The Value of (Chlorzoxazone 250 mg + Paracetamol 300 mg) in Relieving Postoperative Trismus and Pain after Surgical Removal of Impacted Lower Wisdom Teeth (Clinical Study)

[1]Waseem Khalid Mahmood, MSc., [2]Saif Saad Ali Al-Jewari, FIBMS, and [3]Zaid Abdulazeez Muhammad, MSc.
[1, 2, 3] Department of Oral and Maxillofacial Surgery, College of Dentistry, University of Mosul, Iraq.
Corresponding author: Zaid Abdulazeez Muhammad
Email address: Zaidabdulaziz@uomosul.edu.iq

Received March 28, 2021.
Accepted for publication on May 25, 2021.
Published June 06, 2021.

Abstract

Background Reduction of postoperative drawbacks related to extraction of lower wisdom teeth is an important goal in oral surgery. Chlorzoxazone, a centrally acting muscle relaxant, could be use following surgical removal of lower wisdom teeth, to replace other alternative medications such as steroids, non-steriodal anti-inflammatory drugs and diazepam particularly when the access to these medications is limited or contraindicated. **Objectives** this study aims to evaluate a combined therapy (Chlorzoxazone 250 mg + Paracetamol 300 mg), in relieving of postoperative trismus and pain after surgical removal of lower wisdom teeth compared with paracetamol 500 mg.
Materials and Methods thirty healthy patients participated in this prospective clinical study. They were divided into two groups; the test group received the combined therapy (Chlorzoxazone 250 mg + Paracetamol 300 mg) and antibiotic while the control group received just paracetamol 500 mg and antibiotics as postoperative medications. Postoperatively, one independent investigator performed clinical examinations.
Results the combined therapy (Chlorzoxazone 250 mg + Paracetamol 300 mg) presented a good postoperative effect to relief the trismus related to the operation
Conclusions this could justify the use of this combination therapy as an alternative to steroidal and non-steroidal anti-inflammatory agents particularly when these medications contraindicated in certain medically compromised patients.

Keywords: Impaction; chlorzoxazone trismus; pain.

Introduction

To improve the treatment outcome and to reduce the postoperative visits which increase patient satisfaction, reduction of complications resulted following extraction of lower wisdom teeth is the key to achieve these goals. These complications appear in form of pain, swelling, trismus, and alveolar osteitis. Different therapies have been assessed and published in the literature to control postoperative drawbacks related to the extraction of lower wisdom teeth. These therapies are Analgesics (Bailey et al, 2014), Corticosteroid (Alexander et al, 2000), Antibiotics (Ren et al, 2007). Antibacterial mouthwashes such as Chlorhexidine mouthwash (Caso et al, 2005), topical gels of antimicrobial agents (Hita-Iglesias et al, 2008), Irrigation (Daly et al, 2012; Ghaeminia et al, 2016), and cryotherapy (Ibikunle et al, 2016). Cho et al 2017 concluded in their review of multiple evidence-based studies that there is strong evidence for using paracetamol and ibuprofen in the management of postoperative pain. Corticosteroids reduce swelling and trismus after surgery but they should only be used in selected cases. Chlorhexidine mouthwash and gels are proven to be efficient in reducing alveolar osteitis. There is no clear evidence concerning the use of cryotherapy after third molar removal. The impact of using a muscle relaxant to reduce pain, swelling, and trismus following surgical removal of lower wisdom teeth has not been studied well. Chlorzoxazone is a centrally acting muscle relaxant used to treat muscle spasms. It is commonly used after lower spine surgery (Nielsen et al, 2016). The most concerning side effects of this medication are liver toxicity particularly when Chlorzoxazone combined with paracetamol as the latter has the same side effect but this drawback might happen only when consuming these medications for chronic use for several months (Powers et al,1986). Analysis of plasma samples indicated a rapid absorption and rapid elimination of Chlorzoxazone. Average values of the elimination half-life and plasma clearance were 1.12 +/- 0.48 hr and 148.0 +/- 39.9 ml/min, respectively (Desiraju et al, 1983). The purpose of this study was to evaluate the clinical use of combined therapy (Chlorzoxazone 250 mg + Paracetamol 300 mg) in relieving postoperative trismus after surgical removal of wisdom teeth as it can be considered as a replacement of other medications following long oral surgery procedures like NSAID, Steroids and other muscle relaxants such as diazepam particularly when these medications not recommended for certain medically compromised cases excluding patients with liver disease.

Materials and Methods

Study Design

This clinical study was approved and registered by the ethics and scientific committee at the University of Mosul / College of Dentistry, Department of Oral and Maxillofacial surgery. The protocol followed the guidelines in the Declaration of Helsinki and all participants were informed about the details of the procedure in a written informed consent which was signed by all patients before recruitment in this study. A specific selection criterion was applied to avoid unwanted results. Inclusion criteria included Male and females aged 18 years old or above who read and signed the written informed consent for their participation in the study, partial bony impacted mandibular third molars with Class II or III and position A, B, or C, according to Pell and Gregory classification on a radiograph. The patient indicated for lower wisdom tooth extraction without local or/and systemic limitations. The geographic proximity of living should allow adequate follow-up. On the other hand, exclusion criteria involved Patients with liver disease, dental infection such as pericoronitis, medically

compromised patients, and history of allergy or hypersensitivity to the drugs used in this trial, recent use of anti-inflammatory drugs or muscle relaxants, chronic use of any medication (any corticosteroids or NSAIDs), pregnant or lactating females. Regarding sample randomization, thirty patients were recruited in this study and randomly divided into two groups fifteen in each. The first group (the control) received postoperative paracetamol tablets, a maximum of 4, 500 mg when needed. The second group (the experimental) received a postoperative muscle relaxant/ analgesic capsule (Chlorzoxazone 250 mg + Paracetamol 300 mg) three times daily for seven days to ensure complete recovery of the complicated cases. Interincisal distance to assess the mouth opening was measured before and after the surgical procedure to assess trismus after the operation and these readings was measured postoperatively at different time intervals first, the third and seventh day.

Surgical procedure

The study was conducted at the Department of Oral and Maxillofacial Surgery, University of Mosul. Local anesthesia was administered through the inferior dental block and buccal infiltration. A full-thickness mucoperiosteal flap is used in exposing all impacted lower wisdom teeth. Tooth sectioning is applied in difficult inclined teeth to facilitate their removal without traumatic injury to the adjacent structures. Chlorhexidine solution 0.2 % used to clean and disinfect the area following complete removal of impacted teeth. Suturing of the area done with 3/0 black silk suture.

Postoperative assessments and statistical analysis

Postoperative measurement of the mouth opening was performed, to assess trismus, by measuring the Interincisal distance. Visual Analogue Scale measured from (0-10) cm to assess pain severity after the operation and the response to analgesics (Gould et al, 2001). The time of operation from the administration of local anesthesia to the end of suturing was measured for the general assessment of the cases. Mann-Whitney U test was used to compare the effect of different treatments on postoperative trismus and pain. Statistical analysis was performed using SPSS 19 computer software program (SPSS, Cary, North Carolina, USA). Eight males and twenty-two females were recruited in this study with a mean age of 25 ranged from (18- 32) years old. The median of operations time was 36 minutes for the control group and 42 minutes for the treated group and there was no significant difference, $p=0.197$, between the two groups at p-value ≤ 0.05. Tooth sectioning involved eight cases compared to twenty-two teeth extracted without sectioning. No correlation was found between time of operation/tooth sectioning and postoperative trismus/pain.

Results

Demography

Eight males and twenty-two females were recruited in this study with a mean age of 25 ranged from (18-32) years old. The median of operations time were 36 minutes for the control group and 42 minutes for the treated group and there was no significant difference, $p=0.197$, between the two groups at p-value ≤ 0.05. Tooth sectioning involved eight cases compared to twenty-two teeth extracted without sectioning. No correlation was found between time of operation/tooth sectioning and postoperative trismus/pain.

Trismus assessment

The median for Interincisal distance for control and treated group patients preoperatively were 44 for both groups (Table 1). Both medication formulae demonstrated a significant effect following assessment of mouth opening postoperatively. There was no significant difference preoperatively in mouth openings for those who recruited in this study who received later paracetamol 500 mg or Chlorzoxazone 250 mg with paracetamol 300 mg (Table 2). Chlorzoxazone 250 mg with paracetamol 300 mg demonstrated a significant effect compared with paracetamol only in relieving of postoperative trismus following removal of impacted lower wisdom teeth (Table 2).

Table (1): Median of mouth openings (Interincisal Distance mm), after administration of the above mentioned two medications separately.

Median	Paracetamol 500 mg (Control Group				Combined Formula Capsule (Chlorzoxazone 250mg + Paracetamol 300 mg): (Experimental Group)			
	Pre-OP	Day 1	Day 3	Day 7	Pre-Op	Day 1	Day 3	Day 7
	44	22	28	35	44	33	34	42

Table (2): P values for the comparative effect of the above-mentioned two medications on relieving of trismus following removal of lower impacted wisdom teeth. P value significant 0≤0.5.

Comparison of mouth opening following administration of Paracetamol 500 mg and Combined Formula Capsule (Chlorzoxazone 250mg+Paracetamol 300 mg)				
Day (mouth openings)	Pre-Op	Day 1	Day 3	Day 7
P- value	0.829	0.001	0.012	0.037

Pain assessment

Pain measured zero for all recruited patients. Paracetamol 500 mg didn't show to provide enough analgesic effect following extraction of the impacted lower wisdom teeth. On the other hand, the combined formula medication tablet (Chlorzoxazone 250 mg with paracetamol 300 mg) demonstrated an acceptable analgesic effect compared with paracetamol 500 mg after day 1 following the surgical procedure (Tables 3 and 4).

Table (3): Median of Visual Analogue Scale (0-10) cm for pain assessment after administration of the above-mentioned two medications separately. Preoperative readings were zero (no pain).

Median	Paracetamol 500 mg Control Group			Combined Formula Capsule (Chlorzoxazone 250mg + Paracetamol 300 mg): (Experimental Group)		
	Day 1	Day 3	Day 7	Day 1	Day 3	Day 7
	7	4	1	4	3	0

Table (4): P values for comparative effect of the two medications on relieving of pain following removal of lower impacted wisdom teeth. P value significant ≤ 0.05.

Comparison of pain control between Paracetamol 500 mg and Combined Formula Capsule (Chlorzoxazone 250mg + Paracetamol 300 mg)			
Postoperative day	Day 1	Day 3	Day 7
P value	0.006	0.001	0.052

Discussion

Noninfectious pain, trismus, and swelling are commonly expected sequelae after third molar surgery. Surgeons usually tend to stress such complications when preparing informed consents or sheets with postoperative instructions. Patients seem

to focus more attention on functions like chewing, swallowing, and eating. (Martin et al, 2005; Esteller-Martinez et al, 2004). It is crucial that relieving post-operative pain should be effective and the side effects should be reduced by using combination therapy with a different mechanism of action of drugs rather than using a single drug (Kehlet et al, 2003; White et al, 2005; Ong CK et al, 2010). In our study, this reduction in pain intensity may be attributed to the reduction of muscle spasms caused by surgical trauma. So the vicious cycle of (pain-trismus) can be interrupted by providing muscle relaxation. Besides, the surgical removal of impacted teeth procedure is not traumatic as spinal surgery procedure. To the best of the authors' knowledge, this work is the first clinical study to evaluate the use of combined therapy (Chlorzoxazone 250 mg + Paracetamol 300 mg), in relieving post-operative pain and trismus after surgical removal of lower wisdom teeth compared with (paracetamol 500 mg). When patients did not receive any analgesia medications, they show a high pain score on VAS, therefore our study design did not involve the placebo group, because analgesic is critical in such a procedure. The main finding is that Chlorzoxazone 250 mg with paracetamol 300 mg showed significantly less trismus and more ability to open their jaws than paracetamol only in both early (1 to 3 days) after surgery and late (4 to 7 days) after surgery. There was a significant decrease in pain (measured by VAS) in all postoperative days (1st, 3rd, and 7th, postoperatively) in the combined treatment group compared with the control group. Evaluation of trismus was done by measuring Interincisal distance: a non-invasive, simple, cost-effective, and time-saving method, which provides numeric data. The significant positive effect of the combination of Chlorzoxazone with paracetamol on this study can be related to the obvious improvement of postoperative sequelae noted. According to two clinical trials published before 1980, combination therapy of Chlorzoxazone and Paracetamol were more powerful in reducing pain than carisoprodol+ aspirin and methocarbamol + aspirin (Miller et al, 1976; Gready et al 1976). Furthermore, Scheiner, (1976) conducted a trial comparing the analgesic effect of Chlorzoxazone with diazepam they found that Chlorzoxazone was more effective than diazepam in reducing pain and muscle spasm. In contrast to study research conducted by Nelson et al, (2016), where they observed that there was no significant reduction of early acute lower back pain following spinal surgery by using a single dose of Chlorzoxazone. Regarding Chlorzoxazone safety, hepatotoxicity is the most concerning side effect. However, this tends to occur rarely especially in high doses with prolong use of the drug (Jackson et al, 2007; Waldman et al, 1974). Furthermore, addiction is not reported in patients using this drug (Jackson et al, 2007) .in our study there is no remarkable side effects were noted because of using a low dose of the drug for a short period. The relation between swelling and trismus reduction is yet not fully understood (why there was the reduction in swelling when using a muscle relaxant) so further research must be conducted to study the relation between muscle relaxants and postoperative swelling and comparing it to other anti-inflammatory medicines.

Conclusions

The result of our study could justify using a combination of Chlorzoxazone 250 mg with paracetamol 300 mg as a good alternative to the other pharmacological agents that relieve postoperative trismus (like steroidal and non-steroidal anti-inflammatory agents).

Conflict of interest

We are the author's (Waseem Khalid Mahmood BDS, MSc; Saif Saad Ali Al-Jewari BDS, FIBMS; Zaid Abdulazeez Muhammad BDS, MSc stated that the manuscript for this paper is original, and it has not been published previously (or part of MSc. dissertation or PhD thesis) and is not under consideration for publication elsewhere, and that the final version has been seen and approved by all authors.

References

Alexander RE, Throndson RR (2000). A review of perioperative corticosteroid use in dentoalveolar surgery. Oral Surgery Oral Medicine Oral Pathology Oral Radiology Endod; 90: 406-415. https://doi.org/10.1067/moe.2000.109778

Bailey E, Worthington H, Coulthard P. (2014). Ibuprofen and/or paracetamol (acetaminophen) for pain relief after surgical removal of lower wisdom teeth. A Cochrane systematic review. British Dental Journal; 415-455. https://doi.org/10.1038/sj.bdj.2014.330

Caso A, Hung LK, Beirne OR (2005). Prevention of alveolar osteitis with chlorhexidine: A meta-analytic review. Oral Surg Oral Med Oral Pathol Oral Radiol Endod; 99; 155-159. https://doi.org/10.1016/j.tripleo.2004.05.009

Daly B, Sharif MO, Newton T, Jones K and Worthington HV (2012). Local interventions for the management of alveolar osteitis (dry socket). Cochrane Data Base Syst Rev; 12: CD006968. https://doi.org/10.1002/14651858.cd006968.pub2

Desiraju RK, Renzi NL, Nayak RK, Ng KT (1983). Pharmacokinetics of Chlorzoxazone in Humans. J Pharm Sci; 72 (9), 991-4. https://doi.org/10.1002/jps.2600720905

Esteller-Martinez V, Paredes-Garcia J, Valmaseda-Castellon E, Berini-Aytes L, Gay-Escoda C (2004). Analgesic efficacy of diclofenac sodium versus ibuprofen following surgical extraction of impacted lower third molars. Med Oral Patol Oral Cir Bucal; 9:448-53 https://pubmed.ncbi.nlm.nih.gov/15580123/.

Ghaeminia H, Hoppenreijs TJ, Xi T, Fennis JP, Maal TJ, Berge SJ and Meijer GJ (2016). Postoperative socket irrigation with drinking tap water reduces the risk of inflammatory complications following surgical removal of third molars: a multicenter randomized trial. Clin Oral Investigation; 21: 71-83. https://dx.doi.org/10.1007%2Fs00784-016-1751-1.

Gould D, Kelly D, Goldstone L, Gammon J (2001). Examining the validity of pressure ulcer risk assessment scales: developing and using illustrated patient simulations to collect the data. J Clin Nurs 10: 697-706. https://doi.org/10.1046/j.1365-2702.2001.00525.x

Gready DM (1976). Parafon Forte versus Robaxisal in skeletal muscle disorders: a double-blind study. Curr Ther Res Clin Exp; 20: 666–73. https://doi.org/10.1007/s40122-019-0112-6

Hita-Iglesias P, Torres-Lagares D, Flores-Ruiz R, Magallanes Abad N, Basallote Gonzalez M, Gutierrez Perez JL (2008). Effectiveness of chlorhexidine gel versus chlorhexidine rinse in reducing alveolar osteitis in mandibular third molar surgery. J of Oral and Maxillofacial Surgery; 66: 441-445. https://doi.org/10.1016/j.joms.2007.06.641

Ibikunle AA, Adeyemo WL (2016). Oral health-related quality of life following third molar surgery with or without application of ice pack therapy. Oral and maxil-

lofacial surgery; 20: 239-247. https://doi.org/10.1007/s10006-016-0558-1

Jackson J, Anania FA (2007). Chlorzoxazone is a cause of acute liver failure requiring liver transplantation. Dig Dis Sci; 52: 3389–91. https://doi.org/10.1111/aas.12754

Kehlet H, Dahl JB (2003). Anaesthesia, surgery, and challenges in postoperative recovery. Lancet; 362: 1921–8. https://doi.org/10.1016/s0140-6736

Martin MV, Kanatas AN, Hardy P (2005). Antibiotic prophylaxis and third molar surgery. Br Dent J; 198:327-30. https://doi.org/10.1038/sj.bdj.4812170

Miller AR (1976). A comparative study of Parafon Forte tablets and soma compound in the treatment of painful skeletal muscle conditions. Curr Ther Res Clin Exp; 19: 444–50. https://doi.org/10.1111/j.1365-2125.2007.02847.x

Nielsen RV, Fomsgaard JS, Siegel H, Martusevicius R, Mathiesen O, Dahl JB (2016). The Effect of Chlorzoxazone on Acute Pain after Spine Surgery. A Randomized, Blinded Trial. Acta Anaesthesiol Scand; 60 (8), 1152 – 60. https://doi.org/10.1111/aas.12754

Ong CK, Seymour RA, Lirk P, Merry AF (2010). Combining paracetamol (acetaminophen) with nonsteroidal anti-inflammatory drugs: a qualitative systematic review of analgesic efficacy for acute postoperative pain. Anest Analg; 110: 1170–9. https://doi.org/10.1213/ane.0b013e3181cf9281

Powers BJ, USNR MC; Cattau EL, Jr, MC, USN; Zimmerman HJ. (1986). Chlorzoxazone Hepatotoxic Reactions An Analysis of 21 Identified or Presumed Cases. Arch Intern Med.; 146(6):1183-1186. https://doi:10.1001/archinte.1986.00360180197029

Ren YF, Malmstrom HS (2007). Effectiveness of antibiotic prophylaxis in third molar surgery: a meta-analysis of randomized controlled clinical trials. J Oral and Maxillofacial Surgery; 65: 1909- 1921. https://doi.org/10.1016/j.joms.2007.03.004

Scheiner JJ (1976). Muscle relaxants: chlorzoxazone compared with diazepam (a double-blind study). Curr Ther Res Clin Exp.; 19 (1):51-57.

Waldman HJ (1994). Centrally acting skeletal muscle relaxants and associated drugs. J Pain Symptom Manage; 9: 434–41. https://doi.org/10.1016/0885-3924(94)90199-6

White PF (2005). The changing role of non-opioid analgesic techniques in the management of postoperative pain. Anest Analg; 101: S5–22. https://doi.org/10.1213/01.ane.0000177099.28914.a7