platelet function and safe administration in

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patients with a history of peptic ulcers or asthma [7]. Systematic reviews of randomized controlled trials (RCTs) confirm the efficacy of oral paracetamol for acute pain [8, 9]. Oral paracetamol has a slow onset of analgesia and the non-availability of the oral route immediately after surgery limits its value in treating immediate postoperative pain. Currently, two formulations of intra venous (IV) paracetamol are accessible: propacetamol, a prodrug of paracetamol; and the recently approved i.v. paracetamol [9].

The aim of this study was to evaluate, using a single dose of intravenous paracetamol, pain relief after maxillofacial surgery.

Materials and Methods

This is a controlled, randomized, uni-blind, parallel-group clinical trial study to evaluate using a single dose of iv paracetamol, pain relief after maxillofacial surgery between September 1, 2011 and October 31, 2012. The research committee of the medical ethics group of Shiraz Medical Science University approved this study. Subjects eligible for study inclusion were in ASA 1 category, who underwent a maxillofacial surgery with age between 15 and 45 years. Subjects were excluded from study enrolment if they had drug addiction or a documented psychological disorder, concomitant use of sedatives or microsomal enzyme inducers, pregnancy, or women of childbearing potential not using adequate contraception. All subject had a mandibular fracture and underwent open reduction and rigid fixation without intermaxillary fixation (IMF). The surgical approach consisted of intraoral incision, subperiosteal dissection, reduction of fracture site and placement of fixation devices (miniplates and screws). One surgical team performed all the surgeries in the university hospital.

Subjects were randomly allocated according to randomization lists. The subjects were randomly divided into two groups with 40 subjects in each: group I received paracetamol (Apotel)* as a single dose and group II received placebo. None of subjects received any opioid after operation or in the recovery room. Local anesthesia only (lidocain 2 % with epinephrine 1/80,000) ranging from 1.8 to 3.6 mL was used as a local infiltration during standardized surgical procedures to reduce bleeding. An IV cannula for drug administration was placed in the cubital vein of each arm for infusion.

Paracetamol was used as a single dose (20 mg/kg in 100 cc of normal saline which was infused 10 min after surgery in the recovery room just before discharging). We used a visual analogue scale (VAS) to investigate pain relief at 2 h (time 1), 4 h (time 2), 6 h (time 3), 8 h (time 4) after infusion. VAS was considered between 0 and 10 (no pain to severe pain). Normal saline (100 cc within 10 min)

was infused for subjects as a placebo. Operation time was documented for every subject. This study focused on the pain management immediately after maxillofacial surgery during 8 h after operation. Subjects in the both groups received analgesic drugs and were instructed to use them if they had pain after discharge.

Statistical Analysis

Statistical analyses were performed using the statistical package SPSS for Pc, version 19 company. (IBM, USA). Chi square test was used to investigate sex difference between two groups. We used an independent *t* test to assess any difference of operation time, age and weight between the treatment group and the control group. General liner model (repeat measure test) was applied to study time effect on pain relief. Pearson correlation test was used to determine any correlation between duration of operation and pain severity in various VAS measurements.

Results

We studied 40 (26 males and 14 females) subjects in a treatment group and 40 subjects (23 males and 17 females) in a control group. The mean age of the study group was 29.85 ± 8.07 years and the control group was 29.08 ± 8.77 years. Analysis of the data did not show any significant difference between the two groups ($P > 0.05$). The mean of operation time was 103.8 ± 16.37 min in the treatment group and 107.00 ± 15.72 min in the control group. The two groups did not have any difference statistically for the operation time. The mean of subjects' weight was 71.23 ± 9.32 kg in the treatment group and 71.28 ± 11.14 kg in the control group. There was no significant difference between two groups (Table 1). Results showed the mean of VAS was 3.98 ± 0.69 in time 1, 2.7 ± 0.72 in time 2, 2.3 ± 0.75 in time 3, 2.5 ± 1.01 in time 4 for the treatment group and 4.63 ± 1.1 in time 1, 5.10 ± 1.27 in time 2, 5.78 ± 1.3 in time 3, 4.53 ± 1.08 in time 4 for the control group. Results demonstrated that time has a significant effect on pain intensity after operation. Data analysis using a repeat measure test showed significant difference for pain relief between the treatment and the control groups. Evaluation of pain intensity in every time demonstrated a significant difference between the two groups (Table 2). In the treatment group, the intensity of pain declined after infusion for 6 h; then pain intensity increased mildly. In the control group, pain intensity increased for 6 h after infusion of normal saline then pain decreased mildly (Fig. 1). Analysis of the data demonstrated a positive correlation between pain intensity and operation time in every time ($P < 0.05$) (Table 3).

Discussion

Intravenous paracetamol is licensed for the short-term treatment of moderate pain, especially following surgery, and for the short-term treatment of fever. Administration of paracetamol by the IV route is clinically justified when treating pain or hyperthermia is urgently needed and/or when other routes of administration are not possible. The main indications of using IV paracetamol are: when GI motility is reduced in the immediate post-operative period or when rapid establishment of analgesia is required [10].

Generally, patients who undergo maxillofacial surgery have pain in the initial hours after the operations. Consequently, post-operation pain control is crucial [11]. Our study showed that a single dose of paracetamol was effective on pain after operation. The severity of pain reduced for first 8 h after infusion then pain increased mildly. The time course of action for IV paracetamol is quick: it usually reaches peak concentration as soon as infusion is complete (about 15 min). According to the product information, the analgesic effect of paracetamol starts within 5 min, peaks at 1 h and lasts 4–6 h. This is consistent with a plasma half-life of 2.7 h [4]. Furthermore, duration of surgery has a positive correlation with pain severity in various times in the two groups (treatment and control). One of the main limitations of our study was short time evaluation of pain after operation because control of pain according to VAS was difficult after discharging from hospital. Additionally, IV canula was removed and infusion of paracetamol was impossible.

A more recent systematic review compared the effectiveness of paracetamol, NSAIDs and COX-2 inhibitors in reducing cumulative morphine consumption for the first 24 h after surgery, and associated adverse effects, when used as part of multimodal analgesia following major surgery [12]. McNicol et al. performed a systematic search (multiple databases, bibliographies, any language, upto May 2010) for single-dose, randomized, controlled clinical trials of propacetamol or IV paracetamol for acute post-operative pain in adults or children. Thirty-six studies involving 3,896 patients were included. For the primary

Table 1 Comparison of study variables between the treatment group and the control group

Study variables	Treatment group	Control group	<i>P</i> value
Age (years)	29.85 ± 8.07	29.08 ± 8.77	<i>P</i> > 0.05*
Sex	Males (26) Females (14)	Males (23) Females (17)	<i>P</i> > 0.05**
Weight (kg)	71.23 ± 9.32	71.28 ± 11.14	<i>P</i> > 0.05*
Operation time (h)	103.8 ± 16.37	107.00 ± 15.72	<i>P</i> > 0.05*

* Independent *t* test; ** Chi square test

Table 2 Comparison of pain intensity in various times between the treatment group and the control group

Time	VAS		Independent sample test
	Treatment	Control	
Time 1	3.98 ± 0.69	4.63 ± 1.1	<i>P</i> < 0.05
Time 2	2.70 ± 0.72	5.10 ± 1.27	<i>P</i> < 0.001
Time 3	2.30 ± 0.75	5.78 ± 1.3	<i>P</i> < 0.001
Time 4	2.50 ± 1.01	4.53 ± 1.08	<i>P</i> < 0.001

Fig. 1 Comparison of pain intensity according to VAS in the treatment group (1) and the control group (2)

outcome, 37 % of patients (240/367) receiving propacetamol or IV paracetamol experienced at least 50 % pain relief over 4 h compared with 16 % (68/527) receiving placebo (number needed to treat 1/44.0; 95 % confidence interval, 3.5–4.8). The proportion of patients in propacetamol or IV paracetamol groups experiencing at least 50 % pain relief, diminished over 6 h. Patients receiving propacetamol or paracetamol required 30 % less opioid over 4 h and 16 % less opioid over 6 h than those receiving placebo. However, this did not translate to a reduction in opioid-induced adverse events. Similar comparisons between propacetamol or IV paracetamol and active comparators were either not statistically significant, not clinically significant, or both. Adverse effects (AEs) occurred at similar rates with propacetamol or i.v. paracetamol and placebo. However, pain on infusion occurred more frequently in those receiving propacetamol compared with placebo (23 vs 1 %). A single dose of either propacetamol or IV paracetamol provides around 4 h of effective analgesia for about 37 % of patients with acute postoperative pain. Both formulations are associated with few AEs,

Table 3 Correlation between operation duration and pain intensity in various times in both groups

Time		Operation time	Pain (VAS)	Pearson correlation
Time 1	Treatment	103.8 ± 16.37	3.98 ± 0.6	$P < 0.05$
	Control	107.00 ± 15.72	4.63 ± 1.1	$P < 0.05$
Time 2	Treatment	103.8 ± 16.37	2.70 ± 0.72	$P < 0.05$
	Control	107.00 ± 15.72	5.10 ± 1.27	$P < 0.05$
Time 3	Treatment	103.8 ± 16.37	2.30 ± 0.75	$P < 0.05$
	Control	107.00 ± 15.72	5.78 ± 1.3	$P < 0.05$
Time 4	Treatment	103.8 ± 16.37	2.50 ± 1.01	$P < 0.05$
	Control	107.00 ± 15.72	4.53 ± 1.08	$P < 0.05$

although patients receiving propacetamol have a higher incidence of pain on infusion [9].

Another study demonstrated that a single dose of paracetamol was effective only in 37 % of subjects [10]. Toms et al. searched The Cochrane Library, MEDLINE, EMBASE, the Oxford Pain Relief Database and reference lists of articles to update an existing version of the review in July 2008. They concluded that a single dose of paracetamol provided effective analgesia for about half of the patients with acute postoperative pain, for a period of about 4 h, and is associated with few, mainly mild, adverse events [13].

Elia et al. showed that paracetamol (including propacetamol) reduced 24-h morphine consumption by 8.3 mg. However, there was no statistically significant reduction in post operative nausea and vomiting or sedation. Fifty-two randomised clinical trial (4,893 patients undergoing orthopaedic, abdominal, gynaecological, spinal or thoracic surgery) were included. This review also assessed the effect of NSAIDs and COX-2 inhibitors. These were associated with a statistically significant increase in AEs: surgical bleeding complications and renal failure, respectively. No adverse effects were noted for paracetamol [14].

Several studies demonstrated the use of paracetamol in dental surgery and maxillofacial surgery [15–17]. Van Aken et al. conducted the double-blinded, randomized study to assess the analgesic effect of repeated administrations of paracetamol, administered as propacetamol, an injectable prodrug formulation of paracetamol, and to compare these with the analgesic effects of morphine. Results showed after moderately painful surgical procedures, IV paracetamol, administered as propacetamol, may be an asset in the control of acute postoperative pain [15]. Weil et al. studied paracetamol for pain relief after surgical removal of lower wisdom teeth. They concluded that paracetamol is a safe, effective drug for the treatment of postoperative pain following the surgical removal of lower wisdom teeth [16]. A single dose of paracetamol was suggested in orthognathic surgery [17]. A study demonstrated

the same efficacy of oral paracetamol as IV route for pain relief after wisdom tooth extraction [18].

A large proportion of the efficacy data on IV paracetamol is derived from studies of IV propacetamol, a pro-drug of paracetamol. 2 g IV propacetamol has been shown to be therapeutically equivalent to 1 g IV paracetamol. It has been suggested that paracetamol is used in conjunction with other pain relief drugs such as NSAIDs [19].

Caution must be used when IV paracetamol is given to children or adults weighing less than 50 kg, as the dose has to be adjusted according to body weight. The dose should also be reduced in patients with hepatocellular insufficiency, chronic alcoholism, chronic malnutrition, or dehydration. Failure to reduce the dose appropriately may result in paracetamol-induced liver toxicity. This could lead to hepatic failure and death.

IV paracetamol has been shown to be effective and well-tolerated in the management of moderate pain immediately after surgery, but care must be taken to dose according to the licensed recommendations.

Cases of accidental overdose have been reported during treatment with IV paracetamol 10 mg/mL solution for infusion [20]. In most cases this occurred in infants and neonates. Most events have involved a ten fold dosing error in small children caused by calculating the dosage in milligrams, but then administering the solution in milliliters [21]. However there are reports of clinical incidents involving paracetamol overdose in adult patients weighing <50 kg, where the dose was not adjusted according to the patient's weight [21]. Failure to reduce the dose appropriately may result in paracetamol-induced liver toxicity. This could lead to hepatic failure and death [22].

Conclusion

A single dose of paracetamol is effective in pain relieving during 6 h after open reduction of mandibular fractures. Time has a significant effect on pain severity in the treatment and control group. Furthermore, duration of operation has a positive correlation with pain severity in the both groups.

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