Original Article

Efficacy of tranexamic acid in prevention of alveolar osteitis following surgical removal of impacted mandibular third molar

ABSTRACT

Context: Many preventive measures are described to avoid alveolar osteitis (AO) during third molar surgery (TMS), but very few are found to be effective. Tranexamic acid (TA), an antifibrinolytic agent, impedes the proteolytic degradation of fibrin and prevents blood clot disintegration.

Aims: The study was conducted to determine the efficacy of intra-alveolar application of TA soaked in Gelfoam in prevention of AO.

Settings and Design: This was a randomized control trial.

Materials and Methods: A total of 200 patients (100 in control group and 100 in study group) reporting for TMS were allocated randomly. Following surgery, TA soaked in gel foam was placed in socket and sutured in the study group, while in the control group, closure was done by suturing. Patients followed subsequently to observe the incidence of AO, pain severity, and duration of healing after AO.

Statistical Analysis: *Z*-test, Mann–Whitney test, and *t*-test were applied, respectively, to compare the incidence of AO, severity of pain, and duration of healing between the two groups.

Results: The incidence of AO in the control group was 18% and 6% in the study group. Patients in the control group experienced severe pain as compared to patients in the study group. The duration of healing varied from 12 to 16 days in the control group, but in the study group, it was <10 days.

Conclusion: TA significantly reduces the incidence of AO in addition to the reduced severity of pain and enhanced healing. We recommend the routine use of TA, owing to its astonishing rewards.

Keywords: Alveolar osteitis, impaction, prevention, third molar surgery, tranexamic acid

INTRODUCTION

Alveolar osteitis (AO), commonly known as dry socket, is a potential complication of tooth extraction that occurs most commonly in mandibular molar region. Eighteen definitions of AO have been reported. The most accepted and popular definition of AO is "postoperative pain inside and around the extraction site, which increases in severity at any time between the 1st and 3rd days after the extraction, accompanied by a partial or total disintegrated blood clot within the alveolar socket with or without halitosis."[1]

Dry socket occurs in approximately 1%–5% of all extractions and in up to 38%–45% of mandibular third molar extractions.[1,2]

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The symptoms of AO start with onset at 2–4 days after extraction, which includes severe and intense pain that mainly radiates to the ear and neck. The surrounding mucosa becomes erythematous, the alveolar socket is covered with a yellowish gray necrotic tissue layer, and halitosis or a putrid odor is also evident.[3]

Literature suggests many etiological theories and hypothesis of AO, but most widely accepted are the fibrinolytic theory of Birn and the bacterial theory or a combination of both.[4,5] Tranexamic acid (TA), an antifibrinolytic agent, impedes the proteolytic degradation of fibrin by preventing the attachment of plasminogen and plasmin.[6] This helps in stabilization of blood clot and prevents disintegration of clot.

The current study was conducted to determine the efficacy of intra-alveolar application of TA soaked in gel foam for prevention of AO without systemic use of TA.

MATERIALS AND METHODS

The study was conducted from January 2020 to November 2020, on patients requiring mandibular third molar surgery (TMS) for impacted tooth, at our institute. Ethical Clearance was obtained from Institutional Ethical Committee with Ref no 44/20-21/27-02-2020 dated 27.02.2020.

Inclusion criteria

1. Patients diagnosed to have impacted third molar having moderate-to-severe difficulty index (Pederson's Difficulty Index above 5)[7]
2. Healthy patients willing to participate in the study.

Exclusion criteria

1. Patients having systemic diseases such as hypertension, diabetes mellitus, seizure disorder, or under immunosuppressive therapy.
2. Patients on medications for other diseases or reasons like oral contraception
3. Patients having poor oral hygiene and habits such as smoking and alcohol and tobacco use in any form
4. Associated lesions such as odontogenic tumor and pericoronal or periradicular cyst.

Sampling and randomization

A total of 200 participants were included in randomized control trial and randomly distributed in study/treatment group and control group. Simple randomization technique was applied for randomization of patients by flipping a coin (heads – control group and tails – treatment group) that allowed equal distribution of patients in both the groups.

Detailed protocol of conduction of the study

1. After detailed explanation of procedure, informed, written, and verbal consent was taken from patients
2. Surgery was performed by a single maxillofacial surgeon adhering to strict aseptic protocol, under local anesthesia using modified Ward's incision, reflection of flap, bone cutting under copious irrigation of cold saline, separation of tooth crown or roots, and elevation of tooth either in toto or in parts with minimum trauma to surrounding tissues and cleansing of socket
3. In patients of the study group, 1 ml of injection TA soaked in gel foam (a piece of 1 cm × 1 cm) was placed in socket (intra-alveolar) and suturing was done to close the socket. In patients of the control group, wound closure was done simply by suturing
4. Postsurgical instructions were given to the patient along with oral medication containing aceclofenac 100 mg + paracetamol 500 mg BID, amoxicillin 500 mg + clavulanic acid 125 Mg BID, metronidazole 400 mg TDS, and pantoprazole 40 mg OD for 5 days
5. Patients were recalled after 3–4 days, and a detailed clinical examination of socket was carried out to observe the loss of blood clot and exposure of bone whether partial exposure or complete exposure after enquiring about severity of pain. The Visual Analog Scale with values ranging from 1 to 10 was used to record and identify the severity of pain. Value range 1–3 indicated mild pain, 4–6 indicated moderate pain, while 7–10 indicated severe pain. Patients followed subsequently to observe the progression of healing of socket. Pain value at the first visit was considered for statistical analysis.

Thus, the entire surgical procedure, medications, and postoperative follow-up observations were similar in both the groups, except for placement of TA soaked gel pack in postextraction socket in patients of the study group.

Statistical analysis

The data were documented, collected, and analyzed for results. *Z*-test, Mann–Whitney test, and *t*-test were applied, respectively, to compare the incidence of AO, severity of pain, and duration of healing between the two groups.

RESULTS

Among 100 patients in the control group, 56 were male and 44 were female. The age of patients varied from 18 to 52 years, with a mean age of 31.07 years. Eighteen (18%) patients suffered by AO of which 13 had exposure of entire bone socket indicating complete disintegration of blood clot, while 5 patients had bone exposure only at the socket edges and floor of socket was still covered by matured blood clot showing

partial loss of blood clot. All these patients were treated by socket cleansing with betadine and saline solution followed by placement of zinc oxide eugenol dressing and extended course of antibiotics and analgesics for another 3 days. The recovery of patients varied from 12 to 16 days after TMS.

In the study group, among 100 patients, 60 were male and 40 were female. The age of patients varied from 18 to 55 years, with a mean age of 32.28 years. The incidence of AO was 6%, and patients experienced mild-to-moderate pain. All 6 patients showed partial exposure of bone, mainly socket edges, while floor of socket was covered by blood clot. These patients were also treated by socket cleansing with betadine and saline solution followed by placement of zinc oxide eugenol dressing. All patients recovered very well within 10 days after extraction [Table 1].

Comparison between the two groups

Incidence of alveolar osteitis

The incidence in the control group was 18%, while in the study group, it was 6%. *P* value (0.009) was highly significant.

Severity of pain

The median of severity of pain with interquartile range (IQR) was calculated to find the significance of difference. Patients in the study group (6 [IQR = 1.25]) experienced lesser pain as compared to the control group (8 [IQR = 1]). *P* value (0.000) was highly significant.

Duration of healing

The duration of healing after AO was ranging from 12 to 16 days in the control group while the duration of healing was <10 days in the study group, demonstrating significant reduction in duration of healing ($P = 0.005$) in the study group. This fastened healing in the study group helped out in decreased intake of medication, in addition to reduced postoperative discomfort during daily routine.

Furthermore, we noticed that there was complete loss of blood clot and exposure of bone including floor of socket in the control group; on the contrary, in the study group, none of the patient showed complete disintegration of clot and floor of socket was covered by clot except for edges. This might have helped in relatively lesser severity of pain and promoted healing as compared to the control group. This may explain the reason for rapid healing and lesser pain in the study group but requires more research in this regard.

DISCUSSION

Kolokythas *et al*. described a comprehensive review of AO and enumerated various risk factors associated with AO. These factors are surgical trauma and difficulty of surgery, lack of experience, mandibular third molars, physical dislodgement of clot, bacterial infection, excessive irrigation and curettage of socket, systemic disease, oral contraceptives, age, gender, smoking single versus multiple extractions of teeth, local anesthetic with vasoconstrictor, saliva, bone/root fragments remaining in the wound, flap design, and use of suture.[8]

The incidence of AO described in the literature shows significant variability. The lack of objective clinical criteria leads to considerable variability in the reported frequency of AO. Poor study design, miscalculation of data, inadequate sample size, or introduction of variables could also contribute to the variability that has been reported in the literature. For routine dental extractions, the incidence of AO has been reported in the range of 0.5%–5%.[9-12] The incidence of AO after extraction of mandibular third molars varies from 1% to 37.5%.[13,14] It has been well documented that surgical extractions result in about 10 times higher incidence of AO.[1] In our study, the incidence of AO after TMS by routine surgical procedure was 18%.

Different theories of pathogenesis of AO are described in the literature. However, Birn observed high concentrations of plasmin and increased fibrinolytic activity in the alveolar bone lining dry socket lesions.[15,16] Plasminogen, the precursor of plasmin, circulates in the blood and binds to clots at wound sites. Various tissue activators, including tissue-type and urokinase-type plasminogen activators,[17,18] convert

Table 1: Comparison between study group and control group regarding incidence of alveolar osteitis with following parameters

Criteria	Study group	Control group	*P*
Number of patients (male/female)	100 (60/40)	100 (56/44)	
Incidence of AO (male/female)	6 (4/2)	18 (10/8)	0.0090 (*Z*-test)
Median (IQR) of severity of pain on Visual Analog Scale	6 (1.25) xL=5 xU=6.25	8 (1) xL=8 xU=9	0.0000 (Mann-Whitney test)
Clot disintegration			
Complete	0	13	
Partial	6	5	
Mean±SD of duration of healing after AO (range of duration of healing)	9.17±0.75 days (8-10 days)	14.28±1.49 days (12-16 days)	0.0005 (*t*-test)

IQR: Interquartile range, xL: Lower quartile, xU: Upper quartile, SD: Standard deviation, AO: Alveolar osteitis

plasminogen to plasmin.[15,17-19] Plasmin is experimentally identified as an important molecule for inducing inflammation as it induces fibrinolysis to dissolve blood vessel clots, increase local capillary permeability, and attract inflammatory cells and its complements to wound sites.[17,19-21] An alternative theory has emerged based on which in traumatic extractions the bone is subjected to large amounts of compressive forces, these activate signals of apoptosis in the osteoblast, and necrosis from which fibrinolytic activity begins that dissolves the blood clot.[3]

TA exerts its antifibrinolytic action through the reversible blockade of plasminogen molecules, inhibiting its interaction with the heavy chain of fibrin, thereby preventing clot disintegration.[22] In assessing the effect of TA and EACA as inhibitors of plasminogen activation, Melander found that the favorable effect on hemostasis, seen clinically, was due to inhibition of the fibrinolytic activity locally in tissues. This suggests that it is the tissue level of TA that is important in obtaining hemostasis, rather than the plasma levels.[23] This explains rationale for topical use of TA in prevention of AO.

The use of TA after extraction is not new and most commonly used for control of postextraction hemorrhage. Its use in prevention of AO is also described, but meager literature is available with regard to its efficacy.

Naqash *et al*. studied the efficacy of TA in prevention of dry socket and found 26% incidence AO among 50 patients, and it was 62% in the control group.[24] In our study, the incidence was reduced to 6% after the use of TA.

Anand *et al*. also evaluated the use of TA among 60 patients (30 – control group, 30 – study group) undergoing routine tooth extraction. They observed a 6.66% incidence of dry socket in the study group and 30% in the control group. This outcome is comparable with our study, but they have also given oral dose of TA (500 mg) 1 h prior to procedure.[6]

N Gersal-Pederson refuted the use of topical TA in prevention of AO, as they found an incidence of 7.5% on aminomethyl cyclohexane (AMCA, i.e., TA) side and 5% in the placebo side on the same patient. Their result showed that a local inhibition of plasminogen activation by AMCA is insufficient to prevent the development of AO.[25] However, this was an old study done in 1973, and after that, there was extensive research conducted in this regard leading to development of improved techniques in TMS and application of TA inside the socket.

In routine practice, incidence of dry socket is an unavoidable complication of TMS. Prevention is the most important step in management of AO. Several techniques are described in the literature to prevent AO which are described below.

Systemic antibiotics reported to be effective in the prevention of AO include penicillins,[26,27] clindamycin,[26,28] erythromycin,[28] and metronidazole.[29,30] However, their frequent use is not promoted due to possible hypersensitivity, development of resistant bacterial strains, and unnecessary destruction of host commensals.[1,31]

Topical antibiotics

A great number of studies have been performed in order to test the effectiveness of topical medicaments either alone or in combination in preventing AO. There is a lack of consistency, and very few studies are in agreement. Among the many antibiotics studied, topical tetracycline has shown promising results.[32-34] The method of delivery included powder, aqueous suspension, gauze drain, and Gelfoam sponges (preferred). However, foreign body reactions have been reported with the application of topical tetracycline.[35,36] Zuniga and Leist reported a case of a nerve dysesthesia 6 months after mandibular third molar extraction due to the use of medications in the socket.[36] In one study, myospherulosis resulted from petroleum-based carrier used in tetracycline–hydrocortisone combination.[37]

Chlorhexidine

Several studies have reported that the pre- and perioperative use of 0.12% chlorhexidine rinses decreases the frequency of AO.[38,39] Ragno and Szkutnik documented a 50% reduction in the incidence of AO in patients who prerinsed with chlorhexidine solution.[40] Caso *et al*. performed a meta-analysis and concluded that 0.12% chlorhexidine rinse on the day of surgery and for several days thereafter is beneficial.[41]

Steroids

Lele in 1969 found that the use of steroids decreases postoperative complications but failed to prevent development of AO.[42] Recent studies showed that topical application of an emulsion of hydrocortisone and oxytetracycline signi□cantly helps to reduce AO.[43,44]

Eugenol containing dressing

The use of eugenol-containing dressing to prevent the development of AO is suggested by some authors.[45] However local irritant effect of eugenol and the delay in wound healing due to prophylactic dressing of eugenol has been well documented and does not justify its use in prevention of AO.[46,47]

Lavage

Some authors have suggested copious intraoperative lavage to reduce the incidence of AO. Butler and Sweet reported a

significant reduction in AO when 175 mL lavage was used as compared to 25 mL lavage.[48]

Ashvini *et al*. studied the efficacy of TA and concluded that local and systemic administration of TA significantly reduces the incidence of TA.[49] Another study by Mohamed *et al*. demonstrated 0% incidence of AO, postoperative pain, and healing after TMS by using intra-alveolar TA pack.[50] Their results were comparable with results of Svensson *et al*. who found no cases of AO with the use of TA after extraction.[51] In the current study, the use of intra-alveolar TA soaked in gel foam reduced the incidence of AO to as low as 6%. We also found that it significantly reduces the clot disintegration limiting partial loss of blood clot, mainly at the edges of the socket, leading to minimum bone exposure along with decreased severity of pain and fastened healing.

From the current study, we understand the role of TA in prevention of AO, but how it does impact the socket where AO has already occurred is not very clear. No such evidences were found in literature review. Supplementary research is required from this point of view that is what will be role of TA, if any, once AO occurs or in a case where TA was not used but should it be considered at a later stage in treatment of AO in any which ways. Furthermore the current study was limited to only healthy individuals and those having no risk factors for AO. So extended research is recommended by involving patients having systemic illnesses like diabetes o patients carrying risk factors such as elder age, smoking, use of oral contraception and poor oral hygiene.

CONCLUSION

Severe pain, extended course of medication, and delayed healing in AO demand that its prevention is the best way of management. The current study revealed that TA packs after TMS yields promising outcomes in terms of reducing the incidence of AO to 6%, with additional benefits of limiting symptoms to mild-to-moderate range and fastened recovery within 10 days. We recommend that it should be considered as routine practice owing to its astonishing rewards as preventive measure and not so much as curative measure.

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Conflicts of interest

There are no conflicts of interest.

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