Tramadol Versus Ketorolac in the Treatment of Postoperative Pain Following Maxillofacial Surgery

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Abstract Pain plagues daily activity and hence its management would require alleviation at both the mental and physical planes, thus, bringing about comfort. It includes delivering analgesics in parenteral or oral form, or patches depending on the intensity and availability. Best analgesic regimens are ones that offer broad coverage, easy to administer, safe and economical. A drug seemingly appropriate to treat moderate to severe pain would be Tramadol hydrochloride, a centrally acting synthetic opioid analgesic with lower opiate-like dependence than Morphine. Ketorolac, a pyrrolo-pyrrole derivative, possesses analgesic, anti-inflammatory and anti-pyretic activity would also appear equally suitable. Fifty adult ASA grade I and II patients undergoing surgery under GA in the Department of Oral & Maxillofacial Surgery, College of Dental Sciences, Davangere, were included. Ketorolac (30 mg IM) for 25 patients and Tramadol (100 mg IM) for 25 patients were administered at the time of skin closure and repeated after 8 and 16 h from the conclusion of surgery. Pain, using the VAS at the 2nd, 4th, 6th, 12th and 24th post-operative hour, was assessed and compared using χ^2 -test. Vitals were

monitored and adverse events were looked for. Though both the drugs resulted in significant decrease in pain intensity from the 2nd to 24th post-operative hour, Tramadol always resulted in better pain control than Ketorolac at every post-operative hour ($P < 0.050$). To conclude, intramuscular Tramadol seemed useful in controlling pain following surgery, with better levels of tolerance than intramuscular Ketorolac. However, both the drugs produced mild side effects but did not appear to influence the outcome.

Keywords Maxillofacial surgery · General anesthesia (GA) · Analgesia · Tramadol · Ketorolac · Visual analogue scale (VAS)

Introduction

By definition, pain is an unpleasant sensory and emotional experience resulting from tissue damage or described in terms of such damage. Even a tiny amount of pain, irrespective of the cause, can hamper daily activity. But the most apprehending of all pains is that produced by surgery. During surgery, millions of cells are damaged, evoking the pathway of inflammation, releasing thereby abundant chemical mediators that trigger the pain. It is said that “the pain of mind is worse than the pain in body” and its management would require alleviating both the mental and physical pain thus making the patient comfortable. The management of such pain would vary from delivering analgesics in parenteral form, oral form or patches depending on the intensity and availability. Post-operative pain is considered a form of acute pain due to surgical trauma, characterized by incisional damage to skin or mucosa and various other tissues, application of thermal and chemical stimuli to the wound, and often prolonged

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traction and manipulation of soft tissues, with an inflammatory reaction and initiation of an afferent neuronal barrage [1].

The best postoperative regimen is one that offers broad analgesic coverage, easy to administer, is safe and economical. Anesthetists and surgeons must do everything possible to eliminate postoperative pain without causing undesirable effects such as respiratory or vascular depression, gastrointestinal and visceral motility disorders, coagulation anomalies and drug tolerance and dependence [2]. Postoperative pain is currently treated with two classes of drugs: (1) Non-steroidal anti-inflammatory drugs (NSAIDs), which act by prostaglandin synthesis to achieve analgesic and anti-inflammatory actions, but associated with poor gastrointestinal and renal tolerance and risk of interference with coagulation system; and (2) Narcotic analgesics, which act directly on central nervous system opiate receptors, but can cause drug dependence, respiratory depression, constipation, nausea, vomiting and sedation [3] (Graphs 1, 2, 3, 4, 5, 6).

The search for appropriate drugs to treat patients with moderate to severe pain has led to the development of Tramadol hydrochloride, a centrally acting synthetic

Graph 1 Pain incidence in Ketorolac group

Graph 2 Pain incidence in Tramadol group

Graph 3 Comparative pain incidence at 2 h post-operatively

Graph 4 Comparative pain incidence at 4 h post-operatively

Graph 5 Comparative pain incidence at 6 h post-operatively

Graph 6 Comparative pain incidence at 12 h post-operatively

analgesic with a novel mechanism of action: a complementary and synergistic interaction between an inhibition of neuronal monoamine reuptake and a weak affinity for opioid receptors [2]. In humans, Tramadol causes minimal respiratory depression and few gastrointestinal effects, and

has less potential for causing opiate like dependence than morphine. Ketorolac is a member of pyrrolo-pyrrole group of Non-steroidal anti-inflammatory drugs. It possesses analgesic, anti-inflammatory and anti-pyretic activity. The primary action of Ketorolac appears to be inhibition of cyclooxygenase enzyme that metabolizes Arachidonic acid to endoperoxide intermediates and prostaglandins that promote pain. The purpose of this analysis is to comparatively assess the best post operative analgesia outcome in maxillofacial surgery using small doses of Ketorolac (30 mg IM) and Tramadol (100 mg IM). A brief mention of the pharmacology and pharmacokinetics of the respective drugs is also made.

Pharmacology

Ketorolac

Ketorolac belongs to the family of heterocyclic acetic acid derivatives that possesses potent analgesic but moderately effective anti-inflammatory action. It acts by inhibiting prostaglandin synthesis. In its oral and intramuscular formulation, Ketorolac is a racemic mixture of both (*S*)-(–), the active isomer, and (*R*)-(+).

Chemistry

Ketorolac is a pyrrolizine carboxylic acid derivative, structurally related to indomethacin.

Mechanism of Action

The primary action of Ketorolac is the inhibition of prostaglandin synthesis by competitively blocking cyclooxygenase (COX). Like most NSAIDs, Ketorolac is a non-selective COX inhibitor [4, 5].

Indications

Ketorolac is indicated for short-term management of moderate to severe postoperative pain. Maximum duration of treatment should not exceed 5 days for tablets, or 2 days for continuous daily dosing with intravenous or intramuscular formulations [6].

Contraindications

Hypersensitivity is the prime contraindication.

Tramadol

Tramadol, a centrally acting, synthetic analgesic, is a racemic mixture of two pharmacologically active enantiomers, each of which independently contributes to antinociception. Because Tramadol does not affect prostaglandin synthesis, it does not have any antipyretic or anti-inflammatory actions. Interestingly, tramadol-induced analgesia cannot entirely be reversed by naloxone, but tramadol-induced respiratory depression can be reversed by naloxone. Unlike other opioids, tramadol is not usually associated with the development of tolerance, physical dependence or psychological addiction. Tramadol has recently been shown to have local anaesthetic action on peripheral nerves [7, 8].

Chemistry

Tramadol is a synthetic 4-phenylpiperidine analogue of codeine and morphine.

Mechanism of Action

Tramadol has a dual mechanism of action that involves weak affinity for opioid (μ) receptors and also inhibition of reuptake of serotonin and norepinephrine at synapses in the descending inhibition pain pathways [9]. The (+)-enantiomer binds with μ -receptors and inhibits serotonin uptake while the (–)-enantiomer inhibits norepinephrine uptake and stimulates α -2 adrenergic receptors. However, the primary *O*-demethylated metabolite of tramadol is 2–4 times as potent as the parent drug and may account for part of its analgesic effect [10].

Indications

These include moderate to severe intensity short-lasting pain.

Chronic pain including cancer pain.

Contraindications

Tramadol should be avoided in patients with head injury or history of addiction. It should also be avoided in patients taking MAO inhibitors.

Materials and Methods

Fifty adult ASA grade I and II patients were randomized into two groups. The first group of patients (Group-K) was given Ketorolac 30 mg IM at the time of skin closure and repeated after 8 and 16 h from the end of the operation. The second group of patients (Group-T) was given Tramadol 100 mg IM in the same manner. Pain was assessed on the basis of visual analogue scale (VAS) at the 2nd, 4th, 6th, 12th, and 24th post operative hour. The end points of the 100 mm VAS were ‘no pain’ and ‘pain could not be worse’. The mean from VAS were classified as none/no pain 0–10 mm, mild pain 11–30 mm, moderate pain 31–60 mm and severe pain 61–100 mm. All the patients enrolled completed the study. No patient was excluded because of inadequate analgesia.

Inclusion Criteria

1. ASA grade I and II classified patients undergoing major oral and maxillofacial surgeries under general anesthesia.

Exclusion Criteria

1. Patients with history of hypersensitivity to Ketorolac or Tramadol
2. Patients with blood dyscrasias
3. Patients with liver or kidney diseases
4. Patients with history of peptic ulcer disease
5. Patients with history of substance abuse
6. Pregnant or breast-feeding females
7. Patients with head injury
8. Patients undergoing oncologic resective surgeries

Nature of Surgeries

1. ORIF for mid-face and mandibular fractures
2. Enucleation of cysts or tumors of head and neck region
3. TMJ surgeries
4. Transalveolar extraction of all the four third molars

Results

Table 1 shows comparison of characteristics of the patients in both the groups. Mean age of patients for Group-K was 30 ± 13.1 years, and that of Group-T mean age was 33.4 ± 13.2 years. Group-K included 17 males and 8 females while Group-T included 19 males and 6 females. The mean duration of surgery for Group-K was 79.4 ± 50.6 min

Table 1 Patient characteristics

	Group K (N = 25)	Group T (N = 25)	Significance
Age (years)	30.1 ± 13.1	33.4 ± 13.2	$P = 0.39$ N.S. (<i>t</i> test)
Sex (M/F)	17/8	19/6	$P = 0.53$ N.S. (χ^2 test)
Duration of surgery (HOURS)	79.4 ± 50.6	78.6 ± 40.0	$P = 0.95$ N.S. (<i>t</i> test)
ASA—Grades	I—16 II—9	I—15 II—10	$P = 0.77$ N.S. (χ^2 test)

Table 2 Pain incidence in Ketorolac

Time of assessment (h)	No. of cases	Pain incidence		
		Mild pain N (%)	Moderate pain N (%)	No pain N (%)
2	25	14 (56%)	11 (44%)	—
4	25	21 (84%)	4 (16%)	—
6	25	25 (100%)	—	—
12	25	20 (80%)	—	5 (20%)
24	25	8 (32%)	—	25 (100%)
Comparison (h)		Significance		
		χ^2	<i>P</i>	
2–4		4.67	<0.05	
2–6		14.1	<0.01	
2–12		17.1	<0.01	
2–24		29.6	<0.01	

while that for Group-T it was 78.6 ± 40.0 min. The patients in both the groups were similar with regard to age, sex, duration of surgery and ASA grades.

Table 2 shows pain measurement in Group-K on the basis of VAS. The VAS values were recorded at the 2nd, 4th, 6th, 12th, and 24th post-operative hour and interpreted. There was a significant decrease in pain intensity from the 2nd to 24th post-operative hour (χ^2 -test, $P < 0.05$). The maximum pain recording belonged to moderate category and the maximum number of patients experiencing moderate pain was 11 during the 2nd post-operative hour, while at the 24th post-operative hour, 8 patients reported only mild pain while 17 patients were free of any pain.

Table 3 shows pain measurement in Group-T on the basis of VAS at the 2nd, 4th, 6th, 12th, and 24th post-operative hour. There was a significant decrease in pain intensity from the 2nd to 24th post-operative hour (χ^2 -test, $P < 0.05$). In this group also, the maximum pain recording belonged to moderate category but the maximum number

Table 3 Pain incidence in Tramadol

Time of assessment (h)	No. of cases	Pain incidence		
		Mild pain <i>N</i> (%)	Moderate pain <i>N</i> (%)	No pain <i>N</i> (%)
2	25	19 (76%)	4 (16%)	2 (8%)
4	25	18 (22%)	1 (4%)	6 (24%)
6	25	8 (32%)	–	17 (68%)
12	25	3 (12%)	–	22 (88%)
24	25	–	–	25 (100%)
Comparison (h)		Significance		
		χ^2	<i>P</i>	
2–4		3.83	0.15	
2–6		20.3	<0.01	
2–12		32.3	<0.01	
2–24		42.6	<0.01	

of patients experiencing moderate pain was just 4 at the 2nd post-operative hour. All the patients were free of pain at the 24th post-operative hour.

Table 4 shows comparison of pain incidence between Group-K and Group-T. In both groups, the pain intensity was measured on the basis of VAS at the 2nd, 4th, 6th, 12th, and 24th post-operative hour, and the results were compared using χ^2 -test. Though both the drugs resulted in significant decrease in pain intensity from the 2nd to 24th post-operative hour, intramuscular tramadol always resulted in better pain control than intramuscular ketorolac at every post-operative hour ($P < 0.050$).

Table 5 shows adverse events associated with Group-K and Group-T. There were only three adverse events (mild skin reaction, 2; sweating and nausea, 1) in patients taking intramuscular ketorolac while three adverse events (nausea,

Table 5 Side effects seen in Tramadol and Ketorolac groups

Side effects	Group		Significance
	Ketorolac <i>N</i> (%)	Tramadol <i>N</i> (%)	
Mild skin reaction	2 (8.00%)	0 (0.00%)	N.S.
Nausea and vomiting	0 (0.00%)	1 (4.00%)	N.S.
Nausea	0 (0.00%)	2 (8.00%)	N.S.
Sweating and nausea	1 (4.00%)	0 (0.00%)	N.S.
Total	3 (12%)	3 (12%)	N.S.

Table 6 Vital signs recorded

Vital signs	Group		Total
	Ketorolac <i>N</i> (%)	Tramadol <i>N</i> (%)	
Within normal limits	25 (100.00%)	25 (100.00%)	50 (100.00%)

2; nausea and vomiting, 1) were noted among those taking intramuscular tramadol.

Table 6 shows vital signs (blood pressure, pulse rate, respiratory rate and temperature) recorded regularly in both the groups during the initial 24 h. The vital signs were however within normal limits in both the groups.

Discussion

Post-operative pain is considered a form of acute pain due to surgical trauma, characterized by incisional damage to skin or mucosa and various other tissues, application of

Table 4 Comparison of pain incidence between Ketorolac group (Group-K) and Tramadol group (Group-T)

Time (h)	Group	No. of patients	Pain incidence			K vs. T	
			Mild pain <i>N</i> (%)	Moderate pain <i>N</i> (%)	No pain <i>N</i> (%)	χ^2	<i>P</i>
2 h	K	25	14 (56%)	11 (44%)	–	6.03	<0.05
	T	25	19 (76%)	4 (16%)	2 (8%)		
4 h	K	25	21 (84%)	4 (16%)	–	8.03	<0.05
	T	25	18 (72%)	1 (4%)	6 (24%)		
6 h	K	25	25 (100%)	–	–	25.8	<0.01
	T	25	8 (32%)	–	17 (68%)		
12 h	K	25	20 (80%)	–	5 (20%)	23.3	<0.01
	T	25	3 (12%)	–	22 (88%)		
24 h	K	25	8 (32%)	–	17 (68%)	9.5	<0.01
	T	25	–	–	25 (100%)		

thermal and chemical stimuli to the wound, and often prolonged traction and manipulation of soft tissues, with an inflammatory reaction and initiation of an afferent neuronal barrage [1]. Severe postoperative pain may have psychological consequences, increasing the stress response to surgery, seen as a cascade of endocrine-metabolic and inflammatory events that ultimately contribute to organ dysfunction, morbidity, increased in-hospital stay and mortality. Pain often causes the patient to remain immobile, thus becoming vulnerable to deep vein thrombosis, pulmonary atelectasis, muscle wasting, and urinary retention. Besides restlessness, severe pain may contribute to postoperative hypoxemia [11]. The inflammatory mediators released as a result of trauma activate the primary afferent nerves which in turn can evoke changes at the level of spinal cord, a process referred to as “peripheral sensitization”. If acute pain is not properly treated, prolonged activation of pain pathways can lead to further neurophysiologic changes, collectively called “central sensitization,” which may prolong recovery and convert acute pain to a chronic condition [12]. Additionally, patients with moderate to severe pain during the postoperative period, and those having undergone operations with the risk of nerve damage are most likely to develop chronic pain [1].

Postoperative pain is currently treated with two classes of drugs: (1) Non-steroidal anti-inflammatory drugs (NSAIDs), which act by prostaglandin synthesis to achieve analgesic and anti-inflammatory actions, but associated with poor gastrointestinal and renal tolerance and risk of interference with coagulation system; and (2) Narcotic analgesics, which act directly on central nervous system opiate receptors, but can cause drug dependence, respiratory depression, constipation, nausea, vomiting and sedation [3]. Approaches to the measurement and assessment of pain include verbal and numeric rating scales, VAS, behavioral observation scales, and psychological responses. Of these, the VAS is the most frequently used self-rating scale. The most common VAS consists of a 10 cm horizontal or vertical line with the two end points labeled “No Pain” and “Worst Pain”. Patients are asked to place a mark on the 10 cm line at a point that corresponds to the level of pain intensity they presently feel. Advantages of VAS include ease of scoring, its minimum intrusiveness, its greater sensitivity to detect intervention based changes in pain, and its conceptual simplicity [13].

The search for appropriate drugs to treat patients with moderate to severe pain has led to the development of Tramadol hydrochloride, a centrally acting synthetic analgesic with a novel mechanism of action: a complementary and synergistic interaction between an inhibition of neuronal monoamine reuptake and a weak affinity for opioid receptors [2]. In humans, Tramadol causes minimal respiratory depression and few gastrointestinal effects, and has less potential for causing opiate-like dependence than

morphine [14]. Ketorolac is a member of pyrrolo-pyrrole group of Non-steroidal anti-inflammatory drugs. It possesses analgesic, anti-inflammatory and anti-pyretic activity. The primary action of Ketorolac appears to be inhibition of cyclooxygenase enzyme that metabolizes Arachidonic acid to endoperoxide intermediates and prostaglandins that promote pain. The best postoperative regimen is one that offers broad analgesic coverage, is easy to administer, and is safe and economical. The anesthetists and surgeons must do everything possible to eliminate postoperative pain without causing additional problems, such as respiratory or vascular depression, gastrointestinal and visceral motility disorders, coagulation anomalies, drug tolerance and dependence [2].

There are several studies comparing the efficacy of various analgesics used for the control of postoperative pain in maxillofacial surgeries. It is well-known fact that parenteral route is more reliable and effective especially for the patients undergoing surgeries under general anesthesia. The results of this study indicate that adequate analgesic treatment can reduce the intensity and limit the duration of postoperative pain in the population considered. Excellent results were demonstrated with the use of intramuscular Tramadol for treatment of postoperative pain in maxillofacial surgery (Table 4). Tramadol provided effective pain relief in high percentage of cases than ketorolac at every scheduled post-operative VAS record (Table 4). It has been reported that intramuscular Tramadol 100 mg, given post-operatively, has an analgesic effect equivalent to 30 mg of Pentazocine but is less potent than 10 mg of morphine [15]. The maximum pain, as experienced by patients, was of moderate type in both the groups. In the Group-K, moderate pain was reported in 44% of patients at 2nd postoperative hour, and by 16% of patients at 4th postoperative hour, while in Group-T moderate pain was reported by 16% of patients, and by only 4% of cases at 4th postoperative hour. After that, pain was not reported by the patients of either group.

The most common side effects associated with Tramadol are nausea and vomiting. Only 1 patient in Group-T had an episode of vomiting while two patients complained of nausea during initial two postoperative hours (Table 5). These patients were given a single dose intravenous Ondansetron *stat*, following which no further episodes of vomiting were reported. Since these are common post-general anesthesia sequels, it is difficult to conclude whether or not Tramadol had resulted in postoperative nausea and vomiting. An intra-operative parenteral antiemetic and H-1 blocker, Ondansetron, a regular protocol drug in general anesthesia, can explain the insignificant number of these commonest side effects of Tramadol. Therefore, despite the principle side effect being nausea and vomiting, Tramadol can be given safely to patients under the cover of

an antiemetic. Of the 25 patients in the Group-K, two developed mild skin reactions at the site of injection while one patient complained of sweating and nausea (Table 5). However, both the complications were mild and did not require any treatment. Regular monitoring of vital signs was done in both the groups and found to be within normal limits (Table 6). So, on the basis of vital sign recordings and the insignificant number and degree of side effects in both the groups, we could conclude that all patients tolerated their group drug well.

The use of Ketorolac is now contraindicated in patients with hemorrhagic diathesis and in patients undergoing surgery that is associated with a high risk of hemorrhage or with incomplete haemostasis, and the maximum permitted dosage has been reduced from 90 to 60 mg/d in elderly [2]. A recent retrospective trial of more than 20,000 patients showed that parenteral Ketorolac caused a higher incidence of both gastrointestinal and surgical site bleeding than did opioids [16]. Tramadol, on the other hand, causes no significant adverse cardiovascular or respiratory reactions, and has no effect on coagulation either. These advantages bring it closer to an ideal analgesic which would have a high level of activity and a reassuring safety profile [17]. There are several studies comparing the analgesic efficacy of parenteral Tramadol and Ketorolac and most of them are in favor of Tramadol with regard to postoperative pain control. However, few authors have found Tramadol-induced vomiting to be significant [18] which can be controlled by anti-emetics that have been found to be safe in normal healthy adults.

Conclusion

To conclude, though both the drugs were effective in controlling postoperative pain in patients undergoing maxillofacial surgery under general anesthesia, the comparative results of this study clearly demonstrate that intramuscular Tramadol is significantly better than intramuscular Ketorolac ($P < 0.05$). However, both produced side effects that were minor but do not appear to influence the outcome. The duration of action of a drug depends on its half-life but its efficacy is chiefly dependent on its route, consistency and frequency of administration. Side-effects are inevitable however in each case. Future randomized placebo-controlled research trials need to be performed to determine rational dose–response curves, in order to

minimize undesirable side-effects but maximize benefits, economically.

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