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Anti–Nociceptive Efficacy of Tramadol Following Surgical Removal of Impacted Mandibular Third Molar

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الخلاصة

اهداف البحث: يهدف البحث الى تقييم تأثير تسكين الالم باستخدام (١٠٠ملغرام) ترامادول بالعضلة قبل العملية بالمقارنة مع استعمال (١٠٠ملغرام) ترامادول بالعضلة ، بعد العملية، أو مع عدم استعماله بعد عملية قلع سن العقل السفلي المطمور. **المواد وطرائق العمل:** اجريت هذه الدراسة على ٣٠مريضا لقلع سن العقل المطمورلديهم، معدل العمر(٢٤±٢.٢سنة).قسم المرضى الى ثلاث مجاميع، كل مجموعة تكونت من(١٠مرضى). المجموعة الأولى: كل مريض أعطي (١٠٠ملغرام) ترامادول بالعضلة قبل العملية. المجموعة الثانية: كل مريض أعطي(١٠٠ملغرام)ترامادول بالعضلة بعد العملية. المجموعة الثالثة: وهي المجموعة الضابطة، كل مريض حقن بالماء المقطر بالعضلة قبل العملية. بعد العملية أعطي المرضى كبسولات اوكمنتين (٦٢٥ ملغرام) ثلاث مرات يوميا وبراسيتامول حب عند الالم. شدة تسكين الالم قيمت باستعمال المقياس البصري المتناظر ، التقييم الشفوي للالم، مدى رضى المرضى، فترة تسكين الالم بعد العملية، وعدد حبات المسكن. **النتائج:** تسكين الالم باستخدام ترامادول كان أعلى بالمقارنة مع المجموعة الضابطة باستخدام المقياس البصري المتناظر والتقييم الشفوي للالم عند مستوى معنوية(٠,٠٠١). لم يكن هناك فرق معنوي بين استعمال ترامادول قبل أو بعد العملية أو مع المجموعة الضابطة فيما يتعلق بمدى رضى المرضى أو فترة تسكين الالم. **الاستنتاجات:** تسكين الالم باستخدام (١٠٠ملغرام) ترامادول بالعضلة قبل العملية كان أعلى بالمقارنة مع استعمال (١٠٠ملغرام) ترامادول بالعضلة بعد العملية فيما يتعلق برضى المرضى وفترةتسكين الالم والذي يفسر تأثير تسكين الالم قبل العملية.

ABSTRACT

Aims of the Study: To evaluate the efficacy of analgesia mediated by preoperative 100 mg IM Tramadol to the post operative Tramadol and placebo after the surgical removal of mandibular wisdom tooth. **Materials and Methods**: Surgical removal of mandibular third molar was performed in three groups of individuals, total of thirty patients were anticipated in this study. All medically fit, average of age 24 + 2.2; each group consisted of ten patients. Group 1: Preoperative 100 mg Tramadol IM injection 30 minutes prior surgical operation; Group 2: Post operative 100 mg Tramadol IM injection; Group 3: Placebo or control group where distilled water IM injection was applied. All patients received post operatively Augmentin capsules 675 mg tid, and supplementary Paracetamol 500 mg tablet as required. Analgesia was assessed by Visual Analog Scale (VAS) and Verbal Pain Scale (VPS), patient satisfaction (PS), duration of post operative analgesia and total number of analgesic tablet were recorded between groups. **Results:** Analgesia mediated by Tramadol was superior in its efficacy compared to control group in both pre and post operative Tramadol groups, according to VAS and VPS assessment (p= 0.001). There was no significant difference between the preoperative and post operative analgesia according to VAS and VPS; whereas there was a significant difference in PS, and duration of analgesia mediated by the preoperative injection in comparison to the post operative and control groups. **Conclusion:** Preoperative Tramadol analgesia was superior to post operative analgesia in PS and prolonged duration of analgesia that explain its anti–nociceptive effect in controlling post surgical pain.

Key words: Tramadol, mandibular wisdom tooth, surgical removal.

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INTRODUCTION

Pre–operative analgesia, or preventive analgesia or anti–nociceptive effect, is defined as the use of analgesic drug to prevent the establishment of altered central processing of afferent input from the sites of injury. The most important condition for establishment of effective pre–emptive or anti–nociceptive analgesia are the establishment of an effective level of anti–

nociceptive before injury, and the continuation of this effective analgesic level well into the post injury period to prevent central sensitization during the inflammatory phase.[1] Preventive analgesia is a treatment that is initiated before and is operational during the surgical procedure in order to reduce the physiological consequences of nociceptive transmission provoked by the procedure. This type of analgesia has the potential to be more effective than a similar analgesic treatment initiated after surgery. Consequently, immediate post operative pain, development of chronic pain may be reduced,[2] and to prevent or reduce the development of any "memory" of pain stimulation in nervous system.[3]

The removal of impacted teeth is one of the most common procedures performed by oral and maxillofacial surgeons. Surgical removal of third molar is associated with a moderate incidence of complications; about 10% associated with post operative pain. To increase patient satisfaction after third molar extraction it is necessary to avoid a discomfort associated with the removal of the tooth.

Pain is a multidimensional sensory experience vary in its intensity.[4] Extraction of an impacted third molar is a model used commonly to test the efficacy of analgesia for acute dental pain.[5]

Tramadol hydrochloride is clinically effective in the treatment of moderately severe pain with a relative low addition potential, highly effective as post surgical pain killer. It acts at opioid receptors and also seems to modify transmission of pain impulses by inhibition of monoamine reuptake, had affinity for the opioid μ receptor, and inhibitor of serotonine reuptake, and sometimes norepinephrine reuptake inhibitor. The liver metabolism of Tramadol result in one metabolite with greater affinity for the receptor.[6] Tramadol side effects usually very mild compared to other narcotic analgesic in that it lacks the tendency for addiction, yet a mild adverse effect, vertigo, nausea, vomiting, headache and xerostomia.[7] The risk of respiratory depression is significantly lower at equianalgesic doses and does not depress the hypoxic ventilatory response, and does not increase seizure incidence when compared to other analgesic agents.[8]

The aim of the present study was to estimate the anti–nociceptive effect of Tramadol by the use of preoperative Tramadol injection and compare it to post operative analgesia initiated compared to placebo.

MATERIALS AND METHODS

The methodology and procedure of the study had been cleared by the scientific committee in Dentistry College/ Mosul University. All the individuals were well informed about the study, methodology and all the scales (Visual Analog Scale "VAS", Verbal Pain Scale "VPS", Patient Satisfaction "PS", Duration of Analgesia "DA" and Supplement Postoperative Analgesia "SPA"). The individuals were unawared of the analgesic which they had taken during the study. The analgesic and placebo were assigned a code. Patients were randomly assigned into either treatment groups with an assigned code.

The patients were divided into 3 groups containing 10 in each group. All the codes of administered drugs were disclosed only after the pain assessment.

Patients Selection

Thirty healthy non–smoker individuals from both sexes were selected. All required the surgical removal of mandibular third molar that require bone removal, having no history of allergicity to medication, and were asked to discontinue medication 12 hours prior to surgical operation. The procedure was performed by single surgeon in Dentistry College/ Mosul University from 5/6/2010 to 5/12/2010. All patients agreed for their participation in the study and signed specific paper.

Medication Preparation

One hundred milligrams Tramadol injection was prepared in disposable syringes coded A, B disposable syringe consisted of distilled water coded as C to be injected intramuscularly. Decoding of medication was cleared after pain assessment.

Patients Grouping

Double–blind randomized study was performed. Patients were divided into 3 groups:

Group I: Ten patients received Code A (preoperative intramuscular injection of 100 mg Tramadol 30 minutes prior to sur-

gery).
Group II: Ten patients received Code B (post operative intramuscular injection of 100 mg Tramadol immediately after surgical operation).
Group III: Ten patients received Code C (post operative intramuscular injection of distilled water 30 minutes before the surgical operation).

Surgical Procedure

All surgical operations were carried out by the same oral surgeon. Local anesthesia was administered 2% xylocaine with 1:100,000 adrenaline 2 cartridges, nerve block to the inferior alveolar nerve and lingual nerve, and another infiltration anesthesia for the long buccal nerve. Two sided standard mucoperiosteal flap was incised and reflected, bone removal using surgical handpiece, tooth removal, toilet of the socket and suturing of the wound. Patients were instructed to take Augmentin 675 mg tid, and recording the total number of paracetamol (500 mg) for the following 24 hours post operatively and the exact time of the first need for the intake of Paracetamol post operatively.

Pain Scale Measurements

1. VAS:

A 100 mm scale was used to assess pain. It consists of an interval scale range from 0 (represent no pain) to 100 (represent maximal pain).

2. VPS:

The scale consists of: 0: no pain; 1: mild pain; 2: moderate pain; 3: severe pain; and 4: very severe pain.

3. PS:

Regarding pain relief, if the patient underwent pain more than that is suspected it was considered as not satisfied, whereas if the patient underwent pain less than that is suspected it was considered as satisfied.

4. DA:

Patients were instructed to record the first time for the need of analgesia (Paracetamol tablet 500 mg) after surgical operation (time from the end of the surgery until the intake of rescue medication became necessary for the patient).

5. SPA:

Patients were instructed to record the total number of analgesic tablets administered during the 24 hours post operative surgical operation.

6. Adverse Effect:

Any side effect noticed by the patient was recorded in the 24 hours post operative surgical operation.

Statistical Analysis:

Data were loaded on Pentium IV computer and analyzed using Statistical Package for Social Sciences (SPSS) Program Version 13.0. Analysis included descriptive statistics (frequency and percentages for non–parametric data, and mean and standard deviation for parametric ones); and analytical statistics (Mann–Whitney Test for non–parametric data, and independent sample Student's t–test for parametric ones). Differences between groups were considered statistically significant when $p < 0.05$ level.

RESULTS

Distribution of the sample according to age and gender were illustrated in Figures (1) and (2), respectively.

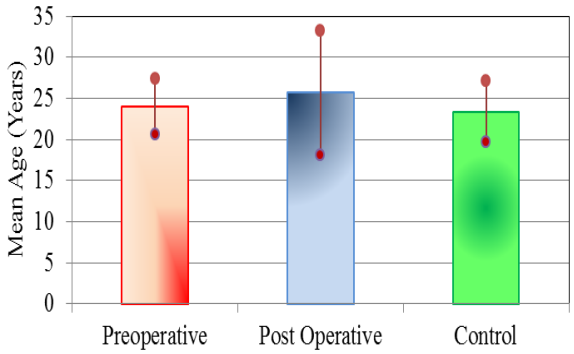

Figure (1): Mean + standard deviation of the sample according to the age of different groups

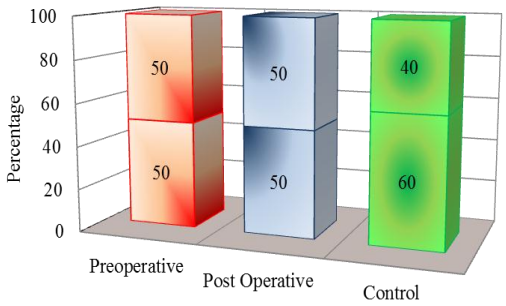

Figure (2): Distribution of the sample according to the gender of different groups

The mean ages of the patients participated in this study were 24.0, 25.7 and 23.4 years for the preoperative, post operative and control groups, respectively.

1. *VAS*:

Eighty percent of preoperative Tramadol group scored 0–25 pain assessment, whereas 20% of patients in this group had 26–50 pain score (Table 1).

In post operative Tramadol group, 50% of patients had 0–25 pain score and 40% of the treated patients' score was 26–50 and 10% of patients in this group had 76–100 score

In placebo or control group, 60% of the patients had 26–50 score, 30% 51–75 score and 10% 76–100 score (Table 1).

Table (1): Distribution of the sample according to visual analog scale of different groups

Group	Scale								Total	
	0–25		26–50		51–75		76–100			
	No.	%	No.	%	No.	%	No.	%	No.	%
Preoperative	8	80.0	2	20.0	0	0.0	0	0.0	10	100.0
Post Operative	5	50.0	4	40.0	0	0.0	1	10.0	10	100.0
Control	0	0.0	6	60.0	3	30.0	1	10.0	10	100.0

There was no significant difference between pre and post operative Tramadol groups whereas a significant difference between preoperative and control groups (p=0.000), and a significant difference between post operative Tramadol group and placebo group (p= 0.02) (Table 2).

Table (2): Mann–Whitney Test among preoperative, post operative and control groups for visual analog scale, verbal pain scale and patients' satisfaction

Criteria	Mann–Whitney Test	Preoperative vs Post Operative	Preoperative vs Control	Post Operative vs Control
Visual Analog Scale	**U–value**	34.000	6.000	21.500
	Z–value	–1.446	–3.565	–2.327
	p–value	0.148	0.000*	0.020*
Verbal Pain Scale	**U–value**	29.000	6.500	17.000
	Z–value	–1.767	–3.455	–2.673
	p–value	0.077	0.001*	0.008*
Patients' Satisfaction	**U–value**	35.000	30.000	45.000
	Z–value	–1.831	–2.179	–0.457
	p–value	0.067	0.029*	0.648

* Significant difference existed between groups at 0.05 level.

2. VPS:

Fifty percent of the preoperative Tramadol group represented no pain, 40% mild, 10% moderate. Ten percent of the post operative Tramadol group expressed no pain, 70% mild, 10% moderate, 10% severe. Whereas 10% of the placebo group represented mild pain, 70% moderate, 20% severe (Table 3).

Table (3): Distribution of the sample according to verbal pain scale of different groups

Group	Pain									
	No		Mild		Moderate		Severe		Total	
	No.	%	No.	%	No.	%	No.	%	No.	%
Preoperative	5	50.0	4	40.0	1	10.0	0	0.0	10	100.0
Post Operative	1	10.0	7	70.0	1	10.0	1	10.0	10	100.0
Control	0	0.0	1	10.0	7	70.0	2	20.0	10	100.0

There was no significant difference between preoperative and post operative groups (p= 0.07), whereas a significant difference between preoperative and control group (p= 0.001), and post operative and control groups (p= 0.008) (Table 2).

3. PS:

One hundred percent of patients in preoperative Tramadol group were satisfied, while 30% of patients in post operative Tramadol group and 40% in the control group were not satisfied (Table 4).

Table (4): Distribution of the sample according to patients' satisfaction of different groups

Group	Patients' Satisfaction					
	Satisfied		Not Satisfied		Total	
	No.	%	No.	%	No.	%
Preoperative	10	100.0	0	0.0	10	100.0
Post Operative	7	70.0	3	30.0	10	100.0
Control	6	60.0	4	40.0	10	100.0

There was no significant difference between the preoperative and post operative Tramadol groups, whereas there was a significant difference between preoperative Tramadol group and control group, but no significant difference between the post operative Tramadol and the control groups (Table 2).

4. SPA:

There was no significant difference among groups in the total number of Paracetamol tablets administered 24 hours post operative surgical operation (Table 5 and Figure 3).

Table (5): Student's t–test among preoperative, post operative and control groups for supplement post operative analgesia and duration of analgesia

Criteria	Independent Sample t–test	Preoperative vs Post Operative	Preoperative vs Control	Post Operative vs Control
Supplement Post Operative Analgesia	**t–value**	0.210	–1.019	–1.165
	df	18	18	18
	p–value	0.836	0.322	0.259
Duration of Analgesia	**t–value**	2.602	3.595	1.965
	df	17	18	17
	p–value	0.019*	0.002*	0.066

* Significant difference existed between groups at 0.05 level.

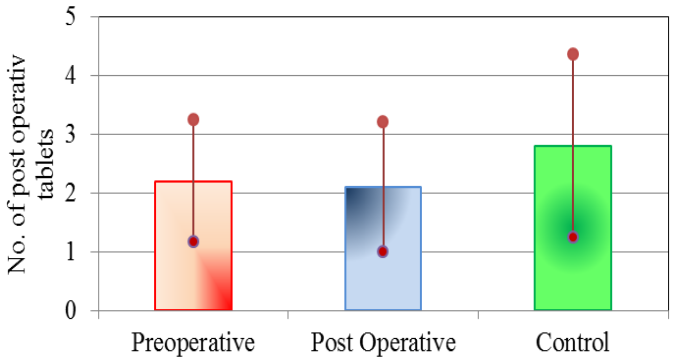

Figure (3): Mean + standard deviation of the sample according to supplement post operative analgesia of different groups

5. DA:

The duration of analgesia was 5.60 + 2.8 hours, 3.0 + 0.86 hours and 2.1 + 1.10 hours for preoperative, post operative Tramadol and the control groups, respectively (Figure 4).

There was a significant difference between preoperative and post operative and control groups (p= 0.001), while no significant difference between post operative and control groups (Table 5).

DISCUSSION

Pain management can be established by the administration of analgesia during either preoperative administration of some analgesic to reduce the onset of post operative pain or administration of analgesia locally at the site of tissue injury to maximize drug level at the site of action and minimize systemic exposure.[10] Patient self–report is the most accurate and reliable indicator of the existence and intensity of pain and any resultant distress.[11] Self–report measurement tools such as adjective or numerical rate scale or VAS can assist the patient in quantifying and characterizing the pain. Assessment of the patient pain is a crucial part of initial evaluation to estimate analgesic requirement.[12] In this study VAS and VPS had been implicated to describe the intensity of pain. The data demonstrated that the preventive or preoperative analgesia was superior to post operative analgesia, yet it is not significant in VAS and VPS, but both scales were significantly superior compared to control as analgesia. Amaury *et al*.[13] demonstrated a superior pre–emptive analgesia to post operative analgesia. Other researchers demonstrated the combination of different types of analgesia at different sites of origin or by combining different routes of administration of the same drug can improve the range of analgesia.[14] As post operative pain after third molar surgery is a frequent used model for acute pain trials.[15] The analgesic efficacy of different analgesia was studied in this field n example preoperative Rofecoxibe 50 mg provides a significantly better analgesic benefit than placebo with regard to post operative analgesia in the first 12 hours compared to placebo and Ibuprofen.[16]

Tramadol is a suitable and safe analgesic for the relief of post extraction pain and is more effective than Ketorolac.[8] In this study, PS was superior and significant compared to post operative analgesia and control. This can be explained by the fact that the analgesic effect of Tramadol before the nociceptive stimuli was more effective than the same dose given later and that the effect of pre–emptive analgesia was to prevent or reduce the development of any "memory" of pain stimulation in the nervous system. This had been manifested by the lower analgesic requirement and a significant longer duration of analgesia and higher PS in the preoperative analgesia group compared to post operative and placebo groups. This finding agreed with other studies.[17, 18]

CONCLUSIONS

Pre operative 100 mg intramuscular Tramadol injection 30 minutes before surgical removal of mandibular third molar showed no significant difference compared to post operative 100 mg intramus-

cular injection of Tramadol as analgesic in accordance to VAS and VPS, whereas both groups were significantly superior than control. Preoperative Tramadol injection was significantly superior in PS and DA than post operative and control groups, whereas there was no significant difference among groups in the total number of Paracetamol intake post operatively.

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