Comparison of anti-inflammatory efficacy of three different therapeutic modalities after mandibular third molar impaction surgery- a cross sectional study

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Abstract

To compare the efficacy of orally administered Prednisolone, Serratiopeptidase and Trypsin-chymotrypsin in supressing inflammatory sequelae after third molar surgery.

The study consisted of three groups of 15 patients who were prescribed oral medication of NSAID along with either Prednisolone, Serratiopeptidase or Trypsin-chymotrypsin. They were evaluated on the third and seventh postoperative days for pain, edema and inter-incisal opening. On the seventh postoperative day the serum C-Reactive Protein was also assessed.

Resolution of pain, edema and mouth opening was best achieved by Prednisolone, followed by Trypsin-chymotrypsin and Serratiopedtidase. Similar results were obtained for serum C Reactive Protein values with Prednisolone and Trypsin-chymotrypsin giving closest to baseline values, while values remained slightly elevated with Serratiopeptidase. Prednisolone was the most effective anti-inflammatory adjuvant to control inflammatory sequelae of third molar surgery followed by Trypsin-chymotrypsin and then Serratiopetidase.

Clinical Significance: Timely control of inflammatory sequelae with appropriate therapeutic modality results in faster functional rehabilitation.

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Introduction

An impacted tooth is any tooth in the dentition that does not erupt past its chronological time of eruption.[1] The transalveolar or 'surgical' extraction of impacted teeth requires soft tissue incision and reflection followed by bone removal, all of which give rise to post-operative inflammation presenting as pain, facial swelling and trismus. The control of post-operative inflammation is an essential requirement to ensure patient comfort and uneventful healing.

The mainstay of treatment of these sequelae has been use of Non-Steroidal Anti-Inflammatory Drugs (NSAIDs). Various adjuvants are also prescribed to bring about faster resolution of inflammation. The adjuvant therapies often used are oral or parenteral perioperative steroids, enzymatic preparations like Serratiopeptidase, Trypsin-chymotrypsin enzyme combinations.

Prednisolone has been widely utilized for relief from inflammatory reactions in various parts of the body. It has been used in orthopaedic surgeries for reduction of post-surgical inflammation. It is used intraoperatively during neck dissections and eye surgeries so that post-operative edema doesn't impinge on or obliterate vital structures.[2,3]

The use of steroids has been well documented in minor oral surgeries be it oral, intralesional injections or intra-venous injections. Serratiopeptidase has a proteolytic effect on inflammatory enzymes and polypeptide mediators of inflammation, thereby decreasing tissue oedema.[4] Trypsin- Chymotrypsin, a proteolytic enzyme combination, available in oral formulations, has anti-inflammatory and anti-edematous properties.[5]

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In this study, we have attempted to compare efficacy of these adjuvant therapies on reduction of postoperative inflammation. The study objectively measures pain, swelling, interincisal opening in the postoperative period as well as serum C-reactive protein (CRP), which is a biochemical marker of inflammation.[6]

Materials and methods

Subjects and Methods:

The study was conducted in the Department of Oral & Maxillofacial Surgery after approval by the Institutional Ethics Committee from December 2018 to October 2020. Adult patients in the age range of 21 to 50 years who presented for removal of impacted mandibular third molars and consented to participate in the study were included, if they met the following inclusion criteria - patient requiring surgical removal of impacted mandibular third molars with Pederson's Difficulty Index of 4 and above, in good physical health with no pre-existing medical co-morbidities, not on any medication and were willing to follow study protocols. Exclusion criteria were patients with co-morbidities or under medication, history of drug allergy and contraindications to use of any of the study medications.

Methodology:

The sample size was 45 patients with 15 patients included in any one of three categories. Written informed consent was obtained. Each subject was given a prophylactic dose of one gram of Amoxicillin (Two Capsules of 500mg) one hour before the procedure. They were then randomly included into one of the three categories - Prednisolone category (Category A), Serratiopeptidase category (Category B) and Trypsin-Chymotrypsin category (Category C). Prior to surgery all patients were given a povidone-iodine mouthwash. Local anesthesia (2% Lignocaine hydrochloride with 1:200000 epinephrine) was administered using 26-gauge needle. Surgical procedure to extract the impacted mandibular third molar was then performed by equally experienced operators, mesioangular, distoangular, vertical and horizontal impactions with a Pederson's Difficulty index of 4 and above were extracted. The steps followed during impaction surgery were mucoperiosteal flap reflection, buccal and distal bone removal with bur, tooth sectioning with bur, extraction followed by debridement. Simple interrupted sutures were placed using 3-0 silk. All patients were instructed to place an ice pack intermittently over the face for the rest of the day. Post- operative anti-inflammatory medications prescribed were:

Category A
1. Tab. Diclofenac 50mg B.D. for 3 days ("Diclogesic, Torrent Pharmaceutical Ltd.")
2. Tab. Prednisolone 10 mg Stat ("Wysolone 10, Pfizer Ltd.")

Category B
1. Tab. Diclofenac 50mg B.D. for 3 days ("Diclogesic, Torrent Pharmaceutical Ltd.")
2. Tab. Serratiopetidase 10 mg T.I.D for 3 days ("Bidansen forte, Glaxosmithkline Ltd.")

Category C:
1. Tab. Diclofenac 50mg B.D. * 3 days ("Diclogesic, Torrent Pharmaceutical Ltd.")
2. Tab. Trypsin-Chymotrypsin 100000 I.U. T.I.D for 3 days ("Chymoral Forte, Torrent Pharmaceuticals Ltd.")

All patients were also prescribed Tab. Ranitidine 150mg O.D for three days ("Rantac, J.B Chemicals & Pharmaceuticals") and Chlorhexidine gluconate mouthwash B.D. for seven days ("Rexidine plus, Indoco Remedies Ltd.")

The patients were recalled for follow up on third postoperative day and seventh postoperative day. On the third post-operative day, patients rated the pain experienced on Visual Analog Scale. A cotton thread was stretched from tragus to pogonion on the side of surgery and measured on a metal scale to indicate the amount of swelling. Interincisal opening was then measured using a metal scale. On the seventh postoperative day, after suture removal, the same measurements were recorded. Additionally, the serum C – reactive protein was estimated from 2ml of intravenous blood drawn from cubital fossa. All the collected data was tabulated and at completion of study, statistically analysed using SPSS Statistics 20 software.

Results

A total of 30 male and 15 female patients were included in the study. Mean age of the male patients was 37 years and female patients, 33 years.

1. Pain (Table 1)

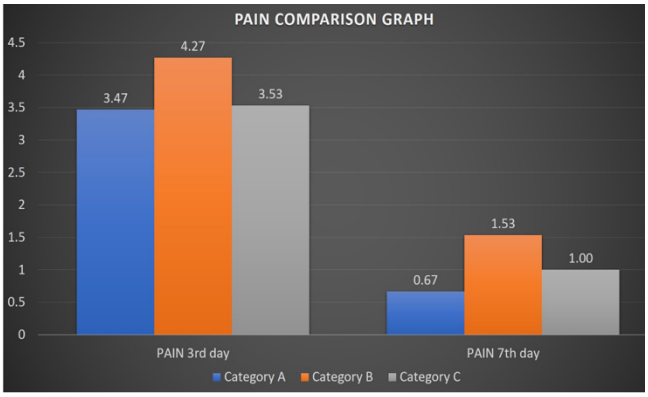
Comparison of Pain Scores on third day between the three groups showed that Serratiopeptidase group (Category B) had the highest of 4.27 and Prednisolone group (Category A) had the least value of 3.47. This difference was statistically significant (p value of 0.002). Patients in the Prednisolone and Trypsin – Chymotrypsin (Category C) groups reported greater pain relief on the third post-operative day as compared to patients in the Serratiopeptidase group.

	Category A (n=15) (as per V.A.S)	Category B (n=15) (as per V.A.S)	Category C (n=15) (as per V.A.S)	ONE WAY ANOVA		POSTHOC TUKEY TEST		
				F value (*=welch test)	P VALUE	Category A vs Category B difference (p value)	Category A vs Category C difference (p value)	Category B vs Category C difference (p value)
PAIN 3rd day	3.47±0.64	4.27±0.7	3.53±0.52	7.569	0.002	-0.8 (0.003)	-0.07 (0.954)	0.73 (0.007)
PAIN 7th day	0.67±0.72	1.53±0.52	1±0.65	7.055	0.002	-0.87 (0.002)	-0.33 (0.334)	0.53 (0.068)
PAIN DIFFERENCE	2.8±0.94	2.73±0.88	2.53±0.74	0.391	0.679	0.07 (0.975)	0.27 (0.675)	0.2 (0.801)

Table 1. Mean values of V.A.S Pain Scores on 3rd and 7th post-operative day and the difference.

	Category A (n=15) (in mm)	Category B (n=15) (in mm)	Category C (n=15) (in mm)	ONE WAY ANOVA		POSTHOC TUKEY TEST		
				F value (*=welch test)	P VALUE	Category A vs Category B difference (p value)	Category A vs Category C difference (p value)	Category B vs Category C difference (p value)
EDEMA 3rd day	9.69±1.68	11.65±0.88	10.55±0.65	11.109*	<0.001	-1.97 (<0.001)	-0.87 (0.113)	1.1 (0.034)
EDEMA 7th day	2.59±0.69	3.27±0.56	2.35±0.58	9.008	0.001	-0.67 (0.012)	0.25 (0.52)	0.92 (0.001)
EDEMA DIFFERENCE	7.09±1.94	8.39±0.91	8.21±0.6	2.683*	0.088	-1.29 (0.023)	-1.11 (0.057)	0.18 (0.922)

Table 2. Mean values of facial swelling on the 3rd and 7th post-operative day and the resultant difference.



Graph 1. Comparing VAS scores on third & seventh postoperative days within each group, labelled as Pain Difference, Category A had the highest value of 2.8 and Category C has the least value of 2.54.

Comparison of Pain Scores on seventh postoperative day between the three groups revealed Category B having the highest value of 1.54 and Category A having least value of 0.67. The difference was statistically significant (p value of 0.002). On the seventh post-operative day, patients in all three categories revealed significant pain relief. Patients in Prednisolone group reported best pain relief. Patients in Serratiopeptidase group also had pain relief but scored higher pain on VAS when compared to Prednisolone group. There was no significant difference in pain scores between Serratiopeptidase and Trypsin-chymotrypsin groups, the reduction in pain being comparable.

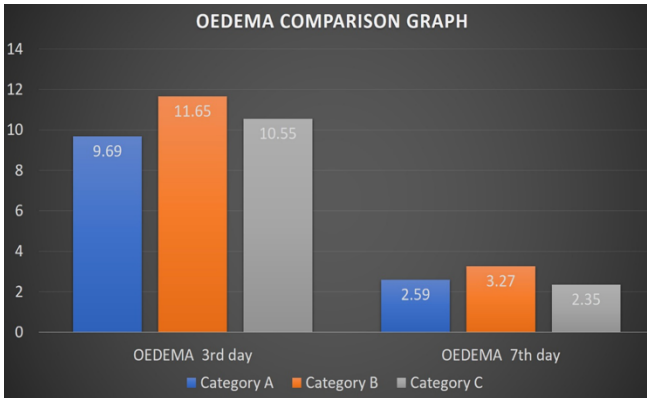
Comparing VAS scores on third & seventh postoperative days within each group, labelled as Pain Difference, Category A had the highest value of 2.8 and Category C has the least value of 2.54. (Graph 1). Comparable reduction of pain scores was obtained across all categories with Prednisolone category achieving the highest amount of pain reduction.

2. Edema (Table 2)

Comparison of edema present on third day between the three categories, revealed patients in the Serratiopeptidase group had the highest value of 11.65mm, and the least value of 9.69mm was found in patients in the Prednisolone group. This difference was statistically significant (p value of <0.001). On the third post-operative day patients in the Prednisolone and Trypsin – Chymotrypsin groups had lesser facial edema as compared to patients in the Serratiopeptidase group.

Comparison of edema on seventh day between the three categories showed that Serratiopeptidase group had the highest value of 3.27 and Trypsin – chymotrypsin group had the least value of 2.35. This difference was statistically significant (p of 0.001). Edema reduction was comparable in Prednisolone and Trypsin – chymotrypsin groups whereas Serratiopeptidase group showed slower resolution of post-operative edema.

Comparison of edema difference between the three groups showed that Serratiopeptidase group had the highest value of 8.39 and Prednisolone had the least value of 7.09. This difference was not statistically significant (p of 0.088). (Graph 2). Extent of decrease in edema is significantly better in Prednisolone and Trypsin – chymotrypsin groups.



Graph 2. Comparison of edema difference between the three groups showed that Serratiopeptidase group had the highest value of 8.39 and Prednisolone had the least value of 7.09.

	Category A (n=15) (in mm)	Category B (n=15) (in mm)	Category C (n=15) (in mm)	ONE WAY ANOVA		POSTHOC TUKEY TEST		
				F value (*=welch test)	P VALUE	Category A vs Category B difference (p value)	Category A vs Category C difference (p value)	Category B vs Category C difference (p value)
TRISMUS 3rd day	28.55±3.3	24.01±1.88	23.98±1.44	12.446*	<0.001	4.54 (<0.001)	4.57 (<0.001)	0.03 (0.999)
TRISMUS 7th day	46.63±2.29	41.98±1.53	45.91±1.93	24.908	<0.001	4.65 (<0.001)	0.73 (0.566)	-3.93 (<0.001)
MOUTH OPENING INCREASE	18.08±3.67	17.97±2.63	21.93±2.97	7.848	0.001	0.11 (0.995)	-3.85 (0.004)	-3.96 (0.003)

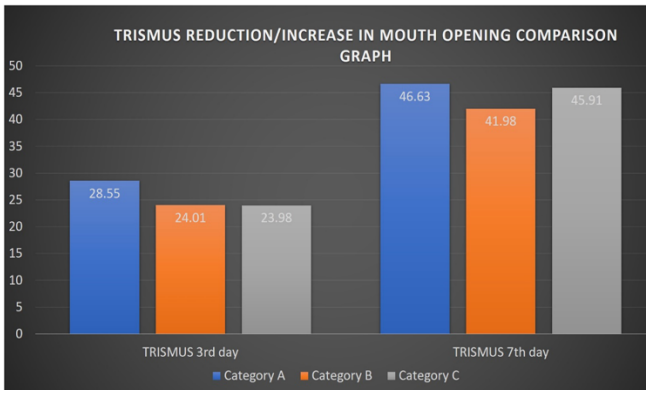
Table 3. Mean values of interincisal opening (as a measure of trismus) as on 3rd and 7th post-operative day and the resultant difference.

3. Trismus (Table 3)

Comparing Interincisal distance on the third day between the three groups shows that Prednisolone group had the highest value of 28.55mm and Trypsin – chymotrypsin group had the least value of 23.98mm. This difference was statistically significant (p<0.001). Comparing Serratiopeptidase with Trypsin – chymotrypsin group, the extent of mouth opening was higher in the Serratiopeptidase group although the difference was not statistically significant.

On the seventh post-operative day, prednisolone group showed marked improvement in mouth opening as did trypsin – chymotrypsin group, whereas patients in the Serratiopeptidase group, did not show statistically significant improvement over the other two categories.

Comparison of mouth opening increase between the three groups (Graph 3), showed patients in all 3 categories achieved increases in mouth opening, Prednisolone and Serratiopeptidase groups demonstrating a gradually increasing mouth opening while Trypsin –chymotrypsin group had lower initial values followed by marked increase in mouth opening.



Graph 3. Comparison of mouth opening increase between the three groups.

	Category A (n=15) (in mg/dL)	Category B (n=15) (in mg/dL)	Category C (n=15) (in mg/dL)	ONE WAY ANOVA		POSTHOC TUKEY TEST		
				F value (*=welch test)	P VALUE	Category A vs Category B difference (p value)	Category A vs Category C difference (p value)	Category B vs Category C difference (p value)
CRP	10.66±0.45	11.39±0.55	10.67±0.57	9.517	<0.001	-0.73 (0.001)	-0.01 (0.997)	0.72 (0.002)

Table 4. Mean values of serum C-RP levels on 7th post-op day.

			N	Mean ± SD	Mean difference ± SD	t	P VALUE
Category A							
	Pair 1	PAIN 3rd day	15	3.47±0.64			
		PAIN 7th day	15	0.67±0.72	2.8±0.94	11.52	<0.001
	Pair 2	EDEMA 3rd day	15	9.69±1.68			
		EDEMA 7th day	15	2.59±0.69	7.09±1.94	14.17	<0.001
	Pair 3	TRISMUS 3rd day	15	28.55±3.3			
		TRISMUS 7th day	15	46.63±2.29	-18.08±3.67	-19.10	<0.001
Category B							
	Pair 1	PAIN 3rd day	15	4.27±0.7			
		PAIN 7th day	15	1.53±0.52	2.73±0.88	11.98	<0.001
	Pair 2	EDEMA 3rd day	15	11.65±0.88			
		EDEMA 7th day	15	3.27±0.56	8.39±0.91	35.75	<0.001
	Pair 3	TRISMUS 3rd day	15	24.01±1.88			
		TRISMUS 7th day	15	41.98±1.53	-17.97±2.63	-26.50	<0.001
Category C							
	Pair 1	PAIN 3rd day	15	3.53±0.52			
		PAIN 7th day	15	1±0.65	2.53±0.74	13.20	<0.001
	Pair 2	EDEMA 3rd day	15	10.55±0.65			
		EDEMA 7th day	15	2.35±0.58	8.21±0.6	52.72	<0.001
	Pair 3	TRISMUS 3rd day	15	23.98±1.44			
		TRISMUS 7th day	15	45.91±1.93	-21.93±2.97	-28.61	<0.001

Table 5. 3rd post-operative day and 7th post-operative day comparison using paired t-test.

4. C-Reactive Protein (C.R.P) (Table 4)

CRP values were highest in Serratiopeptidase group, 11.39 and Prednisolone group had the least value,10.66. This difference was statistically significant (p <0.001). Marginally increased serum C.R.P. levels still persisted on the seventh post-op day. Prednisolone and

Trypsin – chymotrypsin group had lower serum levels and Serratiopeptidase group had higher level of serum C-reactive protein, amongst the groups.

Intragroup comparison of pain, edema and trismus on third day with seventh day reveal significant improvements in scores in all 3 categories. (Table 5)

Discussion

Different adjuvants used in conjunction with NSAIDs help to reduce and control post-operative complications for patients who have undergone impacted third molar surgery. We have attempted to compare and evaluate the efficacy of some of these modalities in our present study.

Corticosteroids are powerful anti-inflammatory agents. Tiigimae-Saar J et al have demonstrated the efficacy of oral prednisolone in reducing post extraction inflammation when given in conjunction with NSAIDs. [7] According to Ibikunle AA et al submucosal injection of prednisolone may also be used, and it had a superior efficacy compared to oral route. [8] In our study, oral prednisolone was most effective in the mitigation of post-surgical inflammation.

The long term use of corticosteroids has been associated with osteoporosis, poor wound healing and increased susceptibility to infection. Kang SH et al have clearly demonstrated that a short course of steroid therapy is useful in controlling inflammatory sequelae without any systemic adverse effects. [9] The potential exhibited in the reduction of pain and swelling post-surgery with the use of a small dose establishes its role as a credible agent in the control of inflammation. Thus it seems to be the mainstay of adjuvant therapy in third molar surgery cases. [10]

Serratiopeptidase exerts its anti-inflammatory action by increasing local vascular permeability and draining edema fluid in the site, clinically seen as reduction in swelling, and is mainly utilized by surgical specialties. [11] Being a proteolytic molecule, Serratiopeptidase modifies cell surface attachment molecules, attracting cells mediating inflammation. [12] Murugesan K et al in their study comparing Serratiopeptidase with Dexamethasone have found serratiopeptidase helped in resolving edema, but rapid symptomatic relief was provided by Dexamethasone. [4] Mouneshkumar Chappi D et al found that compared to methyl prednisolone, it was more effective in controlling post-surgical swelling and trismus. [13] In our study, Serratiopetidase gave a higher extent of mouth opening in patients on the third post-operative day but better symptom relief was obtained in the other groups.

The enzyme combination of trypsin-chymotrypsin has also been used for its anti-inflammatory attributes. Randomized clinical trial conducted by Chandanwale A et al have revealed a very effective action of tryspin-chymotrypsin [14] which is superior to that of Serratiopeptidase (Naddakavukaran D et al) [15] but not superior to Dexamethasone as per Grossi GB et al .[16] In our study, too, Tryspin-Chymotrypsin provided superior resolution of inflammation compared to Serratiopeptidase and can serve as an alternative to use of corticosteroids.

As studies of literature have previously suggested, a combination therapy of NSAID with an adjuvant should be used to effective counter inflammatory sequelae of third molar disimpaction surgery. [17]

Our study has also included a measure of serum CRP as an indicator of anti-inflammatory capability of adjuvants. With this parameter, too, corticosteroids gave superior results followed by trypsin-chymotrypsin, and thirdly Serratiopeptidase.

Some of the limitations of our study is that we did not measure preoperative baseline CRP levels to indicate pre-existing inflammatory condition. Angulations of impacted third molars were not identical thereby contributing to different levels of surgical difficulty and resultant inflammatory sequelae, however, this potential bias was controlled by random distribution in all three groups.

Conclusion

In our study, prednisolone proved to be the most potent and effective medication in order to suppress the inflammatory sequelae that is encountered in the post-operative period after third molar impaction surgery. Trypsin-chymotrypsin also gives a high degree of relief and was comparable to corticosteroid.

Corticosteroids remain the best adjuvants to NSAIDs to help control post-operative

inflammatory sequelae of third molar disimpaction surgery, followed by trypsin – chymotrypsin enzyme. Serratiopeptidase provides slower relief of symptoms, but faster improvement in mouth opening.

Ethical policy and Institutional Review board statement: The study has been conducted in accordance with the ethical principles mentioned in the Declaration of Helsinski (2013) and approved by Institutional Review Board (Ref. No. 18127). Written informed consent was obtained from all patients for participation in the study.

Declaration of Interest

The authors report no conflict of interest.

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