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COMPARISON OF EFFICACY AND TOLERANCE OF PARACETAMOL/TRAMADOL WITH PARACETAMOL/CODEINE IN MANDIBULAR THIRD MOLAR SURGERY

[1]Dr. M. Asim Naqash, [2]Dr.Gulraiz Zulfiqar, [3]Dr.Fatima tuz Zahra
[4]Dr. Fahad Ahmad, [5]Dr. Syed Shumail Ahmad
[1]Senior Registrar Oral & Maxillofacial Surgery, Children Hospital, Faislabad, [2]Assistant Professor Oral & Maxillofacial Surgery, Allama Iqbal Medical College/Jinnah Hospital Lahore, [3,4,5]Resident at Jinnah Hospital, Lahore.

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Abstract:
Mandibular third molar is the most frequently impacted tooth (prevalence 16.7% to 68.6%) [1] and is commonly removed by surgery. The surgical intervention is associated with moderate to severe postoperative pain, swelling and trismus. [2,3] Pain is generated by release of inflammatory endogenous chemical mediators such as bradykinin and prostaglandin. [4] Different anti-inflammatory and antibacterial drugs and insertion of cones or drains saturated with analgesic and antibiotic agents have been used by oral and maxillofacial surgeons for pain control. [5] Drugs of different classes with different mode of actions may also be combined to optimize their analgesic efficacy and tolerability. [6] The efficacy of paracetamol-codeine (PC) combination has proven a superior pain control over paracetamol alone but with associated complications of codeine like sedation, dizziness, nausea, vomiting and constipation. [7] Paracetamol has also been combined with tramadol (PT), an atypical weak opioid with a dual mechanism of action inclusive of a μ-opioid receptor activation and an enhancement of serotonin and norepinephrine transmission, for moderate to severe pain. [8] A significantly lower incidence of constipation, vomiting and other side effects have been reported with PT combination as compared to PC combination. [9] PT combination has not been widely reported for use in oral surgery. our study has several limitations. As one may argue that there is no control group receiving placebo, considering the surgical procedure being invasive one, placebo control group was not even possible. Also in our study, pain was evaluated after 24 hours post op and was not evaluated at different time points, with which more accurate results could have been achieved.

Corresponding author:
Dr. M Asim Naqash
Senior Registrar Oral & Maxillofacial Surgery,
Children Hospital Faislabad, E-mail: asimnaqash@ gmail.com

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INTRODUCTION:

Mandibular third molar is the most frequently impacted tooth (prevalence 16.7% to 68.6%) [1] and is commonly removed by surgery. The surgical intervention is associated with moderate to severe postoperative pain, swelling and trismus. [2,3] Pain is generated by release of inflammatory endogenous chemical mediators such as bradykinin and prostaglandin. [4] Different anti-inflammatory and antibacterial drugs and insertion of cones or drains saturated with analgesic and antibiotic agents have been used by oral and maxillofacial surgeons for pain control. [5] Drugs of different classes with different mode of actions may also be combined to optimize their analgesic efficacy and tolerability. [6] The efficacy of paracetamol-codeine (PC) combination has proven a superior pain control over paracetamol alone but with associated complications of codeine like sedation, dizziness, nausea, vomiting and constipation. [7] Paracetamol has also been combined with tramadol (PT), an atypical weak opioid with a dual mechanism of action inclusive of a μ-opioid receptor activation and an enhancement of serotonin and norepinephrine transmission, for moderate to severe pain. [8] A significantly lower incidence of constipation, vomiting and other side effects have been reported with PT combination as compared to PC combination. [9] PT combination has not been widely reported for use in oral surgery.

Alfano G, et al 2011 [9], in a General Surgery set up, found that the analgesic efficacy of PT was better than that of PC for pain management (pain score 24 hrs after surgery, PC-2.52±0.86 and PT-1.40±0.76, $p<0.001$), tolerability (32.72% patients reporting adverse events with PT versus 90.90% with PC), and need for rescue analgesia (5.5% patients with PT versus 18.2% with PC). PT has been reported as an effective analgesic in an oral surgery setting however tolerability has not been reported. (Fricke et al) Analgesia onset and effectiveness was found to be comparable tramadol/acetaminophen and codeine/acetaminophen have been reported as comparable. (Jung et al). Literature shows the comparison of the analgesic efficacy and tolerability of PT versus PC in outpatient/day case surgeries in a General Surgery setup, but no such study assessing both analgesic efficacy and tolerability were found in an Oral Surgery setup. Since third molar surgery as a day case procedure has become a standard for research in oral surgery, this study was designed to compare PT and PC combinations in third molar surgical procedures.

The rationale of this study was to determine the clinical outcome of the two drug combinations in third molar surgery in terms of analgesic efficacy and tolerability so that a potent analgesic drug with the least incidence of adverse events can be provided to improve the patient care. We hypothesize that there is no difference between paracetamol/tramadol and paracetamol/codeine combinations in terms of less mean pain score and more tolerability for surgical removal of mandibular third molars.

MATERIALS AND METHODS:

This Doubled Blind Randomized Controlled Trial was approved by the Fatima Memorial Hospital – College of Medicine and Dentistry Institutional Review Board and all participants signed an informed consent agreement. The study was aimed to compare the efficacy and tolerability of the fixed combinations of paracetamol/tramadol PT (325/37.25) and paracetamol and codeine (PC (500/30mg).

Two Hundred and sixty patients of both sexes, aged between 18 and 30 years, were registered through Out-patient clinic of Department of Oral and Maxillofacial Surgery, Fatima Memorial Hospital - College of Dentistry (FMHCD), Lahore, Pakistan. All the patients included in the study had mandibular impactions with difficulty score of 5-10 as per Pederson difficulty index and age range of 18 to 30 years old males and females. Patients with allergy or contraindication to use of investigational drugs, compromised immune system, renal and/or liver dysfunction were excluded. PT (325/37.25) combination and PC (500/30mg) combination were packaged by the hospital pharmacy as either Drug A or Drug B labeled with usage instructions for double blinding (researcher and patient).

Randomization was done through random number tables in the beginning and patients were divided into two groups i.e. 1&2 (130 patients in each group). All patients were advised to use a mouthwash chlorhexidine 0.2% before administration of local anesthesia. Patients allocated to Group 1 received drug A and those in group 2 received drug B, one hour before surgery (since the documented therapeutic levels of these analgesic medications i.e. PC and PT is reached 40-120 mins with peak plasma levels attained 2-4 hours after ingestion). An antibiotic (Amoxil 1g or Clindamycin 600mg in case of penicillin allergy) was also given 1 hour before surgery. All surgeries were performed under local anesthesia using inferior alveolar nerve block and buccal infiltration techniques. All mandibular extractions required bone removal with or without tooth sectioning. After surgery the patients were prescribed the assigned drugs in a twice daily dose as per randomization protocol and discharged from the hospital. The drugs were dispensed, pre and post-

operatively, by personnel other than the surgeon for blinding purpose.

The patients were given a structured proforma to be filled up after 24 hours for pain and tolerability. Pain was recorded on a Verbal Rating Scale (VRS) with none marked as 0, mild as 1, moderate as 2, severe as 3 and unbearable/extreme as 4. Tolerability of the drug was evaluated by documenting presence or absence of nausea, vomiting, drowsiness, and constipation as "Yes" or "No". Presence of any of the stated adverse event was considered as poorly tolerated. To reconfirm the validity of VRS and tolerability, the patient was re-interviewed on their follow up visit regarding their experience. Patient data forms were collected on review appointment, and results were analyzed for conclusion. The code for the drugs given to the two groups was broken after the completion of the statistical analysis to ensure double blinding.

The statistical analysis was performed using MATLAB (Mathworks). The collected data was analyzed for outcome variables of mean pain score and tolerability. Mean ±SD was calculated for the quantitative variables like age and mean pain score. Frequencies and percentages were computed for categorical variables like gender, tolerability.

- For mean pain score, t-test (on means) was used to determine statistically significant differences between pain scores for two groups.
- For tolerability, Chi-square test was used to determine statistically significant differences between the proportions (percentages) of the occurrence of adverse events (pooled).

Statistically significant differences between outcome variables from the two groups were determined by using a p-value ≤ 0.05. Confounding variables like age, gender and difficulty index was controlled by stratification to outcome variables.

Table 1: Two-Tailed, Two Sample T-Test to compare means of pain scores of both groups

GROUP	GROUP 1	GROUP 2
Mean	2.38	1.55
SD	0.92	0.83
p-Value	0.------ (Two-Tailed, Two Sample T-Test)	

Table 2: Mean pain scores in PC and PT groups with moderate or very difficult surgical extractions:

	Moderately Difficult	Very Difficult
Group 1(PC)	2.31±0.88	2.70±1.04
Group 2(PT)	1.48±0.81	1.82±0.83

Table 3 Chi-Square Test (without Yate's Correction) on Tolerability

	Raw Values		
	Yes	**No**	**Total**
GROUP 1PC	43	87	130
GROUP 2PT	95	35	130
Total	138	122	260
p-Value	less than 0.0001 (Chi square test)		

RESULTS:

In this study, a total of 260 patients were treated to control postoperative pain and tolerance after surgical extraction of mandibular impacted third molar with combination of codeine/paracetamol and tramadol/paracetamol. Patients were divided into two groups. In group 1 the patients were given a combination of codeine/paracetamol 30/500 mg (Drug A) and in group 2 the patients were given tramadol/paracetamol 37.5/325 mg (Drug B). The drug was given pre-operatively 1 hour before surgery as preemptive analgesia and then as twice daily dose as post-operative analgesia. Females formed the predominant gender 59% while males were 41%. A total of 154 females and 106 males were present in this study. ~~(table 2).~~ In group 1, 38% were males (50), 62%females (80). In group 2, 43%males (56) and 57% were females (74). The mean age of patients was 24.25±2.81 with a minimum and maximum of 18 and 30 years respectively. Sixty percent of the patients were in 23-27 years range. In group 1, mean age was 24.45±2.69 with minimum 18 and maximum age of 30 years, while mean age in group 2 was 24.05±2.92 with minimum 19 years and maximum 30 years. Total number of mandibular molars extracted were 260. Out of these, the percentage of mandibular right third molars was 47% (122) and that of left third molars were 53% (138). Eighty percent of the surgical extractions carried out were moderately difficult (Pederson Criteria) that makes 209 out of 260 extractions done, while 20% of the extractions done were very difficult i.e. 51 out of 260 extractions.

p-Value of mean postoperative pain scores of PC and PT groups according to the Verbal Rating Scale (VRS) 24 hours after the procedure based on Two-Tailed, Two Sample T-Test was highly significant. (Table 1- Giving mean values with standard deviations along with p-value) Thus the null hypothesis can be rejected, and it can be concluded that the efficacy of drug B tramadol/paracetamol combination in minimizing the perception of pain in patients undergoing mandibular third molar extraction surgeries is better than that of codeine/paracetamol combination (Fig.1). Mean pain scores based on level of difficulty in terms of surgical procedure were higher for PC group as against PT group. (Table 2)

Null hypothesis, formulated for tolerability in terms of presence or absence of nausea, vomiting, drowsiness, and constipation between the two groups can be rejected based on extremely statistically significant p-value of less than 0.05 (< 0.0001) based on Chi square test performed on raw values of table 3. We can conclude that the analgesic treatment with tramadol/paracetamol 37.5/325 mg was also better tolerated than codeine/paracetamol 30/500mg. (Table 3)

DISCUSSION:

The results of our study confirmed that a fixed paracetamol/tramadol combination is superior to a paracetamol/codeine combination in terms of higher analgesic efficacy and less post-operative adverse events (tolerability) including nausea, vomiting, constipation and drowsiness. Here we discuss our results and compare them with former studies.

Age being a confounding variable, in investigating the analgesic efficacies of pain medications, needs to be stratified. The inclusion criterion was set between 18-30 years because this is considered as most prevalent age range for clinical presentation of impacted mandibular third molars. (13) In our study, the most common age at the time of presentation was

23-27 years forming 60% of total patients. This is expected because eruption time of mandibular third molars is between 18-25 years of age and if they do not erupt successfully and get symptomatic, people in this age range are the most frequent candidates for third molar removal surgeries' (16). Comparing our age range to previous studies, Jung YS et al (2004) reported mean ages of 23.7 and 23.4 years in two groups treated with tramadol/acetaminophen and codeine/acetaminophen/ibuprofen respectively in dental surgery (17). Fricke JR et al (2002) included 200 "adults" (18 or older) in a study measuring the analgesic efficacy of tramadol/acetaminophen combination tablets, hydrocodone/acetaminophen combination tablets, and placebo after oral surgery (18). In our study, the mean age of patients was 24.25±2.81 (group 1 mean age 24.45±2.69 and mean age in group 2 was 24.05±2.92). A number of studies have shown that impacted mandibular third molars are more common in females than males (22,23). In contrast, the study of Knutsson K, et al (1996) showed that males had more propensity than females to develop mandibular third molar impactions (24). In our study females formed an majority of the patient population with a percentage of 59% accounting for 154 out of the 260 patient. Although a statistically significant relationship between gender and tooth impaction has not been well established in literature, the female predominance in this study can possibly be attributed to social norms, with female patients feeling more comfortable getting treated by a female doctor (the author of this dissertation). In this study, an inclusion criterion was defined for difficulty index which is a quantitative measure of the difficulty of performing the surgery. Difficulty index is obtained from empirical integer numbers associated with clinical and radiologic variables important in predicting surgical difficulty in impacted mandibular third molar extractions (see annexure 2). Surgeries with difficulty indices of 5-7 (moderately difficult) and 7-10 (very difficult) were included in this study. 80% (209 out of 260) of the surgical extractions carried out were moderately difficult while 20% (51 of 260) were very difficult. However, this distribution was conserved in the two groups (Table 4) in order to avoid any effect of difficulty index on determining the efficacy and tolerability of the two drugs. As one would expect, the mean pain scores of very difficult surgeries were higher than those of moderately difficult surgeries (Table 4B) in both groups. This is because patients undergoing very difficult surgeries experienced relatively more surgical intervention (bone cutting and tooth sectioning) and lengthier operative time. Moreover, post-operative sequelae (pain, inflammation, and trismus etc.,) are more pronounced in patients undergoing very difficult surgeries.

Furthermore, the distribution of mean pain scores and occurrence of adverse events ('No' tolerability) was determined for both genders and groups (Table 2B-C). For the whole sample, the mean pain scores and the number of occurrences of adverse events were higher for females than males but in individual groups variations can be seen. The association between clinical pain and gender is not a simple one, but females have reported more frequent pains compared to men in terms of various anatomic regions, neuropathic conditions, chronic musculoskeletal pains, temporomandibular pains, facial pains, and toothaches (25,26). Similarly, the greater sensitivity regarding post-operative pain in females after dental surgery might be attributed to psychosocial factors (mood, sex role beliefs, pain coping strategies, and pain-related expectancies), catastrophizing and sex hormones (26–28). However, Capuzzi et al. (29) reported a greater extent of pain in males, and Yuasa and Sugiura (30) declared that postoperative swelling and morbidity but not pain might be greater in females. Irrespective of gender specific distribution of mean pain scores and tolerability, Group 2 patients treated with paracetamol/tramadol had lower mean pain scores and the number of occurrence of adverse events.

An association between different aspects of surgical difficulty (such as the impaction level and angle, extent of bone removal or length of surgery) and pain or paresthesia has been assessed in most previous studies (31,32). Lago-Méndez et al (33), Pedersen (32), Baqain et al (34), and de Santana-Santos et al (31) stated that lengthier surgeries leave more painful sockets. Haraji and Rakhshan (35), and Yuasa and Sugiura (30) found that more difficult operations were more painful. The release of more inflammatory factors and proximity to the nerve might produce more intense pain in some difficult cases. Seymour et al. (36) stated that the postoperative pain level might not be dependent upon the operator or the extent of surgical trauma as estimated by operating time and radiographic score. In our study, irrespective of the difficulty level of the surgery, mean pain scores in group 2 (for paracetamol/tramadol) were smaller than their counterparts in group 1. Thus, difficulty level of the surgery would not affect our conclusions in comparing the efficacy and tolerability of the two drugs given to patients in both groups.

Our findings are in agreement with the results of other studies which have evaluated the analgesic efficacy in patients treated with paracetamol/tramadol compared with paracetamol/codeine. Numerous studies have confirmed the efficacy and tolerability

of paracetamol plus tramadol in both acute and chronic pain. A meta-analysis of dental pain studies including more than 1,000 patients, Medve RA et al demonstrated that the combination of paracetamol plus tramadol had the same rapid onset of efficacy as paracetamol alone (17 and 18min, respectively), but that this efficacy was sustained for several hours (37). In the same analysis, ibuprofen had an onset of efficacy of 34 min.

Another meta-analysis of five studies in dental pain and two studies in post-surgical pain have demonstrated that paracetamol plus tramadol is more effective than either agent. Almost all adverse effects on paracetamol 650 mg plus tramadol 75 mg were mild to moderate and all were resolved. The main side effects of single-agent tramadol 75 mg or paracetamol 650 mg plus tramadol 75 mg were nausea, dizziness and vomiting.(38)

Comparative trials have shown that paracetamol plus tramadol has comparable efficacy to paracetamol plus codeine, but with reduced somnolence and constipation compared with the codeine combination. The paracetamol plus tramadol combination is also free of organ toxicity associated with selective and non-selective non-steroidal anti-inflammatory drugs (39–41).

Jung YS et al, in their study comparing, Paracetamol/Tramadol (PT) with Paracetamol/Codeine/Ibuprofen (PCIbu) combination came to conclusion that the onset of analgesia and analgesic efficacy of PT was comparable to that of PCIbu combination. PT provided rapid and effective analgesia for acute postoperative dental pain (17)

Frickle et al, in a double-blind, single-dose comparison of the analgesic efficacy of tramadol/acetaminophen (T/APAP) combination tablets, hydrocodone/acetaminophen combination tablets, and placebo after oral surgery found that in addition to T/APA tablets providing effective, rapid (< or = 34 minutes), dose-dependent analgesia for the treatment of postoperative dental pain, the incidence of nausea and vomiting was also reduced to 50% in tramadol/acetaminophen than in hydrocodone/acetaminophen (105).

Aside from dental surgery, various other day care surgeries have proved the superior postoperative analgesic efficacy and tolerability of PT over PC for the management of acute pain. Friedrichsdorf et al (2015) carried out a tonsillectomy of 84 children aged between 4-15 years concluded that as a part of multimodal analgesia, scheduled plus as needed tramadol may be considered for children in postoperative setting due to its analgesic properties and low potential of side effects (42). Alfano G et al (2011) carried out a randomized open study comparing the efficacy of PT vs PC in patients undergoing hemorrhoidectomy, inguinal hernia repair, hallux valgus, and varicose vein surgeries and confirmed the superiority of PT over PC (11).

The need for combination analgesia and its benefits over single analgesic agent for both acute and chronic pain and as postoperative analgesia have been emphasized already and further confirmed by following studies where comparative studies were performed on single analgesic agents;

Moore PA studied the effects of tramadol alone. Tramadol's maximum analgesic efficacy for relieving acute pain after oral surgery appears to be similar to that of 60 milligrams of codeine alone but less than that of a full therapeutic dose of a nonsteroidal anti-inflammatory drug or a codeine combination, such as aspirin/codeine or acetaminophen/codeine and tramadol alone should only be used as an alternative analgesic when gastrointestinal side effects contraindicate the use of nonsteroidal anti-inflammatory drugs and when codeine/acetaminophen combination analgesics are not well-tolerated or are contraindicated (43). In another study Moore pa et al, compared analgesic efficacy of Tramadol hydrochloride with that of codeine, aspirin with codeine, and placebo after dental extraction and found similar results (44).

Similarly single doses of codeine 60 mg provide poor levels of analgesia in acute postoperative dental pain compared with other commonly used analgesics, such as ibuprofen, as measured by both numbers of participants achieving clinically useful levels of pain relief and duration of analgesia; better results are obtained for other types of postoperative pain, though these results are still relatively poor compared with other analgesics (45).

However, our study has several limitations. As one may argue that there is no control group receiving placebo, considering the surgical procedure being invasive one, placebo control group was not even possible. Also in our study, pain was evaluated after 24 hours post op and was not evaluated at different time points, with which more accurate results could have been achieved. One of the limitations of our

study was probably the smaller number of patients, who presented with surgical extraction of impacted third molar. Studies done over a 2-3-year period with around 500 patients or more would have allowed us to have a more conclusive result. A shortage of statisticians with interest in medical epidemiology and who are also ready to help in our region is also a hampering factor while analyzing such data. Further studies are needed to assess the benefits of PT in management of post op pain after surgical extraction of mandibular third molar. An effective analgesic medication like PT in third molar surgery offers a helpful effect on health-related quality of life, so that the patient can return to his normal life as early as possible after the surgical intervention.

CONCLUSION:

In conclusion, the association of codeine and paracetamol has showed a consistently lower analgesic activity than the association of tramadol and paracetamol, in patients undergoing third molar surgical extraction. In addition, the better tolerability of the tramadol/paracetamol association is noteworthy, since it is also confirmed in literature by clinical trials reporting a significantly lower incidence of constipation and other adverse events with tramadol/paracetamol compared to codeine/paracetamol(46). Thus, a fixed association of tramadol/paracetamol is a valuable and safe tool for management of pain, especially in day care surgery like third molar impaction surgery.

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