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Evaluation Study

EFFICACY OF HYALURONIC ACID ON PREVENTION OF ALVEOLAR OSTEITIS: A PRELIMINARY RESULT

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ABSTRACT

Alveolar osteitis (AO) (dry socket) is a permanent tooth extraction complication characterized by intense pain and halitosis. This present study aimed to evaluate the efficacy of hyaluronic acid in preventing alveolar osteitis after tooth extraction in patients with a clinical history of AO. Adults of 18 years or older (patients with a clinical history of AO and/or traumatic extraction) were included. After tooth extraction, the socket was filled with hyaluronic acid in the test group while left empty in the control group. During healing, the patient's pain perception was assessed using a visual analog scale (VAS), and patients were screened for alveolar osteitis. All sites were evaluated clinically at baseline, after 3, 7, and 15 days. No alveolar osteitis (AO) was recorded in the test group, while only one case of AO was recorded in the control group. Within the limitation of our study, the application of hyaluronic acid after tooth extraction seems to be effective in reducing pain among patients with a clinical history of AO.

KEYWORDS: *alveolar osteitis, dry socket, hyaluronic acid, wound healing, socket healing, bone biomaterials*

INTRODUCTION

Alveolar osteitis (AO) (dry socket) was first described in 1986 by Crawford. It is a complication of permanent tooth extraction, which is characterized by intense pain with or without halitosis. It most commonly develops 2-4 days after tooth extraction. It is prevalence ranges from 0.5% to 5% in the case of a regular extraction (1) and from 1% to 45% in the extraction of mandibular wisdom teeth (2). Many names of AO were used in literature such as localized osteitis, necrotic socket, postoperative alveolitis, fibrinolytic alveolitis, localized osteomyelitis, avascular socket, alveolitis sicca, delayed extraction wound healing, dolorosa, and fibrinolytic alveolitis. However, only alveolar osteitis and dry socket continue to be commonly used.

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The incidence of alveolar osteitis is increased in cases with inadequate blood supply, poor oral hygiene, excessive trauma to the bone, mechanical factors such as rinsing or sucking that may cause loss of the clot, foreign bodies or tissue in the socket, and infection (3). Several studies suggest a direct correlation between estrogen use and dry sockets for its effect on the coagulation system (4). Treponema denticola is found abundantly in association with gingival disease and is also involved in the pathogenesis of dry sockets (5). Furthermore, Actinomyces viscosus and Streptococcus mutans showed delayed healing of sockets after inoculation of the organisms in animal models.

Many techniques proposed to reduce the incidence of AO, such as the use of piezosurgery (6, 7) or filling the alveolus with drugs, for example, eugenol (analgesic), alveogyl, iodophorm (antimicrobial), zinc oxide eugenol and polymyxin B sulfate, tyrothricin, neomycin sulfate, or tetracaine hydrochloride (8). The management of AO is symptomatic in nature as AO is self-limiting condition. It is important to control pain control using local measures with or without systemic analgesics (9). Many authors suggest that chlorhexidine 0.12% mouthwash can be used after extraction for the prevention of AO (10, 11). However, evidence is non-conclusive. Recently, it has been proposed the use hyaluronic acid for bone healing and bone regeneration (12). Hyaluronic acid (HA) is a high-molecular glycosaminoglycan (GAG) which can be found as a constituent of the connective tissue, skin, eye, synovial fluid. HA plays an important role in cell migration, differentiation, proliferation, inflammation, wound healing, angiogenesis, cancer, diabetes and many physiological processes (13).

However, there is a lack of reports regarding the effect of HA in the prevention of AO. Therefore, this study was aimed to evaluate the efficacy of hyaluronic acid on the prevention of alveolar osteitis after tooth extraction in patients with a clinical history of AO.

MATERIAL AND METHODS

A pilot study was conducted to assess the efficacy of hyaluronic acid on prevention of alveolar osteitis. Fifty patients were enrolled in the present study; 25 were randomly assigned to the test group and 25 were assigned in the control group. All patients agreed to participate by signing an informed consent form, according to the recommendations of the Declaration of Helsinki. All the patients were treated in the Department of Innovative Technologies in Medicine & Dentistry of the University of Chieti-Pescara, Chieti, Italy.

Inclusion criteria were adult patients of 18 years or older with clinical indications for permanent tooth extraction (due to caries, trauma, or fracture) without the need for flap elevation with a history for alveolar osteitis. Exclusion criteria were patients requiring extraction with flap and rotary instrument, patients with periodontal disease, patients under antimicrobial therapy, or anti-inflammatory drugs.

Dental extractions were performed in accordance with standard procedures(14). All tooth extraction was performed by a single surgeon. After tooth extraction, the socket was filled with hyaluronic acid (Skin-F 26, Ital-Farmacia, Rome, Italy) on the test group, while left empty in the control group. During healing process, the patient's behaviour was evaluated for pain perception using visual analogy scale (VAS) and presence or absence of alveolar osteitis. All sites were evaluated clinically, and photos were taken at baseline, after 3, 7, and 15 days (Fig. 1, 2).

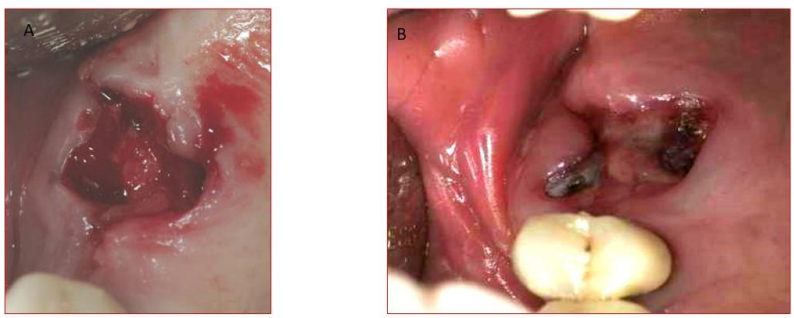

Fig. 1. ***A****): Immediately after the tooth, the socket filled with HA as a baseline.* ***B****): Socket filled with HA after 3 days.*

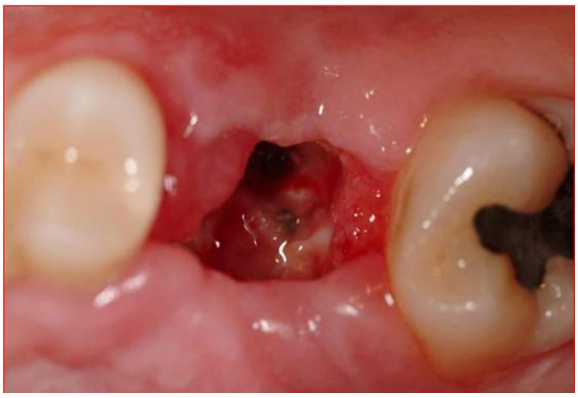

Fig. 2. *Control group. A single case of alveolar osteitis.*

Statistical analysis

A statistical package GraphPad 8.0 (Prism, San Diego CA USA) was used for the statistical analysis. Pain scores were described as VAS means, standard deviations and 95% Confidence Intervals. The Kruskal Wallis followed by the Dunn's test has been applied to compare the VAS scores at the 3 different time points for each group. The Mann-Whitney test has been applied to compare the VAS score levels between the test and control group for each time point. The level of significance was considered for $p<0.05$.

RESULTS

Pain VAS score is a numerical rating scale in which 0 stands for no pain and 10 represents the possible worst pain (Fig. 3).

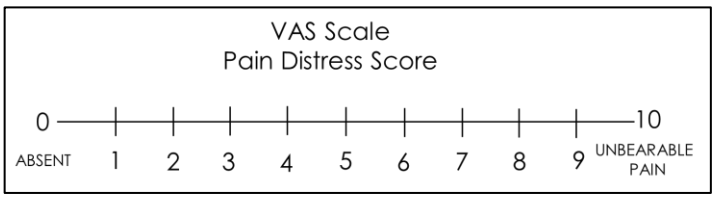

Fig. 3. *Pain VAS: Are you having pain during the post-operative time*?

The VAS values showed that most patients treated with hyaluronic acid had no or mild pain (VAS score: 0–1) at 1st day (96%), 3rd day (100%) and 7th day (100%) after surgery. Pain and mild discomfort were reported in only one case (4%; VAS score 2–4) at day 1 (Table I).

Table I. *Pain VAS distribution at days 1, 3 and 7.*

	VAS Score	1 day	3 days	7 days
Test group	0-1	24 (96%)	25 (100%)	25 (100%)
	2-4	1 (4%)	0	0
	5-7	0	0	0
	8-9	0	0	0
	10	0	0	0
Control group	0-1	14 (56%)	21 (84%)	24 (96%)
	2-4	11(44%)	4 (16%)	1 (4%)
	5-7	0	0	0
	8-9	0	0	0
	10	0	0	0

On the other hand, the control group reported 14 cases with no or mild pain (VAS score: 0–1) on day 1 (56%), 21 subjects on day 3 (84%) and a total of 24 subjects on day 7 (96%) after surgery (Table II). No alveolar osteitis (AO) was recorded in the test group, while only one case of AO was recorded in the control group.

Table II. *Descriptive statistics of the test and control groups VAS at day 1, 3 and 7.*

	Test Group			**Control Group**		
	1 day	3 days	7 days	1 day	3 days	7 days
Mean	0.8	0.56	0.16	1.7	1.4	0.88
Std. Deviation	0.65	0.51	0.37	1	0.91	0.93
Std. Error of Mean	0.13	0.1	0.075	0.2	0.18	0.19
Lower 95% CI of mean	0.53	0.35	0.0056	1.3	0.99	0.5
Upper 95% CI of mean	1.1	0.77	0.31	2.1	1.7	1.3

The means of VAS score of the test group on days 1, 3 and 7 were respectively 0.8±0.65, 0.56±0.51 and 0.16±0.37 (Tab. III). No significant differences were detected when comparing the VAS score of the test group on days 1 and 3 (p=0.6479).

Table III. *Kruskal Wallis followed by Dunn's test comparison of the VAS score at the 3 different time points for each group.*

Test Group- **Dunn's comparisons test**	Mean rank diff.	Summary	Adjusted P Value
1 days vs 3 days	6.64	ns	0.6479
1 days vs 7 days	21.44	***	0.0002
3 days vs 7 days	14.80	*	0.0175
Control Group- **Dunn's comparisons test**			
1 days vs 3 days	8.30	ns	0.3485
1 days vs 7 days	20.08	***	0.0004
3 days vs 7 days	11.78	ns	0.0773

A significant decrease was present comparing days 3 and 7 (p=0.0002) (Table III). The means of VAS score of the control group on days 1, 3 and 7 were 1.7±1, 1.4±0.91 and 0.88±0.93, respectively (Table III). No significant differences were detected comparing the VAS score of the control group on days 1 and 3 (p=0.3485). A significant decrease was present comparing the days 3 and 7 (p=0.0004). A significantly lower VAS pain score was detected comparing the test vs, control group at days 1, 3 and 7 (p<0.01) (Fig. 4).

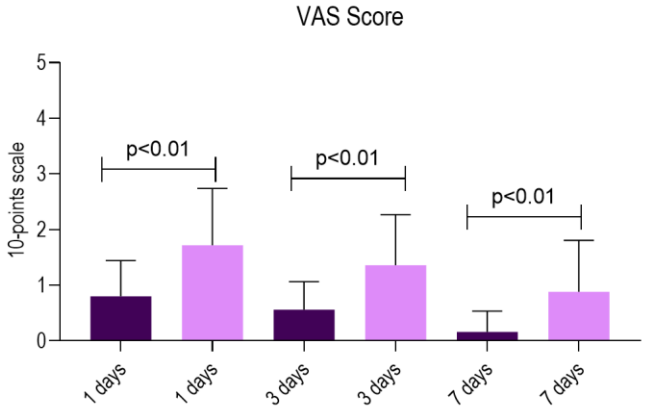

Fig. 4. *Chart of the VAS comparison on days 1, 3 and 7 [Mann-Whitney test].*

DISCUSSION

The results of the present study showed that hyaluronic acid treatment reduce post-extraction pain compared to control group, while no difference was detected for AO incidence. AO incidence in this study was only one case in the control group among patients with history of AO. Thus, the preventive effect was studied in a group known to have a high risk of developing AO.

Healing of extraction sockets is a complex process involving the reconstruction of damaged soft and hard tissues, which are regulated by various cytokines (15). Different factors can alter the healing of extraction sockets such as, gender hormones, diseases, glucocorticoid steroids, non-steroidal anti-inflammatory drugs, chemotherapy, alcoholism, and smoking. For these reasons, we have selected patients who are free from systemic disease and factors that affect tissue healing.

It has been proposed that intra-alveolar application of HA promote the wound healing (16). HA is abundant present in extracellular matrices, and have an important player in vascular disease, wound healing and cancer where fibrin deposition also occurs (17,18). Jointly with fibrin, HA is a major factor of the primary matrix formed following tissue injury. HA fragments increase angiogenesis and inflammatory reactions, which are important events in wound healing and tissue remodelling. HA together human fibrinogen promote formation and modulating the fibrin matrix(19).

HA could be a reliable tool for wound closure and the role of HA in the bone healing has been investigated (20). Recent research including 30 patients with poorly controlled diabetes required tooth extraction, 0.8% HA placed in post-extraction socket enhanced the tissue healing, in particular on the first days after application (21). The decrease in the dry socket rate with use of a hyaluronic acid further supports the significant role of HA in socket healing.

CONCLUSIONS

In conclusion, within the limitation of our study, we concluded that the use of hyaluronic acid after tooth extraction seems to be effective in reducing pain in patients with clinical history for AO. However, additional research with a larger sample size is needed to confirm our findings.

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