

A Comparative Study of Serratiopeptidase & Dexamethasone in Control of Inflammation & Trismus Following Impacted Third Molar – A Double Blind Study

Dr. Nitin Kumar¹, Dr. Nidhi Nagar², Dr. Himanshu Bhutiani³,
Dr. G. Ratna Velugu⁴

¹(BDS, MDS Sr. Lecturer, Department of Oral & Maxillofacial Surgery, Inderprastha Dental College, Ghaziabad (U.P.), India)

²(BDS, MDS Sr. Lecturer, Department of Conservative Dentistry & Endodontics, School of Dental Sciences, Sharda University, Greater Noida (U.P.), India)

³(BDS, MDS Reader, Department of Oral & Maxillofacial Surgery, I.T.S Dental College & Research Centre, Greater Noida, (U.P.), India)

⁴(BDS, MDS Reader, Department of Conservative Dentistry & Endodontics, School of Dental Sciences, Sharda University, Greater Noida (U.P.), India)

Corresponding Author: Dr. Nitin Kumar

Abstract: Health professionals still prefer to give various drug regimens for patients undergoing surgical removal of mandibular third molar to counteract swelling and pain. The study result help in deciding treatment regimen to be followed after third molar surgeries and suggests better patient comfort level is achieved with use of dexamethasone compared to serratiopeptidase for patients undergoing third molar surgeries. In this study serratiopeptidase and dexamethasone had equal and minimal effect on trismus. Serratiopeptidase can be used as an alternative drug to control inflammation in cases where corticosteroids are contraindicated.

Keywords: Swelling, Pain, Trismus, Serratiopeptidase, Dexamethasone

Date of Submission: 18-04-2019

Date of acceptance: 04-05-2019

I. Introduction

Surgical removal of impacted third molars is a common practice for oral and maxillofacial surgeons and usually involves surgical trauma in a highly vascularised area, predominantly constituted by loose connective tissue, leading to expected inflammatory complications, like pain and swelling.⁽¹⁾

Surgical edema is expected sequel of removal of impacted lower wisdom tooth. Swelling usually reaches at its maximum on 2nd & 3rd postoperatively day and should start reducing by 4th day. Swelling completely resolves by 7th to 9th day. The use of intermittent ice pack may limit postoperative swelling and improve patient comfort. The preoperative use of systemic corticosteroids has been advocated to reduce immediate swelling, but debate still exists as to their efficacy.

Trismus is often the result of surgical trauma and is secondary to masticatory muscle irritation and fascial inflammation. As with surgical edema, there is evidence to support the preoperative use of steroids in reducing postoperative trismus.⁽²⁾

Pharmacologic strategies for minimizing the clinical manifestations of surgical injury are therefore, logically directed at blocking the formation or inhibiting the effects of mediators of acute inflammation. Corticosteroids are routinely employed to control the sequelae of inflammation in third molar surgeries.⁽³⁾ The effectiveness of glucocorticoids as anti-inflammatory agents were first reported by Hench and Kendall in 1949, using cortisone to treat rheumatoid arthritis.⁽³⁻⁵⁾

The amount of endogenous cortisol from the adrenal cortex does not appear to alter the process of inflammation significantly; on the other hand, large doses of exogenous cortisol or synthetic steroids appear to block all stages. Steroids prevent diapedesis, the initial leakage of fluids from the capillaries, and stabilize the membranes of the cellular lysosomes which hold large quantities of hydrolytic enzymes. There is also a decrease in the formation of bradykinin, a powerful vasodilating substance.⁽⁶⁾

A prospective study was conducted by Al Khateeb and Nusair on the use of serratiopeptidase for reduction of postoperative swelling, pain, and trismus after third molar surgery.⁽⁷⁾ They concluded that significant reduction in swelling could be achieved with the use of serratiopeptidase. The proteolytic enzyme serratiopeptidase is believed to induce degradation of insoluble protein products like fibrin, biofilm and

inflammatory mediators. It reduces the viscosity, facilitates drainage and alleviates pain by inhibiting the release of bradykinin (a pain inducing amine).⁽⁸⁾

II. Methods

This study was carried out on 100 patients on an out-patient basis in the Department of Oral and Maxillofacial Surgery I.T.S Dental College, Hospital and Research Centre, Greater Noida (Uttar Pradesh). Patients were divided randomly into two groups, irrespective of age and sex - each group consisting of 50 patients. The patients were enrolled for the study consecutively as and when they reported to the hospital. Selected patients were randomly allocated to either the dexamethasone group or the serratiopeptidase group, irrespective of age and sex.

2.1 INCLUSION CRITERIA:

- Patients requiring surgical extraction of mandibular third molar.
- Patients with recurrent pericoronitis
- Patients willing to participate in the study.

2.2 EXCLUSION CRITERIA:

- Patients not willing to participate in the study.
- Extra oral swelling with cellulitis in the area of surgery
- Immunocompromised patients such as uncontrolled diabetes mellitus, pregnancy, AIDS, radiation therapy, chronic renal failure, alcoholism etc.

All the patients signed a written informed consent before participation in the study. Material and method were reviewed and approved by ethical committee. All patients were given full information regarding the purpose of the study and effects of the drugs used. After obtaining consent for participation and completion of preoperative investigations, the patients were taken up for surgery under local anesthesia.

In one group, patients were given 1 mg of dexamethasone, 8th hourly for 3 days postoperatively and, in the other group, patients were given serratiopeptidase 10 mg, 8th hourly for 3 days postoperatively.

In both groups, the patients were recalled on 1st, 3rd, 7th day post operatively to assess the wound healing with clinical variables pain, swelling and maximum mouth opening.

Patient was recalled on 1st, 3rd, 7th post operative day for swelling assessment. Preoperatively and postoperatively swelling was measured at three positions and 5 points were marked According To method of Amin and laskin which uses tape to measure distance at the following reference points, Point **A** from the outer canthus to gonion (angle of mandible). Point **B** from tragus to corner of mouth (oral commissure). Point **C** from tragus to midpoint on chin. For recording the amount of mouth opening, the interincisal distance (distance between the incisal edges of the central incisors) was measured using scale.⁽⁹⁾

Under routine aseptic precautions, local anesthesia was secured with 2% lignocaine hydrochloride with 1: 200000 adrenaline, using the conventional inferior alveolar nerve block, lingual nerve block, long buccal nerve block. A standard Terrance-Ward incision was placed. A mucoperiosteal flap was raised exposing the underlying bone. Bone guttering was carried out buccally and on the distal aspect of the impacted tooth using a round bur. Odontectomy was performed whenever indicated to facilitate tooth removal. The tooth was removed from the socket with the help of dental elevators. The socket was irrigated with povidine iodine and saline after the sharp bony edges were smoothed. Complete hemostasis was achieved and wound closed was obtained using 3-0 silk suture.

The follow up was carried out on the 1st, 3rd, and 7th postoperative days. All the patients were under antibiotic cover for 5 days with amoxicillin (orally) 500 mg 8th hourly, and metronidazole (orally) 400 mg, 8th hourly. For pain, paracetamol 500 mg was prescribed, to be taken as and when required.

The postoperative swelling, mouth opening were measured in the same manner as was done preoperatively and was recorded. Pain assessment was made using a subjective visual analog scale. Mouth opening was measured between the incisal edges of the central incisors.

Statistical analysis was performed with Data was entered into Microsoft Excel spreadsheet and then checked for any missing entries. It was analysed using Statistical Package for Social Sciences (SPSS) version 21. VAS scores, facial measurements and mouth opening were summarized as mean and standard deviation. As the VAS score was measured on an ordinal scale, thus inferential statistics of VAS scores were performed using **non-parametric tests of significance** i.e. Mann Whitney U test, Friedman test and Wilcoxon signed ranks test. Intergroup and intra group comparison of Facial measurements & mouth opening were done by **parametric tests of significance**. Independent Student's t test and repeated measures of Analysis of Variance along with post hoc Bonferroni test respectively. The level of statistical significance was set at 0.05.

III. Results

The present study was aimed at evaluating the efficacy of serratiopeptidase and dexamethasone in reducing postoperative pain, swelling, and trismus after removal of the mandibular third molar. A total of 100 patients were divided randomly in two groups. Group A in which patients were given dexamethasone and Group B in which patients were given serratiopeptidase.

In dexamethasone group there were 38 males and 12 females whereas in serratiopeptidase group there were 37 males and 13 females; which were found to be statistically non significant (P value 0.999) as shown in table 1 and graph 1.

Table 1: Sex wise distribution of study subjects among both the intervention groups

Group		Sex		Total
		Male	Female	
Dexamethasone group	N	38	12	50
	%	76.0%	24.0%	100.0%
Serratiopeptidase group	N	37	13	50
	%	74.0%	26.0%	100.0%
Total	N	75	25	100
	%	75.0%	25.0%	100.0%
P value, Significance		0.999, NS		

Chi square test

Graph 1: Sexwise distribution of study subjects among both the intervention groups

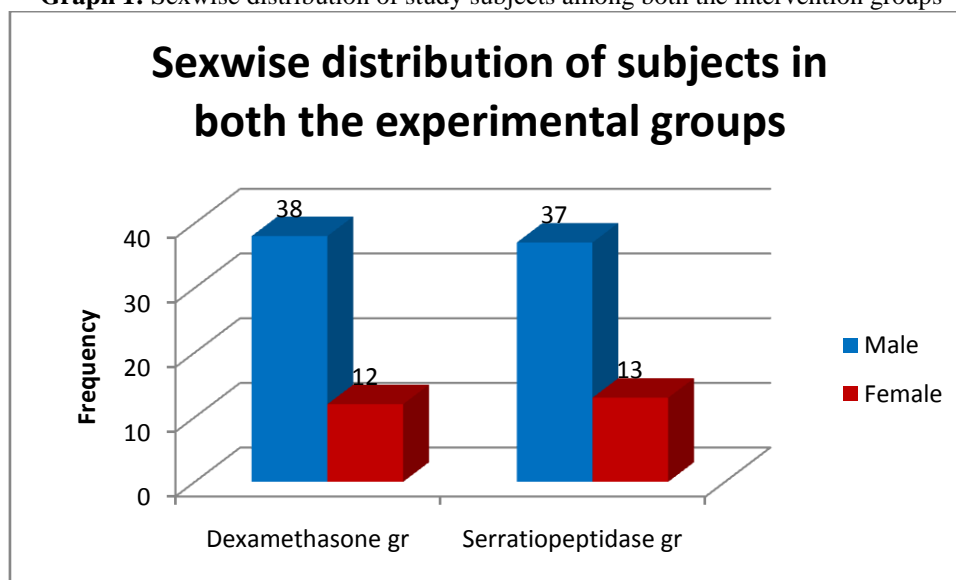


Table 2- represents the degree of pain realized by the two groups of patients from 1st to 7th day. The group of patients on dexamethasone recorded less pain on the first postoperative day (P Value <.001) with mean value of 1.76, (standard deviation was 1.00). Whereas the group of patients on serratiopeptidase recorded more pain on the first postoperative day with mean score of 2.84, (standard deviation is 1.11). This suggests that pain control is better with dexamethasone than with serratiopeptidase on first postoperative day whereas on 3rd and 7th day p value was observed to be 0.100 which is non significant for both groups.

Table 2: Intergroup comparison of VAS scores of pain at pre-operative, first day post-operative, third day post-operative & seventh day post-operative

Group		PAIN (VAS scores)			
		Pre-operative	First day post op	Third day post op	Seventh day post op
Dexamethasone group	Mean	3.00	1.76	0.58	0.26
	SD	1.34	1.00	0.81	0.75
Serratiopeptidase group	Mean	2.82	2.84	0.98	0.14
	SD	1.35	1.11	1.15	0.35
Total	Mean	2.91	2.30	0.78	0.20
	SD	1.34	1.18	1.01	0.59
P ^c value, Significance		0.688, NS	<0.001, S	0.100, NS	0.873, NS

^cMann Whitney U test

Graph 2: Intergroup comparison of VAS scores of pain at pre-operative, first day post-operative, third day post-operative & seventh day post-operative

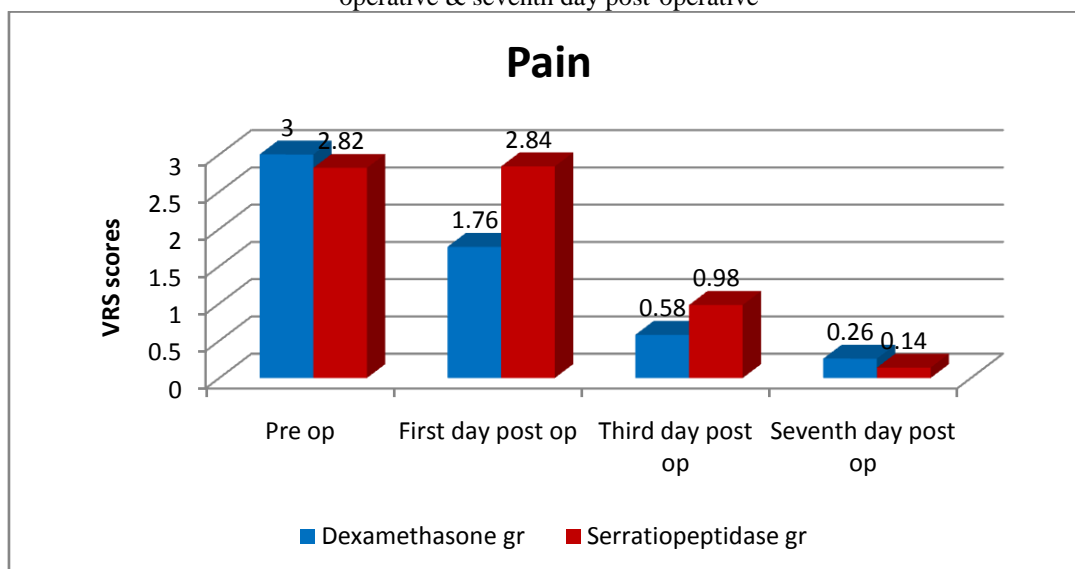


Table 3 and graph 3 illustrate that there was a statistically highly significant swelling in both the groups ($P < 0.001$) on day 1 and day 3, but reduced suddenly to insignificant swelling on 7th day. In comparison, in the serratiopeptidase group, the swelling was highly significant on day 1st and 3rd as well, but reduced suddenly to insignificant swelling on 7th day. But on inter group comparison swelling reduced significantly in dexamethasone group than serratiopeptidase group on 1st and 3rd post operative day. This suggests that dexamethasone has better anti-inflammatory effect than serratiopeptidase.

Table 3: Intergroup comparison of Swelling A at pre-operative, first day post-operative, third day post-operative & seventh day post-operative

		SWELLING		P ^d value
		Mean	SD	
Pre-operative	Dexamethasone group	113.62	6.61	0.786, NS
	Serratiopeptidase group	113.28	5.88	
First day post op	Dexamethasone group	114.88	6.55	0.050, S
	Serratiopeptidase group	117.28	5.95	
Third day post op	Dexamethasone group	113.62	6.53	0.034, S
	Serratiopeptidase group	116.30	5.94	
Seventh day post op	Dexamethasone group	113.60	6.58	0.859, NS
	Serratiopeptidase group	113.38	5.78	

Independent Student's t test

Graph 3: Intergroup comparison of Swelling at pre-operative, first day post-operative, third day post-operative & seventh day post-operative

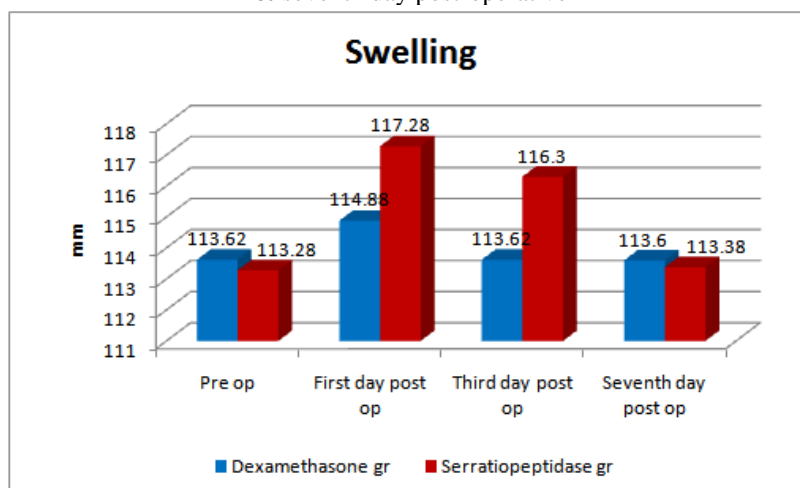


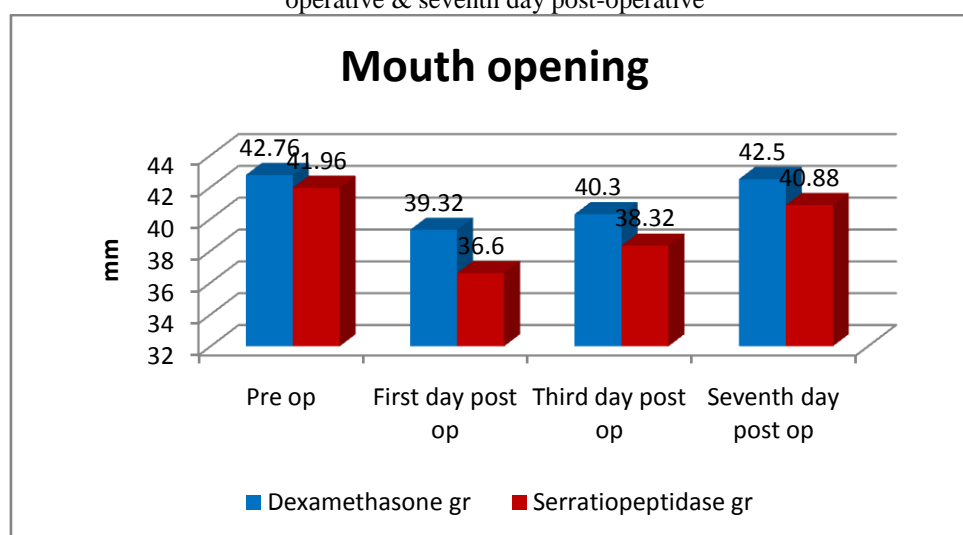
Table 4 and Graph 4 show statistically highly significant restricted mouth opening on 1st and 3rd day (P < 0.001). In both the dexamethasone and the serratiopeptidase groups there was insignificant restricted mouth opening (P < 0.147) on 7th day, suggesting that both the drugs were equally ineffective in relieving trismus.

Table 4: Intergroup comparison of Mouth opening at pre-operative, first day post-operative, third day post-operative & seventh day post-operative

		MOUTH opening			
Group		Pre-operative	First day post op	Third day post op	Seventh day post op
Dexamethasone group	Mean	42.76	39.32	40.30	42.50
	SD	5.44	5.67	5.52	5.94
Serratiopeptidase group	Mean	41.96	36.60	38.32	40.88
	SD	5.07	6.09	5.50	5.12
Total	Mean	42.36	37.96	39.31	41.69
	SD	5.25	6.01	5.57	5.57
P value, Significance		0.449, NS	0.023, NS	0.075, NS	0.147, NS

Independent Student's t test

Graph 4: Intergroup comparison of Swelling A at pre-operative, first day post-operative, third day post-operative & seventh day post-operative



IV. Discussion

The surgical removal of an impacted third molar tooth can result in considerable pain, swelling, and dysfunction. Swelling usually reaches its maximum within 48–72 hours of the surgical procedure.⁽¹⁰⁾

Minimizing tissue damage can control the amount of postsurgical edema. Some believe that ice applied to the operated area decreases vascularity and thereby diminishes transudation. However, no controlled study has verified this practice.^(11,12) The vasoactive amines cause vasodilation, thereby increasing blood flow to the inflamed area. The inflammatory process is necessary if healing is to occur but inflammation also causes edema, pain, and trismus.^(10,13) A meticulous surgical technique can minimize the sequelae of inflammation but will not prevent them. The intensity of the inflammatory process may be reduced by administering corticosteroids.⁽¹¹⁾ Glucocorticoids are a group of steroids that possess anti-inflammatory properties. The primary glucocorticoid secreted by the zona fasciculata of the adrenal cortex is cortisol (hydrocortisone).⁽¹³⁾ Normally, the body produces approximately 15–30 mg of hydrocortisone per day.^(14,15)

Suppression of each stage of the inflammatory response appears to be the major action of the glucocorticoids. There is a decrease in capillary dilatation, leukocyte migration, and phagocytosis, a decrease in the total number of circulating lymphocytes, basophils, eosinophils, and monocytes, and an inhibition of the formation of granulation tissue by retarding fibroblast proliferation and collagen synthesis. Their major role in reducing the inflammatory response is to inhibit the production of vasoactive substances such as prostaglandins and leukotrienes, as well as decreasing the number of chemical attractants such as cytokines. There is also a generalized reduction in the secretion of lipolytic and proteolytic enzymes such as phospholipase, collagenase, and elastase.⁽¹⁶⁾

Enzymes are derived from various sources, including bacteria (e.g., streptokinase and streptodornase). Chymotrypsin is a proteolytic enzyme obtained from the bovine pancreas and is used for management of edema.

Serratiopeptidase or serrapeptase is a protein (proteolytic) enzyme isolated from the non-pathogenic enterobacteria *Serratia E15* found in silkworms. ⁽¹⁵⁾

Swelling involves a three-dimensional volumetric change at the tissue and cellular level. No technique has been proved to be superior or more accurate than any other in analyzing swelling. The desire to include large number of patients, and the practicability of this low cost and reliable technique, made linear measurements a reasonable choice in this study.

In the studies conducted by Elhag et al., Weber and Griffin, and Beirne and Hollander for establishing the anti-inflammatory effects of dexamethasone, the dexamethasone group had mean pain and swelling scores significantly lower than that of the controls. ⁽¹⁷⁻²⁰⁾ our study also showed similar results there was significant reduction of swelling in dexamethasone group on 1st and 3rd post operative day than serratiopeptidase group.

Chopra et al. conducted a randomized, double blind, placebo controlled study to compare the efficacies and safety of acetaminophen, serratiopeptidase, ibuprofen, and betamethasone.

They found that acetaminophen provides statistically significant benefit when compared with placebo for pain relief after third molar surgery. Compared with a nonsteroidal anti-inflammatory drug (ibuprofen), acetaminophen did not prove to be better in terms of reduction of pain scores or rescue medication requirement. The authors also reported that corticosteroids produce analgesic action, albeit with a delay.

In our study we found that in the dexamethasone group the pain was significantly lower than serratiopeptidase group on the 1st postoperative day but on the 3rd and 7th days, it was same for both groups dexamethasone as well as for serratiopeptidase. This observation is consistent with the findings of Chopra et al. ⁽²¹⁾ There was statistically significant reduction of swelling on the 1st and 3rd postoperative days in patients taking dexamethasone than serratiopeptidase group. In this study we noticed that both dexamethasone and serratiopeptidase were effective in minimizing the postoperative inflammation. However, there was a definite difference between dexamethasone and serratiopeptidase, with dexamethasone being superior to serratiopeptidase in reducing inflammation.

V. Conclusion

Two different drugs were compared for efficacy on postoperative swelling, pain, and trismus. In this study serratiopeptidase and dexamethasone had equal and minimal effect on trismus. Dexamethasone was better than serratiopeptidase for the control of pain on 1st post operative day and swelling was reduced significantly on 1st and 3rd post operative day, whereas on 7th day both drugs have similar effects on swelling. Dexamethasone is a better drug of choice in control of pain and swelling post surgical 3rd molar removal. As it was observed in our study that dexamethasone reduces swelling much better than serratiopeptidase, specifically on 1st and 3rd post operative days.

Serratiopeptidase can be used as an alternative drug to control inflammation in cases where corticosteroids are contraindicated. However, a study with a larger sample size is required to validate the results.

Conflict of interest: None

References

- [1]. Filho JRL, Maurette PE, Allais M, Cotinho M, Fernandes C. Clinical comparative study of the effectiveness of two dosages of Dexamethasone to control postoperative swelling, trismus and pain after the surgical extraction of mandibular impacted third molars. *Med Oral Patol Oral Cir Bucal* 2008; 13:E129-32.
- [2]. Markiewicz MR, Brady MF, Ding EL, Dodson TB. Corticosteroids reduce postoperative morbidity after third molar surgery: a systematic review and meta-analysis. *J Oral Maxillofac Surg*. 2008 Sep; 66(9):1881-94.
- [3]. Kaur N, Misurya R, Narula R, Kumar M, Neelkamal, Neeraj. Comparison of the clinical efficacy of methylprednisolone with ibuprofen and ibuprofen alone on the postoperative sequelae of surgical removal of impacted third molar. *Indian J Pain*. 2014; 28:105-10.
- [4]. Ata-Ali J, Ata-Ali F, Peñarrocha-Oltra D, Peñarrocha M. Corticosteroids use in controlling pain, swelling and trismus after lower third molar surgery. *J ClinExp Dent*. 2011; 3:e469-75.
- [5]. Chopra D, Rehan HS, Mehra P, Kakkar AK. A randomized, double-blind, placebo-controlled study comparing the efficacy and safety of paracetamol, serratiopeptidase, ibuprofen and betamethasone using the dental impaction pain model. *Int J Oral Maxillofac Surg*. 2009; 38:350-5.
- [6]. Eugen'e J. Messer, John J. Keller, The use of intraoral dexamethasone after extraction of mandibular third molars. *Oral Surgery, Oral Medicine, Oral Pathology* .Volume 40, Issue 5, November 1975, Pages 594-598.
- [7]. Al-Khateeb TH, Nusair Y. Effect of the proteolytic enzyme serrapeptase on swelling, pain and trismus after surgical extraction of mandibular third molars. *Int J Oral Maxillofac Surg* 2008; 37:264-8.
- [8]. Sherry S, Fletcher AP. Proteolytic enzymes: a therapeutic evaluation. *Clin Pharmacol Ther* 1960; 192); 202-26.
- [9]. Amin MM, Laskin DM. Prophylactic use of indomethacin for prevention of postsurgical complications after removal of impacted third molars. *Oral Surg Oral Med Oral Pathol*. 1983 May; 55(5):448-51.
- [10]. Peterson LJ. Principles of management of impacted teeth. In: Peterson LJ, Ellis E III, Hupp JR, Tucker MR, eds. *Contemporary oral and Maxillofacial Surgery*. 4th ed. St Louis: CV Mosby; 2003:184-213.
- [11]. Sisk AL, Bonnington GJ. Evaluation of methylprednisolone and flurbiprofen for inhibition of the postoperative inflammatory response. *Oral Surg Oral Med Oral Pathol*. 1985 Aug; 60(2):137-45.
- [12]. Stanely F. Malamed Local Complications. In: Malamed SF, editor. *Hand book of local Anesthesia*. 5th ed. St. Louis: Elsevier Mosby Press; 2004.p. 285-302.

- [13]. Gersema L, Baker K. Use of corticosteroids in oral surgery. *J Oral Maxillofac Surg* 1992;50:270-7.
- [14]. Tripathi KD. Corticosteroids. In: Tripathi KD, editor. *Essential of Medical Pharmacology*. 6th ed. New Delhi: Jaypee Brothers Medical Publishers;2006. p. 275-87.
- [15]. Klein G, Kullich W. Short-term treatment of painful osteoarthritis of the knee with oral enzymes. A randomized, double-blind study versus diclofenac. *Chem Drug Invest*. 2000;19(1):15-23.
- [16]. Trummel CL. Antiinflammatory drugs. In: Yagiela JA, Neidle EA, Dowd FJ, editors. *Pharmacology and therapeutics for dentistry*. Mosby; 1998. p. 297-319.
- [17]. Beirne OR, Hollander B .The effect of methylprednisolone on pain, trismus, and swelling after removal of third molars. *Oral Surg Oral Med Oral Pathol*. 1986 Feb; 61(2):134-8.
- [18]. Esch PM, Gerngross H, Fabian A. Reduction of postoperative swelling.Objective measurement of swelling of the upper ankle joint in treatment with serrapeptase- a prospective study. *Fortschr Med* 1989; 107: 67-68.
- [19]. Weber CR, Griffin JM. Evaluation of dexamethasone for reducing postoperative edema and inflammatory response after orthognathic surgery. *J Oral Maxillofac Surg*. 1994 Jan; 52(1):35-9.
- [20]. ElHag M,Coghlan K Christmas P, Harris M.;the anti-inflammatory effects of dexamethasone and therapeutic ultrasound in oral surgery. *Br J Oral Maxillofac Surg*.1985;23:17-23
- [21]. Chopra D, Rehan HS, Mehra P, Kakkar AK. A randomized, double-blind, placebo-controlled study comparing the efficacy and safety of paracetamol, serratiopeptidase, ibuprofen and betamethasone using the dental impaction pain model. *Int J Oral Maxillofac Surg* 2009; 38(4):350-355.

Dr. Nitin Kumar. "A Comparative Study of Serratiopeptidase & Dexamethasone in Control of Inflammation & Trismus Following Impacted Third Molar – A Double Blind Study." *IOSR Journal of Dental and Medical Sciences (IOSR-JDMS)*, vol. 18, no. 04, 2019, pp 78-84.