

A Double-Blind, Placebo Controlled Randomised Comparison of Pre & Post operative administration of Tramadol for Dental Extraction Pain.

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Abstract: To compare, the analgesic efficacy and safety of the single-dose oral Tramadol pre & post operatively for dental extraction pain. 49 Patients who were undergoing third molar extraction (impacted or other causes) were recruited into the study, over a period of one year. The patients were divided into four groups to receive tramadol (100 mg) or placebo either preoperatively or postoperatively (half – an – hour before or half – an – hour after the procedure). Pain assessment was done using a modified Verbal Rating Scale, at 30 minutes, 2 hours, 4 hours and 6 hours after the procedure. A record of whether rescue analgesic (ibuprofen 400 mg) was taken during the 6 hours study period, along with the time it was taken, was made. Record of any adverse effects experienced by the patient was also kept. Maximum pain scores for each of the 4 study groups, over the 6 hours study period. Secondary end points time when rescue analgesic was taken, adverse effects observed. Tramadol was significantly better than placebo, in relieving molar tooth extraction pain. Postoperative administration of tramadol was found to be more efficacious than preoperative administration in relieving the pain. This study demonstrated that tramadol is equally effective as traditional NSAID's in relieving pain in the first 6 hours after molar extraction and therefore can be tried in patients who are intolerant to NSAIDs.

INTRODUCTION

Pain is an unpleasant sensory and emotional experience associated with actual or potential tissue damage or described in terms of such damage¹. Pain can be acute or chronic. Acute pain is produced by an excessive noxious stimulus, giving rise to an intense and unpleasant sensation.

Dental extraction produces moderate to severe pain which is routinely treated with non-steroidal anti-inflammatory drugs (NSAIDs) for 2-3 days^{2,4}. The NSAIDs have the advantage of being analgesic as well as anti-inflammatory and as such are the rational choice for a condition where pain with inflammation occurs^{5,6}. However NSAIDs are known to produce side effects such as gastric irritation leading to ulceration and have a higher propensity to produce bleeding disorders, especially in, patients with pre-existing risk factors for these conditions⁶. Viable alternatives for such patients need to be thought of. Tramadol is an analgesic with weak opioid agonistic activity, in addition to modifying the functioning of other neurotransmitter pathways like nor-epinephrine and 5-hydroxytryptamine and has been shown to provide good analgesic effect after moderate to severe pain⁷⁻¹⁰.

MATERIAL AND METHODS

The study was conducted on 49 patients attending the dental outpatient department of Teerthankar Mahaveer dental college & research centre.

Dental extraction pain is an excellent clinical model for acute pain, especially third molar extraction pain⁵. The patients were recruited from hospital's OPD. Ethical clearance was obtained from Research Centre Ethical Committee. The Verbal Rating scale was chosen for this study because it is very reliable and easy to administer. As placebo was included in this study it was ethically incorrect not to include the rescue analgesic.

As telephonic interviews were needed for the assessment of postoperative pain, patient not accessible by telephone could not be included in the study. The fact that this was a single dose study and pain was assessed only over the first 6 hours, was another limitation. Ideally the duration of a study for assessing the analgesic efficacy of drugs is post extraction pain, should be for a period of 2-3 days, with

multiple dosing.

Ibuprofen-an NSAID has a good anti-inflammatory, analgesic activity. It is one of the most commonly used analgesics for dental pain. Therefore, we introduced ibuprofen as the rescue analgesic. Inclusion & exclusion criteria were made to select the patient for the study. Pain intensity was scored and assessed using a Verbal Rating Scale (VRS). Treatment differences were calculated using Kruskal – Wallis & Mann – Whitney U tests for rank transferred data. Adverse effects were compared using Pearson's Chi squared test.

RESULTS

Demographic Data

A total of 49 patients were recruited during the study. Eight patients were excluded from the efficacy analysis. (Seven patients could not be contacted on the telephone and one patient was found to have high blood pressure after the drug was administered).

Of the 49 patients included in the study 24 were males (48.97%). The mean age of the patients in the study was 31.57y, ranging from 18-65 years, with 92% of the patients in the 25-45 age group. The mean duration of the procedure was 15.93 minutes, ranging from 2-70 minutes. For 38 patients (78%) it took less than 20 minutes for the completion of the procedure. For 1 patients (2%) it took 70 minutes. Local anesthetic (2% lignocaine) was injected to all patients, prior to surgery. The mean dose of the local anesthetic was 2.4 ml ranging 2-8 ml. All except 3 patients (4%) had antibiotic coverage prior to surgery. The indications for the third molar extractions were impacted teeth, infected teeth or both. One patient had a tongue ulcer for which the extraction was indicated. Of the 49 patients, 34 patients (69%) had impacted teeth, 4 patients (9.5%) had infected teeth, and 9 patients (19%) had both. All except 2(4%) were lower molar extractions. All the six patient groups were similar in terms of gender distribution, average age, the amount of local anesthetic administered, the antibiotic coverage given, the position of the molar extracted and the duration of the procedure.

Pain Score

The results of the analysis of the primary end point, namely mean

pain scores show that the Tramadol was more efficacious in reducing the pain as compared to placebo. Mean pain score of tramadol group and placebo group at 30 minutes was 1.250 and 1.312 and at 6 hours was 2.147 and 2.884 respectively. (Kruskal-Wallis Chi-square = 17.2413; P=0.0041).

Analgesic efficacy:- [fig 1]

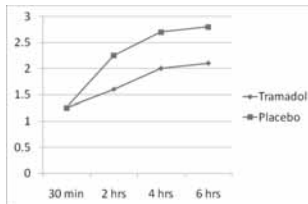


Figure 1: Change in mean pain scores (preoperative and the postoperative group combined) for Tramadol and Placebo over the 6 hour study period.

When the pain scores of analgesic group were compared with those of the placebo group separately, the analgesic group was found to have lower maximum pain scores at each time point as compared to placebo, indicating that the analgesics were superior to placebo in producing pain relief.

On comparison of the pain scores of the preoperative group versus the postoperative group of tramadol, postoperative administration was found to reduce the pain score at each time point, more than preoperative administration at each time point. Mean pain score for preoperative tramadol and postoperative tramadol at 30 minutes was 1.4 and 1.1. and at 6 hours it was 2.42 and 1.875 respectively (Mann Whitney U with Z correction = 1.937; p = 0.05).

Need for rescue analgesic – [Fig :2]

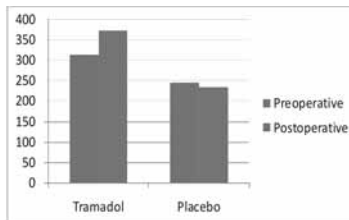


Figure 2: Need for rescue analgesic in the Preoperative versus Postoperative groups of tramadol and placebo as indicated by mean time (in minutes) at which the rescue drug was self administrated.

The secondary end point in the study was the need for rescue analgesic. When tramadol was compared with placebo (both preoperative and postoperative), the analgesic group needed rescue drug less than the placebo group. The average time taken by the patient from the start of the procedure to the time when pain was severe enough for the patient to feel the need to self administer the rescue analgesic was more in the tramadol than in the placebo group, indicates that, more prolonged pain relief was seen in the analgesic group as compared to those receiving placebo (mean time for rescue analgesic in the tramadol–366 minutes, in the placebo group – 240 minutes (Kruskal – Walis Chi-Square = 17.7;p = 0.00337)

It was seen that on comparison of preoperative placebo with preoperative tramadol, there appeared to be no significant difference in need for rescue analgesic. (Mean time for rescue in the preoperative placebo group- 245 minutes, mean time for rescue in the preoperative tramadol group – 313 minutes) Mann Whitney U – 1.4; p = 0.241) When postoperative placebo was compared with postoperative tramadol, the need for rescue analgesic was significantly lower in the tramadol group. (mean time for rescue in the postoperative placebo group –233 minutes, mean time for rescue analgesic in the postoperative tramadol group 372 minutes) (Mann Whitney U Test = 6.2;p = 0.012).

When preoperative tramadol was compared with postoperative tramadol, there was no significant difference in the need for rescue analgesic (Mean time for rescue in the preoperative tramadol group –313 minutes, mean time for rescue in the postoperative tramadol group – 372 minutes) (Mann Whitney U test = 1.5; p = 0.217) were no serious adverse events reported for any of the study groups.

Adverse Effects

Only 8 patients (16.3 %) of the total of 49 reported side effects. Of these 8 patients that reported side effects, 7 belonged to the tramadol group and 1 to the placebo group. One patient from tramadol complained of feeling sleepy. Five patients in the tramadol group felt dizziness/giddiness. One patient from the tramadol group felt weakness/tiredness. One patient in the tramadol group felt nausea/vomiting one patient in the placebo group complained of tingling sensation.

For purposes of analysis, occurrence of adverse effects were represented as nominal data that is, either ‘any adverse effect occurred’ or ‘no adverse effect occurred’. Pearson’s chi square test (without Yale’s continuity correction) showed a significant difference between groups (Chi square – 12.6083; p =0.0018)

Comparison of adverse effect reportage of tramadol versus placebo groups showed that tramadol was significantly more likely to produce adverse effects, compared to placebo (Fisher’s exact test; p = 0.0006) as shown in table.

Table: Adverse Events

| Adverse Effects | Tramadol n = 25 | Placebo n = 24 |
|------------------------|--------------------|-------------------|
| Sleepy | 1 | 0 |
| Dizziness/giddiness | 5 | 0 |
| Weakness/Tiredness | 1 | 0 |
| Nausea/Vomiting | 0 | 0 |
| Tingling sensation | 0 | 1 |
| Serious adverse events | 0 | 0 |
| Total n % | 7(28) | 1(4.16) |

DISCUSSION

Third molar extraction produces moderate to severe pain and a fair amount of inflammation. It is routinely treated with non-steroidal anti-inflammatory drugs (NSAIDs) for 2-3 days. NSAIDs are known to produce side effects such as gastric irritation leading to ulceration and bleeding disorders. Despite the inflammatory component, the drug used in this study was a non-NSAID, so that the side effects produced by the anti-inflammatory analgesics could be avoided. The analgesic efficacy of non NSAIDs to Placebo was compared in this study. We also attempted to compare the adverse effects of non NSAID with Placebo, when given as single dose. Another aspect, which was looked at in this study, was pre-empting the expected pain by preoperative administration versus countering pain after it sets in by postoperative administration.

This study has succeeded in demonstrating the analgesic efficacy of single oral doses of tramadol, for impacted third molar extraction, with an acceptable incidence and severity of side effects, over the first 6 hours following extraction. Tramadol was found to be more effective postoperatively than preoperatively.

We looked at whether there is any need for analgesics for post extraction pain as the patient is already receiving a local anesthetic prior to surgery, and found that a significant proportion of patients do experience pain severe enough to require analgesics. Single dose of either tramadol was more efficient than placebo in relieving pain,

over the first 6 hours. Other studies corroborate this finding. Keeping the concept of pre-emptive analgesia in mind, we expected preoperative administration of analgesics to be more efficacious in relieving the pain than postoperative administration. Our results show that postoperative administration of tramadol appears to be more efficacious than preoperative administration, in terms of pain relief. Analgesic effect of tramadol begins within 1 hr and reaches a peak in approximately 2-3 hours (physician's Desk Reference, 1999) It is likely that the post extraction pain reaches a peak in the first 2-4 hours. Pharmacodynamics and pharmacokinetics of most administered drugs are time dependent. Therefore here, in the absence of severe pain, optimum use of tramadol has not been made. Opioid activity of tramadol is due to both low affinity binding of the parent compound and higher affinity binding of the O-demethylated metabolite to m opioid receptors. As it is extensively metabolized by a number of pathways the bio-availability of the active metabolite is high. Therefore it has a quick onset of action. Though tramadol was given preoperatively with the idea of preempting the expected pain, it appears that giving it before the procedure is too early to be of any benefit. This may be an explanation, why it is less effective when administered preoperatively than postoperatively, as the peak analgesic effect and the time of maximum pain after tooth extraction may not be coinciding with each other. This could also be a reflection of the inadequacy of the dose used preoperatively.

From our results showing that analgesic group required the rescue drug (ibuprofen 400 mg) less than the placebo group, we once again demonstrated that the pain following impacted tooth extraction is severe enough to require analgesics. Tramadol group require less rescue analgesic than the placebo group.

Looking at pre-emptive analgesia from the stand point of need for rescue, our study shows that preoperative tramadol did not appear to have sufficiently long lasting effects to be significantly different from preoperative placebo. As explained earlier, the analgesic effect of tramadol begins within 1 hours and reaches a peak in approximately 2-3 hours. In this study tramadol was administered half-an-hour before the procedure, hence the peak analgesic effect and the maximum pain produced by dental extraction might not be coinciding with each other when tramadol is administered preoperatively at the dose used in our study.

When postoperative placebo and tramadol were compared, tramadol was found to be more efficacious as indicated by the lower need for rescue in the analgesic groups. This result reinforces that sufficient residual pain remains despite adequate local anesthesia.

Tramadol being an opioid and nor-epinephrine modulator, more CNS related side effects as expected was found as 6 patients is tramadol

group had CNS related side effects and none in placebo group reported. Overall, the side effects reported by tramadol was significantly more than that reported by the placebo group. Tramadol's effects on the gastrointestinal tract is fairly minor and its CNS effects are more prominent. Some of the reported side effects include anxiety, confusion, euphoria, sleep disorders, visual disturbance and dependence.

Pain assessment using a verbal rating scale (VRS) was appropriate for this study. Jensen et al⁹ assessed the utility of 10 indices (including the verbal rating scale) in the subjective experience of acute pain. The results indicated that each of the measures of pain intensity is adequately valid. Jensen & Karoly¹⁰ have also said that because pain intensity is a relatively easy dimension of pain experience for patients to report, most self-report measures of pain intensity are strongly related to one another, and so can probably be used interchangeably in many situations.

CONCLUSION

This study demonstrated that tramadol is equally effective as traditional NSAID's in relieving pain in the first 6 hours after molar extraction and therefore can be tried in patients who are intolerant to NSAIDs. A firm conclusion regarding the time of intervention (i.e., pre-extraction post-extraction) for optimal pain control is a point for clarification and needs further analysis.

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