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Comparative evaluation of submucosal injection of hyaluronidase with dexamethasone on postsurgical effects after surgical removal of bilateral impacted mandibular third molar

[1]Dr. Raghvendra singh Arvind Narela, Consultant Oral and Maxillofacial Surgeon, Sagar, Madhya Pradesh

[2]Dr. Vardan Maheshwari, Associate Professor, Department of Dentistry, American international Institute of medical sciences Udaipur, Rajasthan, India

[3]Dr. Bipin A. Bulgannawar, Professor and Head, Department of Oral and Maxillofacial Surgery, Pacific Dental College and Hospital, Udaipur, Rajasthan, India.

[4]Dr. Pooja Sarda, Consultant Oral and Maxillofacial surgeon, Ambajogai, Maharashtra

Corresponding Author: Dr. Vardan Maheshwari, Associate Professor, Department of Dentistry, American international Institute of medical sciences Udaipur, Rajasthan, India

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Abstract

Background: The purpose of this study was to compare the effect of submucosal administration of hyalurondase versus dexamethasone on discomfort after mandibular third molar surgery.

Method: 20 patients with bilaterally impacted mandibular third molars requiring surgical removal were included in the study. Patients were given 2 ml of dexamethasone on one side and 2 ml hyaluronidase was given on the remaining side via submucosal route by the operator before starting the surgical extraction. The patients were recalled for follow-up visits on 3rd and 7th day of postsurgical extraction. Pain and swelling were assessed postoperatively. All the data was tabulated and statistical analysis was carried out using paired t-Test.

Result: The comparative difference of mean pain and swelling were assessed using paired t - test and it showed statistically significant difference in all patients at each time interval i.e. 3rd day and 7th day ($p \leq 0.05$) on left and right sides.

Conclusion: The administration of hyaluronidase is valuable following oral and maxillofacial surgery with a significant reduction in pain and swelling thus improving the quality of life of patients. Furthermore laboratory based research and clinical trials are needed to confirm these favourable and expected outcomes.

Keywords: Bilateral impacted third molar, Dexamethasone, Hyaluronidase (HA).

Introduction

Amongst the anticipated complications of mandibular impacted third molar extractions, the most common are the post-operative pain, edema and trismus as the post-operative inflammatory sequel. The scope of management of impacted third molars is varied. The treatment options include observation, exposure, transplantation and removal. Various measures (hot and cold applications, diathermy, systemic antibiotics, and chemotherapeutic agents) have been employed in an attempt to prevent or minimize traumatic swelling after oral surgery.1 During the past 10 years, the most commonly used and studied corticosteroids are Dexamethasone, Methyl prednisolone, Prednisolone and Betamethasone due to its potent anti-inflammatory properties and yet no effect on the fluid electrolyte balances. These drugs have been administered through various routes such as oral, intravenous, intramuscular, submucosal and endoalveolar. Studies have proved Dexamethasone to be an effective agent for reducing pain, swelling and trismus to a certain degree, irrespective of the route and the timing of administration. No serious adverse effects, namely acute alveolar osteitis, post-operative infection and nausea, have been reported following the administration of dexamethasone in the study samples. The effect of hyaluronidase in aiding diffusion and consequent resorption of local fluid accumulation caused by operative or other traumas have also been studied.2 Hyaluronic acid is naturally present in an unbound liquid form that is metabolized within twelve hours. In contrast, crosslinked HA has a gel consistency and a prolonged metabolism allowing it to last for up to seven days.3 The effect of cross-linked HA gel on facial swelling, pain, and trismus after surgical extraction of impacted mandibular third molars has been rarely reported in the literature. The study was carried out at Department of Oral and Maxillofacial Surgery, Darshan Dental College and Hospital, Udaipur, Rajasthan. 20 patients within the age group of 18years to 70years of either gender with bilaterally impacted mandibular third molars with same difficulty index were included in the study. All patients underwent surgical extraction of mandibular impacted third molar under LA with patients consent taken prior to the treatment. Patients who were medically compromised patients, allergic to HA or patients with pre-existing swelling, edema or trismus were excluded from the study. All patient received 2ml (1500 IU) hyaluronidase submucosally (SM) on one side and 2ml (8mg) of dexamethasone (SM) on the another side before starting the procedure. The patients were recalled for follow-up visits on 3rd and 7th postoperative day.

Clinical parameters assessed

1. **Analysis of Pain -** The pain was assessed using a 10cm visual analogue scale (VAS) at intervals of day 3rd and 7th post-operative **(Figure 1)**

2. Analysis of swelling - Swelling was evaluated using linear measurements pre-operatively and on post-operative day 3 and day 7. **(Figure 2)**

a. Distance in centimeters from the external canthus of the eye to the soft tissue gonion (AD).
b. Distance from the lower border of the tragus to the mouth commissure on the operated side (AC).
c. Distance from the lower border of the tragus to soft tissue pogonion (BE).

The mean value of the sum of all the three measurements (a+b+c) was considered for the assessment of post-operative swelling.

Results

The mean pain score was evaluated using paired t – test. The results showed that pain was significantly reduced on

the HA injection side as compared to dexamethasone at each time interval i.e, 3rd day and 7th day ($p \leq 0.05$).

The comparison of mean swelling on 3rd and 7th postoperative day revealed that the effect of HA in reducing swelling was more effective than dexamethasone in all the patients at all-time intervals of postoperative follow up and it was statistically significant ($p \leq 0.05$).

Discussion

Impaction may be due to multiple contributing factors such as dense overlying bone, soft tissue, teeth bone discrepancy, abnormal positioning of tooth bud, differential root growth and curvatures or associated pathological lesions.[4] The most important cause for the impacted third molar is the lack of space distal to the second molars and mesial to the ascending ramus. There are literatures supporting the evidence that removal of pre-molars for the purpose of orthodontic treatment has significantly reduced the frequency of impacted third molars attributing to the mesial migration of the teeth during the treatment.[5] This suggests that most common reason for a tooth to be impacted is loss of space.

The post-operative inflammation results in edema due to increased vascular permeability and recruitment and migration of leucocytes into the surgical site and the release of chemical mediators of inflammation at the surgical site by the leucocytes. Pharmacological agents that have provided a promising result in the management of such post-operative inflammatory sequelae are corticosteroids. Corticosteroids reduce inflammation via the inhibition of phospholipase A2, which is the first enzyme involved in the conversion of phospholipids into arachidonic acid, therefore blocking the synthesis of other products such as prostaglandins, leukotrienes and substances related to thromboxane A2.[6] They also have the ability to stabilize lysozyme membranes, decrease the release of inflammation-causing lysozymes, and decrease the permeability of capillary which thus prevents diapedesis, i.e. the initial leakage of fluids from the capillaries and loss of plasma protein into tissue space. There is also a decrease in the formation of bradykinin, a powerful vasodilating substance. Various studies have been done to evaluate the usage of these corticosteroids for third molar surgery in different formulations, dosings, routes and sites of administration. These corticosteroids include dexamethasone (per oral/p.o.), dexamethasone acetate (intramuscular), dexamethasone sodium phosphate (intravenous and intramuscular), methylprednisolone (p.o.), and methylprednisolone acetate and methylprednisolone sodium succinate. During the past 10 years, the most commonly used and studied corticosteroids are Dexamethasone, Methyl prednisolone, Prednisolone and Betamethasone. These drugs have been administered through various routes such as oral, intravenous, intramuscular, submucosal and endoalveolar. Studies have proved Dexamethasone to be an effective agent for reducing pain, swelling and trismus to a certain degree, irrespective of the route and the timing of administration. The lowest dose possible to achieve an anti-inflammatory effect was 4 mg. No serious adverse effects, namely acute alveolar osteitis, post-operative infection and nausea, have been reported following the administration of dexamethasone in the study samples. Variations in the results may be because of differences in surgical methods, differences in individual response to treatment and differences in the methodology used.[7] Hyaluronan is a linear polysaccharide comprising alternating glucuronic acid and N-acetyl-glucosamine residues, repeated approximately 2000 times.[8,9] It belongs to a group of substances known as glycosaminoglycans. The hyaluronan molecule was first described in the 1930s, and was linked with other members of the glycosaminoglycans group, including chondroitin

sulphate, keratan sulphate and heparin sulphate.[10] Since then hyaluronan's properties and function have been investigated, but to date much remains unclear about its role in wound healing.[11] Hyaluronan is synthesised on the cell membrane via the activity of hyaluronan synthase, and secreted into the extracellular space. The newly synthesised molecule protrudes directly into the extracellular environment, promoting a highly hydrated micro- environment because of its hygroscopic properties.[12] It is removed from the plasma via the lymphatics and liver by the activity of specific endocytic receptors.[13]

It is thought that the functions of HA are to expand the extracellular space by binding to salt and water,its hygroscopic properties attract water, resulting in expansion. It interacts with a variety of extracellular molecules to form the extracellular matrix which is rich in glycosaminoglycans, and hyaluronan provides stability and elasticity [14]. It activates intracellular signaling pathways via the activity of cell surface receptors, such as CD44 and RHAMM.[15] However, during normal cell division hyaluronan synthesis rises, helping the dividing cell to disassociate from its substratum, thereby permitting cell movement. Hyaluronan's ability to do this is directly linked to its hygroscopic properties, which allow it to attract large amounts of water to an area.[1] After the cell has undergone mitosis and dissociation and the epithelial cells mature and migrate, hyaluronan levels gradually return to normal.[16]

Hyaluronan levels also rise during the earlier phases of wound healing.[17,18] Oksala et al. demonstrated this using in vitro human tissue biopsied from healing mucosal wounds.[4] Results suggested that levels rose in early wound healing, before reducing again by day seven, post-injury. Higher levels were also found in newly forming granulation tissue. As this was a human wound model, it could be inferred that these findings have more value and are more reflective of normal wound healing than studies carried out using in vitro animal models. The synthesis of different glycosaminoglycans is also time-dependent. During this time the process of angiogenesis begins, with endothelial cells developing capillary buds.[19]

HA consists of a tissue component with numerous roles in the early[20] inflammatory stages. It started to be used in the treatment of cutaneous and subcutaneous wounds in the 90's when its properties were investigated in the medical sciences through the promotion of analgesia, functional improvement and to assist in[21] intra-articular lubrication of the knee and ankle. In dentistry, in the 50s, researchers believed that the degradation of hyaluronic acid through the injection of the hyaluronidase enzyme could provide less postoperative complications after tooth [6,21] . The studies showed that hyaluronidase compared to saline solution extractions provided better clinical parameters of pain, edema and trismus extraction of third molars. However, later studies pointed out that HA had anti-inflammatory properties and discussed its real effect in preventing inflammatory post-operative[18,22] complications after surgical procedures after, in the treatment of Temporomandibular Disorders – TMD [23,24] and improvement of periodontal status

Various studies have supported the pre-operative administration of Dexamethasone over post-operative administration based on the fact that, corticosteroids should be given before the onset of the inflammatory process. Post- operative administration may only prevent further propagation of inflammation but is unable to reverse inflammation that has occurred. Various routes of administration have been studied such as intravenous, intramuscular, pterygomandibular space, submucosal injections, oral administration and endo-alveolar administration. Amongst these, local administration such

as submucosal injection is most favoured to reduce the post- operative sequelae.[25]

In this study hyaluronidase injection was significantly good in reducing pain as compared to dexamethasone. A possible justification for this result is that HA decreases the amount of prostaglandins, resulting in less painful symptoms[26]. In addition, in a histological analysis of a tissue sample collected on margins of surgical wounds from extractions, the use of 0.8% HA showed a lower inflammatory response when compared to no treatment, which justifies the lesser amount of pain.[35] However in our study we have not conducted histological analysis. The differences reveals that the swelling at given time interval was less for HA side as compared with dexamethasone side and it was statistically significant. The literature points out that surgical trauma results in the accumulation of fluids at the extraction site that results in the formation of edema and HA seems to confer a faster resolution of the edema due to its hydrophilic nature[27]. This antiedematous effect can also be related to osmotic activity that eliminates prostaglandins and metalloproteinases.[22] Similar results were also shown by Bayoumi A et al. (2018)[27].

The main limitation of this review is the small number of clinical trials that compared the application of HA to the use of dexamethasone in third molar surgeries. Thus, the results should be interpreted with caution due to the proximity of the confidence interval to the statistical non-significance. Furthermore, the absence of a standardized approach in the presentation of data between studies in the assessment of pain, edema and trismus outcomes may have contributed for the methodological heterogeneity.

The quality of the studies included in this review was generally classified as good to uncertain, with the allocation concealment criterion being the most neglected by the studies. It is noteworthy that concealment of allocation is considered an important criterion in clinical trials that compare therapeutic modalities, as it prevents systematic errors and makes it impossible to predict which group the patient will be allocated to. [39] In assessing the certainty of the evidence generated by this review through the GRADE system, the decrease in the level of evidence of the pain outcome occurred in the analysis of risk of bias (one study, similar in weight to the other studies in the effect estimate, had a high risk of selection bias), inconsistency (in which a statistically significant moderate heterogeneity was observed) and indirect evidence (in which most studies excluded smoking patients, decreasing the external validity of the study covering these patients through the clinical question).

Therefore, it is suggested that more randomized clinical trials comparing HA to the dexamethasone solution lower third molars should be performed. These studies should seek to better define the eligibility criteria, perform a sample calculation and a standardized approach in presenting data on the clinical outcomes of pain, edema and trismus, and should be evaluated from the first post-operative day, subsequently until the seventh day.

Conclusion

The observed results show that HA seems to provide no pain and swelling on the third and seventh postoperative days and has no influence on postoperative trismus after extractions of third molars. Further studies with stronger methodology examining these parameters are necessary to present more useful outcomes.

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Legend Figures

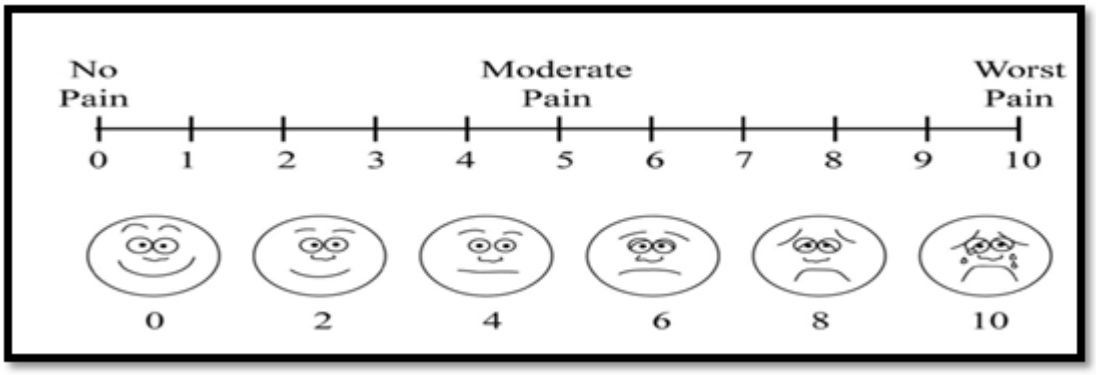

Figure 1: Measurement of Pain

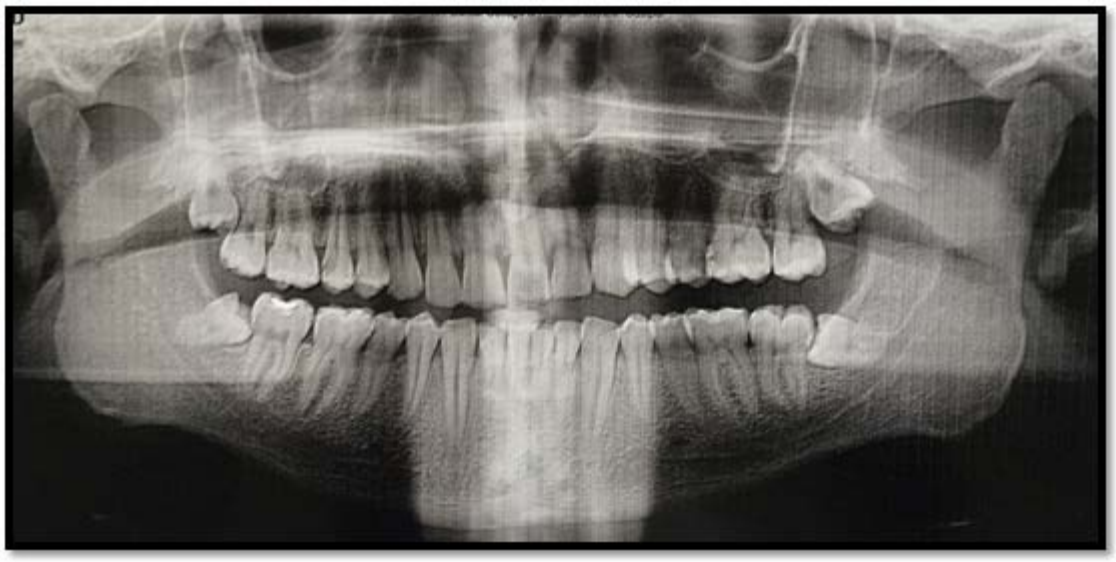

Figure 2: Preoperative OPG with bilateral impacted mandibular third molar

Figure 3-1: Measurements of swelling on 3rd postoperative day on right side at HA injection site

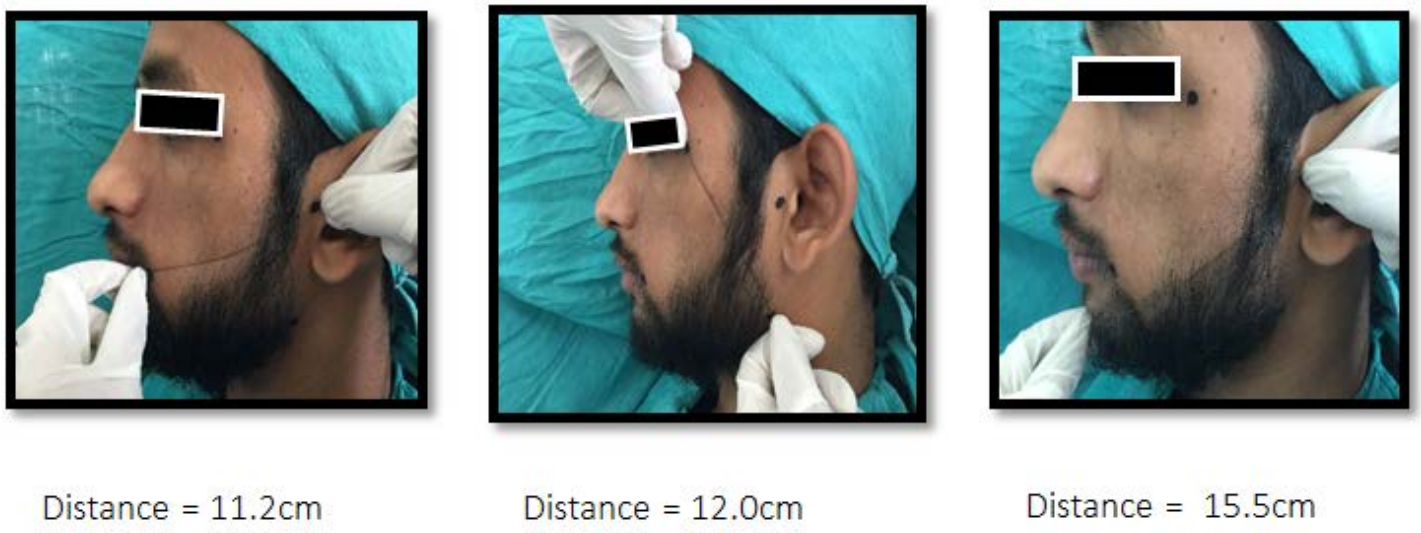

Figure3-2 : Measurements of swelling on 3rd postoperative day on left side at dexamethasone injection site

Figure 3 (a) Point A – C Most anterior point in midline of tragus to most lateral point on corner of mouth.

Figure 3 (b) Point B - E Lateral canthus of eye to most inferior point on angle of mandible.

Figure 3 (c) Point A – D Most anterior point in midline of tragus to soft tissue pogonion on chin.

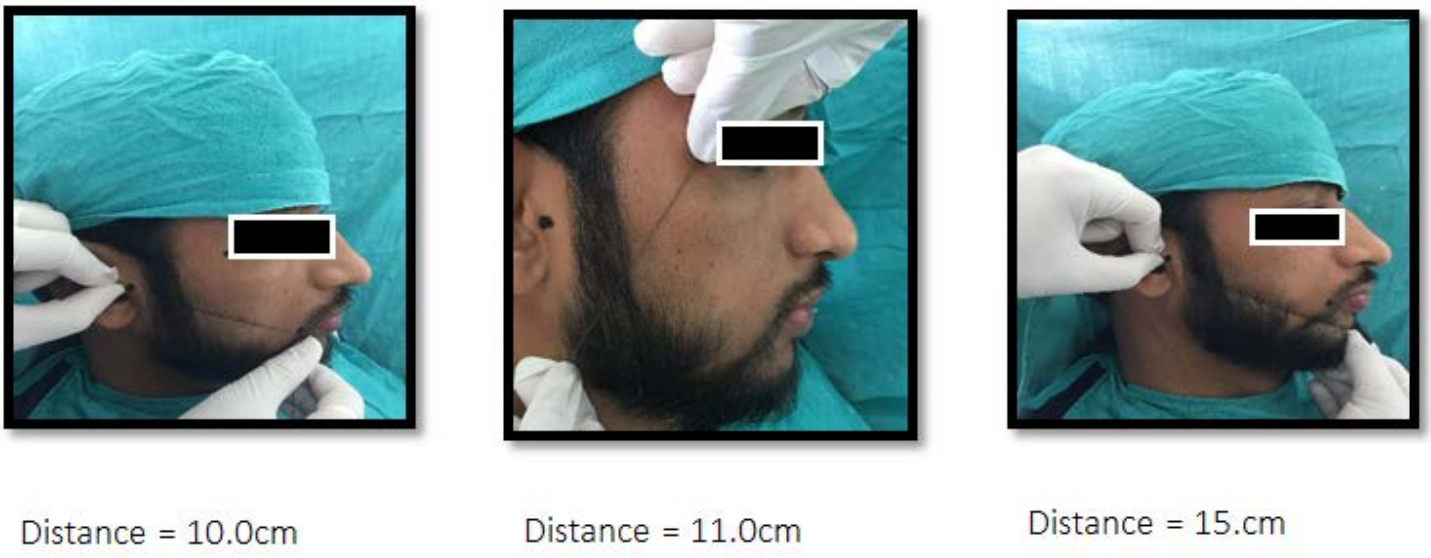

Figure 4-1 Measurements of swelling on 3rd postoperative day on right side at HA injection site

Figure 4-2 : Measurements of swelling on 3rd postoperative day on left side at dexamethasone injection site

Figure 4 (a) Point A – C Most anterior point in midline of tragus to most lateral point on corner of mouth.

Figure 4 (b) Point B - E Lateral canthus of eye to most inferior point on angle of mandible.

Figure 4 (c) Point A – D Most anterior point in midline of tragus to soft tissue pogonion on chin.

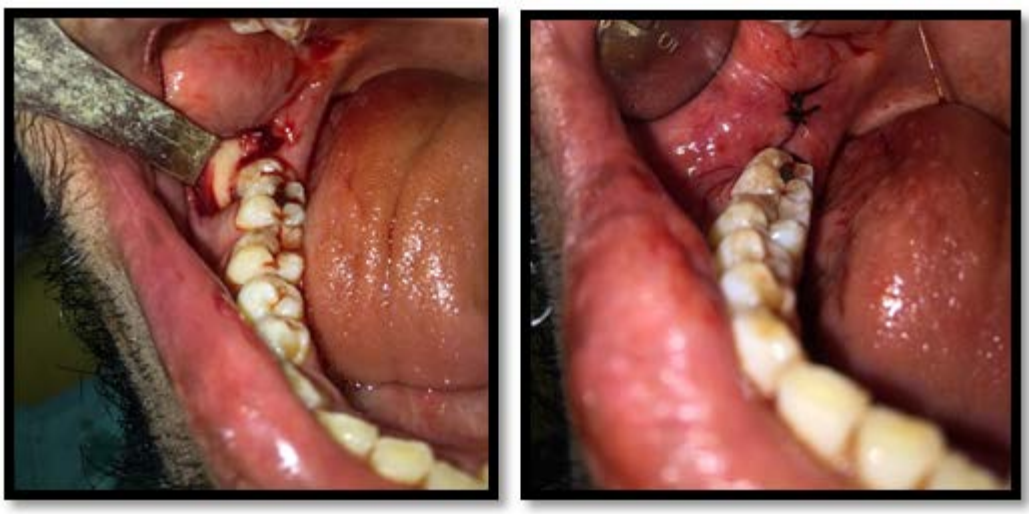

Figure5-1 : surgical exposure and extraction at HA injection site

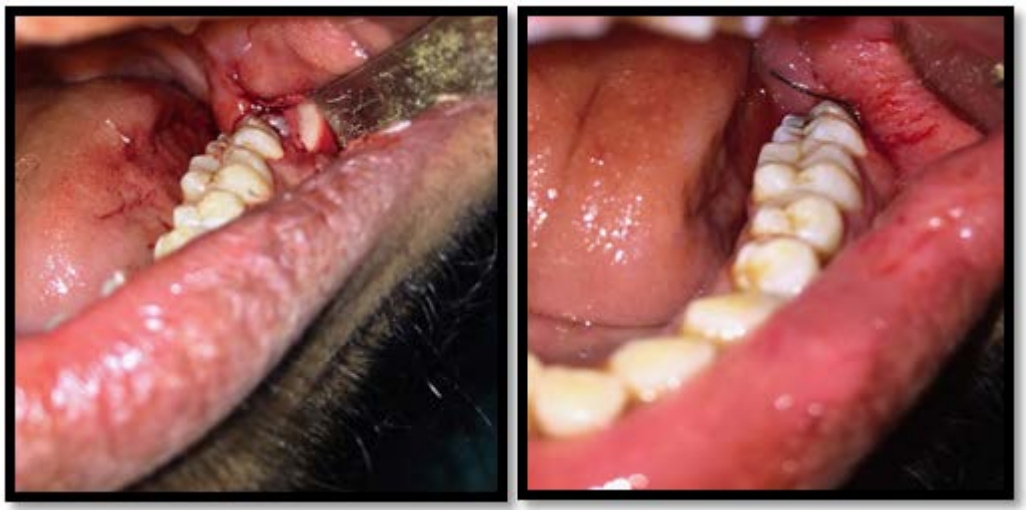

Figure 5-2 : surgical exposure and extraction at dexamethasone injection site