(e) ISSN Online: 2321-9599

(p) ISSN Print: 2348-6805

# ORIGINAL ARTICLE

## EFFECT OF SUBMUCOSAL APROTININ INJECTION ON COMPARATIVE EVALUATION OF POSTOPERATIVE COMPLICATIONS AFTER SURGICAL REMOVAL OF MANDIBULAR 3rd MOLAR

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**ABSTRACT:**

**Purpose**: Surgical removal of third molar is frequently associated with significant discomfort in oral health related quality of life in immediate postoperative period. There is frequent complain of pain, swelling and trismus due to acute inflammatory response to the surgical procedure. Aprotinin, an antifibrinolytic naturally occurring protease inhibitor was assessed for its efficacyin reducing post surgical complications after surgical removal of Mandibular 3rd molar. **Methodology**: 85 randomly selected patients who required simultaneous surgical removal of bilateral impacted mandibular third molars were included in the study. Before the procedure, randomly selected side of the patient was injected at buccal side with 1ml (10,000 IU) of aprotininsubmucosally around the surgical siteand the contra lateral side with 1ml of isotonic saline as a control. After adequate surgical anesthesia, the surgical removal of third molar was conducted in a similar manner on both sides in all the patients. Post-operatively the patients were evaluated for pain, trismus and swelling for one week (1st, 3rd and 7th day). **Results:** It was observed that there was noticeable clinical reduction in post-operative pain, swelling and trismus & there were no adverse effects of aprotinin. **Conclusion:**Current pharmacologic agents which are used , have adverse effects and associated morbidity which still pose a problem, Aprotinin, a naturally occurring agent could be efficiently used after surgical removal of third molar removal in management of post surgical symptoms and improve patient comfort and quality of life.

**Key Words:** Aprotinin; Pain; Proteolytic enzyme; Swelling; Trismus.

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This article may be cited as: Raval R, Singh P, Choudhary A, Kundu A, Kaur M, Shergill DK, Kaur J. Effect of submucosal aprotinin injection on comparative evaluation of postoperative complications after surgical removal of mandibular 3rd molar. J Adv Med Dent Scie Res 2017;5(4):26-31.

| Access this article online | |
|---|---|
| Quick Response Code | Website: www.jamdsr.com |
| | DOI: 10.21276/jamdsr.2017.5.4.7 |

## INTRODUCTION:

The surgical removal of impacted third molars is considered as one of the most frequent minor surgical procedures in oral and maxillofacial surgery. Removal of an impacted lower third molar causes pain, swelling and difficulty in opening of the mouth (trismus) due to acute inflammatory response to surgical trauma. Reduction of this discomfort becomes essential for the success of surgical practice.[1,2] Prolonged periods of pain and inflammation are mediated by release of local prostaglandins.[3]Post operative oedema is the consequence of tissue injury during surgery, the raising of muscular attachments, and as a result of direct trauma to blood and lymph vessels. This condition represents fluid accumulation in the interstitial area due to transudation from the injured blood vessels and fibrin obstruction of lymph drainage. [4]

The ideal pharmacological agent to use after third molar surgery should lighten pain, reduce swelling and trismus. Presently, surgeons use corticosteroids[3, 5] NSAIDS, enzyme preparations, cold packs [6] low level laser therapy[7] to reduce postoperative discomfort. Even thoughall these agents areproficient in management of post operative complications, adverse effects still pose a serious problem.[8,9] Soclinicians are seeking some superior drug for the same.

Aprotinin, a naturally occurring protease inhibitor isolated from bovine lung tissue, containing 58 amino acid residues, inhibits mainly the trypsin, chymotrypsin like enzymes including those concerned with the formation of mediators of acute inflammation[10]. Aprotinin indirectly inhibits bradykinin, inactivates plasmin, a proteolytic enzyme responsible for digesting fibrin and other plasma proteins. It activates the potent anaphylotoxin C3a in the complement cascade.[11,12]

This study aims at assessing the efficacy of this polypeptide, aprotinin in reducing the post surgical pain and swelling, in patients undergoing surgical removal of impacted lower third molars under local anesthesia.

**METHODOLOGY**:

Total 85 patients between the age group of 16-35 years irrespective of cast, gender and socio-economical status were included in the study on random basis with bilaterally impacted mandibular third molars with similar degree of impactions (moderate to difficult according to Pederson's scale[13]) All the patients were undergone surgical removal of impacted third molars on both sides simultaneously. Patients with systemic diseases were excluded. All patients were explained the details about the surgical procedure and the possible complications associated with the same. A written informed consent was obtained from all the patients prior to surgical procedure. All the patients were checked for allergic reaction to Aprotinin injection by skin patch test. Preopeartively, The case study side of the patient was selected on random basis to be injected with 1ml of 10,000 IU/ml injection of aprotinin (Fig-1) submucosally around surgical site and the contra lateral side with 1ml of isotonic saline (control side).

**PROCEDURE:**

All the patients underwent surgical removal of bilaterally impacted mandibular 3rdmolar under local anesthesia. Inferior alveolar, lingual and long Buccal nerve block wasadministered first on right side and next on left side.The small 'V' shaped incision was made with one point at the distobuccal lineangle of the second molar. One distal limb, which follows the external oblique ridge, andanterior limb avoids the gingival sulcus of second molar and extends downward to the

mucogingival junction Mucoperiosteal flap was reflected and retracted with austin's retractor. Bone was removed with rose head bur and tapered fissure bur no. 702 adapting guttering technique. Constant irrigation using sterile isotonic saline solution was used to reduce the heat generated. The teeth were removed by odontectomy or intoto. The irregular bone and the gingival margins margins were parried; the wound was irrigated with sterile isotonic saline solution. Flap was repositioned and sutures were placed on the distal arm for primary healing, using non-resorbable 3-0 black braided silk. (Figure 2) Post operatively, all patients received amoxicillin 500mg TID and Diclofenac sodium 50 mg TID for 3 days. Patients were advised to use chlorohexidine mouth wash (0.12%) thrice daily post operatively for 7 days post-operatively. The sutures were removed on the seventh post operative day. All patients were given feedback forms with daily pain records to be filled during postoperative 1st,3rd and 7th day and Trismus & swelling were also evaluated on the same days.

**POSTOPERATIVE EVALUATION-**

Pain was evaluated and recorded in the postoperative period using a visual analog scale from value 0 to 10. (Figure-3) The maximum mouth opening was evaluated by measuring the distance between the incisal edges of the upper and lower central incisors, using divider in centimeters. (Figure-4)

Evaluation of the facial swelling was performed using a horizontal and vertical guide as four reference points: attachment of the ear lobe, corner of the mouth, outer canthus of the eye and angle of the mandible.(Figure-5)The horizontal measurement corresponds to the distance between the corner of the mouth to the attachment of the ear lobe following the bulge of the cheek.The vertical measurement corresponds to the distance between the outer canthus of the eye to the angle of the mandible.The arithmetic means of the two measurements determine the facial measure. The percentage of facial swelling was obtained from the difference between measurements made in the preoperative and postoperative periods, dividing the result by the value obtained in the preoperative period and multiplying it by 100.

$$\frac{\text{Postoperative value} - \text{preoperative value}}{\text{Preoperative value}} \times 100$$

= % of facial swelling.

The mean value and standard deviation for each of the parameters was considered and checked for statistical significance using the Mann Whitney test, which is used for non-parametric values.

**RESULTS:**

All 85 patients completed the study.

**Post operative pain and pain distribution:**

When pain was assessed, 70 (82%) of the patients chose aprotinin side to be less painful than the control. 8 (9%) patients chose control side less painful and 7 (8.5%) patients found no difference between study and control side . Mean readings were taken on each 1st, 3rd, and 7th post operative days according to the degree of pain the patients described verbally as No pain, mild, moderate, severe, very severe and worst pain (0, 1, 2, 3, 4 and 5). No patients complained of very severe pain and worst possible pain. Mann-Witney U test was used to calculate the difference in pain between aprotinin and control side. Subjects experienced less pain on the aprotinin side compared to control side post operatively. On the post operative days the mean pain scores on the

aprotinin side was less compared to the control side (Table 1 and Graph 1)

**Measurement of Swelling:**
The swelling was measured on pre operative, 1st, 3rd and 7th post operative days. On the 1st post operative day, the mean swelling was ~2.85 on the aprotinin side, whereas on the control side the mean was ~5.39. On 3rd post operative day the mean swelling was ~4.34 on the aprotinin side, whereas on the control side the mean was ~7.65. On the 7th post operative day the mean swelling was ~1.68 on the aprotinin side, whereas on the control side the mean swelling was ~ 2. The difference in swelling was statistically significant. (Table 2 & Graph 2) It can be observed that swelling size is evidently lesser in the aprotinin(case) side compared to control.

**Measurement of Trismus:**
Maximum interincisal opening was noted pre operatively and on follow up visits. There is ~5 mm of reduction of maximum interincisal opening overall on last follow up visit. (Table 3)

**Figure 1:** Vial of Aprotinin injection

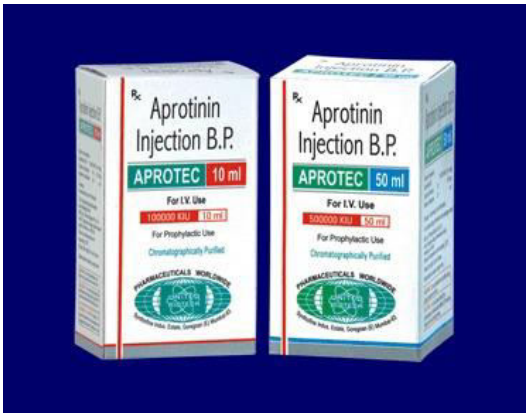



**Figure 2:** Surgical steps for the removal of impacted mandibular 3rd molar

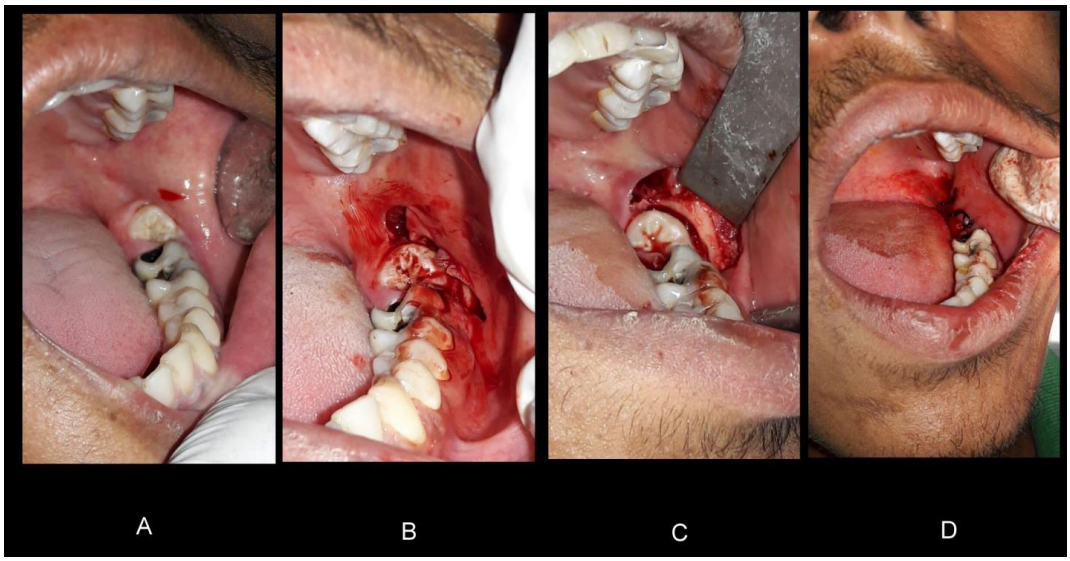



**Figure 3:** Visual analogue scale

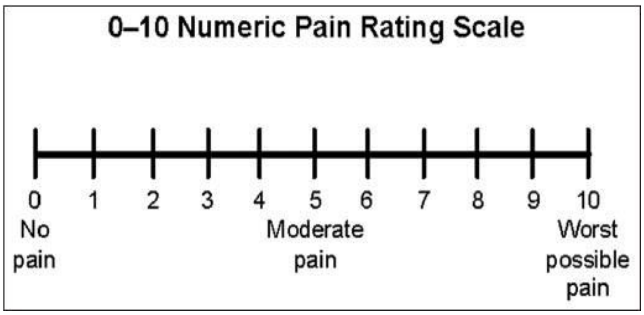



**Figure 4:** Maximum mouth opening measurement by Caliper

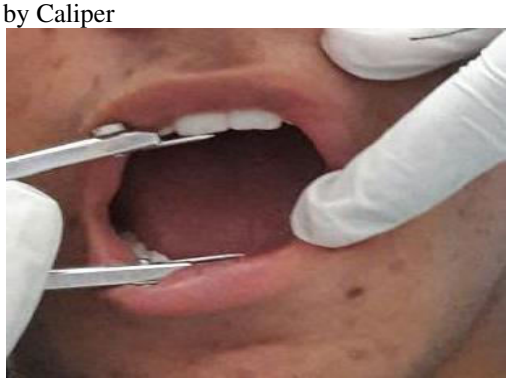
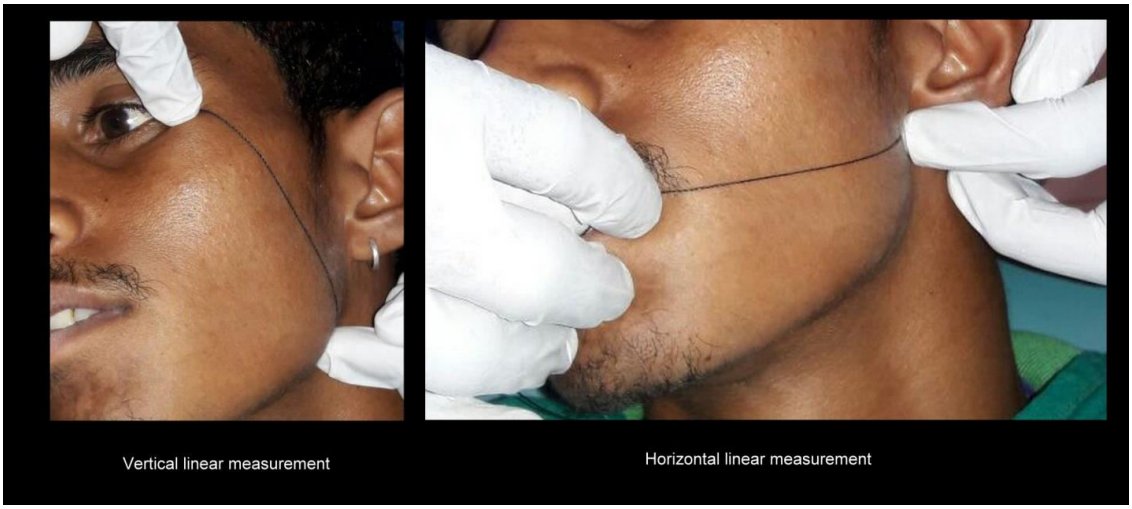
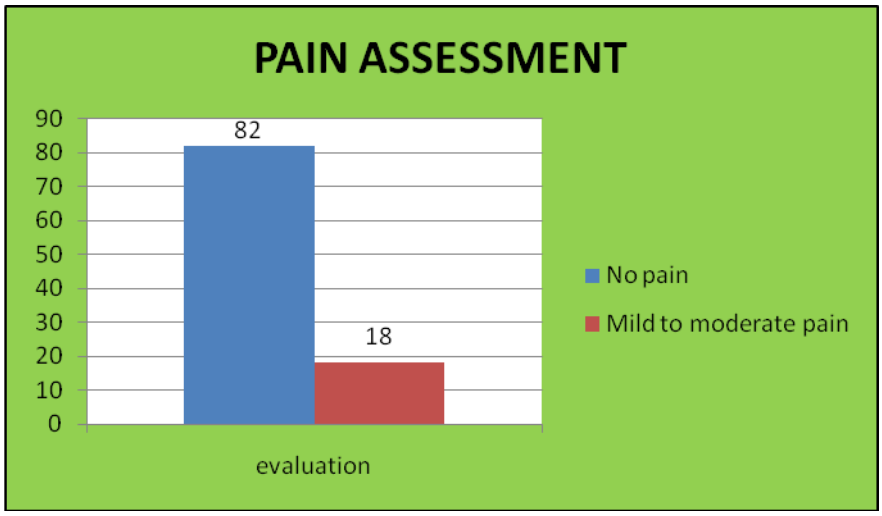


**Figure 5:** Linear measurement of swelling transferred to scale




**Graph 1-** showing the pain assessment on case side

**Table 1:** Pain distribution in study and control side for all the patients on the 1st, 3rd& 7th post-operative days.

**STUDY SIDE** (n=85)

| PAIN SCORE | No. of patients 1st post-op day | No. of patients 3rd post-op day | No. of patients 7th post-op day |
|---|---|---|---|
| **NO PAIN** | 69 | 64 | **70** |
| **MILD PAIN** | 11 | 14 | **13** |
| **MODERATE PAIN** | 5 | 7 | **2** |
| **SEVERE PAIN** | **0** | **0** | **0** |

**CONTROL SIDE** (n=85)

| PAIN SCORE | No. of patients 1st post-op day | No. of patients 3rd post-op day | No. of patients 7th post-op day |
|---|---|---|---|
| **NO PAIN** | 23 | 15 | **20** |
| **MILD PAIN** | 54 | 62 | **58** |
| **MODERATE PAIN** | 5 | 8 | **7** |
| **SEVERE PAIN** | **3** | **0** | **0** |

**TABLE 2:** Descriptive statistics of the study & control groups of swelling (percentage of swelling)

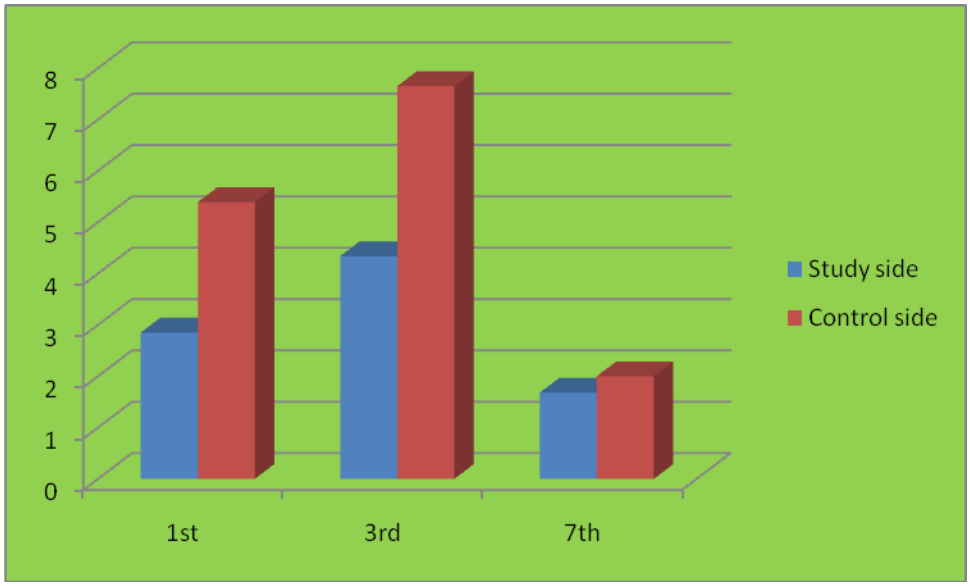
| Study groups | Study | | Control | |
|---|---|---|---|---|
| | Mean | SD | Mean | SD |
| 1st Day | 2.85 | 0.76 | 5.39 | 1.54 |
| 3rd Day | 4.34 | 0.67 | 7.65 | 1.86 |
| 7th Day | 1.68 | 0.64 | 2.00 | 1.73 |

NOTE: SD = Standard Deviation.

**TABLE 3:** Descriptive statistics of mouth opening

| Max mouth opening (mm) | Value | |
|---|---|---|
| | Mean | SD |
| Pre operative | 38.16 | 4.78 |
| 1st Day | 30.2 | 5.16 |
| 3rd Day | 32.76 | 5.24 |
| 7th Day | 35.92 | 4.67 |

NOTE: SD = Standard Deviation.




**Graph 2:** Showing assessment of swelling on case and control side (in percentage) on follow up days

## DISCUSSION

Surgery of the impacted third molars is one of the most frequently performed procedures in the oral and maxillofacial surgical practiceand can lead to a variety of immediate and late postoperative discomfort. These postoperative discomforts may be related to the surgical technique.[1]

In the present study the efficacy of aprotinin in management of post operative pain, swelling and trismusafter mandibular third molar surgery was evaluated. It has been observed that use of aprotinin clinically seldom causes hypersensitivity reaction[10]. Surgical removal of impacted third molar causes moderate to severe pain and forms a practical model for assessing the efficacy of analgesics [4, 14].The interpretation of pain, experienced by the patients has always been a challenge since it is based on individual perception. Based on studied methods of pain assessment the Visual Analogue Scale (VAS) was used to evaluate pain in the present study[14]. Evaluation of facial swelling resulting from surgical procedure was difficult as swelling involves a three dimensional volumetric change at the tissue and cellular level. Methods used to estimate swelling include photographic analysis, modified face-bow, linear measurementsand subjective assessment[16-19]. It has been observed that linear measurements are sensible, practical &reliable technique for measuring swelling[16]. In support to these, linear measurement for assessing post-operative facial size was incorporated in the present study. Linear measurements of swelling on the 1st, 3rd and the 7th post-operative days were comparatively lesser on the side of the face in which aprotinin was injected than the control side The facial size clinically was seen to reach normal on the aprotinin side by the 7th post-operative day but not on the control side.

The post operative pain assessment reflected that pain was considerably reduced on aprotinin side of the mouth

following extraction of third molars on all follow up days. The pain reduction by aprotinin was highly significant on the 1st and 2nd post-operative days and significantly lesser on the 7th post-operative day. The results of the present study was similar to a previous study conducted to evaluate the value of aprotinin in third molar surgery and which concluded that aprotinin reduced pain and swelling post-operatively[20].

Trismus following mandibular 3rd molar surgery is also a complication which makes the patient uncomfortable in post operative period. Due to injection of aprotinin reduction of trismus has also been noticed. Otherwise the amount of trismus is somewhat more in routine surgical procedure of 3rd molar removal. [2,4,18.]

A question was there regarding healing of the sockets on the side where aprotinin was given which might be compromised because of inhibition of the initial acute inflammatory reaction. However, when sockets were checked for adequate healing after 1 week, both the sides showed satisfactory healing in all the patients. When the patients were reviewed a week following extractions, most confirmed that aprotinin side of the mouth had been less painful and the discomfort was lesser than the control side. Results from this investigation may be correlated with the unique property of aprotinin in inhibiting the mediators of acute inflammation. These mediators, which cause pain when applied to nerve endings and increase vascular permeability, were not activated and therefore the tissue reaction to trauma was reduced. In view of this observation injection of 1ml aprotininsubmucousally around the surgical site 5 minutes before the surgical procedure markedly reduces post-operative pain and swelling clinically, thereby helping the patient resume his/her routine. Based on these observations it may be concluded that aprotinin proved to have definite benefits for relief of postoperative pain and swelling clinically, but the limitations recommend further studies with the use of aprotinin in a larger number of patients undergoing surgical removal of mandibular third molar and comparative studies with other drugs like corticosteroids to ascertain its efficacy conclusively.

## CONCLUSION:

This study concluded that, the use of submucosalaprotinin injection in and around surgical site , especially preoperatively while surgical removal of impacted mandibular third molars will reduce postoperative facial swelling, pain and trismus. Those patients were more comfortable than control group after third molar surgery. Due to this, acceptance of surgical procedure can be improved overall.

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**Source of support:** Nil **Conflict of interest:** None declared