



RESEARCH ARTICLE

COMPARISON OF EFFICACY OF COMBINATION OF PROTEOLYTIC ENZYMES WITH DICLOFENAC SODIUM VERSUS DICLOFENAC SODIUM ALONE IN PATIENTS UNDERGOING SURGICAL EXTRACTION OF MODERATELY DIFFICULT IMPACTED MANDIBULAR THIRD MOLARS

¹Dr. Gokkulakrishnan, S., ²Dr. Satyabhushan, ³Dr. Meera Thinakaran, ⁴Dr. Rajaram Abishek balaji, ⁴Dr. Vivek Kannaiyah, ⁵Dr. Gunasekaran Manikandan, ⁶Dr. J Benjamin Premkumar, ⁴Dr. Alex Varghese and ^{*}⁷Dr. Sankalp Verma

¹Department of Oral Maxillofacial Surgery, Adhiparasakthi Dental College and Hospital, Melmaruvathur

²GITAM Dental College, Vishakapatnam

³Department of OMFS, Karpaga Vinayaga Institute of dental sciences, Mumundur

⁴Senior Lecturer, Department of OMFS, Adhiparasakthi Dental College and Hospital, Melmaruvathur

⁵Sri Satya Sai Medical College and Research Institute, Nellikuppam, Tamil Nadu

⁶Senior Lecturer, Vinayaka Mission Dental College and Hospital, Puducherry

⁷Sri Sai Hospital, Moradabad, India

ARTICLE INFO

Article History:

Received 10th July, 2016
Received in revised form
22nd August, 2016
Accepted 18th September, 2016
Published online 30th October, 2016

Key words:

Impacted third molar,
Postoperative Complication,
Proteolyticenzyme, Trismus.

ABSTRACT

Objectives: Surgical extraction of impacted mandibular third molar in many cases leads to debilitating post-operative complications which are routinely managed with drugs like corticosteroids, NSAID's and opioids. Unfortunately these drugs carry their share of side effects; hence a natural, effective and safe remedy that lacks undesired side effects is desired. The aim of this study is to evaluate the efficacy of various proteolytic enzymes (trypsin, bromelain, rutoside trihydrate and serratiopeptidase) with diclofenac sodium in comparison with diclofenac sodium alone in reducing the postoperative complications like pain, swelling, trismus.

Material and methods: This study was conducted in 30 patients randomly selected and divided into 3 groups of 10 patients each. The postoperative complications were recorded and evaluated on 1st, 3rd, 5th and 7th postoperative days.

Results: In group II patients, significant improvement in reduction of pain, trismus and quality of life was seen on 1st, 3rd, 5th and 7th postoperative days as compared to group I and III. In group III patients' significant improvement in mouth opening and reduction of pain was observed on 5th and 7th postoperative days however significant improvement on quality of life was seen on 3rd, 5th and 7th postoperative days.

Conclusion: In surgical extraction of moderately difficult impacted teeth ; bromelain, trypsin, rutosidetrihydrate with diclofenac sodium was effective in pain control, increased mouth opening and improved quality of life than seratiopeptidase with diclofenac sodium when comparing with diclofenac sodium alone.

Copyright © 2016, Dr. Gokkulakrishnan et al. This is an open access article distributed under the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

Citation: Dr. Gokkulakrishnan, S., Dr. Satyabhushan, Dr. Meera Thinakaran et al. 2016. "Comparison of efficacy of combination of proteolytic enzymes with diclofenac sodium versus diclofenac sodium alone in patients undergoing surgical extraction of moderately difficult impacted mandibular third molars", *International Journal of Current Research*, 8, (10), 39842-39845.

INTRODUCTION

Surgical extraction of impacted mandibular third molar is one of the most common minor surgical procedures performed by the Oral and Maxillofacial Surgeons (Al-Sandook et al., 2014). The surgical procedure produces a significant level of soft tissue and bone injury that causes intense post-operative inflammatory reaction.

These complications are usually managed by using various drugs like corticosteroids, NSAID's and opioids. Though opioids are effective analgesics but their sedative effect masks their efficacy. Corticosteroids are potent anti-inflammatory drugs but have disadvantage of adrenal suppression and usually cause delayed wound healing (Premkumar, 2012). Post-operative pain and inflammation can be managed by NSAID's but some patients do not get adequate relief and moreover long term use of them have the adverse effect on gastric mucosa (Dionne, 1999). Hence a natural, effective and safe remedy that lacks undesired side effects would offer a

*Corresponding author: Dr. Sankalp Verma
Sri Sai Hospital, Moradabad India

welcome alternative in controlling the post-operative complications. This study was undertaken to evaluate the efficacy of various proteolytic enzymes (trypsin, bromelain, rutosidetrihydrate and seratiopeptidase) with diclofenac sodium in comparison with diclofenac sodium alone in reducing the postoperative complications like pain, swelling, trismus and their adverse effects on the quality of life after surgical extraction of impacted mandibular third molars.

MATERIALS AND METHODS

Healthy patients with moderately difficult impacted mandibular third molars according to modified Pederson's difficulty index (Table 1) and patients who were willing to accept the inform consent and willing to participate in the study with its subsequent follow-ups were included in this study. Pregnant mothers, medically compromised patients, patients with renal and liver diseases, patients who were allergic to NSAIDs and patients taking hemostasis altering medications, history of allergic to drugs, history of pericoronitis and recent anti-inflammatory treatment were excluded from the study. Facial measurements and maximal mouth opening were recorded pre operatively. Parameters recorded were swelling, pain, trismus and quality of life on 1st, 3rd, 5th and 7th days post operatively. Facial swelling was measured by a modification of tape measuring method described by Gabka and Matsumara. Three measurements were made between 5 reference points viz tragus of the ear, soft tissue pogonion, lateral corner of the eye, angle of the mandible and outer corner of the mouth. The pre-operative sum of all the three measurements was considered as the base line and the difference between each post-operative and the base line measurements was recorded as changes in the facial swelling. Trismus was evaluated by measuring the distance between the mesial incisal corners of the upper and lower central incisors at maximum mouth opening with the help of divider. Pain was evaluated subjectively by Von Baker's Faces pain rating scale (VAS). Quality of life was evaluated by using LIKERT type scale with oral health related questionnaire and its domains. Intraoral periapical radiographs were obtained to determine the type of impaction. Inferior alveolar, lingual and long buccal nerve anaesthesia was achieved using a 2ml solution of 2% lignocaine hydrochloride and vasoconstrictor (1:80,000).

Following a ward's incision a full thickness mucoperiosteal flap with releasing incision on the distobuccal aspect of the second molar was raised. After buccal and distal guttering the tooth was sectioned and gently elevated from the socket with subsequently flushed with normal saline and betadine. The flap was closed with 3-0 silk sutures in an interrupted fashion. Group I patients received diclofenac sodium 50mg alone (*VORIK*[®] 50 from Glenmark), Group II patients received trypsin 48mg, bromelain 90mg, rutosidetrihydrate 100m with diclofenac sodium 50mg (Rutoheal-D from Mankind). Group III patients received a combination of seratiopeptidase 15mg and diclofenac sodium 50mg (DiclomolSP from WinMedicare). In addition to that all patients received amoxicillin trihydrate 500mg and clavulanate potassium 125mg three times a day for 5 consecutive days. The data collected was tabulated and subjected to SPSS version 16 for statistical analysis. The statistical tests employed were ANOVA with Bonferroni Post hoc test and Chi-square test. P value less than 0.05 was accepted as statistical significant.

RESULTS

Total 30 patients (15male and 15 female) participated in the study. The mean age of the patients was 28.90. None of the patients reported adverse events and drugs under study were well tolerated. The distribution of patients in three groups is shown in Table 2.

Table 1. Modified Pederson's difficulty index

Classification	Value
Spatial relationship	
Mesio angular	1
Horizontal / Transverse	2
Vertical	3
Disto angular	4
Depth	
Level A – High occlusal level	1
Level B – Medium occlusal level	2
Level C – Low occlusal	3
Ramus relationship / Space available	
Class 1 – Sufficient space	1
Class 2 – Reduce space	2
Class 3 – No space	3
Difficulty index	
Very difficult	7-10
Moderately difficult	5-6
Slightly difficult	3-4

On Preoperative day the mean swelling scores were 12.48 in group I, 12.47 in group II and 12.88 in group III. On 1st, 3rd, 5th and 7th post-operative day the mean swelling score was comparatively less in group II but it was not statistically significant ($p > 0.05$). (Table 3) Statistically significant mean reduction in pain scores was noticed at postop days 1,3 and 7 (Table 3). It means that in group II patient's pain was significantly reduced on these three days than group I and group III. The maximum increase in mean mouth opening score was seen in group II followed by group III and I. With respect to quality of significant difference was observed between three groups on 1st, 3rd, 5th and 7th postoperative days. In group II patients, quality of life is improved significantly than group I and group III (Table 3).

DISCUSSION

Surgical removal of impacted mandibular third molar causes significant pain, swelling and trismus even when done atraumatically (Dionne *et al.*, 1999 and Milles *et al.*, 1999) and is quite annoying to the patient and affects their quality of life by delaying the period of recovery. These complications are attributed to the inflammation produced as a result of surgical trauma. The levels of immunoreactive bradykinin have been reported to increase three- to four-fold during oral surgery (Hargreaves *et al.*, 1988). These chemical mediators trigger the subsequent physiological processes, which include vasodilatation, vasoconstriction, leukocyte migration, chemotaxis, and generation of pain impulses. Though inflammation is a reparative process it causes significant distress due to pain and swelling. Trismus, which is due to intramuscular inflammation, could be an associated distressing factor for the patient. Hence, to minimize the unwanted effects of inflammation, it becomes essential to regulate the process of inflammation. Prostaglandins generated after trauma appear to play a major role in sensitizing afferent nerves that mediate pain. Inhibitors of prostaglandin synthesis such as diclofenac have been shown to be effective in many studies (Wuolijoki *et al.*, 1987). Diclofenac sodium is a commonly prescribed

NSAID that works well to reduce mild to moderate postoperative pain. In the third molar surgeries its efficacy is well documented (McGrath *et al.*, 2003), so we chose diclofenac sodium in the present study as a control group.

as fibrin; it thins the fluids formed from inflammation and injury as well as facilitating their drainage that speeds the tissue repair process. It alleviates pain by inhibiting the release of specific pain-inducing amines called bradykinin.

Table 2. Distribution of patients in three groups

Sex	Group I			Group II			Group III		
	No	%	Mean age	No	%	Mean age	No	%	Mean age
Male	2	20 %	31	5	50%	31.2	8	80%	27.25
Female	8	80%	27.85	5	50%	20.4	2	20%	22
Total	10	100%	28.5	10	100%	25.8	10	100%	26.2

Table 3. Comparison of three groups with respect to swelling, pain, trismus and quality of life at pre-operative, 1st, 3rd, 5th and 7th postoperative days

Variables	Facial swelling			Pain		Trismus		QOL	
	Group	Mean± SD	P	Mean± SD	P	Mean± SD	P	Mean± SD	P
1 st Postop	I	13.71±0.45	0.410	4.00	0.001	18.30±4.21	0.001	28.10±5.74	0.001
	II	13.33±0.75		2.60±0.51		23.70±2.63		15±6.92	
	III	13.55±0.63		3.40±0.51		19.10±1.34		20.4±7.13	
3 rd Postop	I	13.39±0.42	0.118	3.40±0.5	0.001	23.20±1.35	0.001	19.20±4.89	0.001
	II	12.87±0.58		1.80±0.42		30.20±4.98		6.40±3.09	
	III	13.34±0.73		2.20±0.42		26.70±2.76		8.60±3.65	
5 th Postop	I	13.12±0.45	0.127	2.60±0.51	0.127	27.20±4.01	0.001	9±4.34	0.001
	II	12.67±0.49		1.00		36.60±3.89		2.2±1.22	
	III	13.10±0.64		1.80±0.42		33.40±4.75		2.8±1.54	
7 th Postop	I	12.81±0.40	0.109	1.50±0.52	0.001	32.20±4.35	0.001	3.30±2.163	0.001
	II	12.51±0.45		0.60±0.5		41.10±2.91		0	
	III	13.00±0.62		1.00		38.00±4.93		0.9±0.73	

Proteolytic enzymes reduce inflammation by blocking the release of pain mediators from inflamed tissue and other clotting cascade intermediates. However previous clinical reports indicate that proteolytic enzymes reduced the mean pain scores in comparison to placebo and the difference was not statistically significant (Morita *et al.*, 1979). Hence the present study aimed to identify synergetic effect of proteolytic enzymes when combined with diclofenac sodium in impacted third molar surgery. Proteolytic enzymes are defined as physical substances that catalyze the hydrolysis of proteins. In the medical literature of the past ten years, these enzymes have been said to be therapeutically indicated for reducing the soft tissue edema and inflammation secondary to trauma. These enzymes include pancreatic proteases chymotrypsin, trypsin, bromelain, papain and serratio peptidase. The anti-inflammatory action of Proteolytic enzymes results from blocking bradykinin and its modulation of prostaglandin synthesis (F.Q. Cunha *et al.*, 1999 and Kakinuma *et al.*, 1982). Bromelain is an aqueous extract obtained from the stem and fruit of the pineapple plant that contains high levels of proteolytic enzymes. It directly influences pain mediators such as bradykinin and reduces swelling, bruising, pain and healing time after trauma and surgical procedures. Evidence has shown that bromelain can digest fibrin thereby allowing elimination of edema (Morita *et al.*, 1979). Serratiopeptidase is an endopeptidase, having molecular weight of about 60 K Dalton. It is obtained from microorganism Serratia E 15 and HY-6, which lives in the gut wall of the silkworm (Yamasaki *et al.*, 1967). It is one of the most promising proteolytic enzymes in treatment of various types of inflammations. In a study, serrapeptase was compared to trypsin, chymotrypsin, and pronase in a rat model of scalding, which is known to induce abnormal activation of fibrinolysis and Serrapeptase was found to be far more effective than any other enzyme in repressing fibrinolysis in this model as an anti-inflammatory agents (Kakinuma *et al.*, 1982). It reduces inflammation in three ways (Yamasaki *et al.*, 1967 and Sherry *et al.*, 1920), it breaks down the insoluble protein by-products of blood coagulation known

This natural anti-inflammatory agent has had wide clinical use spanning over twenty-five years throughout Europe and Asia as a viable alternative to salicylates, ibuprofen and the more potent NSAIDs (Vicari *et al.*, 2005 and Tokumine *et al.*, 1999). German researchers conducted one double-blind study to determine the effect of serrapeptase on post-operative swelling and pain. This study involved sixty-six patients who were treated surgically for fresh rupture of the lateral collateral ligament of the knee. On the third postoperative day, the group receiving serrapeptase exhibited a fifty percent reduction of swelling, compared to the controls (Esch *et al.*, 1989). A clinical study by PremKumar *et al.* (Dionne *et al.*, 1999), suggested that proteolytic enzymes treatment as adjunct was found to be better than diclofenac alone. In this study patients taking bromelain-trypsin, rutosidetrihydrate experienced reduced pain and swelling on 1st and 3rd post-operative days as compared to other 2 groups. Moreover serratio group patients had better improvement when compared to diclofenac group suggestive that, bromelain group was more effective than other groups.

Al-Khateeb *et al.* reported that following third molar surgery; there was significant reduction in the extent of cheek swelling and pain in serratiopeptidase group at 2nd, 3rd and 7th post-operative days. There was significant reduction in pain on 3rd and 5th days and improvement in mouth opening on 5th and 7th post-operative days when compared to diclofenac but no significant difference in swelling was found between 2 groups (Al-Khateeb *et al.*, 2008). Cameron *et al.* conducted a study to evaluate efficacy of chymotrypsin to reduce swelling and trismus after removal of third molar. Results showed that there was no effect on post-operative swelling and trismus throughout the post-operative period in chymotrypsin group. In the present study in addition to chymotrypsin, bromelin and rutosidetrihydrate was added & it showed statistically significant difference in reducing pain and found improvement in mouth opening after extraction of third molar. Barrera Nunez *et al.* did a study to evaluate the anti-inflammatory and

analgesic effect of bromelain in the postoperative phase after extraction of impacted lower third molars. Although there was no statistically significant differences between the treatment groups, a trend towards less inflammation and improved oral aperture was observed in the group that received bromelain, compared to placebo group (Maria del Carmen de la Barrera-Nunez *et al.*, 2014). In the present study, trypsin and rutosidetrihydrate were added to bromelain. Pain, swelling, trismus and quality of life were recorded on 1st, 3rd, 5th and 7th postoperative days. There was significant difference in reducing pain and improved mouth opening on 1st, 3rd and 5th post operatively when compared to control group. WaleedO *et al* did a study to compare the effect of oral bromelain versus diclofenac sodium in postop pain, swelling, trismus, quality of life after surgical removal of impacted lower 3rd molars. Results demonstrated that oral bromelain is an effective therapy to improve the quality of life after surgical removal of impacted lower 3rd molars. In the present study compared bromelain, trypsin, rutoside was compared with diclofenac sodium (control group). Results showed that the patients who were receiving bromelain, trypsin, rutoside showed better results such as swelling and improvement in mouth opening on 3rd, 5th, and 7th days which was significant statistically. Quality of life was also improved significantly in patients who were receiving bromelain, trypsin, rutoside with diclofenacsodium. So in this study, oral bromelain, trypsin, rutoside with diclofenac sodium was found to be an effective therapy to improve quality of life after surgical removal of impacted mandibular 3rd molars (Omer WaleedMajid *et al.*, 2014).

Limitations and future challenges

Limitations of the present study includes smaller sample size, cases were operated by different surgeons, did not compare the bilateral symmetrical impacted teeth and did not include other types of difficulty among impacted mandibular third molars according to modified Pederson's index. Hence there is a need for further studies with larger sample size to evaluate the efficacy in other minor surgical procedures other than third molar surgeries.

Conclusion

It can be concluded from our study that in surgical extraction of moderately difficult impacted teeth bromelain, trypsin, rutosidetrihydrate with diclofenac sodium was effective in pain control, increased mouth opening and improved quality of life than seratiopeptidase with diclofenac sodium when comparing with diclofenac sodium alone.

REFERENCES

- Al-Khateeb, T. H., Nusair, Y. 2008. Effect of the proteolytic enzyme serrapeptase on swelling, pain and trismus after surgical extraction of mandibular third molars. *Int. J. Oral Maxillofac Surg.*, 37: 264–268.
- Al-Sandook, T.A., Tawfik, N.O., Qassim, D.A. 2014. Clinical evaluation of the efficacy of orthal-forte (proteolytic enzymes, trypsin and chymotrypsin) on postoperative sequel following the removal of lower impacted third molar. *International Journal of Enhanced Research in Science Technology & Engineering.* 3(2): 169-173.
- Cunha, F.Q., S. Poole, B.B. Lorenzetti, F.H. Veiga, S.H. Ferreira. 1999. Cytokine-mediated inflammatory hyperalgesia limited by interleukin-4. *British Journal of Pharmacology.*, 126: 45 – 50
- Dionne, R.A. 1999. Additive analgesic effects of Oxycodone and ibuprofen in the oral surgery model. *J Oral Maxillofac Surg.*, 57(6): 673-8.
- Esch, P.M., Gerngross, H., Fabian, A. 1989. Reduction of postoperative swelling Objective measurement of swelling of the upper ankle joint in treatment with serrapeptase- A prospective study. *Fortschr Med.*, 107:67-8.
- Hargreaves, K.M., Troullos, E.S., Dionne, R.A., Schmidt, E.A., Schafer, S.C., Joris, J.L. 1988. Bradykinin is increased during acute and chronic inflammation: Therapeutic implications. *Clin Pharmacol Ther.*, 44:613-21.
- Ian, W. 1980. Cameron. An investigation into some of the factors concerned in the surgical removal of the impacted lower wisdom tooth, including a double blind trial of chymoral. *British Journal of Oral Surgery*, 18: 112-124.
- Kakinuma, A., Moriya, N., Kawahara, K., Sugino, H. 1982. Repression of fibrinolysis in scalded rats by administration of Serratia protease. *Biochem Pharmacol.*, 31:1-6.
- Maria del Carmen de la Barrera-Nunez, Rosa-Maria Yanez-Vico, Antonio Batista-Cruzado, Jean-Michel Heurtebise-Saavedra, Raquel Castillo-de Oyague, Daniel Torres-Lagares. 2014. Prospective double-blind clinical trial evaluating the effectiveness of bromelain in the third molar extraction postoperative period. *Med Oral Patol Oral Cir Bucal.*, 19(2):157-62.
- McGrath, C., Comfort, M.B., Lo, E.C. 2003. Changes in life quality following third molar surgery The immediate postoperative period. *Br. Dent. J.*, 194:265.
- Milles M, Desjardins PJ, Reduction of postoperative facial swelling by low dose methylprednisolone. *J Oral Maxillofac Surg.* 1993; 51:987-991.
- Morita, A.H., Uchida, D.A., Taussig, S.J. 1979. Chromatographic fractionation and characterization of the active platelet aggregation inhibitory factor from bromelain. *Arch Inter Phar Ther.*, 239:340-350.
- Omer Waleed Majid, Bashar Adil Al-Mashhadani. 2014. 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. *J. Oral Maxillofac. Surg.*, 72:1043-1048.
- Premkumar, B., Amanda Fernandez, Gayathri, T. 2012. Proteolytic Enzymes as Adjuncts to Diclofenac in Third Molar Tooth Extraction. *Clinical Research*, 2(3):43-47
- Sherry, S., Fletcher, A.P. 1960. Proteolytic enzymes: a therapeutic evaluation. *Clin Pharmacol Ther.*, 1:202-26.
- Tokumine, F., Sunagawa, T., Shiohira, Y., Nakamoto, T., Miyazato, F., Muto, Y. 1999. Drug-associated cholelithiasis: a case of sulindac stone formation and the incorporation of sulindac metabolites into the gallstones. *Am J Gastroenterol.*, 94:(2)285-8.
- Vicari E, La Vignera S, Battiato C, Arancio A. 2005. Treatment with non-steroidal anti-inflammatory drugs in patients with amicrobial chronic prostatic vesiculitis: transrectal ultrasound and seminal findings. *Minerva UrolNefrol.* 57:53-9.
- Wuolijoki, E., Oikarinen, V.J., Ylipaavalniemi, P., *et al*: Effective postoperative pain control by preoperative injection of diclofenac. *Eur. J. Clin Pharmacol.*, 32:249, 1987.
- Yamasaki, H., Tsuji, H., Saeki, K. 1967. Anti-inflammatory action of a protease, TSP, produced by Serratia. *Folia Pharmacol Japon.*, 63:302-14.