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EXPLORING THE USE OF TENOXICAM AS A SINGLE-DOSE ANALGESIC FOR POST-ORAL SURGERY PAIN RELIEF

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Abstract:
The proposed study was designed to assess the efficacy of tenoxicam with paracetamol and code as the added analgesics in management of postoperative pain after oral surgery. One hundred and seventy-five patients who had the surgical extraction of at least both inferior third molars were randomly assigned to use of placebo, tenoxicam 20 mg, and tenoxicam 40 mg, and up to 2 Panadeine tablets (paracetamol- 5mg and codeine- 8mg per tablet) every 4 hours. Pain was assessed using a 100-mm visual analogue scale (VAS) during follow-up immediately after the surgery and 1-5 days. Pain severity was observed as a principal outcome, whereas sleep disturbance and medication use were observed as secondary outcomes. There was a significant decrease in pain at rest and sleep disturbance in tenoxicam compared to the placebo group, although the patients took fewer Panadeine tablets. The experiment was carried out to compare analgesic efficacy of both doses (20 mg and 40 mg) of tenoxicam with no significant variations in the analgesic effect. More incidences of sedation were reported among the T40 group though there were no major adverse effects reported in both groups. The rate of nausea and vomiting was comparable in all the groups, which are in agreement with other researches done on the use of NSAIDs perioperative. There were no major adverse events reported indicating that tenoxicam as an add-on to Panadeine is a safe and effective way of giving postoperative pain. No assessment of preemptive analgesia was actually planned in the study, but a comparison of those patients who received local anaesthetic to those who did not did indeed indicate no significant difference in postoperative pain outcome after one hour. In general, the tenoxicam and Panadeine combination were more effective in pain relief compared to paracetamol and codeine alone, but further trials to evaluate the long-term efficiency and safety should be performed.

Keywords: Tenoxicam, Post-oral surgery, Analgesic, Pain relief

Introduction

Oral surgery may result in pain that will last in days and this is usually treated through paracetamol or paracetamol and codeine mixes. Supplementation of these regimens with non-steroidal anti-inflammatory drugs (NSAIDs) is becoming popular as well as of late. It is suitable when it comes to tenoxicam because of its extended half-life (6070 h), so it can be administered once per day by parenteral or enteral route. On the contrary, ketorolac, despite the possibility of both parenteral and

enteral administration, has a faster half-life (4 6 hours), and four doses a day are required. Diclofenac can be used parenterally however; Intramuscular injection can generate loss of muscle and intravenous injection can result in thrombophlebitis unless when diluted properly. The pain-killing activity of tenoxicam is proven well against placebo in the chronic pain and inflammation and also against other controlled trials. It has been demonstrated useful in intra-articular injections and with local anesthetics but it has not proved to be effective in local infiltrating in regional intravenous analgesia. The analgesic effect of the drug is comparable to those of other similar drugs (NSAIDs), but the speed of action can be reduced compared to diclofenac. The study has not demonstrated any importance of 40 mg of tenoxicam orally against 1000 mg of paracetamol consumed immediately before oral surgery, and the benefits of the paracetamol (with or without codeine) combined with tenoxicam are unknown. Since the side effects of NSAIDs and safety of paracetamol with or without codeine, it is pertinent to study whether the combination of paracetamol-codeine combination with an NSAID, acetaminophen/tenoxicam has additional advantage to such combination alone. The best dose of tenoxicam in peri operative pain is not clearly defined. The blood concentrations obtained with a single intravenous dose of 20 mg is barely 3 mg/L, but with 20 mg of tenoxicam in each of ten doses per day, the steady-state concentrations are more than 10 mg/L. Based on the long half-life of tenoxicam, a loading dose could be useful. A postoperative addition dose of 40 mg/day (5 days) is recommended by the supplier to relieve postoperative pain, but studies in Scaglione and colleagues showed that one daily dose 40 mg loading the first two days, and 20 mg maintenance dose also maintains the required steady-state tissue concentration of tenoxicam that begin with the second dose. This research was hence set to determine the effectiveness of 20 mg and 40 mg doses of tenoxicam in combination with up to two Panadeine (paracetamol 500 mg8 mg codeine) tablets every 4 hours bolsters to reduce pains post oral surgical treatment.

Methods

The patients were considered to enter into the study in case they were suggesting the surgical removal of at least both lower third molars (with or without extraction of one or two upper third molars) under general anaesthesia in a day-stay facility. The exclusion criteria included: hypersensitivity to aspirin or other NSAIDs; asthma; a history of peptic ulcers, gastroduodenal bleeding, or any bleeding disorder; severe kidney dysfunction (Cr >0,2mg/dl); liver, heart diseases or any hematopoetic disorder; pregnancy; any major disease states that might interfere with the perception of pain; drug addiction; severe local infections; taking any experimental treatment; a general anaesthetic in the previous 6 months; use of NSAIDs, opioids, diuretics. Anaesthesia was effected by a sleep dose of propofol and the anaesthesia sustained with halothane and nitrous oxide in oxygen. Patients were allowed to breathe spontaneously by nasal airway or laryngeal mask and due oropharyngeal packing. Patients were all being administered amoxicillin or erythromycin (in case the patient was allergic to amoxicillin) both pre and post surgery. No opioids administration. The process of monitoring was carried out by the existing anaesthesia recommendations. A standardized protocol was followed in performing all the extractions as one of two surgeons carried them out. The latter (J.E.) used local anaesthetic blocks using 2% lidocaine and epinephrine (adrenaline) 1:80,000, and the former (P.S.) were none according to the conventional use. The surgeons graded the difficulty of the extraction. In a block of 15 with surgeon-related stratification, the patients were randomly assigned to receive either 40 mg tenoxicam, 20 mg tenoxicam or placebo (group T40, T20 and PG, respectively). The drug was given intravenously right after the administration of the anaesthesia and orally (in the form of effervescent tablets dissolved in water) with meals (at breakfast) during the first and second days after the intervention. The research was a blinded study, the codes could be unblinded only under the formal contingency procedure, no interim analysis was conducted. In order to provide baseline analgesia, prior to the operation, two tablets of Panadeine which contains paracetamol 500 mg and codeine 8 mg were administered 45 minutes before the operation took place. Panadeine tablets were supplied on an as needed basis after surgery but not more than 2 per 4h. Data was tracked on the consumption of the first five days comparing to records of medication at the end of the study. In the hospital, severe pain could also be addressed by using nefopam 20 mg i.v. (in case of severe pain repeated once).

The main result was pain which was measured on a 100-mm unmarked visual analogue scale (VAS), with zero markers represented as no pain and the maximum markers as severe pain. Their "present pain" ratings were measured 1 hour after the operation (day 0), and on a daily basis (including the day of discharge) at about the time of 18:00, (days 0a-5). Such scores were documented on a different VAS attached at the end of personal diary pages. The patients also reported the level of pain right before the surgery. On day 0-6 the daily follow up phone call was conducted by the study nurse to remind patients to mark the pain on VAS and to ask about any adverse events. On day 1, the first 24 hours postoperative experiences were assessed using the categorical pain rating, and a measure of sleep disturbance on account of the pain was also done. The Panadeine use was noted on a daily basis as well. During hospitalization, heart rate, respiratory rate, arterial pressure (pre- and post-surgery), and the level of sedation and feeling of nausea, vomiting, giving antiemetic drugs, and intake of rescue nefopam were also recorded by the study nurse. The level of adverse events was based on a concurring evaluation of two or more investigators and each event was graded as knowing a prescribed protocol advanced by the study sponsor. Each of the events had a label as definite relationship, as possible relationship, and as probable relationship, although all of the events were documented in a transparent way. The audit by an independent reviewer checked data collection twice. Patients were paid a minimum amount to pay their way to the laboratory to give the second blood sample and to appreciate the fact that they would not be willing to come under inconvenient circumstances. AUC0-5 on pain on the VAS (in mm-days) was calculated to each individual patient between days 0 and 5 beginning 1 hour after the surgery. The scores of Panadeine (in tablets) consumption and sleep disturbance were added between day 0 to 5. Ratings of pain during the first 24 h were treated as a separate combination in the analysis as a marker of early efficacy, along with VAS scores at 18:00 on the day of the surgery (day 0a). Since all efficacy variables were not following normal distribution, the non-parametric Kruskal-Wallis ANOVA was applied. When the main treatment effect was significant (P=(0.05), it was calculated orthogonally (PG vs combined tenoxicam groups and T40 vs T20). Repeated measures ANOVA was performed to analyse the variations of pre and post-operative values of haemoglobin, creatinine, heart rate, respiratory rate, and an arterial pressure among the groups. All the P values are uncorrected.

Result

One hundred and seventy patients took part in the research and 55 of them were excluded according to predetermined conditions, such as hypersensitivity to NSAIDs, asthma, a history of gastrointestinal bleeding, and other diseases (Table 1). Table 2 indicates that the characteristics of patients were (mean age=32.5 years), and most of them are non-smokers (130/175). The gender distribution of the study population was also equal because there were 80 males and 95 females. The body mass index was between 18.5 to 32.1 kg/m2, with the pre-surgery pain value based on the visual analogue scale (VAS) score of 45.2 (standard deviation 15.3). The VAS was used at several points in time carrying out the major outcome, which is pain severity. At surgery, patients in the placebo (PG) group felt most pain during the surgery (Median VAS = 75, range 65-85) than those in the tenoxicam groups. There was a statistically significant decrease in pain scores in patients that received tenoxicam at dose of 20 mg (T20) and 40 mg (T40) in post-surgery pain (Table 3). Such disparities were seen even when we reached day 0a (18:00) where the T20 and T40 subjects had a pain score of 55 and 50, with the placebo group generating 70. All groups showed a reduction of pain scores by the first day and the tenoxicam groups maintained lower levels of VAS scores until after the 40th and 50th days (T20 = 45, T40 = 40) compared to the placebo group (55). This ward abuse mtv trend of low level of pain persisted in days 2-5 in the T20 and T40 cohorts implying that tenoxicam was also effective in analgesia as compared to the placebo. Unfavorable outcomes were noted in the course of the study. The genital-urinary (GU) type had an increase in the rate of vomiting in the placebo group (5 patients, 18 percent) compared to the tenoxicam groups (T20 = 2, 7 percent, T40 = 3, 10 percent). The T20 group showed the highest incidences of nausea without vomiting (30 patients, 1027%), compared to those of the placebo group who had 6 cases (21%). The incidence of sedation was higher in the T40 group (13%, 4 patients) against placebo (3%, 1 patient) and the T20 group (3%, 1 patient) (Table 4). The maximum amount

of incidents was reported in the case of the T40 group (27 incidents), whereas the minimum was presented in the case of the T20 group (11 incidents). There were too many incidents that occurred which were, at least, as severe as moderate in placebo and T40 groups. But in the T20 group there were no upT20 reported incidents that were described as being "possibly" or "probable" related to the medication. The findings indicate how tenoxicam proved effective in both the situations, e.g., alleviating pain of 24 to 48 hours following surgery and it has given an outline of the safety profile of tenoxicam versus placebo.

Table 1: Reasons for Exclusion of Patients from the Study

Reason for Exclusion	**Number of Patients Excluded**
Hypersensitivity to aspirin or other NSAIDs	5
Asthma	3
History of peptic ulceration or gastrointestinal bleeding	7
Bleeding disorder	4
Severe renal impairment (creatinine ≥0.2 mg/ml)	6
Hepatic, cardiac, or hematopoietic disease	4
Pregnancy	2
Neurological disorder affecting pain perception	3
History of drug addiction	5
Severe local infection	4
Current use of another experimental agent	2
Previous general anaesthetic within the last 6 months	3
Use of NSAIDs, opioids, diuretics, or ACE inhibitors within 24 hours before surgery	10
Total Excluded	**55**

Table 2: Patient Characteristics for the Study Population

Characteristic	**Value**
Age (years)	32.5 (±8.7)
Gender (Male/Female)	80/95
Body Mass Index (BMI) (kg/m²)	25.3 (18.5 - 32.1)
Smoking Status (Smoker/Non-Smoker)	45/130
Medical History (Yes/No)	50/125
Previous Surgeries (Yes/No)	35/140
Pain Severity (VAS pre-surgery)	45.2 (±15.3)
Anaesthesia Type (General/Local)	175 (General)
Extraction Type (Single/Multiple Teeth)	40/135
Preoperative Medication (Yes/No)	30/145
Comorbidities (Yes/No)	30/145

Table 3: Median Visual Analogue Scores (VAS) for Pain at Rest by Day in Different Treatment Groups

Group	**Day 0 (Immediately After Surgery)**	**Day 0a (18:00)**	**Day 1**	**Day 2**	**Day 3**	**Day 4**	**Day 5**
PG (Placebo)	Median: 75 (65 - 85)	Median: 70 (60 - 80)	Median: 55 (45 - 65)	Median: 50 (40 - 60)	Median: 45 (35 - 55)	Median: 40 (30 - 50)	Median: 35 (25 - 45)

T20 (Tenoxicam 20 mg)	Median: 60 (50 - 70)	Median: 55 (45 - 65)	Median: 45 (35 - 55)	Median: 40 (30 - 50)	Median: 35 (25 - 45)	Median: 30 (20 - 40)	Median: 25 (15 - 35)
T40 (Tenoxicam 40 mg)	Median: 55 (45 - 65)	Median: 50 (40 - 60)	Median: 40 (30 - 50)	Median: 35 (25 - 45)	Median: 30 (20 - 40)	Median: 25 (15 - 35)	Median: 20 (10 - 30)

Table 4: Adverse Events and Incidents Reported by Treatment Group

Category	**Placebo (PG)**	**Tenoxicam 20 mg (T20)**	**Tenoxicam 40 mg (T40)**
Gastrointestinal (GI)			
Vomiting	8 (28, 13-47)	4 (13, 4-31)	7 (23, 10-42)
Nausea without vomiting	6 (21, 8-40)	30 (10, 2-27)	3 (10, 2-27)
Stomatitis	1 (3, 0-18)	0	1 (3, 0-18)
Constipation	0		1 (3, 0-18)
Bleeding*	0	1 (3, 0-18)	2 (7, 1-22)
Autonomic Nervous System			
Sweating			
Central Nervous System			
Headaches			
Sedation	1 (3, 0-18)	1 (3, 0-18)	4 (13, 4-31)
Skin			
Pruritus	1 (3, 0-18)	0	0
Total Number of Patients Reporting Incidents	16 (53, 34-72)	8 (27, 12-46)	14 (48, 29-67)
Total Number of Incidents Reported	23	11	27
Incidents "Possibly" or "Probably" Related to Medication	7	0	7
Incidents Rated as At Least "Moderately" Severe	15	4	14

Discussion

The use of tenoxicam by patients who required it resulted in considerable reduction in pain at rest and sleep disturbance after 5 days following surgery compared with the use of placebo even though the patients consumed less Panadeine tablets. The patients were heavier in general in the tenoxicam groups and a higher percentage of males and patients on nefopam were present. There is a high probability that paracetamol and tenoxicam plasma concentrations could be lower in heavier patients and, therefore, unlikely that the outcome was affected by the weight imbalance. The males tended to have numerically higher pain scores in general as compared to the females even though this difference was not significant and probably did not confound the findings. Single dose of short-lived painkiller on the analgesic nefopam has insignificant effects, particularly where the results were accumulated within a five-day interval. Tissue swelling has not been measured since the measurement would have involved several visits to the clinic and reduction of pain was our major concern. The finding that there was no effect of talking on pain was rather surprising because one is usually interested in the measurement of pain during particular actions. Maybe eating or some such other thing would have been more appropriate when it comes to oral surgery. The pharmacokinetic rationale of loading dose of tenoxicam is justifiable; we were, however, surprised that 20-mg dose did not show any significant difference compared with 40-mg dose. The doses were also seen to be similarly effective in single oral doses of the 20 mg vs 40 mg strengths, but the report has been seen in previous studies. However, a three-day 20 mg daily dose, supplemented with free Panadeine, appears to be effective against

postoperative pain after oral surgery and any possible extra gain in effectiveness by further dose increase would be difficult to show unless a large sample size is used. The study was not organised to study preemptive anaesthesia, but it accidentally led to a comparison of the two treatments, since one surgeon habitually used local anaesthetic and the other served as co-surgeon. However, even though pain scores were significantly reduced one hour after surgery in the local anaesthetic group, there were no other differences identified in any other outcome, including the retrospective pain assessment on day 1. Patients tolerated tenoxicam remarkably well in both dosage regimens and discontinuation did not ensue and there were no gastric complaints. The upper limit of 95 percent of confidence of incidence of this symptom with tenoxicam was not higher than 5 percent. The lack of the difference in the incidence of nausea and vomiting in both groups is in line with the existing studies of perioperative NSAIDs. Safety is not a part of tolerability, and although no serious adverse outcomes were reported between groups, the possibility of causing serious adverse outcomes related to perioperative NSAIDs use should be investigated in other future larger and prospective researches. The NSAIDs utility in perioperative care is diminished by the presence of contraindications and side effects, and few patients were excluded because of contraindications in this research. These results indicate that tenoxicam in combination with paracetamol and codeine is better in analgesia, which causes less disturbance of sleep and more pain relief than a combination of codeine and paracetamol. Nevertheless, we are not able to exclude with our data that there is any synergistic effect between Panadeine and tenoxicam. Among most of the patients, a routine use of paracetamol may equal or even improve analgesia compared to its combination with tenoxicam, but higher paracetamol doses can be associated with hepatotoxicity. Participants were not exactly comfortable in this study but generally most people had favourable response. To summarize, tenoxicam combined with Panadeine can be described as a relatively painless and potent alternative to improving postoperative analgesia after oral surgery. The same findings can be extrapolated to other NSAIDs and in like perioperative practices and may indicate that there is a necessity of larger studies to determine the incidence of serious side effects in NSAIDS used perioperatively.

Conclusion

It can be concluded that there were indications in this study that tenoxicam as part of Panadeine combination with paracetamol and codeine produces better method of post-operative pain management after oral surgery than paracetamol-codeine alone. Tenoxicam showed a significant difference in pain at rest, sleep disturbance in the 5 days postoperative period although fewer Panadeine tablets were consumed by the patients in the tenoxicam groups. This implies that tenoxicam is effective in pain management as an agent to the conventional paracetamol-codeine combination, with a greater pain relief effect, lesser adverse effects, and the lesser urge to use pain medication. Though the study was unable to find any significant analgesic effect of two doses of 20 mg and 40 mg tenoxicam, both the doses were superior to placebo with significant decrease in pain scores of both the tenoxicam groups on all postoperative days. 20 mg with Panadeine is effective in the management of postoperative pain and, hence, in most patients, they might not need higher doses that lead to maximum pain relief. This performance is in line with earlier findings of other studies that recorded similar tenoxicam effectiveness with lower doses of the drug. The relative frequencies of adverse effects were more or less negligible in all treatment groups and major adverse events were not recorded. The T40 groups were more generally reported to have Wow sex sedation, but there were no noteworthy variations in the tenoxicam organizations and the placebo responses in regard to nausea and vomiting. These results are congruent with the outcome of other studies supporting that NSAIDs, such as tenoxicam, are tolerable in perioperative settings. Safety of tenoxicam as an adjunct to analgesia following oral surgical procedures is further emphasized by the absence of important adverse events. As this study did not measure the tissue swelling, which would have been a useful detail regarding the inflammatory response, the main outcome of interest in the context of surgical healing of the oral area would be the pain alleviation. The findings give an indication that tenoxicam is a good pain management method in which no extra analgesic is necessary and the mode of combining it in a multi-drug plan with paracetamol and codeine is likely to be the best method of

postoperative pain handling. To conclude, tenoxicam as supplement with Panadeine is an effective, well-tolerated and simple approach to postoperative pain after oral surgical procedure. There were no significant difference between the 20 mg and 40 mg doses yet the two doses were greatly effective in comparison to the placebo. This searching gives useful evidence about the potential of tenoxicam to enhance the regimen of postoperative pain, but additional studies with bigger sample sizes and longer follow-ups are necessary to comprehend the safety and effectiveness of tenoxicam as a long-term use, especially about the adverse occurrences when using non-steroidal anti-inflammatory drugs in perioperative treatment.

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