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Comparison of effectiveness of metronidazole, chlorhexidine, and lignocaine combination gel with that of zinc oxide eugenol dressing for the treatment of alveolar osteitis

Kavita Wadde[1], Ashwini Chhapane[1], Sanpreet Singh Sachdev[2,*], Ashish Sarda[1], Asha Chowdhar[1], Siddhesh Latke[3]

[1]*Dept. of Oral and Maxillofacial Surgery, Government Dental College and Hospital, Mumbai, Maharashtra, India*
[2]*Dept. of Oral Pathology and Microbiology, Government Dental College and Hospital, Mumbai, Maharashtra, India*
[3]*Dept. of Oral and Maxillofacial Surgery, Swargiya Dadasaheb Kalmegh Smruti Dental College & Hospital, Nagpur, Maharashtra, India*

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ABSTRACT

Introduction: Alveolar osteitis (AO) is the most common complication of dental extractions, especially, the mandibular third molar. Zinc oxide eugenol (ZOE) is commonly used as a surgical dressing for the treatment of AO. However, the search for better dressing materials is still underway. Therefore, the present study aims to evaluate the impact of the intra-alveolar application of Metronidazole (MN), Chlorhexidine (CHX), and Lignocaine (LC) on the treatment of alveolar osteitis and compare it with that of ZOE.
Materials and Methods: A total sample of n=32 patients was randomly assigned into the experimental group treated with MN+CHX+LC combination, while the control group was treated with ZOE paste dressing. Pain, discomfort, and healing were assessed on 3-day and 2-week follow-ups.
Results: A statistically significant difference was noted in the number of individuals with pain (p=0.006) and halitosis (p=0.002) on the third day follow-up with higher number of individuals in the control group still experiencing the symptoms. By the end of two weeks, all the patients in the experimental group (n=16) had relief from pain and discomfort while they persisted in n=4 patients and halitosis was noted in n=9 patients treated with ZOE dressing.
Conclusion: The experimental combination has a clear advantage as a medicament dressing because of its superior antibacterial and anesthetic properties over ZOE dressings. The combination reduces the time period required for healing the socket in AO, while greatly adding to the patient's comfort and overall well-being.

1. Introduction

Extraction of third molars is one of the most frequently performed procedures in the field of Oral and Maxillofacial Surgery. Dry socket, which typically develops 2-4 days after is one of the most frequent postoperative consequences following tooth extraction.[1] Numerous terms, such as Dry Socket, Localized Osteitis, Osteomyelitis Syndrome, Alveolitis Sicca Dolorosa, Avascular Socket, and Fibrinolytic Alveolitis, are used to refer to alveolar osteitis (AO).[1,2] It is characterized by the presence of pain in the socket region from which a tooth was extracted one to three days ago. The pain increases in severity over time and is accompanied by a blood clot disintegrated to a varying extent.[3]

* *Corresponding author*.
E-mail address: sunpreetss@yahoo.in (S. S. Sachdev).

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Dry socket is so common that it develops in about 3% of all extractions and 30% of cases of mandibular extractions, with the mandibular third molar region being most commonly involved. The signs of AO include a foul odor, visible bony socket without any granulation tissue, radiation of pain to nearby sites, and may radiate to nearby locations, and absence of suppuration.[1] Trauma, microbial contamination, and nutritional deficiency are a few potential etiological factors that lead to fibrinolysis in the socket.[4]

Use of obtundents such as zinc oxide eugenol (ZOE) in dressing form, analgesics in systemic/topical forms, and irrigation by various agents have been suggested to relieve the symptoms of AO.[5] Eugenol, which is a prime component of ZOE, is found to be have calming and anodyne characteristics as well as antimicrobial capabilities.[6] Despite generous efforts, there is yet a need to find an optimal chemopreventive agent against the formation of a dry socket. An ideal obtundent dressing would hinder the growth of microorganisms, prevent fibrinolysis, and aid in healing the socket wound.

Given the fact that anaerobic bacteria such as treponema denticola and fusiform bacilli are implicated in the etiology of AO, antibiotic mouthwashes and dressings are recommended before and after surgery to prevent its formation.[7] Metronidazole (MN), a nitroimidazole anti-microbial drug has specialized efficacy against these anaerobic pathogens.[8] On the other hand, chlorhexidine (CHX), a biguanide antiseptic utilized in bio-adhesive gels or mouthwashes, is effective against several aerobic and anaerobic microbial species with an added advantage of substantivity.[9]

The symptoms of AO can be relieved to some extent by 2% lidocaine (LC) jelly.[10] The nerve endings stimulated during the surgical procedures would be quickly anesthetized by such topical usage. Intra-alveolar insertion is beneficial because it enables greater bioavailability, resulting in a longer-lasting release of the active ingredient and a more direct impact on the alveolus.

Mouthwashes incorporating CHX have been demonstrated to be only moderately effective against AO formation, while MN alone has been shown by many authors to be ineffective.[11] While many combinations of antibiotics and other chemicals have been tried, none of the studies have attempted to combine MN, CHX, and LC for the combined action against AO. Therefore, the present study aims to evaluate the impact of the intra-alveolar application of LC, MN, and CHX on the treatment of alveolar osteitis and compare it with that of ZOE.

2. Materials and Methods

The present randomized clinical trial was conducted in the institutional Department of Oral & Maxillofacial Surgery from July 2019 to May 2020. Patients reporting to the department were randomly assigned into either the experimental group or the control group (n=16 each respectively). Patients were allocated to either of the groups using a table of random sequence generator, using GraphPad software (v. 8.0). The procedure of allocation was carried out by a pre-determined investigator (SS) not involved in any part of data collection or surgical procedure, thus maintaining allocation concealment and triple blinding of the trial. The random sequence was not revealed to any investigator and was known only to that expert.

Patients who were clinically diagnosed with AO were enrolled in the current study after giving their informed written consent in accordance with the Helsinki Declaration. Medically compromised patients, mentally challenged patients, pregnant/lactating patients, patients allergic to Lidocaine, metronidazole or chlorhexidine, and those having bone pathology or taking oral contraceptives were excluded from the study.

The diagnostic criteria used for AO included: (i) Patient with severe pain arising after 24hrs to 3^{rd} day of extraction, localized to extraction socket and sensitive to even gentle probing. (ii) Absence of a normal healthy post-extraction blood clot in the socket which may be empty or contain yellowish/grayish fragments of disintegrated blood clot (Figure 1), and (iii) Halitosis. For each patient, a thorough case history was obtained before the clinical examination and radiological evaluation. The afflicted socket was gently irrigated with warm saline to dislodge or remove all debris or dissolved clot after any root pieces or foreign body remains were ruled out.

The patients in both the groups received dressing of the corresponding medication as described below under standard aseptic protocol: Experimental group: Rexidine M Forte gel, which contained 1% chlorhexidine gluconate and metronidazole, lignocaine hydrochloride 2% w/w and benzoate 1% w/w. Control group: ZOE paste comprising of Zinc oxide powder and Eugenol liquid components.

The patients were recalled on the 3^{rd} day and 2^{nd} week after placing the medicament dressing for follow-up. The pain levels at every visit were evaluated by means of Visual Analog Scale (VAS). Other parameters such as healing of socket, discomfort & presence/absence of halitosis were also assessed.

3. Statistical Analysis

Data collected was compiled into an MS Office excel worksheet & was subjected to statistical analysis using SPSS software. Frequency (n) & percentage (%) of various responses in each group was compared using a chi-square test. For numerical continuous data (following a normal curve) t-test for inter-group comparison was used. P value < 0.05 was considered statistically significant.

Table 1: Comparison of outcome variables between the patients treated with experimental combination and ZOE dressing

Variable	Category	Rexidine M Forte	ZOE	Chi square value	P value of chi square test
Pain Baseline	Yes	16	16	—	—
3D	No	15	8	7.575	0.006**
	Yes	1	8		
2W	No	16	6	14.545	0.000**
	Yes	0	10		
Discomfort Baseline	Yes	16	16	—	—-
Discomfort 3D	No	14	13	0.237	0..626#
	Yes	2	3		
Discomfort 2W	No	16	12	4.571	0.033*
	Yes	0	4		
Socket baseline	NH	16	16	—	—-
Socket 3D	Healing	16	16	—	—-
Socket 2W	Healing	15	8	7.575	0.006**
	NH	1	8		
Exposed bone baseline	Yes	16	16	—	—-
Exposed bone 3D	Covered	16	16	—	—-
Exposed bone 2W	Covered	15	7	9.309	0.002**
	Exposed	1	9		
Halitosis baseline	Yes	16	16		
Halitosis 3D	Absent	15	7	9.309	0.002**
	Present	1	9		
Halitosis 2W	Absent	15	7	9.309	0.002**
	Present	1	9		
Socket baseline	Empty	16	13	3.310	0.069#
	Pieces	0	3		
Socket 3D	Empty	16	16	—	—-
Socket 2W	New bone	16	7	12.522	0.002**
	No change	0	5		
	Remodel	0	4		
Lamina dura baseline	Intact	14	16	2.133	0.144#
	Not intact	3	0		
lamina dura 2W	Intact	14	7	6.788	0.009**
	Not intact	2	9		

* = statistically significant difference (p<0.05)
** = statistically highly significant difference (p<0.01)
# = non-significant difference (p>0.05)

4. Results

The total sample size of n=32 comprised of 16 males and 16 females. The age of the patients ranged from 18 to 50 years with a mean age of 31.64 + 8.98 years. A statistically non-significant difference (p>0.05) between the mean age and the number of individuals of each gender indicated that the baseline demographic characteristics of both groups were identical, thereby minimizing variations due to these confounding factors.

Starting from the baseline wherein all the patients (n=16) presented with pain in both groups, on the third day, the pain persisted in eight patients treated with ZOE dressing and only in one patient treated with the experimental combination of MN, CHX, and LC. A statistically significant difference was noted in the number of individuals with pain (p=0.006) and halitosis (p=0.002) on the third day follow-up with higher number of individuals in the control group still experiencing the symptoms.

By the end of two weeks, all the patients in the experimental group (n=16) had relief from pain and discomfort; only one patient had exposed bone and halitosis, but surprisingly, without associated symptoms. On the other hand, discomfort persisted in n=4 patients treated with ZOE dressing and halitosis was noted in n=9 patients. The socket was found to be non-healing in only one patient in the experimental group while in n=8 patients in the control group.

A statistically highly significant difference (p<0.001) was noted between the number of individuals experiencing pain in both groups with a greater number of individuals experiencing pain after two weeks in the control group. Interestingly, there was no significant difference found in

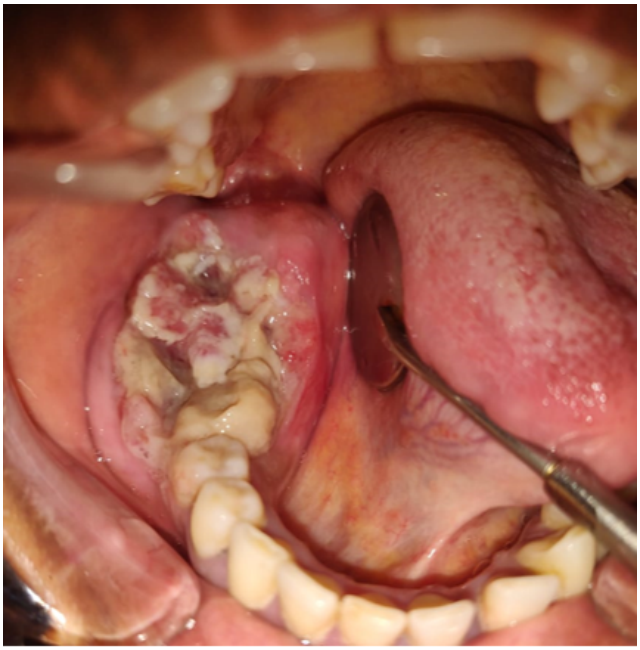

Fig. 1: Presence of yellowish disintegrated clot and food material in the unhealed dry socket

the pain levels denoted by VAS by patients in both groups. The bone was still found to be exposed and the socket not healed with a disrupted lamina dura after two weeks in a significantly higher number of individuals ($p<0.05$ each parameter, respectively) in the control group.

The overall results are comprehensively listed inTable 1.

5. Discussion

To tackle AO efficiently and effectively, it is essential for the agents used in surgical dressing to destroy the wide variety of bacterial species present in the oral microflora. At the same time, reducing the symptoms of pain, discomfort, and halitosis is of utmost importance for the patient. Our results indicated that the combined dressing of MN, CHX, and LC was effective in alleviation of pain in 93.75% of patients by the third day itself. On the contrary, only 50% of patients treated with ZOE were completely free of pain.

It can, therefore, be discerned from our results that the experimental combination is much more effective in treatment of AO as compared to ZOE. This is because of its antimicrobial components, MN and CHX, and anesthetic component (LC) that rid of the contaminant microbes while alleviating the patient's symptoms. The low redox potential electron transfer protein, Ferredoxin, in MN binds to polar products which lack nitro groups present in the microbial genetic material. The reduction product disrupts DNA and prevents the formation of nucleic acids essential for the sustenance of bacteria, particularly, the anaerobic species, resulting in cytotoxic damage.[12]

In a research paper, the potential role of anaerobic microorganisms in the pathogenesis of alveolar Osteitis was demonstrated by Nitzan et al.[13] In the study by Kaur et al., the bactericidal effects of metronidazole on these microorganisms and the antiseptic effects of chlorhexidine on bacteria producing fibrinolysisis are found to be beneficial.[11] Mitchell evaluated the effectiveness of a 10% metronidazole gel for the treatment of dry socket which resulted in speedier healing when the gel was applied.[13] Poi et al. in his clinical trial concluded that the paste containing metronidazole and lignocaine was successful in the treatment of infection and did not interfere with the regular chronology of the healing process based on these findings.[14]

In a research published by Shad et al, the antimicrobial properties of chlorhexidine were discovered to be effective in cases of AO.[15] According to the literature, by-products of bacterial infection boost antifibrinolytic activity, leading in clot breakdown and loss, which leads to AO. This fibrinolytic mechanism can be suppressed by chlorhexidine, resulting in prevention of AO.[1,3] Haraji et al. concluded that topical chlorhexidine gel significantly reduces dry socket incidence and postsurgical pain in patients with and without dry socket in their study.[16]

The number of patients free of discomfort by the third day was almost similar with 87.5% of patients in the experimental group and 81.25% of patients in the control group. The eugenol component in ZOE is a safe obtundent having calming and anodyne characteristics as well as antimicrobial capabilities to some extent.[6,17] The reduction of pain levels as well as discomfort was found to be similar by eugenol and LC.

Our study presents itself with a few limitations. Firstly, the sample size may be inadequate to extrapolate the findings to the general population. The authors, therefore, advise caution before interpretation of the results to their face value. Secondly, the pain levels reported by VAS may be subjective and thus, vary according to each patient's level of perception rather than being a standard scale of reference. Lastly, long-term follow-up of patients would have been beneficial to identify flare-ups or recurrences as well as completion of healing.

Nevertheless, our findings would serve to guide researchers to further test the new combination in the treatment of AO. The evidence generated by our results should suffice to encourage clinicians to practice use of the combination of MN, CHX, and LC as a surgical dressing for patients with AO.

6. Conclusion

To the best of our knowledge, the present study was the first in the literature to evaluate the effectiveness of combination of MN, CHX, and LC to treat AO. The experimental combination has a clear advantage as a medicament

dressing because of its superior antibacterial and anesthetic properties over ZOE dressings. The combination reduces the time period required for healing the socket in AO, while greatly adding to the patient's comfort and overall well-being.

7. Source of Funding

None.

8. Conflict of Interest

None.

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Author biography

Kavita Wadde, Associate Professor

Ashwini Chhapane, Post Graduate

Sanpreet Singh Sachdev, Post Graduate https://orcid.org/0000-0001-7655-8180

Ashish Sarda, Post Graduate

Asha Chowdhar, Post Graduate

Siddhesh Latke, Post Graduate

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