Effects of Prednisolone and Kotase on Post-Disimpaction Sequelae of Mandibular Third Molars In General Hospital, Lagos: A Randomized Controlled Trial

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Key words*:* Third molar disimpaction, postoperative sequelae, prednisolone, Kotase.

ABSTRACT

Background:

The sequelae of surgical disimpaction of mandibular third molars negatively impact patients' quality of life in the immediate post-operative period. Some clinicians have shown reluctance to use steroids in oral surgery, though they provide excellent control of the postoperative inflammatory triad following third molar disimpaction. Kotase, a fixed-dose combination of two enzymes (Bromelain and Trypsin), has also been effective in reducing postoperative inflammation.

Methods:

We conducted a randomized controlled trial at the General Hospital, Lagos Island. Eighty-four participants were randomized into two treatment groups: Prednisolone and Kotase. Pain was assessed using a visual analogue scale (VAS). Facial swelling was measured using linear distances from the tragus to pogonion, tragus to the angle of the mouth, and gonial angle to the lateral canthus of the eye. Trismus was measured using a pair of dividers. Data were analyzed using SPSS version 20. Chi-square and Student's t-tests were used for comparisons, with $p < 0.05$ considered significant.

Results:

The socio-demographic and clinical characteristics of participants were similar in both groups. The highest intensity of sequelae occurred on the first postoperative day in both groups. Pain was not statistically significant ($t = 0.067$, $p = 0.946$). Facial volumetric variation in the tragus–oral commissure plane ($t = 0.369$, $p = 0.713$), tragus–pogonion plane ($t = 0.959$, $p = 0.341$), and outer canthus–gonial plane ($t = 1.523$, $p = 0.132$) showed no significant differences. Trismus was also not statistically significant ($t = 0.890$, $p = 0.376$).

Conclusion :

Kotase was observed to be as effective as prednisolone in mitigating postoperative inflammatory sequelae following mandibular third molar disimpaction.

INTRODUCTION

Surgical disimpaction of impacted mandibular third molars is a frequently performed intraoral procedure under local anesthesia, contributing to the increased prevalence of dentoalveolar surgeries in maxillofacial and general dental clinics.[1-4] This procedure is accompanied by postoperative sequelae such as pain, trismus, and edema, which negatively impact patients' quality of life in the first 48–72 hours postoperatively.[5-8] Efforts to control these sequelae include non-pharmacologic techniques (e.g., cryotherapy, drains, surgical closure techniques) and pharmacologic agents such as corticosteroids, non-steroidal anti-inflammatory drugs (NSAIDs), and systemic enzymes (Trypsin and Bromelain).[6-9]

Prednisolone, a potent intermediate-acting synthetic cortisol analogue, suppresses inflammation.[10] However, it affects water and electrolyte balance, glucose metabolism, and immune competence.[15] Corticosteroids can elevate blood glucose, exacerbating morbidity in diabetic patients, and their sodium-retaining effects may complicate hypertension.[5] These concerns have led to reluctance in their use for postoperative sequelae, necessitating alternative pharmacologic agents with fewer adverse effects.

Kotase, a fixed-dose combination of Bromelain and Trypsin, has demonstrated efficacy in reducing postoperative inflammation. [11 - 12] The enzymes in Kotase complement each other, providing more complete inflammation inhibition and faster resolution of postoperative sequelae. [12]

Objective of the Clinical Trial:

This trial aimed to compare the anti-inflammatory effects of Prednisolone and Kotase on post-disimpaction sequelae of mandibular third molars.

Hypotheses :

H_0: There is no significant difference in the anti-inflammatory effects of Prednisolone and Kotase.

H_1: There is a significant difference in the anti-inflammatory effects of Prednisolone and Kotase.

METHODS

Ethics: Ethical approval was obtained from the Health and Research Ethics Committee of Lagos State University Teaching Hospital. Informed consent was obtained from all participants. The study was conducted and reported in accordance with the Consolidated Standards of Reporting Trials (CONSORT) guidelines and in adherence to the Declaration of Helsinki.

Trial Design: A randomized double-blind controlled trial conducted at the Department of Oral and Maxillofacial Surgery, General Hospital Lagos Island.

Participants

Inclusion Criteria

- Systemically healthy participants aged ≥18 years.
- Participants requiring mandibular third molar surgical disimpaction.

Exclusion Criteria

- Patients aged <18 years.
- History of systemic diseases (hypertension, diabetes, hepatitis, asthma, heart disease).
- Pregnant women.
- Subjects on anticoagulants, steroids, or NSAIDs 24 hours prior to surgery.

Recruitment Methods:

Consenting participants were consecutively recruited and randomized via balloting into Prednisolone and Kotase groups.

Baseline Characteristics:

Recorded preoperatively.

Sample Size Calculation:

The sample size was determined using the method described by Kirby et al.[13] This yielded a total of 84 participants.

Interventions:

Kotase Group: Received two tablets (each containing 40 mg Bromelain and 1 mg Trypsin) 30 minutes preoperatively (Day 0), then six-hourly for 3 days.

Prednisolone Group: Received 20 mg oral Prednisolone 30 minutes preoperatively (Day 0), followed by 10 mg daily for the next 2 days. All participants received a stat dose of 550 mg Naproxen Sodium for immediate postoperative pain. Local anesthesia was administered using 2% lidocaine with 1:100,000 adrenaline via inferior alveolar, lingual, and long buccal nerve blocks.

Outcomes and Measurements:

Pain: Assessed using VAS (0–10 scale: 0 = no pain, 0.5–2.5 = mild, 2.5–6.5 = moderate, 6.5–9.5 = severe, >9.5 = unbearable).

Facial Swelling: Measured using three linear planes adapted from previous studies.[8,9,14]

1. Tragus–pogonion (AD).
2. Tragus–oral commissure (AC).
3. Outer canthus–gonial angle (BE).

Trismus: Measured as maximum interincisal distance using dividers.

All measurements were taken preoperatively (Day 0) and postoperatively (Days 1, 3, and 7).

Randomization:

Participants were randomized via a balloting system to ensure unbiased allocation into the Prednisolone and Kotase groups.

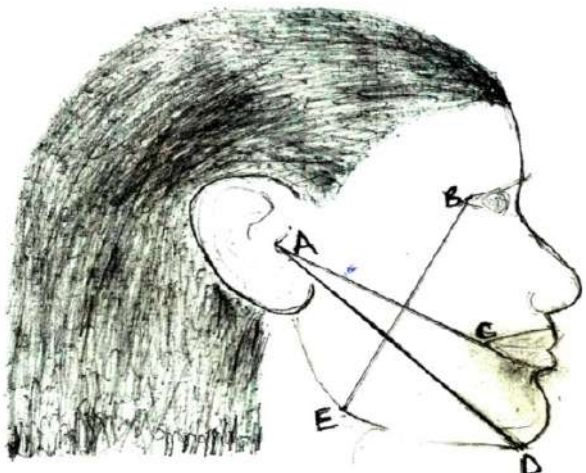


Figure 1: Showing linear planes measurement of facial volumetric changes.

Allocation Concealment and Blinding:

To maintain blinding, a pharmacist prepared and dispensed the medications, ensuring that neither the principal researcher nor the participants knew the group assignments (double-blind design).

Statistical Analysis:

An intention-to-treat (ITT) approach was adopted for data analysis, as the study focused on effectiveness rather than efficacy. There were no dropouts or protocol deviations, ensuring full adherence to the protocol. Data were analyzed using SPSS version 20. Descriptive statistics, including percentages, means, and standard deviations, were computed. The Kolmogorov–Smirnov test was used to assess the normality of distribution for the outcome variables (pain, trismus, and swelling). Independent Student's t-test was used to compare means between the two treatment groups. Paired t-test was used to evaluate preoperative versus postoperative changes within each group. Chi-square test was applied for categorical variables, such as pain severity categories. A p-value of < 0.05 was considered statistically significant.

CONSORT Flowchart:

Enrollment

Assessed for eligibility (n = 100)
Excluded (n = 16)
- Not meeting inclusion criteria (n = 0)
- Declined to participate (n = 16)
- Other reasons (n = 0)

Randomized (n = 84)

Allocation

Allocated to intervention A (n = 42)
- Received allocated intervention (n = 42)
- Did not receive allocated intervention (reasons) (n = 0)

Allocated to intervention B (n = 42)
- Received allocated intervention (n = 42)
- Did not receive allocated intervention (reasons) (n = 0)

Follow-Up

Lost to follow-up in group A (reasons) (n = 0)
Discontinued intervention in group A (reasons) (n = 0)
Lost to follow-up in group B (reasons) (n = 0)
Discontinued intervention in group B (reasons) (n = 0)

Analysis

Analyzed in group A (n = 42)
- Excluded from analysis (reasons) (n = 0)

Analyzed in group B (n = 42)
- Excluded from analysis (reasons) (n = 0)

RESULTS

Socio-demographic and Clinical Characteristics

The study enrolled 84 participants, equally randomized into Prednisolone and Kotase groups. The mean ages were comparable between the groups: 30.6 ± 7.6 years (Prednisolone) versus 31.7 ± 8.2 years (Kotase). Both groups demonstrated similar gender distributions, with male-to-female ratios of 1:1.5 (Prednisolone) and 1:1.6 (Kotase) (p = 0.823). Educational attainment was high among participants, with 71.4% in the Prednisolone group and 66.7% in the Kotase group having completed tertiary education. The primary indication for surgical disimpaction was dental caries, accounting for 31.0% of cases in the Prednisolone group and 40.5% in the Kotase group. Most extractions were performed on the left mandibular side: 59.5% (Prednisolone) and 69.0% (Kotase) (p = 0.362) (Table 1).

Table 1: *Socio demographic and clinical characteristic of respondents*

Variable	Prednisolone n = 42 (%)	Kotase n =42 (%)	χ2	p
Age group (years)				
<25	10 (23.8)	8 (19.0)	0.610	0.962
25 – 29	12 (28.6)	11(26.2)		
30 – 34	8 (19.0)	9 (21.4)		
35 – 39	6 (14.3)	6 (14.3)		
≥ 40	6 (14.3)	8 (19.0)		
Mean (SD)	30.6(7.6)	31.7(8.2)		
Sex				
Male	17 (40.5)	16 (38.1)	0.050	0.823
Female	25 (59.5)	26 (61.9)		
Educational status				
Primary	4 (9.5)	10 (23.8)	3.974	0.137
Secondary	8 (19.0)	4 (9.5)		
Tertiary	30(71.4)	28 (66.7)		
Reason for exodontia				
Dental caries	13 (31.0)	17 (40.5)	5.289	0.382
Pericoronitis	12 (28.6)	14 (33.3)		
Facial Pain	12 (28.6)	7 (16.7)		
Periodontal reason	5 (11.9)	2 (4.8)		
Orthodontic reason	0 (0.0)	1 (2.4)		
Tumor/ Cyst	0 (0.0)	1(2.4)		
Side of Mandible				
Right	17 940.5)	13 (31.0)	0.830	0.362
Left	25 (59.5)	29 (69.0)		
Type of impaction				
Mesioangular	16 (38.1)	16 (38.1)	0.000	1.000
Distoangular	9 (21.4)	9 (21.4)		
Vertical	9 (21.4)	9 (21.4)		
Horizontal	8 (19.0)	8 (19.0)		

VAS scores at different treatment milestones

Pain Outcomes: Both treatment groups demonstrated similar pain progression patterns, with intensity increasing from baseline to peak levels on postoperative day 1 (1.77 in the Prednisolone group and 1.74 in the Kotase group) (Figure 2).

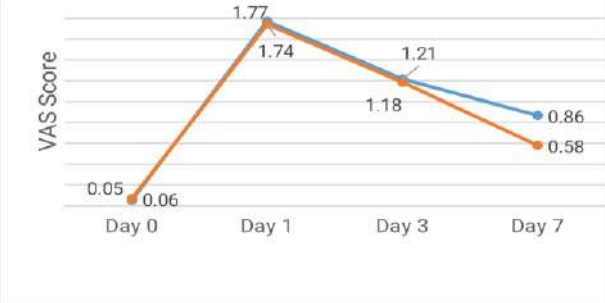


Figure 2: The mean of VAS score in Prednisolone and Kotase groups at different treatment milestones.

Tragus-Oral commissure length of participants:

Facial volumetric variation along the tragus-oral commissure plane peaked on postoperative day 1 in both groups (Figure 3).

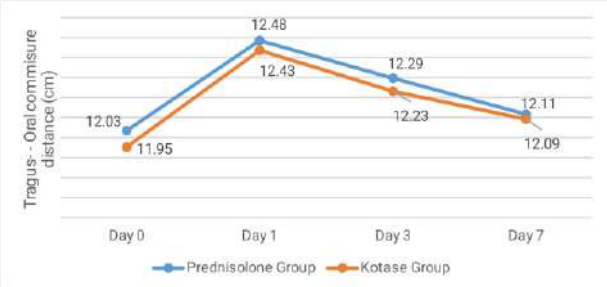


Figure 3: The mean Tragus-Oral commissure length (cm) in Prednisolone and Kotase groups at different treatment milestones.

Tragus-Pogonial length of participants: The facial volumetric change along the tragus-pogonion plane crescendoed for both groups on postoperative day 1(Figure 4)

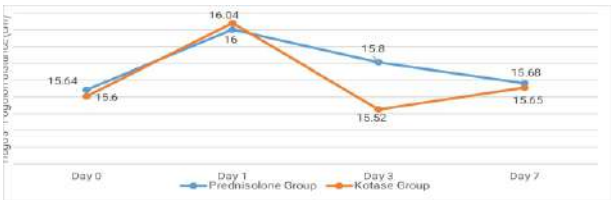
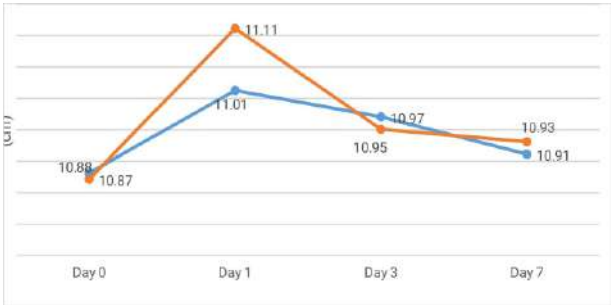


Figure 4: Mean Tragus-Pogonial length (cm) in Prednisolone and Kotase groups at different treatment milestones.

Facial volumetric change along the outer canthus-gonial plane

The facial volumetric change along the outer canthus–gonial plane peaked on postoperative day 1 in both treatment groups (Figure 5 – mean outer canthus–gonial length [cm] by group and time-point).



Interincisal distance measures (mm)

Participants in this study experienced varying degrees of trismus, measured by interincisal distance, across the postoperative assessment days. The interincisal distance decreased from the preoperative baseline (Day 0), reaching its lowest point on postoperative Day 1, and progressively improved from Day 3 to Day 7 in both groups. No statistically significant differences in trismus were observed between the Prednisolone and Kotase groups on postoperative Days 1, 3, and 7 (Table 2).

DISCUSSION

Findings: Surgical extractions of impacted mandibular third molars result in a detrimental clinical triad of pain, swelling, and trismus, largely due to the inflammatory response triggered by the procedure. The intensity of these sequelae peaks within the first 48–72 hours postoperatively. [15,16] These complications significantly impair patients' quality of life during the immediate recovery period.[2] Researchers have explored various techniques to minimize these effects, ranging from non-pharmacological interventions (cryotherapy, surgical closure techniques, drains, transcutaneous electric nerve stimulation) to pharmacological agents (corticosteroids, antibiotics, non-steroidal anti-inflammatory drugs, antibacterial mouth rinses, and topical gels).[6] Corticosteroids, administered either parenterally or orally (e.g., dexamethasone, betamethasone, methylprednisolone, and prednisolone), have demonstrated substantial efficacy in reducing postoperative sequelae following mandibular third molar disimpaction.[12,15]

The use of proteolytic enzymes in oral surgery to mitigate postoperative complications is gaining attention due to their therapeutic efficacy and safety profile.[17] These

Table 2: *Mean difference in Interincisal distance (mm) between the Prednisolone and Kotase groups.*

Mean difference of Interincisal distance	n	Mean (SD)	t	p
Day 1 and Day 0				
Prednisolone group	42	14.74(9.00)	0.890	0.376
Kotase group	42	16.56(9.72)		
Day 3 and Day 0				
Prednisolone group	42	12.39(9.33)	1.169	0.246
Kotase group	42	14.72(8.92)		
Day 7 and Day 0				
Prednisolone group	42	8.79(9.81)	1.226	0.224
Kotase group	42	11.29(8.91)		

Keys: n=sample size in each group; p=p-value; t= student 't' test; mean (SD) = mean (standard deviation)

enzymes are derived from bacterial, fungal, plant, and animal sources. Serratiopeptidase, for instance, is extracted from the bacterium Serratia species E-15.[17] Chymotrypsin and trypsin are obtained from bovine pancreas.[1] Bromelain, another proteolytic enzyme, is derived from pineapple stems (Ananas comosus).[19] Kotase, a fixed-dose enzyme combination, contains 40 mg bromelain and 1 mg trypsin.[18] Kumar highlighted the therapeutic benefits of serratiopeptidase in his review.[17]

Socio-demographics were assessed in this study. The largest proportion of participants (25–29 years) was in their third decade of life, accounting for 28.6% and 26.2% in the prednisolone and Kotase groups, respectively. This aligns with findings by Odusanya et al.,[20] Otuyemi et al.,[21] Almpani et al.,[22] and Edetanlen et al.,[23] who reported the highest incidence of mandibular third molar impactions in individuals aged 20–29 years in Ile-Ife, northern Nigeria, and Benin City. The male-to-female ratio in this study was 1:1.5, suggesting a higher prevalence of third molar impactions requiring disimpaction in females, consistent with Edetanlen et al.[23] However, other studies have reported conflicting findings regarding sex distribution.[24,25]

Most participants in this study had tertiary education (71.4% in the prednisolone group and 66.7% in the Kotase group), with impaction peaking between ages 25–29. This demographic trend may reflect dietary shifts from fibrous to processed foods, common among tertiary students, which may contribute to inadequate mandibular growth and subsequent impaction.[25]

The primary reason for disimpaction in this study was dental caries (31% in the prednisolone group and 40.5% in the Kotase group). Mesioangular impaction was the most common type observed, likely due to food accumulation in the undercut between the impacted third molar and the second molar, leading to caries formation.[27,28] This contrasts with Gbotolorun et al.,[29] who identified pericoronitis as the leading indication for third molar disimpaction.

Postoperative pain peaked within the first three days, with visual analogue scale (VAS) scores rising to 1.77 and 1.74 on day 1 for prednisolone and Kotase, respectively, before declining to 0.86 and 0.56 by day 7. Although Kotase demonstrated slightly better analgesic efficacy, the difference was not statistically significant. This finding aligns with studies by Ibikunle et al.[9] and Murugesan et al.,[15] suggesting that Kotase is as effective as prednisolone in managing postoperative pain. Limited studies have evaluated Kotase for third molar disimpaction sequelae, but research from Egypt,[30] Asia,[31,35] and Europe[36,37] supports the efficacy of enzymes in pain reduction. Inchigolo et al.[36] and Majid et al.[11] reported bromelain's effectiveness, while Murugesan et al.[15] found serratiopeptidase inferior to dexamethasone. Conversely, de la Barrera et al.[37] observed no significant difference between bromelain and placebo, suggesting dose-dependent effects. Al-Sandook et al.[35] noted that Orthal Forte (trypsin-chymotrypsin combination) outperformed placebo in pain reduction. Kotase may mitigate pain by inhibiting cytokine release (e.g., bradykinin) and degrading necrotic tissue.[17]

Postoperative swelling, a hallmark of inflammation, peaks within 48–72 hours and subsides by day 7[38,39] Facial volumetric changes were assessed using three linear planes (tragus-oral commissure, tragus-pogonion, and outer canthus-gonial), adapted from Bello et al.,[8] Gaata et al.,[14] and Ibikunle et al.[9] No significant difference was observed between prednisolone and Kotase in any plane, though both groups showed reduced swelling over time. These findings are consistent with studies in Nigeria,[8] Asia,[40] and Europe.[41,42]

Kotase's anti-inflammatory mechanism may involve hydrolysis of histamine, serotonin, and bradykinin, improving microcirculation and reducing edema.[17] While some studies[37] reported bromelain's ineffectiveness compared to placebo, others [11,30] highlighted serratiopeptidase and bromelain's efficacy in swelling reduction.

Trismus, resulting from postoperative pain and edema, peaked within the first three days.[15,17] Both groups exhibited limited mouth opening, with no significant difference between prednisolone and Kotase, consistent with Murugesan et al.[15] However, Chappi et al.[32] and Basheer et al.[33] reported superior trismus relief with serratiopeptidase compared to methylprednisolone and diclofenac, respectively. Kotase's efficacy may stem from its combined anti-inflammatory and microcirculatory effects on masticatory muscles.

ADVERSE EFFECTS

No adverse effects were recorded in either group.

Implications

- Kotase is as effective as prednisolone in reducing postoperative pain.
- Kotase demonstrates comparable efficacy to prednisolone in minimizing postoperative edema.
- Kotase is equally effective in alleviating postoperative trismus.

Trade-Offs (Limitations)

Despite being a randomized controlled trial, this study has limitations viz;

- Single-center design may limit generalizability.
- Subjective outcome measures may be influenced by individual variability.
- Lack of long-term follow-up limits assessment of prolonged effects.

Take-Home (Conclusion)

This study found a higher prevalence of mandibular third molar impaction among educated urban dwellers in their third decade of life. Kotase, combining bromelain and trypsin, proved as effective as prednisolone in mitigating postoperative sequelae.

Expectations For Future Research:

Future studies should explore long-term outcomes and multicenter validation.

Recommendation:

We recommend multicenter trials with larger samples and extended follow-up to validate these findings.

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Conflicts of Interest:

The authors declare no conflicts of interest.

REFERENCES

1. Tiigimee-Saar J, Leibur E, Tamme T. The Effects of Prednisolone on reduction of complaints after impacted third molar removal. Stomatology, Baltic Dental and Maxillofacial Journal 2010; 12:17-22.
2. Bamgbose BO, Akinwande JA, Adeyemo WL et al. Effects of co-administered Dexamethasone and Diclofenac Potassium on pain, swelling and trismus following third molar surgery. Head and Face Medicine 2005; 1:11.
3. Santosh P. Impacted Mandibular Third Molars: Review of Literature and Proposal of a Combined Clinical and Radiological Classification. Ann Med Health Sci Res; 2015; 5(4): 229-234.
4. Akinbami BO, Ifolama LI. Pattern of Lower Third Impaction and Outcomes of Treatment in a New Tertiary Center- A 5 Year Survey. East and Central African Journal of Surgery 2011; 16(3): 80-84.
5. Bamgbose BO, Akinwande JA, Adeyemo WL et al. Prospective, Randomised, Open-label, Pilot Clinical Trial comparing the effects of Dexamethasone co-administered with Diclofenac Potassium or Acetaminophen and Diclofenac Potassium monotherapy after third molar extraction in adults. Curr Ther Res 2006; 67 :229-240
6. Osunde OD, Adebola RA, Omeje UK. Management of inflammatory complications in Third Molar Surgery: A literature review. African Health sciences 2011; 11(3): 530-537.
7. McGrath C, Comfort MB, Lo ECM, Luo Y. Changes in Life Quality following third Molar Surgery- the immediate Post-operative Period. BDJ 2003; 194:265 -268.
8. Bello SA, Adeyemo WL, Bambgose BO, Obi EV, Adeyinka AA. Effect of age, impaction types and operative time on inflammatory tissue reactions following lower third molar surgery. Head and Face medicine 2011,7:8
9. Ibikunle AA, Adeyemo WL, Ladeinde AL. Effect of Submucosal or Oral administration of Prednisolone on Post-operative sequelae following surgical extraction of impacted mandibular third molar: A randomised control study. Niger Med J 2016; 57(5): 272- 279.
10. Data sheet Prednisone. Retrieved from www.medsafe.govt.nz/profs/datasheet/p/prednisonetabs.pdfon 10/03/2016.

11. Majid OW, Almashhadani BA. Perioperative Bromelain reduces pain and swelling and improves quality of life measures after mandibular third molar surgery. A randomized, double blind, placebo-controlled clinical trial. Journal of Oral and maxillofacial Surgery. 2014; 72(6):1043-1048.

12. Ezeome ER, Aghaji AC. A Prospective Randomised trial of Kotase (Bromelain and Trypsin) in the management of post-operative abdominal wounds at the University of Nigeria Teaching Hospital, Enugu, Nigeria. Journal of College of Medicine 2005; 10(2): 61-66.

13. Kirby A, Gebski V, Keech AC. Determining the sample size in a Clinical Trial. Med J Aust. 2002; 177(5): 256-257.

14. Gaata IS, Nemat AH. Evaluation of the effectiveness of two methods using methylprednisolone on post-operative sequelae following lower third molar Surgery. Kufa Med. Journal 2009; 12(2): 257-266.

15. Murugesan K, Sreekumar K, Sabapathy B. Comparison of the Roles of Serratiopeptidase and Dexamethasone in the Control of Inflammation and Trismus following Impacted Third Molar Surgery. Indian J Dent. Res 2012; 23(6): 709-713.

16. Ata-Ali J, Ata-Ali F, Peñarrocha-Oltra D et al. Corticosteroids use in Controlling Pain, Swelling and Trismus after lower Third Molar Surgery. J. Clin Exp Dent. 2011; 3(5): e469-75.127.

17. Kumar S. The emerging role of serratiopeptidase in oral surgery: Literature update. Asian J Pharm Clin Res 2018; 11(3): 19- 23.

18. Kotase Retrieved on 16th March, 2016 from rxnigeria.com /items? task=view &id=1125.

19. Tochi B, Wang Z, Xu S et al. Therapeutic Application of Pineapple Protease [Bromelain]: A Review. Pakistan Journal of Nutrition 2008; 7(4): 513- 520.

20. Odusanya SA, Abayomi IO. Third Molar Eruption among Rural Nigerians. Oral Surg Oral Med Oral Pathol 1991; 71: 151-4.

21. Otuyemi OD, Ugboko VI, Ndukwe KC, Adekoya-Sofowora CA. Eruption Times of the Third Molars in Young Rural Nigerians. Int Dent J 2011; 47(5).

22. Almpani K, Kolokitha O. Role of Third Molars in Orthodontics. World Journal of Clinical Cases. 2015; 3(2): 132-140.

23. Edetanlen BE, Igbinosa LO. Pattern of presentation of impacted third molar in a Nigerian tertiary health facility: a prospective study. Nig J Med Dent Educ; 2024, 6(2):45-50.

24. Tsebedze VN. Prevalence of Impacted Mandibular Third Molar Teeth at Medunsa Oral Health Center. Thesis Submitted and Accepted for Award of Masters in Dental Science in the Department of Maxillofacial and Oral Surgery, University of Limpopo. 2012.

25. Wahid A, Mian FI, Bokhari SAH et al. Prevalence of Impacted Molars. JUMDC 2013; 4(2): 22- 31.

26. Olasoji HO, Odusanya SA. Comparative Study of Mandibiular Third Molar Impaction in Rural and Urban Areas of South-western Nigeria. Odonto-Stomatologie Tropical, 2000; pp: 25-28.

27. Bataineh AB, Albashaireh ZS, Hazzaam AM. The Surgical removal of mandibular third molars: a story in decision making. Quitessence int. 2002; 33(8): 613-617.

28. Abdulai AE, Nuamah IK, Sackeyfio J et al. Indications for Surgical Extraction of Third Molars: a Hospital-Based Study in Accra, Ghana. Int J Med Biomed Res 2014; 3(3): 155-160.

29. Gbotolorun OM, Olojede AC, Arotiba GT et al. Impacted Mandibular Third Molars: Presentation and Post-Operative Complications at the Lagos University Teaching Hospital. Nig Q J Hosp Med 2007; 17(1): 26-9.

30. Mustafa AAS. Effect of Serrapeptase on Post Surgical Sequelae after Surgical Removal of Impacted Wisdom teeth. Thesis submitted and accepted for the award of Bachelor of Dental Surgery by University of Cairo, 2012.

31. Al-khateeb TH, Nusair. Effect of Proteolytic Enzyme Serrapeptase on Swelling, Pain and Trismus after Surgical Extraction of Mandibular Third Molar. Int J Oral Maxillofac Surg; 2008; 37(2): 264-268.

32. Chappi DM, Suresh KV, Patil MR et al. Comparison of Clinical Efficacy of Methylprednisolone and Serratiopeptidase. J Clin Exp Dent 2015; 7(2): e 197-e202.

33. Basheer SA, Mohan GM, Vijayan S. Efficacy of Medication on postoperative pain, swelling &trismus after impaction of mandibular third molar. International Journal of Applied Dental Sciences 2017; 3(3): 96- 99.

34. Kannan R, Kabitha R. A Comparative study of the anti-inflammatory properties of Bromelain/Serratiopeptidase as add-on therapy to conventional treatment following impacted third molar surgery. World Journal Pharmaceutical Research. 2015; 4(8): 2595- 2607.

35. Al-Sandook TA, Tawfik NOM, Qassim DA. Clinical evaluation of the efficacy of Orthal-forte (proteolytic enzyme, Trypsin and Chymotrypsin) on postoperative sequel following the removal of lower impacted third molar. International Journal of Enhanced Research in Science Technology & Engineering 2014; 3(2): 169-173.

36. Inchigolo F, Tatullo M, Marrera M et al. Clinical trial with Bromelain in third molar exodontias. Eur Rev Med Pharmacol Sci. 2010; 14(9): 771-4.

37. de la Barreta-Núñez MC, Yañez-Vico RM, Batista-CruzadoA et al. Prospective double-blind Clinical trial evaluating the effectiveness of Bromelain in the third molar extraction postoperative period. Med Oral Pathol Cir Buccal. 2014; 19(2): e157- 62.

38. White RP, Shugar DA, Shafer DM et al. Recovery After Third Molar Surgery: Clinical and Health-

related Quality of Life Outcomes. J Oral Maxillofac Surg 2003; 61: 535-544.

39. Chaushu S, Becker A, Zelter R et al. Patients' Perceptions of recovery after Surgical exposure of impacted maxillary teeth treated with an open-eruption Surgical-Orthodontic technique. European Journal of Orthodontics; 2004, 26(6): 591-596.

40. Kang SA, Choi YS, Byun IY, Kim Mk. Effect of Pre-operative Prednisolone on Clinical Post-operative symptoms after Surgical Extraction of Mandibular Third Molars. Aust. Dent. J 2010; 55(4): 462-7.

41. Sortino F, Cicciù M. Strategies used to inhibit post-operative swelling following removal of impacted third molar. Dent Res J 2011; 8(4): 162-171.

42. Milles M, Desjardins J. Reduction of Post-operative facial swelling by low dose methylprednisolone. J Oral and Maxillofac Surg 1993; 51(9): 987-991.