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EFFICACY OF OZONE GEL, DOXYCYCLINE SATURATED CHITOSAN DRESSING VERSUS ALVEOGYL IN PAIN ALLEVIATION AND HEALING OF ALVEOLAR OSTEITIS IN DIABETIC PATIENTS DOUBLE BLIND RANDOMIZED CLINICAL TRAIL

Tarek Abdelbary Abdellatife*

ABSTRACT

Aim of the study: To assess the efficiency of ozone gel or doxycycline-saturated chitosan dressing compared to Alvogyl in alleviating pain & promoting recovery of alveolar osteitis in cases with diabetes.

Methodology: A total of 60 type II diabetic patients of either gender aged from 20-60 years who were suffering of alveolar osteitis following dental mandibular molar teeth extraction. The patients were equally divided according to material used to pack the dry socket. Following gentle irrigation and curettage of affected Socket; [(group A) Ozone gel, (group B) doxycycline hyclate saturated chitosan dressing (HHD) HemCon dental dressing and for (group C) Alvogyl paste] was applied. Pain scores was recorded on VAS. The healing score of the extraction socket was documented using Landry wound healing index.

Results: for (VAS) comparison between the three groups at different time points shown that significant differences in VAS scores emerged between groups at all subsequent time points P value < 0.05. Group C consistently showed higher VAS scores, indicating more pain, while Group B generally had the lowest scores, comparison of healing score of the socket showed significant variations between groups from day 4 to day 14 ($p<0.001$). Groups A & B demonstrated faster healing than Group C during this period. By day 21, all groups eventually achieved similar healing outcomes.

Conclusion: ozone gel and doxycycline saturated chitosan dressings are effective treatment modalities for management of dry socket cases in type II diabetic cases and proved to be more effective than the conventional Alvogyl dressing

Keywords: Dry socket, Ozone gel, Doxycycline, Alvogyl

* Lecturer of Oral and Maxillofacial Surgery, Faculty of Dentistry, Minia University

INTRODUCTION

Alveolar Osteitis; a common complication following extraction or surgical removal of tooth; also known as dry socket characterized by postoperative pain of severe intensity and clot disintegration which occur between the first and third day after the tooth extraction, [1]. Five percent of routine dental extractions develop the condition which rises up to 30% in cases of impacted mandibular wisdom tooth extraction [2, 3]

In diabetic patients; many changes occur in all tissues of the body specially in capillaries where the basement membrane develops thickening directly altering permeability, hinder leukocytes migration causing under perfusion when tissue suffer from hypoxia. These tissue alterations are directly related to the poor and/ or delayed wound healing which may be superimposed with infection for these responses diabetic patients are more susceptible to developing dry socket. [4] Numerous local and systemic factors contribute to alveolar osteitis; however, the exact pathogenesis is not yet well understood even, in this era of advanced cell and molecular biology, [5, 6]

Many treatment modalities have been recommended to manage alveolar osteitis, [7,8,9] however, traditional treatment approaches only address the symptoms but do not immediately eliminate pain and other symptoms. Recently; different maneuvers of wound management in other surgical specialties including use of low intensity pulsed US therapy [10], low level laser therapy [11,12], ozone therapy [13, 14] and the use of platelet rich plasma (PRP) are now been administrated to treat alveolar osteitis.

Ozone has long been used in different medical and environmental fields due to its antimicrobial efficiency and no of adverse effects. Ozone gas has been effectively utilized as surface disinfectant for implants instruments and prostheses. It is also suitable during surgical interventions as it promotes wound healing and epithelization. [14]

The HemCon Dental Dressing (HDD) is a compressed chitosan acetate dressing designed for hemostatic applications [15]. It is a chitin based dressing, produced from shrimp shells. [16, 17] Chitosan possesses a (+ve) charge and attracts and adheres to red blood cells and platelets, via ionic interaction; thereby sealing of the wound site. [18] This supportive, initial seal enable the body to start coagulation process effectively. It also functions as a support frame work for the platelets and red blood cells till hemostasis is achieved. [19] Moreover; Chitosan is biocompatible, antimicrobial agent against a broad range of gram(+ve) and gram(+ve) bacteria and fungi. [20] Doxycycline has long been utilized as a local medicament and a dressing in dry socket cases by itself exhibiting varying success rates [21]

Therefore, the null hypothesis was that there was no difference in the efficacy of ozone gel or doxycycline saturated HDD compared to Alvogyl regarding pain relief and wound healing of dry socket in type II diabetic patients.

AIM OF THE STUDY

Assess the Efficacy of ozone gel or doxycycline saturated chitosan dressing versus Alvogyl on pain alleviation and healing of alveolar osteitis in type II diabetic patients

MATERIALS AND METHOD

The research adhered to the medical protocol and ethics of Declaration of Helsinki; Ethics Committee clearance was granted by Faculty of Dentistry, Minia University under no **(94/ 713)** DATE 28/ 2/ 2023, additionally; the investigation protocol was registered on **ClinicalTrials.gov** with **ID (NCT05875506),** all participants signed a written informed consent after they were informed about the nature of the study.

Sample size calculation was performed using G*Power version 3.1.9.7. applied to the null

hypothesis based on the results of a previous study [4]; the predicted sample size (n) was a total of 56 cases which was increased to 60 cases to compensate for any dropout (i.e., 20 cases per group).

Selection of participants and Recruitment strategy

A Consecutive sampling was done through screening of patients; in outpatient clinic of the Oral and Maxillofacial Surgery Department – Faculty of Dentistry- Minia University; according to the predetermined inclusion criteria. This was continued until the target population was achieved. **Inclusion criteria**: patients ages between 20 - 60 years of either gender, that are controlled type II diabetic patients, with signs and symptoms of dry socket (having tooth extraction with-in past 48-72 hours), participant willing to carefully control their blood glucose level all through the period of the study. **Exclusion criteria:** patients with any significant medical condition other than type II diabetes mellitus, patients on drugs that affect the central nervous systems, and those who are pregnant or lactating, or have hypersensitivity to local anesthetics.

Randomization and blinding

A random sequence was generated by computer software (Microsoft Excel) where all groups were denoted and randomly distributed. The patients were blinded to the assigned group as well as the assessor that score healing of the socket.

Grouping

The participants were randomly divided into three equal groups according to the dressing applied: **group A** (20 patients), who received Ozone gel: (Ozene; Premier Research Labs, USA. 78728) application in to the dry socket, **Group B** (20 patients), who received chitosan dressing (HHD) HemCon dental dressing Pro (Tricol Biomedical, Inc. USA) which was impregnated with doxycycline hyclate (Atridox 10% Tolmar Inc, USA) and **group C** who received Alvogyl paste (Septodont, inc, FRANCE) application in to the dry socket

Intervention

Following adequate anesthesia was reached, a brief saline irrigation of the socket with 2ml of (0.9% solution) normal saline to flush out any debris followed by gentle and carful curettage of the socket then further irrigated with 6mL warm saline. Gentle damping with sterile gauze to control bleeding then The dressing was applied according to the assigned group. Stress reduction protocol during the procedure was performed

Dressing application:

Group A: Ozone gel was carefully administrated into the dental socket utilizing a blunt-ended sterile disposable 1 ml syringe. The gel was injected slowly into the socket up to the gingival level. A Sterile gauze was placed over the socket and patient was instructed to keep it in place for 30 minutes.

Group B: A Custom-cut chitosan dressing was cut to fit loosely into extraction socket to a standard dimension (10 mm x 12 mm x 5.5 mm) for all cases of this group. then it was immersed into a sterile tube with 10% doxycycline hyclate gel and allowed to set for 30 minutes before use. The doxycycline saturated dressing was gently then seated loosely into the socket. A Sterile gauze with gentle finger pressure was applied over the filled socket site for 60 seconds.

Group C: The socket was packed with appropriate amount of fibers from the Alvogyl paste. A Sterile gauze with gentle finger pressure was placed over the socket site for 60 seconds.

Postoperative instructions: Paracetamol 500 mg every 6 hours was prescribed as analgesic for 2 days. All patients were motivation to maintain a good oral hygiene and hot fomentation after 24 hours following the procedure.

Subjective Assessment

The patients were educated and instructed to recorded Pain scores on (VAS) visual analog scale using a zero to ten pain score where 0 indicate no pain and 10 indicate the worst pain the patient had ever felt. (record were documented every 24h for 7 days).

For Healing score of the dry socket site; one blinded operator performed the scoring for all cases at the following (4 days, 7 days, 14 days and 21 days) time intervals using Landry wound healing index [22, 23]. The Landry wound healing index was utilized to assess the tissue healing process at the dry socket sites. The index classifies into five different categories: (1) very poor, (2) poor, (3) good, (4) very good, and (5) excellent healing

Data collection and statistical analysis

Data were collected and tabulated and statistically analyzed

RESULTS

Consort flow diagram of the participants throughout this clinical trial is shown in Fig. (1). A total of 78 patients were assessed. Seven cases did not meet the inclusion criteria and eleven declined to participate so they were excluded. No cases were lost during the study or the follow up.

The age and sex distribution across the three groups (A, B, & C), each with 20 participants. The p-value > 0.05 indicates no statistically significant difference in age and sex distribution between the groups. The groups are well-matched in terms of age and sex distribution. **Table (1)**

Visual Analogue Scale (VAS) scores comparison between the three groups at different time points shown in **Table (2), Fig. (2)** provided that There were no differences preoperatively, significant differences in VAS scores emerged between groups at all subsequent time points. Group C consistently showed higher VAS scores, indicating more pain, while Group B generally had the lowest scores.

Table (1): Comparison of age and sex distribution between study groups

		Group A	Group B	Group C	P value
		No =20	No =20	No =20	
Age	Range	(20-59) [a]	(20-59) [a]	(21-59) [a]	0.840
	MEAN ± SD	35.6±11.8	35.5±11.5	37.4±12	
Sex	Male	7(35%) [a]	7(35%) [a]	7(35%) [a]	1
	Female	13(65%)	13(65%)	13(65%)	

One Way ANOVA test for normally distributed quantitative data between the three groups followed by Post Hoc LSD test between each two groups

Chi square test for qualitative data between groups

Superscripts with different small letters refer to significant differences between each two groups

Significant level at P value < 0.05

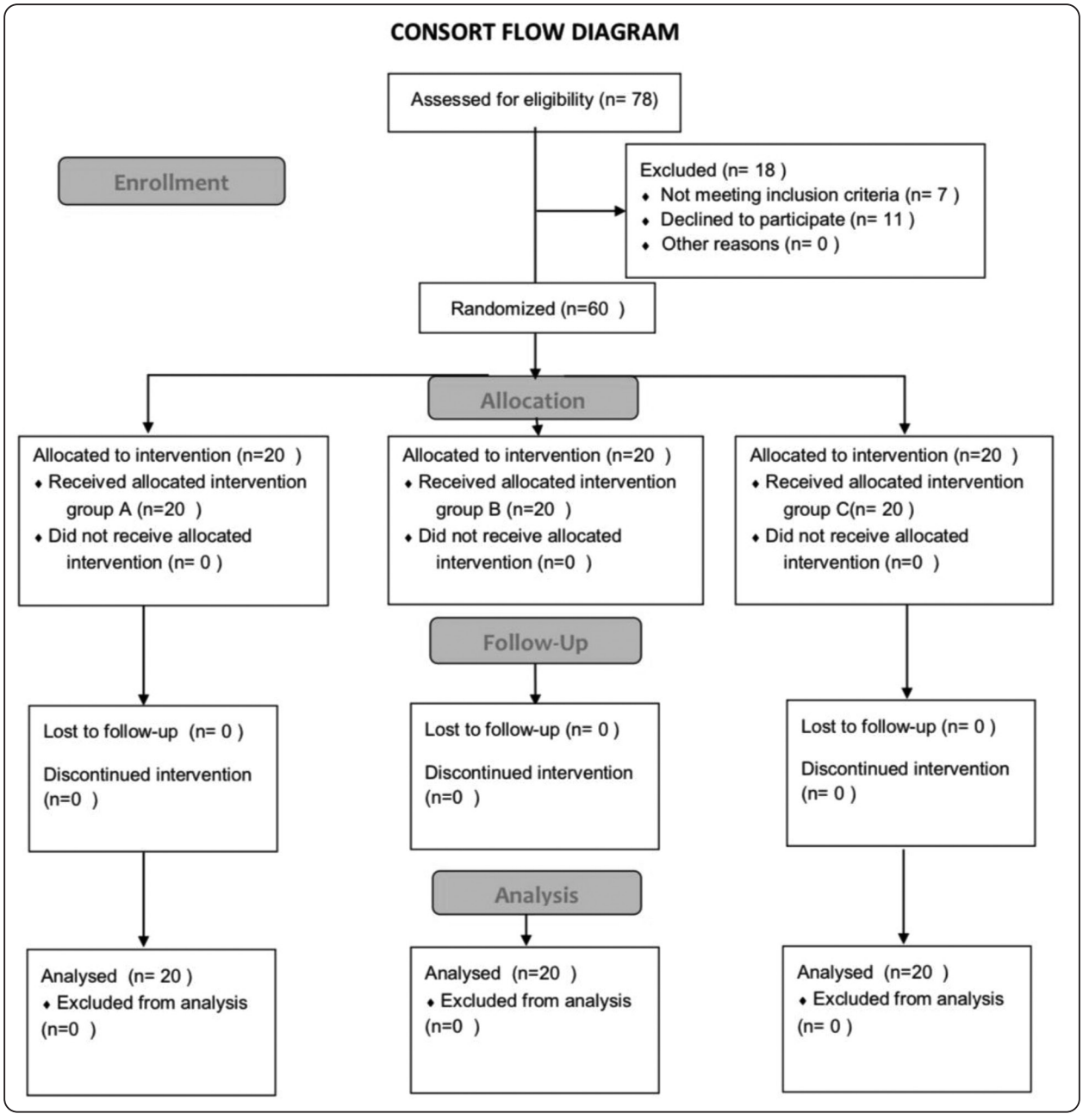

Figure (1): Consort flow diagram

TABLE (2) Comparison of VAS between different groups at different intervals

VAS		Group A	Group B	Group C	P value
		No =20	No =20	No =20	
Preoperative	Median	8 [a]	8 [a]	8 [a]	1
	IQR	(7-8)	(7-8)	(7-8)	
At 24 hours	Median	6 [a]	5 [a]	7 [b]	<0.001*
	IQR	(5-6.8)	(5-6)	(6.3-7.8)	
At 48 hours	Median	4 [a]	3 [b]	6 [c]	<0.001*
	IQR	(4-5)	(3-4)	(5-6)	
At 7 days	Median	2 [a]	2 [a]	2 [b]	0.001*
	IQR	(1-2)	(1-2)	(2-3)	

Kruskal Wallis test for not normally distributed quantitative data between the three groups followed by Mann Whitney test between each two groups

Superscripts with different small letters refer to significant differences between each two groups

****: Significant level at P value < 0.05***

Tables (3,4,5) show the statistical significance of VAS score changes within each group over time. For all three groups, there are statistically significant differences with p value < (0.001) between all-time points (preoperative, 24 hours, 48 hours, and 7 days); indicating pain reduction was evident though all time intervals.

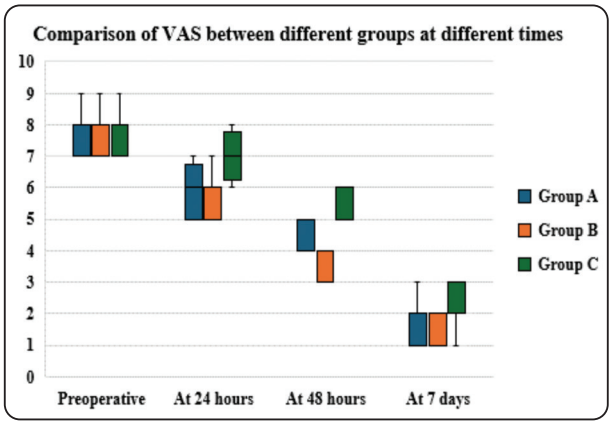

Fig. (2): box plot showing comparison of VAS between different groups

TABLE (3) P value for comparison of VAS between different times within group A

Group A	Preoperative	At 24 hours	At 48 hours
At 24 hours	<0.001*		
At 48 hours	<0.001*	<0.001*	
At 7 days	<0.001*	<0.001*	<0.001*

Wilcoxon signed rank test

****: Significant level at P value < 0.05***

Table (4): P value for comparison of VAS between different times within group B

Group B	Preoperative	At 24 hours	At 48 hours
At 24 hours	<0.001*		
At 48 hours	<0.001*	<0.001*	
At 7 days	<0.001*	<0.001*	<0.001*

Wilcoxon signed rank test

****: Significant level at P value < 0.05***

Table (5): P value for comparison of VAS between different times within group C

Group C	Preoperative	At 24 hours	At 48 hours
At 24 hours	<0.001*		
At 48 hours	<0.001*	<0.001*	
At 7 days	<0.001*	<0.001*	<0.001*

- ***Wilcoxon signed rank test***
- ****: Significant level at P value < 0.05***

Healing scores followed a similar pattern, with no significant differences preoperatively (p=0.866) but showing significant variations between groups from day 4 to day 14 with p value less than 0.001. Groups A & B demonstrated faster healing compared to Group C during this period. By day 21, these differences were no longer statistically significant with p value of (0.126), suggesting all groups eventually achieved similar healing outcomes. **Tab (6), Fig (3)**

Table (6): Comparison of healing score between different groups at different times

Healing score		Group A	Group B	Group C	P value
		No =20	No =20	No =20	
Preoperative	Very poor	17(85%) [a]	17(85%) [a]	18(90%) [a]	0.866
	Poor	3(15%)	3(15%)	2(10%)	
	Good	0(0%)	0(0%)	0(0%)	
	Very good	0(0%)	0(0%)	0(0%)	
	Excellent	0(0%)	0(0%)	0(0%)	
At 4 days	Very poor	0(0%) [a]	0(0%) [b]	4(20%) [c]	<0.001*
	Poor	14(70%)	6(30%)	16(80%)	
	Good	6(30%)	14(70%)	0(0%)	
	Very good	0(0%)	0(0%)	0(0%)	
	Excellent	0(0%)	0(0%)	0(0%)	
At 7 days	Very poor	0(0%) [a]	0(0%) [a]	0(0%) [b]	<0.001*
	Poor	0(0%)	0(0%)	11(55%)	
	Good	7(35%)	7(35%)	9(45%)	
	Very good	13(65%)	13(65%)	0(0%)	
	Excellent	0(0%)	0(0%)	0(0%)	
At 14 days	Very poor	0(0%) [a]	0(0%) [a]	0(0%) [b]	0.001*
	Poor	0(0%)	0(0%)	0(0%)	
	Good	0(0%)	0(0%)	2(10%)	
	Very good	9(45%)	6(30%)	16(80%)	
	Excellent	11(55%)	14(70%)	2(10%)	
At 21 days	Very poor	0(0%) [a]	0(0%) [a]	0(0%) [a]	0.126
	Poor	0(0%)	0(0%)	0(0%)	
	Good	0(0%)	0(0%)	0(0%)	
	Very good	0(0%)	0(0%)	2(10%)	
	Excellent	20(100%)	20(100%)	18(90%)	

Chi square test for qualitative data between groups

Superscripts with different small letters refer to significant differences between each two groups

****: Significant level at P value < 0.05***

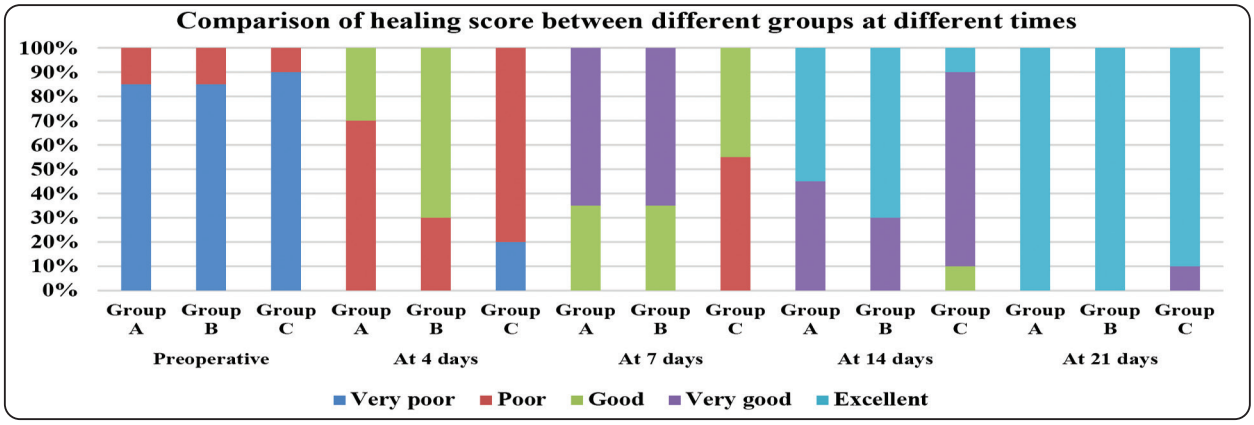

Fig. (3) Bar chart showing comparison of healing score between different groups at different time intervals

DISCUSSION

Alveolar Osteitis; an oral condition which is a common complication following extraction or surgical removal of tooth; also known as dry socket characterized by postoperative pain of severe intensity and clot disintegration. The exact pathogenesis has been subjected to significant controversy and is not yet well understood. Complete healing of the socket requires a well-established blood clot after tooth extraction. Premature disintegration of the blood clot prevents the essential healing process leading eventually to development of alveolar osteitis. [24.]

Diabetic patients are more susceptible to developing dry socket. This is attributed to changes in different tissues of the body specially the capillaries which develop basement membrane thickening that alters permeability and disturbs leukocytes migration causing impaired perfusion and hypoxia; all of which result in poor and/or delayed wound healing and increases wound infection risks and further increasing the incidence of dry socket in such patients. [4]

Due to the intense pain and impaired healing accompanied with dry socket added to the critical condition of the tissues in diabetic patients; comprehensive clinical approach to treating such lesions is of utmost importance. For the present study three different materials were applied to dry socket cases to reach the most optimum treatment modality for management of such cases.

Regarding pain alleviation significant differences in VAS scores emerged between groups at all subsequent time intervals. Group A showed significantly lower pain score than group C while Group B generally had the lowest pain scores.

Concerning cases treated with ozone gel group (A); significant decrease in postoperative pain was shown which comes in accordance with **Ebensberger et al** [25] **and Khan et al** [26] Whom demonstrated that ozone not only reduces the inflammation, but also activates angiogenesis in the inflamed tissue which effectively decreases pain.

Further; **Huth etal.** [27] examined the effectiveness of ozone aqueous solution against pathogenic periodontal microbes compared to chlorhexidine digluconate of different concentrations; it was determined that both agents were effective in eliminating pathogenic microorganisms.

Moreover; it comes in agreement with **Ahmedi etal** [28] whom compare the ability of both ozone and CHX gel in preventing dry socket development after surgical extraction of impacted mandibular wisdom tooth and found that ozone was of superior efficacy

This may be explained that ozone not only is a potent disinfectant but also Ozone induces moderate and controlled oxidative stress that can generate second messenger molecules that activate different transcription factors that regulate different biological and physiological cellular responses triggering the antimicrobial, antioxidant, anti-inflammatory, immune modulating and anti-hypoxic mechanisms of action of ozone [29]

In addition; ozone possesses anti-inflammatory and antioxidant actions which leads to reduced release of inflammatory mediators; serotonin and endogenous opioids increase also lead to stimulation of antinociceptive pathways, thus intermediating an analgesic effect [30, 31]

While group A (treated with ozone) was effective in relieving pain; group B (treated with doxycycline saturated chitosan dressing) still recorded significantly more pain reduction than did group A. Chitosan dressing is a widely used dressing for surgical wound. The findings of the current study are consistent with **Malmquist etal.** [19] whom previously evaluated the postoperative pain after utilizing the chitosan dressing in dental extraction socket and found it to be superior than control group where no dressing was applied.

Chitosan not only possesses noticeable antimicrobial effects; by destabilizing the outer membrane and increasing plasma membrane permeability of the bacterial cell; but also modulates the activity of inflammatory cells, fibroblasts and osteoblasts leading to accelerated wound healing. This innovative semipermeable biological dressing maintains an uncontaminated wound, preventing dehydration of the wound optimizing conditions for optimum healing. [32, 33, 34]

In the present study Immersion of the chitosan dressing into doxycycline hyclate allowed the dressing to eventually perform more efficiently; Doxycycline is well known synthetic derivative of tetracycline with broad-spectrum antimicrobial properties. Bacteria that are frequently associated with dry socket include *Enterococcus, Streptococcus viridians, Streptococcus mutans, Pseudomonas aeruginosa, Antinomies viscous, Citrobacter freundii, Escherichia coli, and Treponema denticola*. These microorganisms provoke alveolar osteitis as they delayed healing of extraction sites due to plasmin-like fibrinolytic activities, and indirect fibrinolysis associated with such microorganisms. Doxycycline has antimicrobial effect on the growth of these microorganisms. Further; it additionally has the capability to inhibit proinflammatory cytokines that lead to the protein kinase C pathway downregulation. At low doses, it is known to suppress collagenase, gelatinase and metalloproteinases; all which are known to be predisposing factors stimulating the initiation of alveolar osteitis cases. [35, 36]

The present study is consistent with **Rusu and Buta** [37] whom studied doxycycline anti-inflammatory properties, they found it to inhibit neutrophil and T-lymphocytes activation and migration, and came to conclude that it eventually inhibits phospholipase and granuloma formation, along with the suppression of inflammatory cytokines release (IL-6, TNFα, IL-1β, IL8). **Liu et al** [38] similarly demonstrated that doxycycline act as an inhibitor of matrix metalloproteinase (MMP) activity. Doxycycline hyclate possesses the dual action of promoting regeneration while simultaneously suppresses infectious processes, rendering it a promising treatment option for wounds of different etiologies.

Consistent results were found by **Sanchis etal** [39] whom Studied the effect of placement of intra-alveolar tetracycline on improvement of postoperative pain. The authors found that patients receiving intra-alveolar tetracycline experienced less pain and trismus and needed less analgesics than the those who did not have tetracycline treatment.

Although group C, treated with alvogyl dressing, had the lowest pain reduction and the slowest healing compared to the other test groups; it still showed significant alleviation of pain and by time improved healing. Many studies have provided evidence that it is an effective treatment modality; not only does it decrease pain and inflammation, but also by promoting alveolar mucosa healing. [40, 41]

The findings align with **Almayiah etal** [42] whom compared Alvogyl to 0.2% chlorhexidine gel application following surgical removal of impacted lower third molar. Alvogyl paste showed superior efficacy in pain reduction. This may be attributed to the components of the formula of alvogyl that include; eugenol which contains sedative, antibacterial, and anodyne effects. Further, butamben- one of the components- is an anesthetic substance along with iodoform which is a potent antibacterial agent. Alvogyl's properties render it a beneficial dressing material for postoperative pain alleviation specially in cases suffering from dry sockets [43, 44]

Groups (A & B) demonstrated faster healing compared to Group C during the period up to 14 days. This comes in agreement with findings by **Alpan etal** [45] whom investigate, through morphometrically and immunohistochemically technologies, the impact of gaseous ozone on bone healing in diabetic rat calvarial defects and concluded that ozone gas promotes bone healing particularly in the early stages of bone healing , and consistent with **Ozdemir etal** [46] whom found similar results when they utilized ozone gel in osseous defects in calvarial of rats where increase bone healing was observed both with histomorphometric assessments and histological analyses. This was evident in terms of increase proliferation of osteoblasts and enhanced new bone formation, another animal study conducted by **Buyuk etal** [47] where oxygen-ozone therapy was applied to bone defects; the results confirmed bone stimulation and regeneration, further showing that concentration of 25 μg/mL was the most efficient dose.

Laçin etal [48] showed similar results stating that the more bone formation in defects created in calvarial bone was produced when ozone was used in combination with bone graft. This may be due to increased hemostasis in the region, its ability to promote osteoblastic proliferation, formation of new bone matrix and enhances both angiogenesis and osteogenesis.

Similarly, in group B, using doxycycline saturated chitosan dressing a significant accelerated healing was observed. This semipermeable dressing, maintains a clean wound, minimizing dehydration and contamination thus optimizing conditions for healing acceleration. **Li etal.** [49] assessed the efficacy of chitosan based fiber membrane impregnated with flagyl on wound healing following tooth extraction. Their results demonstrated accelerated wound healing and reduced incidence of dry socket; they attributed their findings to the biocompatibility and anti-inflammatory properties of the chitosan dressing which also provided support for the forming blood clot in the tooth socket and the antimicrobial effect of flagyl that suppressed infection. Histological investigations confirmed the clinical findings showing enhanced wound healing. Additionally; it serves as a scaffold for fibroblast proliferation, thereby accelerating granulation tissue growth and inducing new bone formation. the incorporation of Doxycycline; a matrix metalloproteinase inhibition; reduces collagen breakdown and enhances new collagen deposition, thus improving wound healing as previously demonstrated by **Palasuk etal** [50]

Finally, Doxycycline can modulate the fibroblast activity and collagen deposition with in the wound bed, resulting in healing with decreased scar formation **Karna etal** [51] Doxycycline inhibits several bacterial strains that produce beta-lactamases, which are predominantly found in deep periodontal pockets as noted by **Connell etal** [52] which creates an optimum environment for progress of healing. Thus the null hypothesis for the current study was rejected.

CONCLUSION

Ozone gel and doxycycline saturated chitosan dressings are effective treatment modalities for management of dry socket cases in type II diabetic patients and proved to be more effective than the conventional Alvogyl dressing

DECLARATION OF INTERESTS

The study is self-funded and there is no conflict of interest.

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