Effects of intraoperative placement of tetracycline, tetracycline + gelatin sponge, and placebo on postoperative pain after mandibular molar extraction: A comparative prospective study

ABSTRACT

Background: Painless postoperative period is a major requisite following routine dental extractions. Reduction in the postextraction complication is beneficial to both clinician and patients. Hence, emphasis should be given to the techniques and agents that help reduce the complications for better postoperative recovery.

Materials and Methods: Three groups of 30 patients each requiring mandibular molar extractions were randomly selected with intrasocket placement of tetracycline, tetracycline plus gelatin sponge, and placebo control after extraction. A small piece of collagen membrane was used on the superior surface of the socket after the placement of the medicament in Group A and Group B. The postoperative pain scores were evaluated at 24 h, 48 h, and 7 days postoperatively.

Results: Ninety patients requiring mandibular molar teeth extraction were enrolled as the study participants. Forty-two patients (55.26%) were male and 34 (44.73%) were female. Tetracycline alone and tetracycline + gelatin sponge group shows no statistical significant difference in reducing postoperative pain after 7 days, but the pain score values were less in Tetracycline + gelatin sponge group. The comparison between tetracycline alone and control group showed no significant difference observed between the groups at 24 h but showed statistically significant difference between the groups after 48 h and 7 days, whereas comparison between tetracycline + gelatin sponge and control group showed statistically significant difference between the groups after 48 h and 7 days (P = 0.009, 0.001, and 0.017, respectively).

Conclusion: Tetracycline and gelatin sponge intrasocket placement provides a good substitute to the prolong use of analgesics and as a good adjuvant in reducing pain in the first few days after routine dental extraction.

Keywords: Gelatin sponge, pain, postextraction, tetracycline

INTRODUCTION

Exodontia is the most frequently surgical procedure performed in dentistry, and its success is equally important both to patient and the dental surgeon. For patients, the most common reason for the extraction of teeth is pain, and hence, it is important for patient as well as for the surgeon to manage the perioperative as well as postoperative pain. Researches have shown that pain, swelling, and dry
socket are the common complications after the extraction of teeth.\textsuperscript{[2]} Dry socket is more frequently seen in mandibular molars compared to any other teeth.\textsuperscript{[3]} Alveolar osteitis more commonly known as “dry socket” is a frequent complication which occurs after extraction. This condition remains a common postoperative problem as it results in severe postoperative pain. Repeated hospital visits can also be problematic to patients with this condition. AO is known to occur between 1 and 3 day after tooth extraction and literature believes that almost 95\%-100\% of all the cases have reported within a week. Pathogenesis of dry socket is not very well understood in the literature. Birn’s published literature suggested that the etiology of this condition being an increase in the local fibrinolysis which further leads to disintegration of the blood clot in the socket.\textsuperscript{[4]} The pain experienced with it is debilitating and effects daily function.

Many intrasocket antibiotics have been tried in the literature to prevent or to reduce the postoperative complications after extraction. Topical tetracycline placed in the extraction socket is known to reduce postoperative pain, trismus compared to the one’s undergoing routine dental extraction without its placement.\textsuperscript{[5]}

Tetracyclines discovered in 1940s show activity against a wide variety of microorganisms including both Gram-positive and Gram-negative bacteria. Chlamydia, rickettsia, mycoplasmas, and protozoan parasites are also under its spectrum. Mechanism of action of tetracyclines is that it inhibits protein synthesis in bacteria by preventing the association of aminoacyl-tRNA with bacterial ribosome.\textsuperscript{[6]} Matrix metalloproteinases (MMPs) are a group of >20 Zn-dependent enzymes which regulate inflammation. Pathologically, the elevation of MMPs causes connective tissue and bone loss in various inflammatory diseases. Tetracyclines are effective inhibitors of mammalian MMPs. Tetracyclines can inhibit both intracellular and extracellular MMPs. Tetracycline inhibits MMPs on specific sites that has been identified as the calcium and zinc-binding site at C-11 and 12. The anti-inflammatory nature of tetracycline is utilized in the various dermatological diseases and in periodontitis too.\textsuperscript{[7]} The anti-inflammatory property of tetracyclines can be useful in the reduction of postoperative sequelae following extraction. It has also been reported that, gelatin sponge too reduces postoperative complications after oral surgical wounds. Gelatin sponge serves as a mechanical hemostatic agent which obliterates dead space which hastens healing of wound.\textsuperscript{[8]}

There is no comparative study available in the literature to evaluate the efficacy of tetracycline and tetracycline + gelatin sponge to reduce postoperative pain after extraction in patients without any systemic antibiotic coverage. Although studies regarding the use of topical tetracycline as well as gelatin sponge independently placed in the extraction socket\textsuperscript{[5,8]} have been done but no comparative study is available in literature to evaluate their combined usage in extraction socket. This study evaluates the efficacy of tetracycline alone and tetracycline + gelatin sponge to reduce post extraction pain in patients without any systemic antibiotic coverage.

**MATERIALS AND METHODS**

**Aims and objectives**

Assessment of postextraction pain in patients after mandibular molar extraction divided into three groups (with or without intra-socket tetracycline, tetracycline + gelatin sponge).

Ninety patients requiring mandibular molar teeth extraction of the age group of 18–60 years who reported to the Department of Oral and Maxillofacial Surgery, from December 2015 to July 2017 were included in the study. Written informed consent was obtained in a given format before the treatment. Institutional ethical clearance was obtained before the study was conducted. Patients were divided into three groups in a random manner:

- Group A – Patients treated with intrasocket tetracycline alone (n = 30)
- Group B – Patients treated with intrasocket tetracycline + gelatin sponge (n = 30)
- Group C – Patients treated without any intrasocket medicaments (n = 30).

Patients who were immunocompromised, with acute abscess, mobile teeth, allergic to tetracycline mentally challenged patients, patients unable to communicate, who is already on systemic antibiotics for other purpose and pregnant and lactating women were excluded from the study. Teeth requiring transalveolar extractions were excluded from the study. Third molars requiring bone guttering or sectioning of the tooth were excluded too.

Preoperative analysis was done using the intraoral periapical radiograph [Figure 1]. Under strict aseptic condition, surgical procedure was carried out by the same operator. Tetracycline capsule (250 mg) was mixed with 0.5 ml of saline and placed in the socket in Group A [Figure 2], whereas in Group B, this mixture was impregnated on gelatin sponge which was cut according to the extraction socket size and was placed in the same. Group C was kept as such. Preoperative mouthwash rinsing was done with Perioguard mouthwash (1 min) and...
extraoral skin scrub was also done. The surgeries were performed under local anesthesia (lignocaine 2% with epinephrine 1:80,000).

Extraction was done carefully, while preserving the alveolar bone plates around the teeth.

**Reflection of mucoperiosteal flap**
A periosteal elevator is used to elevate the mucoperiosteum surrounding the tooth. The loosening of the soft tissues around the tooth also permits the elevators or forceps to be applied more apically.

**Luxation of the tooth using elevator (in case of root stumps)**
An appropriate elevator was used to detach the tooth from its soft-tissue attachment. The elevator was applied to expand the alveolar socket and tear the periodontal ligament which helps in the luxation of the tooth from its socket.

**Adaptation of forceps and removal of the tooth**
Appropriate forceps were chosen depending upon the shape and location (maxilla or the mandible) of the tooth, appropriate forces were delivered and the extraction was completed.

There was no need for surgical bone removal in any of the cases.

After extraction, thorough debridement of the extraction socket was done with fine curettes. Visible granulation tissue was curetted from the socket. Irrigation was done with sterile saline.

A small piece of the collagen membrane was used on the superior surface of the socket after placement of the medicament in Group A and Group B. Socket was closed by figure of 8 sutures with 3 black silk suture in all three groups.

Pain was recorded after 24 h, 48 h, and 7 days postoperatively. Systemic antibiotics were not prescribed in any of the three groups, but all patients were kept on oral analgesics (Tab Diclofenac sodium (Reactin 50 mg, Cipla) 50 mg twice daily for 3 days and from first postoperative day onward). Perioguard mouth wash was also prescribed twice daily for 7 days. For pain, scores were taken on a Visual Analog Scale (VAS) of 10 cm [Figure 3], from the patients, after 24 h, 48 h, and again after 7 days [Table 1].

Recording of the VAS scores was done by the patient himself.

**RESULTS**

A total of 90 patients requiring mandibular molar tooth extraction were enrolled as the study participants.

The clinical photographs are included from Figures 4-9. Figure 4 shows preoperative records, whereas Figures 5 and 6 shows intraoperative procedure. Figures 7-9 shows 24 h, 48 h, and 7 days follow-up of the case. In addition, 14th day follow-up photograph of the case is also shown in Figure 10.
The age of the patients included in the study was between 16 years and 60 years, out of which 50 patients (55.55%) were male and 40 (44.44%) were female [Graph 1].

The Kruskal–Wallis test [Table 2] shows statistically significant difference among three independent groups in relation to pain scale VAS ($P = 0.024$, 0.003, and 0.018, respectively). Further statistical test (Mann–Whitney U) was applied to the same data. The Mann–Whitney U-test in between tetracycline alone and tetracycline + gelatin sponge group, which shows no statistical significant difference between them ($P = 0.069$; 0.061; 1.00, respectively), this indicates tetracycline alone and tetracycline + gelatin sponge are equally effective in reduction of pain after 7 days postoperatively [Graph 1].

Comparison between tetracycline alone and control group was done using the Mann–Whitney U-test for VAS_24, VAS_48, and VAS_7D were performed. There is no significant difference observed between the groups at 24 h ($P = 0.060$), but showed statistically significant difference between the groups after 48 h and 7 days ($P = 0.031$ and 0.017, respectively). This indicates both the groups experienced same amount of pain at first 24 h and observed significant pain reduction in tetracycline alone group compared to the control group at 48 h and 7 days interval [Table 4 and Graph 3].

Comparison between tetracycline + gelatin sponge and control group was done using the Mann–Whitney U-test for VAS_24, VAS_48, and VAS_7D were performed. The test
results showed statistically significant difference between the groups after 24 h, 48 h, and 7 days ($P = 0.009$, 0.001, and 0.017, respectively). This indicates that tetracycline + gelatin sponge group [Table 5 and Graph 4] showed better pain reduction compared to the control group at 24 h, 48 h, and 7 days interval.

Table 2: Kruskal–Wallis test

| Group                  | n  | Mean rank | P       |
|------------------------|----|-----------|---------|
| VAS_24                 |    |           |         |
| Control                | 30 | 54.98     | 0.024*  |
| Tetracycline alone     | 30 | 43.47     |         |
| Tetracycline + Abgel   | 30 | 38.05     |         |
| Total                  | 90 |           |         |
| VAS_48                 |    |           |         |
| Control                | 30 | 57.27     | 0.003*  |
| Tetracycline alone     | 30 | 43.5      |         |
| Tetracycline + Abgel   | 30 | 35.73     |         |
| Total                  | 90 |           |         |
| VAS_7D                 |    |           |         |
| Control                | 30 | 54.77     | 0.018*  |
| Tetracycline alone     | 30 | 40.87     |         |
| Tetracycline + Abgel   | 30 | 40.87     |         |
| Total                  | 90 |           |         |

*Significant association set at ≤0.05. VAS: Visual Analog Scale

Table 3: Represents the Visual Analog Scale score (pain) between Group A and Group B

| Pain scale | Group                  | n  | Mean rank | P       |
|------------|------------------------|----|-----------|---------|
| VAS_24     | Tetracycline alone     | 30 | 32.32     | 0.069   |
|            | Tetracycline + Abgel   | 30 | 28.62     |         |
| VAS_48     | Tetracycline alone     | 30 | 33.15     | 0.061   |
|            | Tetracycline + Abgel   | 30 | 28.87     |         |
| VAS_7D     | Tetracycline alone     | 30 | 25.87     | 1.00    |
|            | Tetracycline + Abgel   | 30 | 25.87     |         |

*Significant association set at ≤0.05. VAS: Visual Analog Scale

Table 4: Represents the Visual Analog Scale score (pain) between Group A and Group C

| Pain scale | Group                  | n  | Mean rank | P       |
|------------|------------------------|----|-----------|---------|
| VAS_24     | Tetracycline alone     | 30 | 32.32     | 0.060   |
|            | Control                | 30 | 36.67     |         |
| VAS_48     | Tetracycline alone     | 30 | 33.15     | 0.031*  |
|            | Control                | 30 | 39.62     |         |
| VAS_7D     | Tetracycline alone     | 30 | 25.87     | 0.017*  |
|            | Control                | 30 | 35.13     |         |

*Significant association set at ≤0.05. VAS: Visual Analog Scale

Table 5: Represents the Visual Analog Scale score (pain) between Group B and Group C

| Pain scale | Group                  | n  | Mean rank | P       |
|------------|------------------------|----|-----------|---------|
| VAS_24     | Tetracycline + abgel   | 30 | 28.62     | 0.009*  |
|            | Control                | 30 | 36.67     |         |
| VAS_48     | Tetracycline + Abgel   | 30 | 28.87     | 0.001*  |
|            | Control                | 30 | 39.62     |         |
| VAS_7D     | Tetracycline + Abgel   | 30 | 25.87     | 0.017*  |
|            | Control                | 30 | 35.13     |         |

*Significant association set at ≤0.05. VAS: Visual Analog Scale
DISCUSSION

According to the International Association for the Study of Pain, pain is defined as “Unpleasant sensory and emotional experience associated with actual or potential tissue damage.” Pain after extraction is a common complication. Pain is common body response to wound anywhere in the body. Postextraction pain occurs in extraction wound as it is not different from other body wound, and this pain results from the inflammation at the site of extraction which is a part of normal wound healing.

Effort to minimize postoperative complications after the extraction of tooth is going on from long time. Maintaining asepsis, soft-tissue handling, achieving hemostasis, and proper postoperative instructions may reduce these but not completely eradicate it. The use of intrasocket placement of bioactive substances by many authors to reduce postoperative sequelae and regenerative purposes has been very well documented.

Gabler and Creamer shows that tetracycline causes the suppression of human neutrophil function, this can be on the basis for fact that intra-socket tetracycline reduces postoperative pain by reduction in the postoperative inflammation.

Tetracyclines are known to cause inhibition of MMPs which contribute to tissue destruction. Tetracyclines have the ability to scavenge reactive oxygen species (ROS) and act as anti-inflammatory agents. Increase formation of ROS is seen in chronic inflammatory diseases and it leads to oxidative damage and also causes dysfunction of cells. Tetracyclines ability to scavenge free radicals, overcomes this oxidative stress. This anti-inflammatory action reduces the amount of pain postoperatively. The antihypernociceptive effects of tetracyclines are well documented in the literature too.

Gelatin sponge functions as a supportive and mechanical agent which provides structural support for the clot. This surface-mediated hemostatic device hastens the clot formation because of its spongy physical properties. Platelets are present blood clot and provide natural growth factors (BMP, platelet-derived growth factor, and transforming growth factor-beta) which are essential for tissue healing and regeneration.

Pain was assessed in our study on the VAS after 24 h, 48 h, and after 7 days postoperatively. The results show significant reduction in postoperative pain in tetracycline alone as well as in tetracycline + gelatin sponge groups compared to group which did not receive any intrasocket medicament. On the other hand, postoperative pain was less in tetracycline + gelatin sponge group compared to tetracycline alone group but difference was not statistically significant. According to Sanchis et al., also, the patients in whom intra-alveolar tetracycline was administered experienced
less pain and consumed few analgesics than compared to the patients who did not received intraalveolar tetracycline, although the results were not statistical significant.\cite{3}

In our results, pain was more at 24 h after extraction in all the three groups with highest pain scores for the control group and the lowest scores for group in which tetracyclines plus gelatin sponge was given. A study conducted by Hussain and Alnahar\cite{4} on postoperative pain after intraalveolar extraction concluded that mild pain was experienced by 38.6% cases, whereas 12.8%, 22% experienced shooting pain, constant pain at evening of extraction with 15.2% cases still suffering mild pain after 7 days too. This study also concluded that 6.8% cases used analgesics even after 7 days. In our study, tetracycline usage reduced the postoperative pain levels significantly low than the control group.

Dry socket with bone exposure, halitosis, and necrotic debris was noted in 2 out of 30 patients in Group C (control group) representing an incidence of 6.66% which is slightly higher compared to 2%–5% as mentioned in the literature for routine extraction.\cite{5,6,7} Both two cases of dry socket were noted in the region of tooth no 38; out of which one case was in 37-year-old female and other was in 48-year-old male and managed by daily socket irrigation with betadine and zinc oxide eugenol pack for 3 days.

In tetracycline alone and tetracycline + gelatin sponge group, not a single case of complicated wound healing or dry socket was found. This result is accordance with studies mentioned in literature about intrasocket tetracycline. Sanchis et al. show that, intra-alveolar placement of tetracycline compound after the surgical removal of impacted mandibular third molars did not affect the incidence of dry socket.\cite{8} Gabriela Jude Fernandes et al. published a case in which doxycycline/local anesthetic-soaked Gelfoam sponge was placed into the apical portion of the socket after extraction. Postoperative pain or discomfort was not reported in that case. The patient was able to carry out his normal routine activities. No evidence of dry socket was noted on follow-up of that case also. The author concluded that Doxycycline/local anesthetic/Gelfoam sponge seems to be an effective technique in the prevention of dry sockets.\cite{9} According to Julius et al., piece of Gelfoam impregnated with 0.5 ml of Terra‑Cortril which combined with oxytetracycline and hydrocortisone can be used as intrasocket medicament to reduce the incidence of localized osteitis.\cite{10}

A double-blind study was carried out by Swanson to evaluate the effectiveness of topical tetracycline used as a suspension in a square of gelatin sponge for the prevention of dry socket in 100 impacted mandibular molars. The study results show that, the incidence of dry socket was decreased markedly in patients who received dressing of topical tetracycline used as a suspension in a square of gelatin sponge.\cite{11}

As the role of dry socket in causing postextraction pain and discomfort cannot be ruled out, so efforts should be made to minimize this complication which ultimately will reduce the postoperative pain. The placement of intraalveolar tetracycline and gelatin sponge reduces the incidence of it as in our study 60 extractions were carried in Group A and B combined with no incidence of dry socket.

No other complications with the use of tetracycline and gelatin sponge were reported in our study.

CONCLUSION

The use of intraalveolar tetracycline and gelatin sponge reduces the postextraction complication of pain and dry socket. Hence, this modality of treatment should be employed following extraction, especially in the areas prone to dry socket formation as well as during traumatic extractions.

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Conflicts of interest

There are no conflicts of interest.

REFERENCES

1. Reich F, Hiller KA. Reasons for tooth extraction in the western states of Germany. Community Dent Oral Epidemiol 1993;21:379-83.
2. Pierce JE, Dym H, Clarkson E. Diagnosis and management of common postextraction complications. Dent Clin North Am 2012;56:75-93.
3. Heasman PA, Jacobs DJ. A clinical investigation into the incidence of dry socket. Br J Oral Maxillofac Surg 1984;22:115-22.
4. Kolokythas A, Olech E, Miloro M. Alveolar osteitis: A comprehensive review of concepts and controversies. Int J Dent 2010;2010:249073.
5. Sanchis JM, Sáez U, Peñarrocha M, Gay C. Tetracycline compound placement to prevent dry socket: A postoperative study of 200 impacted mandibular third molars. J Oral Maxillofac Surg 2004;62:587-591.
6. Chopra I, Roberts M. Tetracycline antibiotics: Mode of action, applications, molecular biology, and epidemiology of bacterial resistance. Microbiol Mol Biol Rev 2001;65:232-60.
7. Tilakaratne A, Soory M. Anti-inflammatory actions of adjunctive tetracyclines and other agents in periodontitis and associated comorbidities. Open Dent J 2014;8:109-24.
8. Silverman LM. An investigation of gelatin sponge with thrombin and penicillin in the treatment of oral surgical wounds. Oral Surg Oral Med Oral Pathol 1949;2:260-88.
9. Gabler WL, Creamer HR. Suppression of human neutrophil functions by tetracyclines. J Periodontal Res 1991;26:52-8.
10. Golub LM. Introduction and background. Pharmacol Res 2011;63:99-101.
11. Webster G, Del Rosso JQ. Anti-inflammatory activity of tetracyclines. Dermatol Clin 2007;25:133-5.
12. Bastos LF, de Oliveira AC, Watkins LR, Moraes MF, Coelho MM.
1. Patil, et al.: Tetracycline effects on postoperative pain after mandibular molar extraction

2. Tetracyclines and pain. Naunyn Schmiedebergs Arch Pharmacol 2012;385:225-41.

3. Kabashima H, Sakai T, Mizobe K, Nakamuta H, Kurita K, Terada Y. The usefulness of an autologous blood clot combined with gelatin for regeneration of periodontal tissue. J Oral Sci 2013;55:363-6.

4. Hussain AT, Alnahar A. Pain experience after simple tooth extraction. J Oral Maxillofac Surg 2008;66:911-7.

5. Bonine FL. Effect of chlorhexidine rinse on the incidence of dry socket in impacted mandibular third molar extraction sites. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 1995;79:154-7.

6. Fernandes GJ, Hatton MN. Prevention of alveolar osteitis. A case report and review of literature. N Y State Dent J 2016;82:21-5.

7. Julius LL, Hungerford RW, Nelson WJ, McKercher TC, Zellhoefer RW. Prevention of dry socket with local application of Terra-Cortril in Gelfoam. J Oral Maxillofac Surg 1982;40:285-6.

8. Swanson AE. A double-blind study on the effectiveness of tetracycline in reducing the incidence of fibrinolytic alveolitis. J Oral Maxillofac Surg 1989;47:165-7.