

Efficacy of Preemptive Analgesia on Post-operative Pain and Quality of Life among Patients Undergoing Mandibular Third Molar Surgery.

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ABSTRACT

Background: It is unclear if pre-emptive analgesia is effective in pain control and improved quality of life following third molar surgery. The objective of this study was to determine the efficacy of pre-emptive plus postoperative versus postoperative analgesia alone on postoperative pain and quality of life (QoL) following lower third molar surgery.

Methods: This was a randomized, controlled, double blinded study performed at a Nigerian teaching hospital. Patients were randomly allocated in ratio 1: 1 into test group that received 50 mg diclofenac potassium 30 minutes pre-emptively and same drug post-operatively, 12 hourly for five days and the control group that received 50 mg diclofenac potassium postoperatively, 12 hourly for 5 days. The pain was assessed with a visual analogue scale at 4 hours, 8 hours, 12 hours, 24 hours, 48 hours, 72 hours, and day 7 postoperatively. The quality of life (QoL) was assessed with OHIP-14 questionnaire on days 1, 3 and 7 postoperatively. Both descriptive and inferential statistics were performed. A p value of less than 0.05 was considered statistically significant.

Results: The median age was 24 years and the male-to-female ratio was 1:1.4. At all-time points (4 hours, 8 hours, 12 hours, 24 hours, 48 hours, 72 hours and day 7), the pain scores were significantly lower in the test group compared to the control group ($p < 0.05$). The QoL was significantly better in the test group compared to the control group on day 1 ($p = 0.002$) and day 3 ($p = 0.006$) but not different on day 7 ($p = 0.135$).

Conclusion: Pre-emptive plus postoperative analgesia was more efficacious in the control of postoperative pain and in improving the quality of life of patients than postoperative analgesia alone following mandibular third molar surgery.

Keywords: Third molar surgery, diclofenac potassium, preemptive, postoperative, analgesia, pain, quality of Life.

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INTRODUCTION

The Surgical extraction of an impacted mandibular third molar is a common procedure in dental practice. (Eklund et al., 2001, Keneko et al., 1997). This surgical procedure is relatively invasive and often times associated with post-operative pain, swelling trismus and ultimately the quality of life of the patient.

(Woolf, 2004) In particular, post-operative pain increases the suffering and anxiety of the patient, which can demoralize both the patient and surgeon, and can disrupt the homeostasis of the circulatory and endocrine system. (Odai et al., 2015) Pain is an unpleasant sensory or emotional experience or a sensory modality that signals the existence of

destructive stimuli, triggering protective reflexes and reactions. (Schwartzmann., 2003) It is a key symptom associated with possible impairment of oral health-related quality of life. (Sear et al., 2010) Health related quality of life (HRQoL) is essentially the subjective perception about the ability to perform those activities important for the individual which is influenced by the current health status. (Joshi et al., 2004)

Preemptive analgesia is defined as a treatment that is initiated before surgery in order to prevent the establishment of central sensitization evoked by the incisional and inflammatory injuries occurring during surgery and in the early post-operative period. (Kissin., 2003) It is thought that by initiating analgesic interventions before the surgical procedure, intraoperative and post-operative nociception can be mitigated to the central nervous system and provide superior benefits in comparison to the same analgesics if given post-operatively. (Woolf et al., 1993) Managing pain can be challenging for the surgeon, with many patients being at risk of developing chronic pain if poorly managed. Chronic pain is a disabling condition that affects every aspect of a patient's life, contributing to a loss of both physical and emotional function, affecting a patient's level of activity, ability to function in the workplace, home and engage in social and recreational pursuits. (Tuck et al., 2011) There is also an economic downside to poorly controlled pain as there are increased health care expenses, purchase of analgesics and a potential decrease in financial income as work time is reduced. (Rice et al., 2016) Controversy remains as regards the efficacy of pre-emptive analgesia following third molar surgeries. While some authors have reported pre-emptive analgesia to be effective in reducing post-operative pain, others have also reported otherwise. (Schwartzmann., 2003, Woolf et al., 1993, Shah et al., 2012, Rangaswamy et al., 2016, Zacharias et al., 1996, Liporaci., 2012) The aim of this study was to determine the efficacy of pre-emptive plus postoperative versus postoperative analgesia alone on postoperative pain and quality of life following impacted mandibular third molar surgery.

METHODS

This was a randomized, controlled, double blinded study performed at a Nigerian teaching hospital that recruited all patients that required surgical removal of their impacted mandibular third molar. While informed consent was taken from the patients, ethical approval was obtained from the institutions

ethical and research committee (ADM/E22/A/VOL.VII/14831098) Those excluded from the study were patients less than 18 years, allergic to the preemptive analgesia (diclofenac potassium), acute local infection and those with severe difficulty index according to Pederson's index. From a previous study (Shah et al., 2012) minimum sample size and 10% attrition was estimated to be 66 using the formula of Zhong., 2009. Eligible patients were enrolled by the researcher

Study variables: The predictor variable was the timing of analgesia (pre-emptive plus postoperative or postoperative alone) used in each group. The outcome variables were self-reported pain (visual analogue scale; VAS) and oral health related quality of life (OHROqL) using OHIP-14 questionnaire. The other study variables were demographic variables including age, gender, indication for extraction, site of impaction, type of impaction, and duration of surgery

Enrolment, randomization and blinding: Sixty-six participants were enrolled into the study by the researcher. An independent observer performed sequence generation with the aid of computer and concealed them in opaque sealed envelopes which were assigned into test (50 mg diclofenac potassium (Novartis, Switzerland) 30 minutes pre-emptively and same drug post-operatively, 12 hourly for five days; n=33) and control (50 mg diclofenac potassium postoperatively, 12 hourly for 5 days; n = 33) groups using blocked randomization.

Operative procedure: All surgical procedure was done by a single surgeon (the researcher) using same surgical protocol for all patients. The surgical extraction of the mandibular third molars was done under local anesthesia using 2% lignocaine with 1:100,000 adrenaline. A three sided mucoperiosteal flap was raised, and with the buccal guttering technique adequate bone was drilled to allow for elevation of the tooth from the socket. Tooth delivery was followed by adequate irrigation of the socket with 0.9% normal saline. Hemostasis was achieved and the flap repositioned and sutured in place using a 3.0 vicryl suture material. All patients were placed on a five day antibiotic regimen (500 mg Amoxicillin (Smithkline Beecham UK), 3 times daily and 400 mg Metronidazole, Aventis 3 times daily.

Pain assessment: The visual analogue scale (VAS) was used for pre-operative and post-operative pain assessment. It had a horizontal line having a 10 cm length with 0 at one end and 10 at the other end (0 represents 'no pain 10 represents 'severe pain'). The blinded patients were asked to mark anywhere

across the line representing their pain intensity. The higher the score, the higher the pain intensity. A ruler is then used by the researcher to measure the distance from the no pain mark to the patient's marking in order to arrive at the score. Post-operatively, pain assessment was recorded after 4 hours, 8 hours, 12 hours, 24 hours, 48 hours, day 3, and day 7.

OHRQoL assessment: The oral health related quality of life (OHRQoL) was assessed using the oral health impact profile 14 (OHIP-14) questionnaire that was administered to all blinded patients before the surgery and subsequently after 24 hours, day 3, and day 7 post-operatively. OHIP-14, in spite of being a short questionnaire, is used worldwide and has been shown to possess a certain amount of evidence for its validity and reliability, sensitivity to changes and has adequate cross-cultural consistency.

Statistical analysis: Both descriptive and inferential statistics were performed. In the descriptive analysis, the range, mean and standard deviation or the inter-quartile range and median of the numerical data were estimated while the frequency and percentage

of the categorical data were estimated. In the inferential statistics, normality of continuous data between the two groups was tested with the Shapiro-Wilk test. The Mann-Whitney U test was used of intergroup comparison of the VAS scores and OHIP-14 scores. Repeated measure ANOVA analyses were conducted on the Rank transformed values of VAS and OHIP 14 scores. Chi-square test was used for categorical variables. Data were analyzed on per-protocol bases using Statistical Package for the Social Science (SPSS) software version 22 (SPSS Inc., Chicago, USA). $P < 0.05$ was considered significant.

RESULTS

A total of 66 participants equally distributed in both groups completed the study and were analyzed. The median age was 24 years and range 18-45 years. The female to male ratio was 1.4:1. The most common indication for extraction was dental caries (51.5%), and the most common type of impaction was mesioangular impaction. There was no significant difference between the two groups as shown in Table 1.

Table 1: Clinical and operative parameters for the study participants

Parameters	Groups		Total	Test statistic	P-value
	Pre + Post	Post			
Indication for Extraction					
Pericoronitis	16 (48.5%)	14 (42.4%)	30 (45.5%)	Fisher's=2.022	0.805
Dental caries	17 (51.5%)	17 (51.5%)	34 (51.5%)		
Prosthetic Reason	0 (0%)	1 (3%)	1 (1.5%)		
Orthodontic reason	0 (0%)	1 (3%)	1 (1.5%)		
Total	33 (100%)	33 (100%)	66 (100%)		
Site of Impaction					
Right	18 (54.5%)	8 (24.2%)	26 (39.4%)	$\chi^2 = 6.346$	0.012*
Left	15 (45.5%)	25 (75.8%)	40 (60.6%)		
Total	33 (100%)	33 (100%)	66 (100%)		
Type of Impaction					
Mesioangular	16 (48.5%)	18 (54.5%)	34 (51.5%)	Fisher's=1.321	0.806
Distoangular	3 (9.1%)	1 (3%)	4 (6.1%)		
Vertical	10 (30.3%)	11 (33.3%)	21 (31.8%)		
Horizontal	4 (12.1%)	3 (9.1%)	7 (10.6%)		
Total	33 (100%)	33 (100%)	66 (100%)		
Duration of Surgery	21.0 (IQR:19-22)	22.0 (IQR:19.5-23)	22 (IQR:19-23)		0.936
Sex					
Male	15 (45.5%)	12 (36.4%)	27 (40.9%)	$\chi^2 = 6.346$	0.453
Female	18 (54.5%)	21 (63.6%)	39 (59.1%)		
Total	33 (100%)	33 (100%)	66 (100%)		
Age categories(years)					
≤20	4 (12.1%)	7 (21.2%)	11 (16.7%)	Fisher's=5.773	0.215
21-25	11 (33.3%)	14 (42.4%)	25 (37.9%)		
26-30	7 (21.2%)	3 (9.1%)	10 (15.2%)		
31-35	9 (27.3%)	4 (12.2%)	13 (19.7%)		
≥35	2 (6.1%)	5 (15.2%)	7 (10.6%)		

*Statistically significant at $p < 0.05$; †=Mann-Whitney U test

Figure 1 highlights the trend of the visual analogue scale (VAS) scores between the study groups

Table 2 presents the comparison of pain scores between the study groups. The highest pain scores among the study participants were recorded 4 hours post-operatively; with median VAS scores of 7 and 8 in the Pre + Post and Post analgesia groups respectively. Post-operatively, the pain scores were higher in the participants who received Post analgesia alone, on all the assessment days. There was statistically significant differences in the pain scores at 4 hours ($p=0.022$); 8 hours ($p<0.0001$),

12 hours ($p<0.0001$), 24 hours ($p<0.0001$), day 2 ($p<0.0001$), day 3 ($p=0.001$), and day 7 ($p<0.0001$)

Figure 2 presents the trend of the oral health impact profile 14 (OHIP-14) scores between the study groups.

Table 3 shows the comparison of the oral health related quality of life between the study groups. On all the assessment days, we recorded lower OHIP 14 scores in the Pre + Post-operative analgesia group compared to the group that received Post-operative analgesia alone. The observed difference was statistically significant on days 1 and 3 but was not statistically significant on day 7.

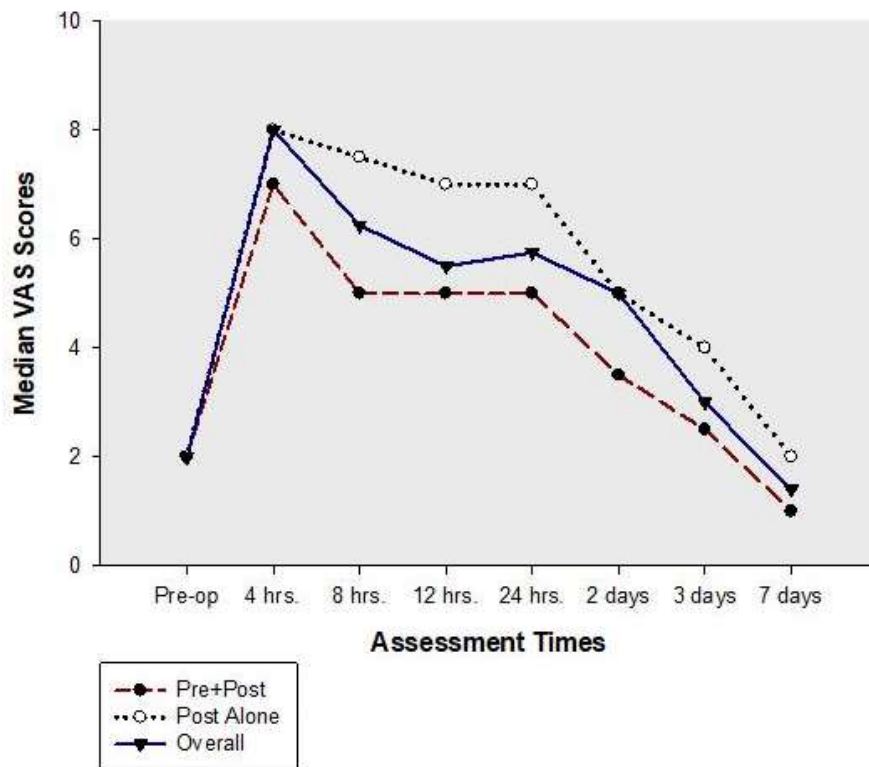


Figure 1: Trend of VAS scores pre-operatively and post-operatively between the study groups.

Table 2: VAS scores between the study groups

Time	Groups		Difference	†Test statistic	P-value
	Pre + Post	Post			
Pre-op	2.0 (IQR:1.0-3.0)	2 (IQR:1.0-4.0)	0 (IQR:-1 - 1)	Z=-0.098	0.922
4 hrs.	7.0 (IQR:5.6-8.0)	8 (IQR:6.0-9.0)	-1 (IQR:-1.75--1.25)	Z=-2.294	0.022*
8 hrs.	5.0 (IQR:4.5-6.3)	7.5 (IQR:6.3-8.0)	-2 (IQR:-2.25--1.75)	Z=-4.330	<0.0001*
12 hrs.	5.0 (IQR:3.8-5.8)	7 (IQR:5.3-8.0)	-2 (IQR:-1.25--2.9)	Z=-4.597	<0.0001*
24 hrs.	5.0 (IQR:3.8-5.8)	7 (IQR:5.5-8.0)	-2 (IQR:-1.2--2.3)	Z=-4.528	<0.0001*
2 days	3.5 (IQR:2.3-5.0)	5 (IQR:4.5-7.0)	-1.5 (IQR:-2.6--2.25)	Z=-3.590	<0.0001*
3 days	2.5 (IQR:1.9-4.0)	4 (IQR:3.0-5.0)	-2 (IQR:-2.4--0.5)	Z=-3.201	0.001*
7 days	1 (IQR:0.0-2.0)	2 (IQR:1.0-4.0)	-1 (IQR:-1--2)	Z=-3.644	<0.0001*
†P value	<0.00001*	<0.00001*	-	-	-

†Mann Whitney U test; *statistically significant, A= Friedman test for intra group comparison of VAS scores in each group (an omnibus test)

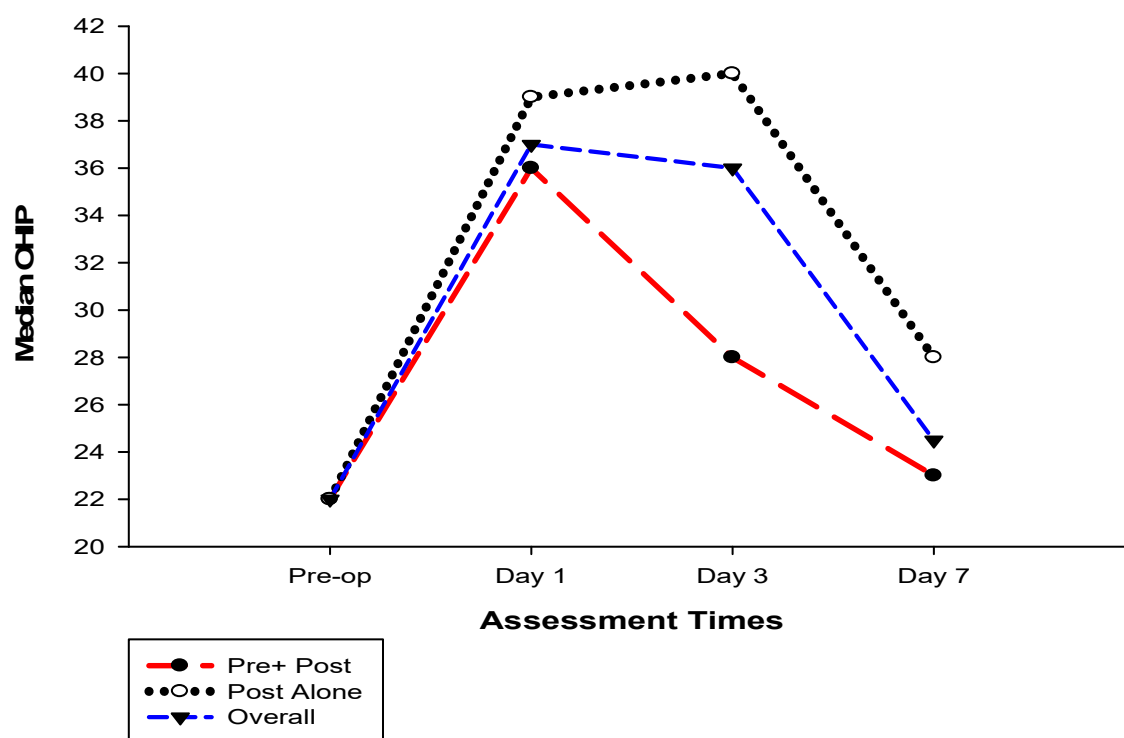


Figure 2: Trend of OHIP scores preoperatively and postoperatively between the study groups.

Table 3: OHIP-14 scores between the study groups

	Groups			†Test statistic	P-value
Time	Pre + Post	Post	Difference		
Pre-op	22.0 (IQR:17.0-26)	22 (IQR:19.0-26.0)	0 (IQR:-2-0.5)	Z= -0.675	0.500
Day 1	36.0 (IQR:26.5-46.0)	39.0 (IQR:28.5-44.5)	-3 (IQR:-2-2.5)	Z= -3.057	0.002*
Day 3	28.0 (IQR:24.0-41.0)	40.0 (IQR:20.0-39.0)	-9 (IQR:-4.5-1)	Z= -2.743	0.006*
Day 7	23.0 (IQR:14.0-31.5)	28.0 (IQR:14.0-31.5)	-6 (IQR:0-0.5)	Z= -1.496	0.135
^P-value	<0.0001*	<0.0001*			

†Mann Whitney U test; *statistically significant. A= Friedman test for intra group comparison of VAS scores in each group (an omnibus test)

DISCUSSION

In a bid to effectively manage post-operative pain, various methods have been explored, one of which is the timed administration of non-steroidal anti-inflammatory drugs (NSAIDs). The mechanism postulated for the effectiveness of NSAIDs is that when they are administered prior to the onset of pain, the drug absorption begins, and therapeutic blood level is achieved. (Bauer et al., 2013) Thus the presence of a cyclooxygenase inhibitor (an NSAID) at the surgical site may limit the production of prostaglandin and prostacyclin. (Bauer et al., 2013) Diclofenac Potassium is an NSAID with analgesic and antipyretic effects, inhibits the production of

prostaglandin, and decreases the synthesis of inflammatory mediators such as bradykinin, substance P, serotonin, histamine thus preventing hyperalgesia and edema. (Sear et al., 2010) It has been reported that pre-operative use of an analgesic agent can be beneficial in greatly reducing post-operative pain. (Isordia et al., 2011) hence the concept of preemptive analgesia.

The first 12-24 hours after surgical extraction of an impacted mandibular third molar are considered to be the worst in terms of perceived pain. (Schwartzmann., 2003, Joshi et al., 2004, Kissin., 2003) and one of the goals of preemptive analgesia is to ameliorate pain sensation during this peak pain

period. (Kissin., 2003) It is believed that non-steroidal anti-inflammatory drugs exhibit their preemptive analgesic effect by inhibiting peripheral and central sensitization resulting in reduced intra-operative nociception and subsequently reducing both acute and chronic post-operative pain. (Joshi et al., 2004, Kissin., 2003, Bauer., 2013, Isordia et al., 2011)

The preemptive analgesia used Diclofenac potassium, is a derivative of phenylacetic acid, inhibits the activity of cyclooxygenase (COX) 1 and 2 and prostaglandin production, which converts arachidonic acid to prostaglandin precursor (Bauer et al., 2013) this action provides anti-inflammatory, antipyretic, and analgesic effects. The maximal plasma drug concentration is obtained within 30 minutes of dosing, and its half-life is around one to two hours (Bauer et al., 2013) It is economical, relatively safe with minimally reported allergies. (Bauer et al., 2013)

The preemptive plus post-operative analgesia group had a significantly better pain control than the postoperative analgesia alone group throughout the post-operative period (4 hours, 12 hours, 24 hours, 48 hours day 3 and day 7. This study denotes that the use of diclofenac potassium as a preemptive analgesic agent in the experimental group had a significant effect, as both groups also received it post-operatively with similar local anesthetic agent and vasoconstrictor. This effect can be attributed to Diclofenac Potassium being easily absorbed in the gastrointestinal tract, having a rapid onset of action that reaches maximum plasma drug concentration 30 minutes after administration, and a mean terminal half-life of 1-2 hours, allowing for a 4- to 6-hour duration of activity. The positive preemptive effect of this study is in consonance with the findings made by Shah et al., 2012; Bauer et al., 2013. Rangaswamy et al., 2016. However, the results from this study contradicts the findings documented by Zachariah et al., 1996, Liporaci., 2012 as they reported that the use of preemptive analgesia had no significant effect in pain control. The reason for the non-agreement may be due to the fact that in this present study, there was extended inhibition of reactive inflammation as a result of administering diclofenac potassium post-operatively in addition to the initial preemptive administration, as preemptive analgesia has been considered to be effective (Kissin., 2003; Joshi et al., 2004; Isordia et al., 2011) in preventing peripheral sensitization which is implicated in potentiating central sensitization.

Furthermore, in this study, patients who received preemptive plus post-operative analgesia had a

significantly better quality of life compared to those who had post-operative analgesia alone. This may be attributed to the better post-operative pain control by the pre-analgesic administration of diclofenac potassium, as studies have shown that effective pain management can lead to a better quality of life in the postoperative period, resulting in faster recovery and a quicker return to daily activities. (Smart et al., 2010, Gan., 2010, Khawaja., 2006, Tuzuner et al., 2011, White et al., 2003) There are just a few studies that have evaluated the impact of administering preemptive analgesia before third molar surgery on the patient's oral health-related quality of life post-operatively. It is challenging to make comparisons because of the paucity of data on this topic. However, the following studies corroborates our findings: a study conducted by Cetira et al., 2022 showed that preemptive photobiomodulation, combined with nimesulide (an NSAID), had a positive impact on the quality of life of patients after third molar surgery. The study utilized the OHIP-14 questionnaire and revealed that preemptive analgesic therapies reduced the peak increase in OHIP-14 scores immediately after surgery significantly in the treatment group. Another study by Ibikunle et al., 2016 evaluated the oral-health-related quality of life following third molar surgery with either oral administration or submucosal injection of prednisolone. Patients who received either form of prednisolone had a significantly better quality of life compared to the control group.

CONCLUSION

This study has shown that compared to post-operative analgesia alone; implementing preemptive plus postoperative analgesia using oral diclofenac potassium provides a more effective approach to reducing the impact of third-molar surgery on oral-health related quality of life and in post-operative pain management.

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Conflicts of interest

There are no conflicts of interest

REFERENCES

Bauer HC, Duarte FL, Horliana AC, Tortamano IP, Perez FE, Simone JL, Jorge WA (2013). Assessment of preemptive analgesia with ibuprofen co administered or not with dexamethasone in third molar surgery: A randomized double-

- blind controlled clinical trial. *Oral Maxillofac Surg*; 17(3):165-171.
- Cetira Filho EL, Silva PGB, Wong DVT et al (2022). Effect of preemptive photobiomodulation associated with nimesulide on the postsurgical outcomes, oxidative stress, and quality of life after third molar surgery: a randomized, split-mouth, controlled clinical trial. *Clin Oral Invest*; 26:6941-6960
- Eklund SA, Pittman JL (2001). Third molar removal patterns in an insured population. *J Am Dent Assoc*; 132(4):469-475
- Gan TJ (2010). Diclofenac: An update on its mechanism of action and safety profile. *Curr Med Res Opin*; 26:1715-1731
- Ibikunle AA, Adeyemo WL (2016) Oral health related quality of life following third molar surgery with or without application of ice pack therapy. *Oral Maxillofac Surg*; 20:239-247
- Isordia-Espinaza MA, Pozos-Guillen AJ, Martinez-Rider R, Herrera-Abarca JE, Perez-Urizar J (2011). Preemptive Analgesic effectiveness of oral Ketorolac plus local tramadol after impacted mandibular third molar surgery. *Med Oral Pathol, Oral Cir Bucal*; 16:776-780.
- Joshi A, Parara E, MacFarlane TV (2004). A double blinded randomized controlled trial of the effect of preoperative Ibuprofen, Diclofenac, Paracetamol with Codeine and placebo tablets for relief of postoperative pain after removal of impacted third molars. *Br J Oral Maxillofac Surg*; 42(4):299-306
- Joshi A, Parara E, MacFarlane TV (2004). A double blinded randomized controlled trial of the effect of preoperative Ibuprofen, Diclofenac, Paracetamol with Codeine and placebo tablets for relief of postoperative pain after removal of impacted third molars. *Br J Oral Maxillofac Surg*; 42(4):299-306.
- Kaneko Y, Ichinohe T, Ishikawa T. Vicious cycle of pain. Clinical practice of the oral and maxillofacial pain. Tokyo. 1997;69-74
- Khawaja AN (2006). Third molar impaction. A review. *Pak Oral Dent J*; 15:97-101.
- Kissin I (2003). Preemptive analgesia. *Anesthesiol*; 93:1138-1143
- Liporaci Junior J (2012). Assessment of preemptive analgesia efficacy in surgical extraction of third molars. *Rev Bras Anesthesiol*; 62:502-510
- Odai ED, Ehizele AO, Enabulele JE (2015). Assessment of pain among a group of Nigerian patients. *BMC Research Notes*; 8:251-252.
- Rangaswamy S, Sheshappa K.N, Srikanthan P (2016). Preemptive Analgesic efficacy of Diclofenac Sodium for surgical Removal of Impacted third molars. *J Health Sci Res*; 7(2);38-41.
- Rice AS, Smith BH, Blyth FM (2016). Pain and the global burden of disease. *Pain*; 157(4):791-796
- Schwartzmann L (2003). Quality of Life Related to Health: Conceptual aspects. *Science Suck* (online); 2:9-21
- Sear JT, Liebur E, Tamme T (2010). The effect of prednisolone on reduction of complaints after impacted third molar removal. *Balt Dent Maxillo Fac Jr*; 12:17-22
- Shah R, Mahajan A, Shah N, Dadhanian A (2012). Preemptive analgesia in third molar impaction surgery. *Natl J Maxillofac Surg*; 3:144-147
- Smart KM, Blake C, Staines A, Doody C (2010). Clinical indicators of nociceptive peripheral neuropathic and central sensitization as mechanisms based classifications of musculoskeletal pain. A Delphi survey of expert clinicians. *Manual Therapy*; 15:80
- Turk DC, Wilson HD, Cahana A (2011). Treatment of non-cancer pain. *Lancet*; 377(9784):2226-2235
- Tuzuner Oncul AM, Yazicioglu D, Alanoglu Z, Demiralp S, Ozturk A, Uçok C (2011). Post-operative analgesia in impacted third molar surgery: the role of preoperative diclofenac sodium, paracetamol and lornoxicam. *Med Pric Pract*; 20(5):470-476.
- White RP Jr, Shugars DA, Shafer DM, Laskin DM, Buckley MJ, Philips C et al (2003). Recovery after third molar surgery: Clinical and health related quality of life outcomes. *J Oral Maxillofac Surg*; 61:535-544.
- Woolf CJ, Chong MS (1993). Preemptive analgesia treating post-operative pain by preventing the establishment of central sensitization *Anesth Analg*; 77:362-379.
- Woolf CJ (2004). Pain: Moving from symptom control towards mechanism specific pharmacologic management. *Ann Intern Med*; 140:441-451.
- Zacharias M, Hunter KM, Baker AB (1996). Effectiveness of preoperative analgesics on postoperative dental pain: a study. *Anesth Prog*; 43(3):92-96.
- Zhong B (2009). How to calculate sample size in randomized controlled trial. *J Thorac Dis*; 1:51-54.