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ORIGINAL ARTICLE

A Double Blind Trial to Assess the Clinical Efficacy of Aprotinin in Control of Pain, Edema and Trismus in Mandibular Third Molar Surgery

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ABSTRACT

Introduction: *The removal of impacted mandibular third molar and the resultant tissue, and cellular destruction brings about the production and release of several inflammatory mediators such as a histamine, bradykinin, leukotrienes, prostaglandins, andetc., and produce pain, edema and trismus. Aprotinin is a naturally occurring protease inhibitor isolated from bovine lung tissue, containing fifty-eightaminoacyl residues, and inhibits many of the trypsin like enzymes including those concerned with the formation of certain mediators of acute inflammation. Considering all, a double blind trial was conducted on forty healthy patients to assess the efficacy of aprotinin in control of pain,edema, and trismus in bilateral symmetrical impacted mandibular third molar surgery.*

Materials and Methods: *A double blind clinical trial compared the effects of local infiltration of 1 mL of saline on one side of mouth and aprotinin (10.000 international units) on the other side in patients requiring extraction of both mandibular third molars. Pain, edema and trismus were assessed.*

Results: *In overall comparison of the patients with pain and no pain, at the end of seventh post-operative day, 97.5% patients had no pain in the aprotinin group, whereas 12.5% patients had no pain in the control group. Regarding the assessment of swelling with the aprotinin side, aprotinin reduced post-operative edema both on the second and seventh days. Opening the mouth was significantly better in the aprotinin treated group.*

Conclusion: *When analyzed statistically, aprotinin showed significantly reduced post-operative pain, edema, and trismus compared to the control group.*

Key words: *Aprotinin, Plasmin, Kallikrein*

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ÖZET

Mandibuler Üçüncü Molar Cerrahi Sonrası Ağrı, Ödem ve Trismusun Kontrolünde Aprotininin Etkinliğini Değerlendiren Çift Kör Çalışma

Giriş: *İmpakte üçüncü molar diş ve remant dokunun çıkarılması sonucu oluşan hücresel yıkıma bağlı olarak histamin, bradikinin, lökotrien, prostaglandin ve benzeri maddeler salınarak ağrı, ödem ve trismusa neden olur. Aprotinin büyük baş hayvanların akciğerinden izole edilmiş doğal olarak bulunan bir proteaz inhibitörüdür. Elli sekiz aminoasil rezidüleri içerir ve tripsin gibi enzimleri*

baskılayarak akut inflamasyon mediyatörlerinin oluşumunu etkiler. Bu veriler ışığında kırk sağlıklı bireye bilateral impakte üçüncü molar diş çekimi sonrası ağrı, ödem ve trismusun kontrolünde aprotininin etkinliği çift kör randomize çalışma ile değerlendirildi.

Materyal ve Metod: *Çift kör çalışmada bilateral üçüncü molar dişleri çekilen 40 sağlıklı bireyde bir tarafa salin diğer tarafa aprotinin (10.000 internasyonal ünite) lokal olarak infiltre edilmesiyle gerçekleştirildi. Ağrı, ödem ve trismus değerlendirildi.*

Bulgular: *Ameliyat sonrası yedinci günde ağrı değerlendirilmesi yapılan hastalarda aprotinin grubunda %97'sinde ağrı yoku. Kontrol grubunun %12.5'inde ağrı saptanmadı. Ödem ve buna bağlı şişlik değerlendirmesinde aprotinin verilen grupta ameliyat sonrası ikinci ve yedinci günlerde şişlik daha azdı. Ayrıca bu gruptaki hastaların çene açıklıkları diğer gruba göre daha fazlaydı.*

Sonuç: *Sonuçların istatistiksel analizi aprotinin verilen grupta ağrı, ödem ve trismusun kontrol grubuna oranla belirgin şekilde daha az olduğunu gösterdi.*

Anahtar kelimeler: *Aprotinin, Plazmin, Kallikrein*

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INTRODUCTION

In oral surgery, the major causes of post-operative difficulty are edema, trismus, and pain. The removal of impacted mandibular third molar and the resultant tissue, and cellular destruction brings about the production and release of several inflammatory mediators such as histamine, bradykinin, leukotrienes, prostaglandins, and etc., and produce pain, edema and trismus. Aprotinin is a naturally occurring protease inhibitor isolated from bovine lung tissue, containing 58 aminoacyl residues, and it inhibits many of the trypsin like enzymes including those concerned with the formation of certain mediators of acute inflammation. Considering all, a double blind trial was conducted on forty healthy patients to assess the efficacy of aprotinin in control ofpain, edema, and trismus in bilateral symmetrical impacted mandibular third molar surgery.

APROTININ

Aprotinin is isolated from bovine lung and other tissues. This serine protease inhibitor is a single polypeptide of 6512 deltons, showing 4 lysine residues responsible for the inhibition of trypsin like enzymes,as shown in Figure 1. It was discovered by Kraut et al. (1930), and Kunitz and Northrup (1936) to inhibit kallikrein and trypsin. Aprotinin was introduced in clinical use in the 1950s. Its role was limited only in the treatment of pancreatitis. Recently, its ability to reduce bleeding has been discovered. It has been used in the field of cardiovascular surgery where aprotinin has dramatically reduced surgical bleeding and the need for donor blood transfusion. Aprotinin has also been used in hemorrhagic shock, obstetric and gynecological disorders, urological surgery, and etc. Aprotinin acts as a potent inhibitor of serine proteases, including human trypsin, plasmin, plasma kallikrein, and tissue kallikrein. Aprotinin inhibits kinin generation and activation of complement system through enzyme kallikrein, thus acting as a potent anti-inflammatory agent. Bradykinin, a non-peptide, is 10 times more potent asa vasodilator than histamine, and causes intense pain when applied to tissue. Since bradykinin is dependent on kallikrein for its activation, aprotinin inhibits this mediator. Plasmin, responsible for the degradation of fibrin, is inhibited by aprotinin (Figure 2). After a 24-hour IV infusion of aprotinin at a dosage of 250.000 KIU/hour (35 mg), a constant plasma concentration of 40-50 KIU/mL is obtained in patients. Aprotinin is metabolized to shorter peptides by lysosomal activity in kidneys. Unchanged aprotinin excreted in urine, a biphasic elimination pattern with an initial half-life of 0.7 hours and terminal half-life 7 hours, was observed.

MATERIALS and METHODS

The present study was conducted in the Department of Oral and Maxillo facial Surgery PMNM Dental College, Bagalkot. Forty healthy patients, with an age group of 16-30 years and a symmetrical impacted mandibular third molar, were included into the study. Pre-operative pain assessment was recorded verbally as nil, mild, moderate, and severe. Mouth opening was measured by interincisal distance. The external facial measurement was made by taking five fixed points on the face as,

S1-From the angle of mandible to lateral canthus of the eye.

S2-From the angle of mandible to ala of the nose

S3-From the angle of mandible to corner of the mouth

S4-From the angle of the mandible to the menton

S5-From the ala of the nose to tragus of the ear.

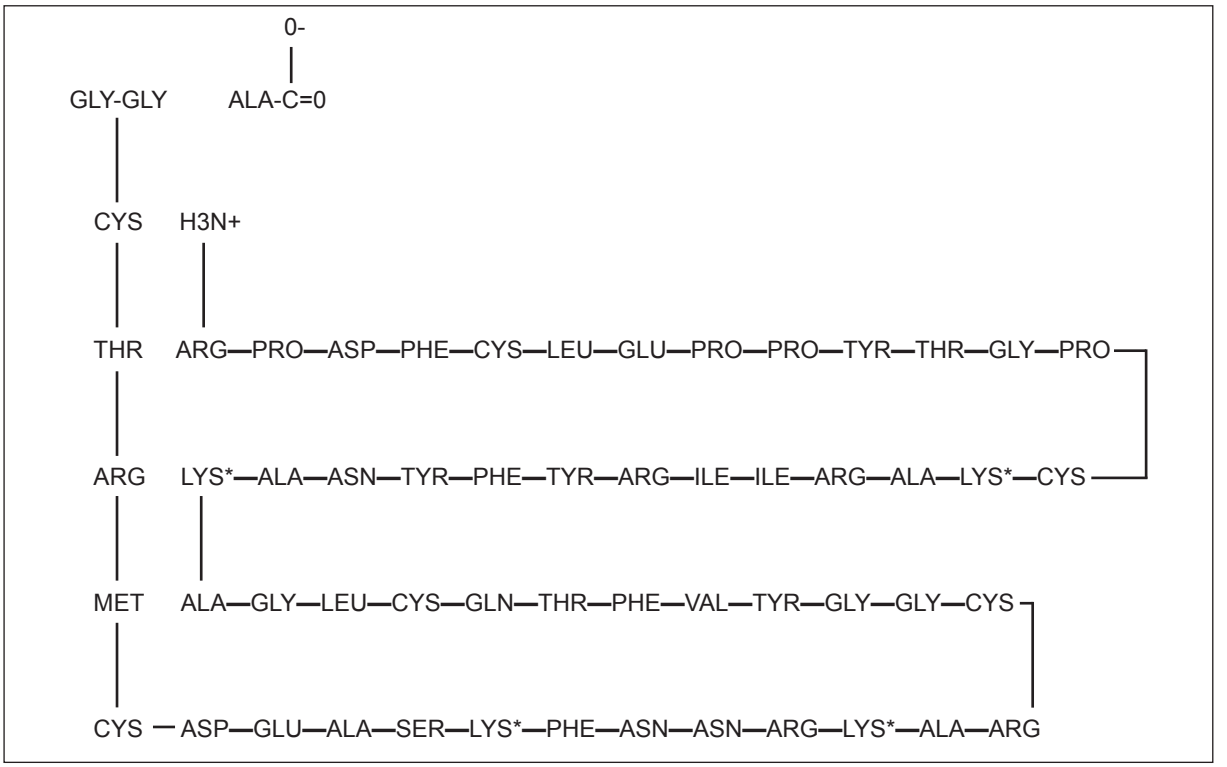

Figure 1. The structural formula of aprotinin.

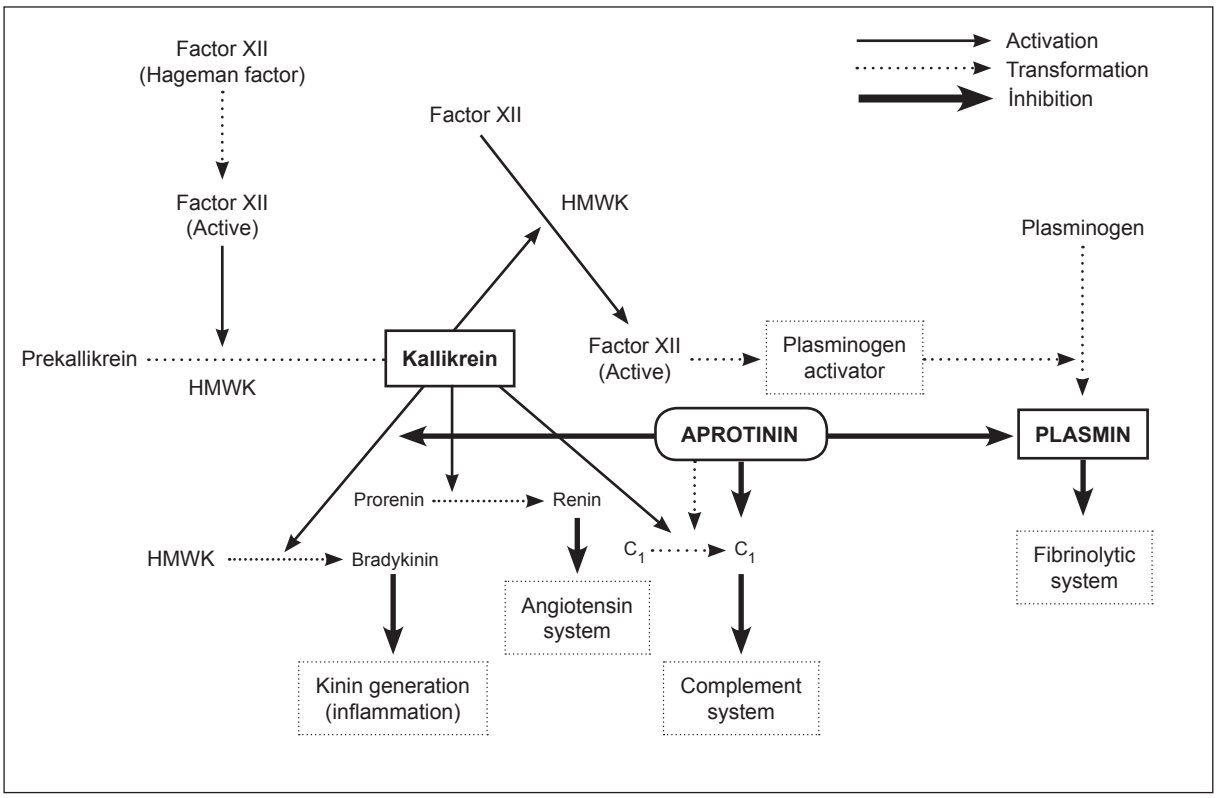

Figure 2. Action of aprotinin.

The procedure included 1 mL of drug A or drug B infiltrated locally at surrounding tissues of the mandibular third molar five minutes before the operation, and patients were called after two weeks for the extraction of the other side. It was only at the end of the study that the drugs were decoded consequently, and patients were divided into aprotinin and control groups. The study consisted twenty-eight male and twelve female patients.

RESULTS

In overall comparison of the patients with pain and no pain, at the end of seventh post-operative day, 97.5% patients had no pain in the aprotinin group, whereas 12.5% patients had no pain in the control group, as shown in Figure 3. Regarding the assessment of swelling with the aprotinin side, aprotinin reduced post-operative edema both on the second and seventh days, as shown in Figures 4 to 8. Opening the mouth was significantly better in aprotinin treated group, as shown in Figure 9.

DISCUSSION

The post-operative sequel of impacted mandibular third molar surgery is manifestations of inflammation due to tissue injury. Strategy for managing these clinical symptoms is aimed at interfering with the inflammatory process to limit the intensity and shorten the duration of clinical signs of inflammation pain, trismus, and edema. Aprotinin inhibits many of trypsin like enzymes including those concerned with the formation of certain mediators of acute inflammation[1]. Kallikrein, which forms the potent chemical mediator bradykinin by enzymatically cleaving high molecular weight kininogen in the blood, is one such enzyme inhibited by aprotinin. Bradykinin, a nonpeptide, is 10 times more potent as a vasodilator than histamine, and causes intense pain when applied to tissue. Since bradykinin is dependent on kallikrein for its activation, aprotinin indirectly inhibits these mediators[1]. The proteolytic enzyme, plasmin, responsible for digesting fibrin and other plasma proteins, and activating the potent anaphylotoxin C3a in the complement cascade, is also inactivated by aprotinin. The digestion products of fibrin which have anticoagulant properties and ability to increase vascular permeability are therefore also inhibited[1]. Aprotinin also inhibits L-selectin and P-selectin. Thus, aprotinin has a potential anti-inflammatory and analgesic properties. Systemic administration of aprotinin is employed to reduce blood loss and blood use after cardiopulmo-

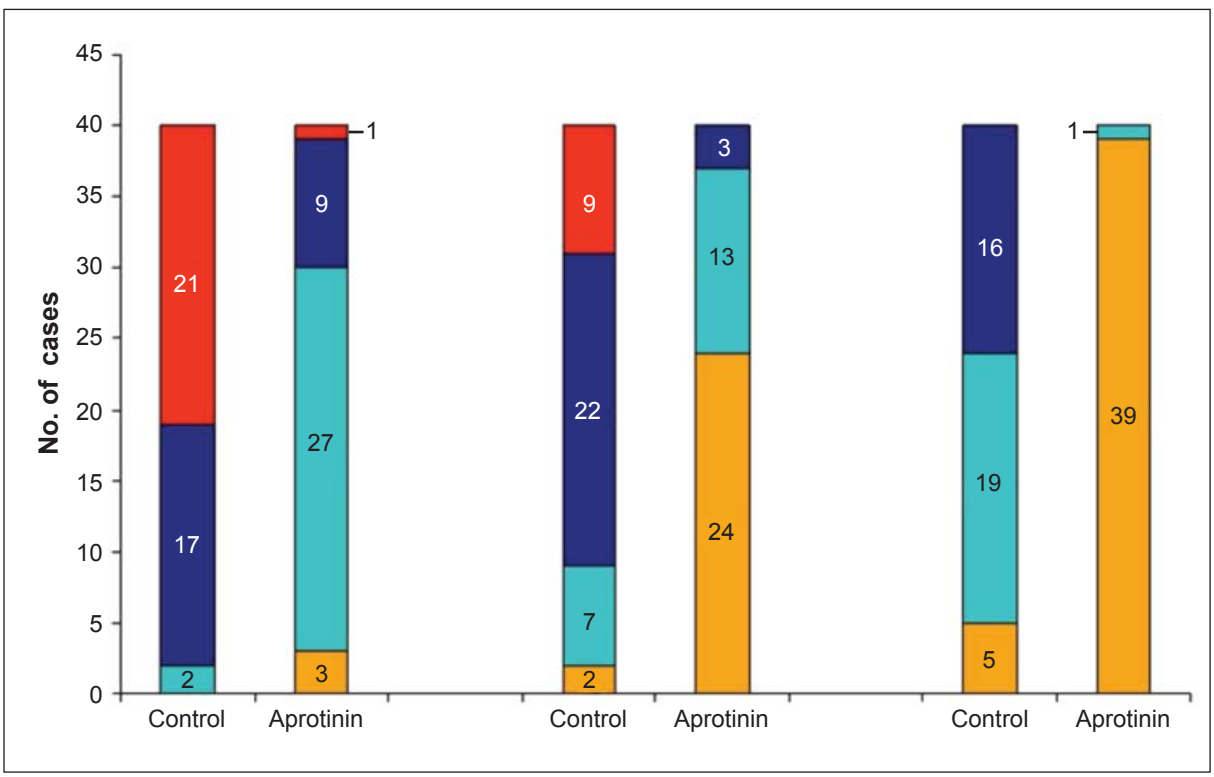

Figure 3. Comparison of pain.

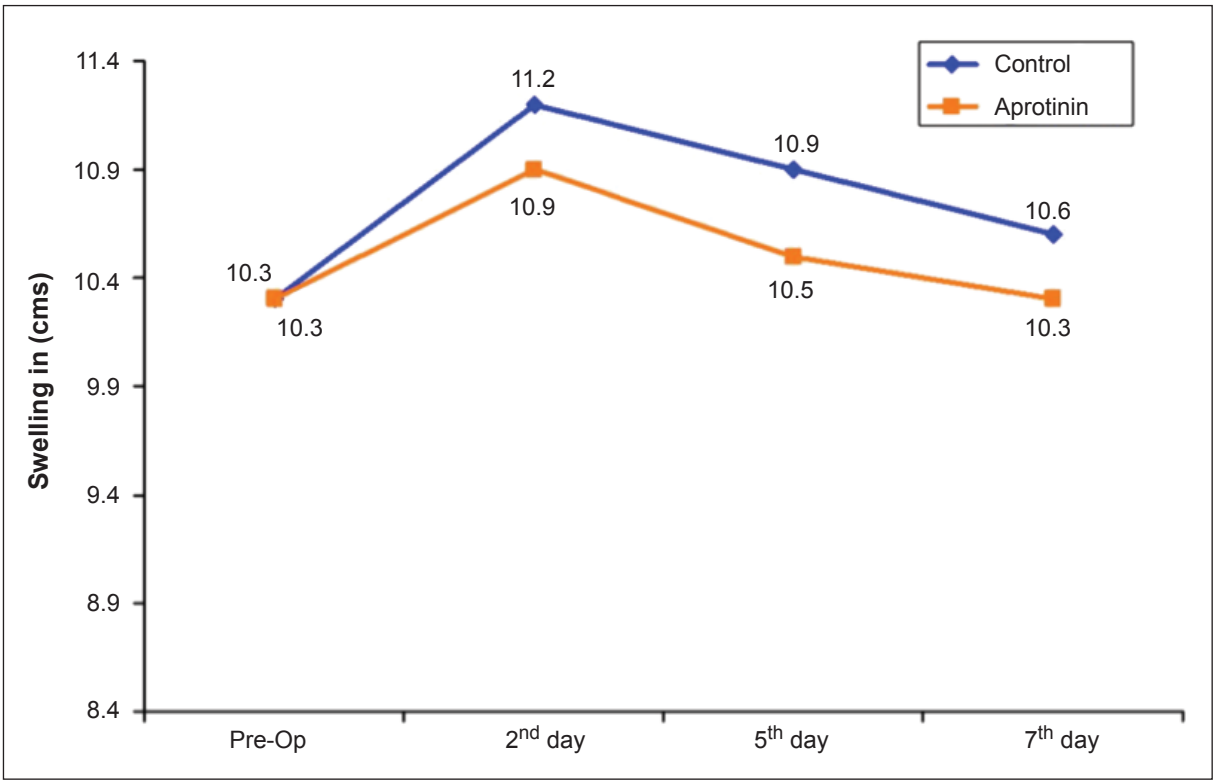

Figure 4. S1 swelling comparison.

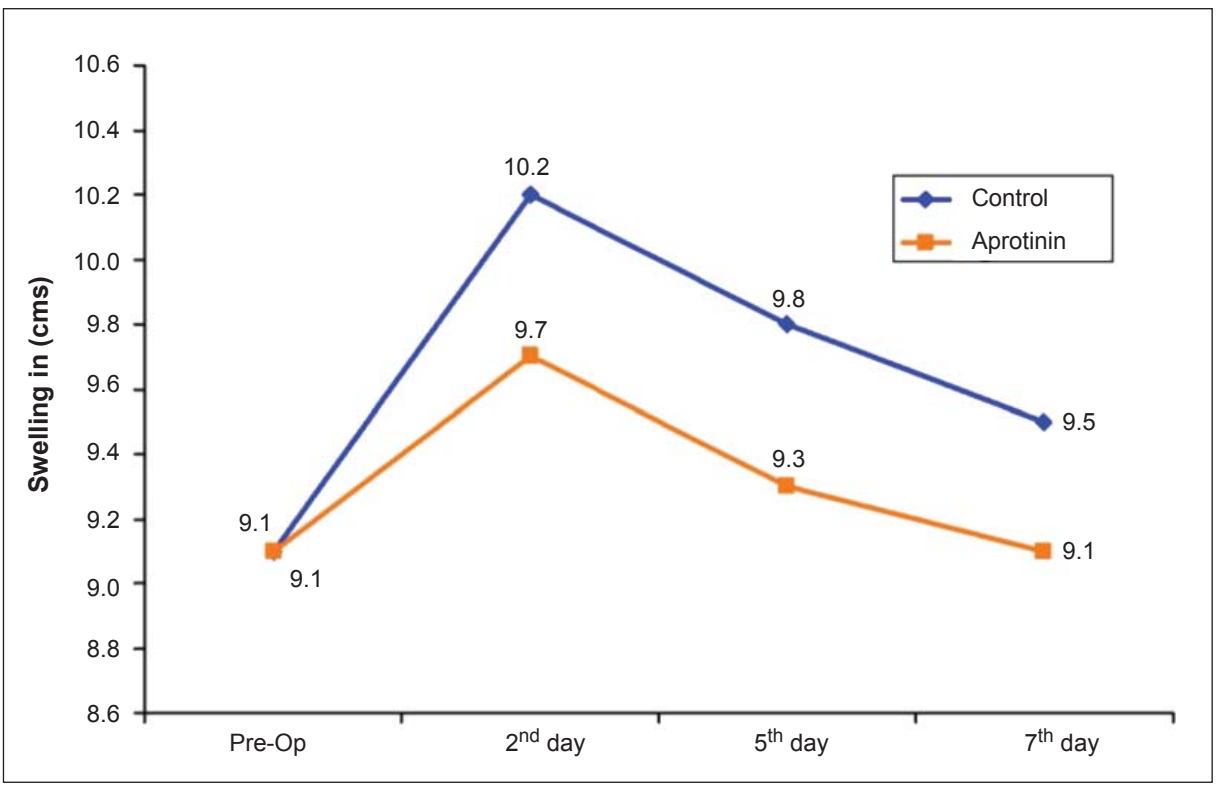

Figure 5. S2 swelling comparison.

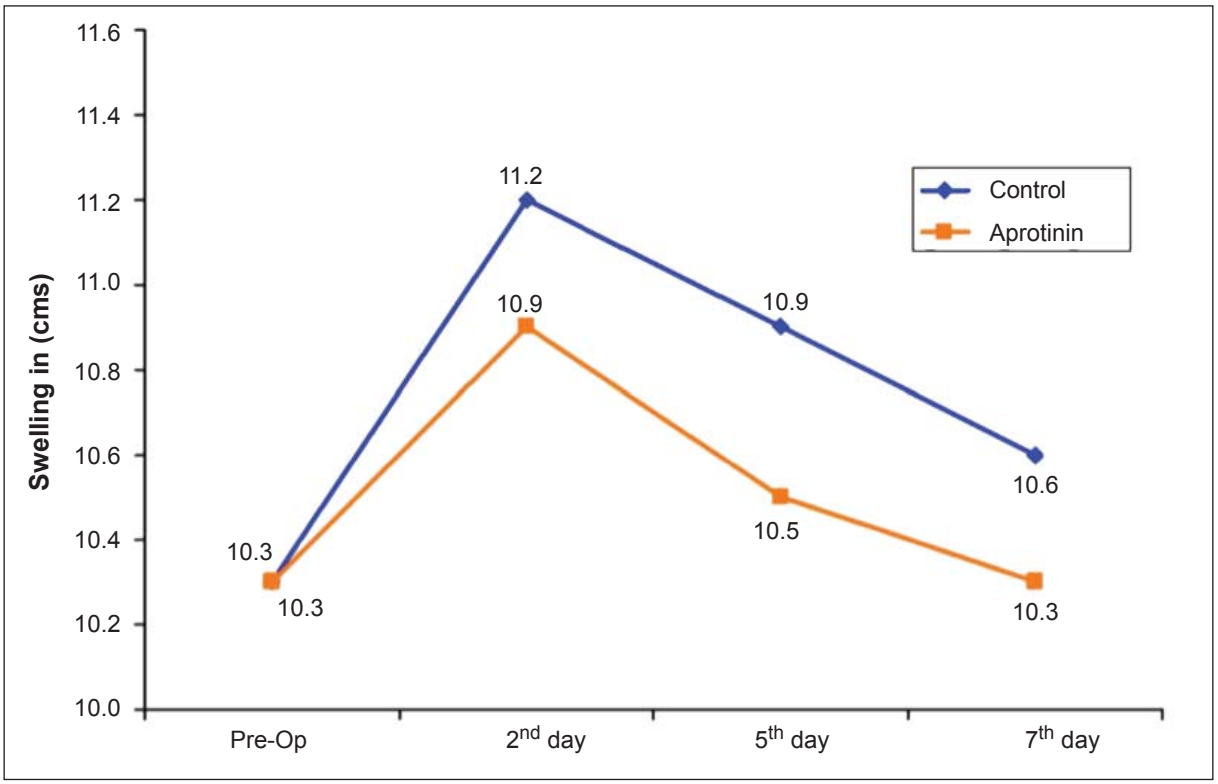

Figure 6. S3 swelling comparison.

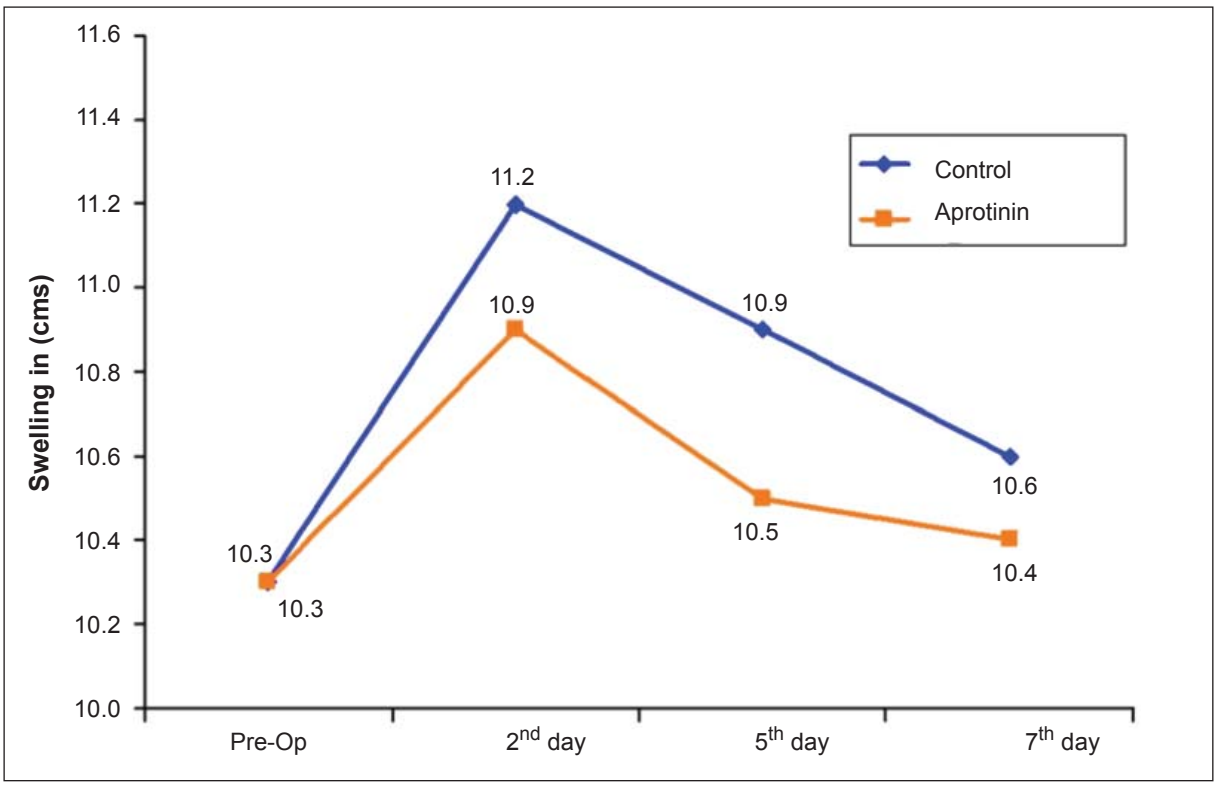

Figure 7. S4 swelling comparison.

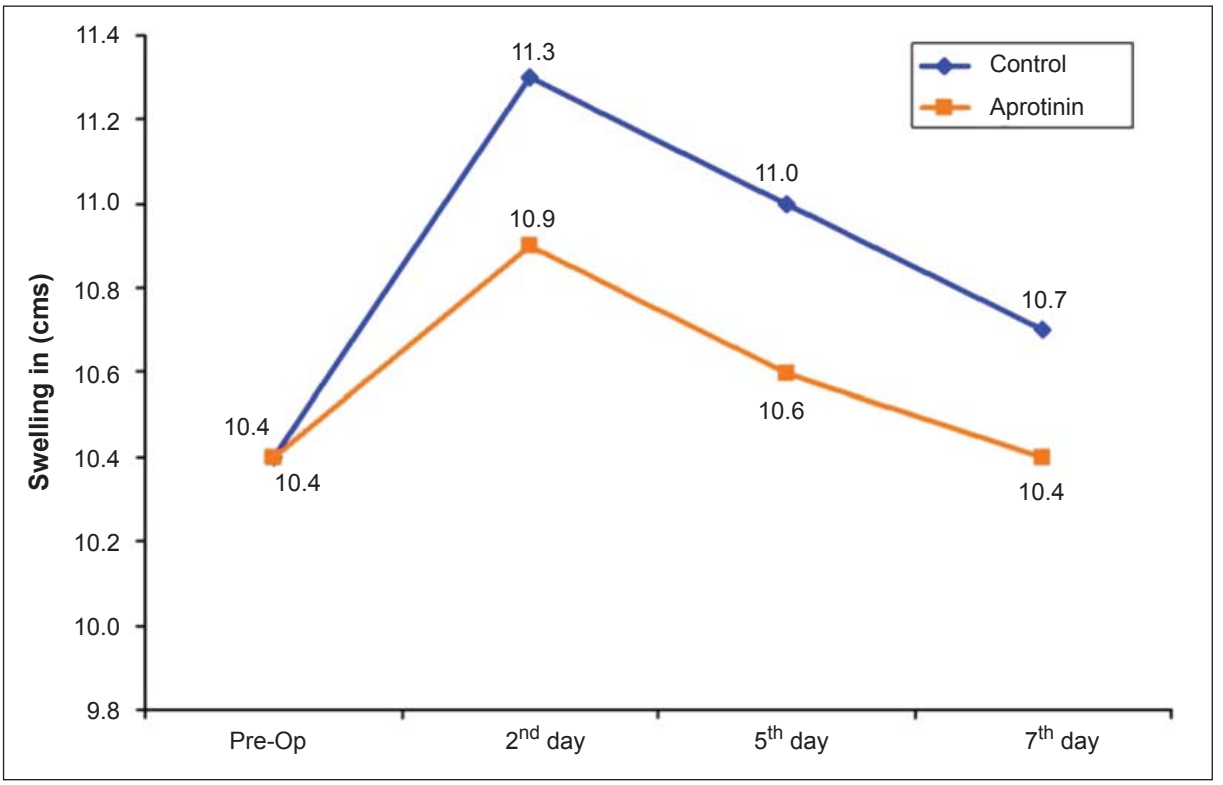

Figure 8. S5 swelling comparison.

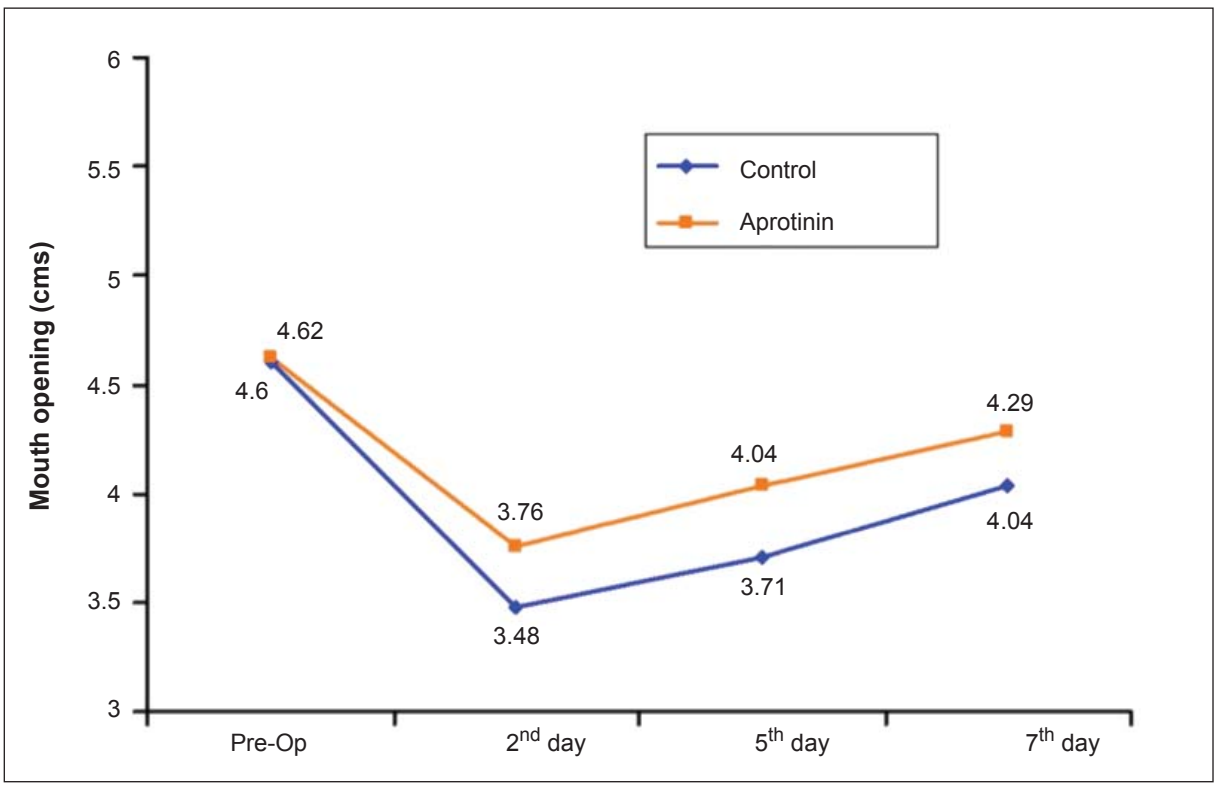

Figure 9. Comparison of mouth opening.

nary bypass, liver transplantation, and orthognathic surgery[2-4]. The drug is available in the form of suspension as 10 mL in 1 ampoule containing 14 mg of aprotinin corresponding to 1, 00, 000 KIU in sterile solution, and as 50 mL in 1 vial containing 70 mg aprotinin corresponding to 5, 00, 000 KIU in sterile isotonic solution.

In our study, 1 mL of aprotinin was infiltrated locally into soft tissues surrounding mandibular third molar. Aprotinin proved to be clinically, statistically, and significantly better over control group in the management of post-operative pain, swelling, and trismus. The same operator, who was using the same technique, same type of impaction, injecting the drug in a double blind manner as the color of both drugs are the same and are stored in a same sized container, ruled out any deviation or discrepancy in the manner this study was conducted.

CONCLUSION

It was concluded that aprotinin, a protease inhibitor, was effective in controlling post-operative pain, edema, and trismus. Though this study was standardized to the maximum possible extent, it is humbly suggested and hoped that more studies are undertaken to compare the anti-inflammatory properties of aprotinin and corticosteroids.

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