ORIGINAL ARTICLE

UDC: 616.314-089.87-06-08
DOI: 10.2298/VSP150304125D

The use of hyaluronic and aminocaproic acid in the treatment of alveolar osteitis

Primena hijaluronske i aminokapronske kiseline u terapiji alveolitisa

Dejan Dubovina*, Branko Mihailović*, Zoran Bukumirić†, Zoran Vlahović*, Milan Miladinović*, Nikola Miković‡, Zoran Lazić§‖

***Department of Oral Surgery, Faculty of Medicine, University of Priština Kosovska Mitrovica, Kosovska Mitrovica, Serbia; †Institute of Medical Statistics and Informatics, Faculty of Medicine, University of Belgrade, Belgrade, Serbia; ‡Clinic of Maxillofacial Surgery, Faculty of Dentistry, University of Belgrade, Belgrade, Serbia; §Clinic of Dental Medicine, Military Medical Academy, Belgrade, Serbia; ‖Faculty of Medicine of the Military Medical Academy, University of Defence, Belgrade, Serbia**

Abstract

Background/Aim. Alveolar osteitis (AO), also known as "dry socket", is relatively common post-extraction complication. It probably occurs due to excessive fibrinolytic activity in the coagulum and is characterized by intense pain sensations. The aim of this clinical study was to examine the role of hyaluronic acid and aminocaproic acid in the treatment of AO. **Methods.** The study included 60 patients with the clinical diagnosis of AO. All the patients were divided into two groups of 30 patients each according to the applied non-pharmacological measure: irrigation – irrigation of dry socket with sterile saline; curettage – careful curettage. Both of these groups were further divided into three subgroups regarding the applied treatment (hyaluronic acid; hyaluronic acid + aminocaproic acid; Alvogyl®, an anesthetic and antiseptic paste), each with 10 patients, according to the following protocol: 0.2 mL of hyaluronic acid in the form of a 0.8% gel; 2 mL of aminocaproic acid and hyaluronic acid; Alvogyl®. During each visit, scheduled for every two days until complete absence of painful sensations, the patients had the therapeutic method repeated as at the first examination. At each control visit the number of present symptoms and signs of AO was recorded, as well as the level of pain (measured with a visual analogue scale). **Results.** With the use of hyaluronic acid, with or without aminocaproic one, a statistically significantly faster reduction in pain sensations was achieved, along with the reduction in the number of symptoms and signs of AO compared to the use of Alvogyl®. **Conclusion.** Hyaluronic acid, applied alone or in combination with aminocaproic acid significantly reduces pain sensation, thus it can be successfully used in the treatment of AO.

Key words:
tooth extraction; postoperative complications; dry socket; hyaluronic acid; aminocaproic acids; curettage.

Apstrakt

Uvod/Cilj. Alveolitis je relativno česta postekstrakciona komplikacija. Nastaje, najverovatnije, usled izrazite fibrinolitičke aktivnosti u koagulumu, a karakteriše se pojavom intezivnog bola. Cilj ove kliničke studije bio je da se ispita mogućnost primene hijaluronske i aminokapronske kiseline u terapiji alveolitisa. **Metode.** Studija je uključila 60 pacijenata sa kliničkom dijagnozom alveolitisa. U odnosu na primenjenu nefarmakološku meru svi pacijenti su bili podeljeni u dve grupe sa po 30 pacijenata: ispiranje – ispiranje obolele alveole sterilnim fiziološkim rastvorom; kiretaža – pažljiva kiretaža. Obe ove grupe, u odnosu na primenjeni tretman [(hijaluronska kiselina, hijaluronska kiselina + aminokapronska kiselina, Alvogyl® (kombinacija anestetika i antiseptika u obliku paste)], bile su podeljene u tri podgrupe sa po 10 pacijenata po sledećem protokolu: 0,2 mL hijaluronske kiseline u obliku 0.8% gela; 2 mL aminokapronske kiseline i hijaluronske kiseline; Alvogyl®. Na kontrolnim pregledima, zakazanim na svaka dva dana do potpunog prestanka bolnih senzacija, pacijentima je ponavljana terapijska opcija sa prvog pregleda. Evidentiran je broj prisutnih simptoma i znakova alveolitisa kod pacijenata, kao i nivo bola (meren pomoću vizuelno-analogne skale). **Rezultati.** Primenom hijaluronske kiseline, sa ili bez aminokapronske kiseline, postignuto je statistički značajno brže sniženje bolnih senzacija kao i smanjenje broja prisutnih simptoma i znakova alveolitisa u odnosu na upotrebu Alvogyl®-a. **Zaključak.** Hijaluroska kiselina, samostalno ili u kombinaciji sa aminokapronskom kiselinom, značajno snižava bol, te se može uspešno primenjivati u terapiji alveolitisa.

Ključne reči:
zub, ekstrakcija; postoperativne komplikacije; alveolitis, suvi; hijaluronska kiselina; aminokapronske kiseline; kiretaža.

Correspondence to: Dejan Dubovina, Department of Oral Surgery, Faculty of Medicine, University of Priština, Anri Dinana bb, Kosovska Mitrovica, Serbia. E-mail: dejandubovina@yahoo.com

Introduction

Alveolar osteitis (AO) sometimes occurs after tooth extraction due to the disturbances in the healing processes. It is characterized by the appearance of postoperative pain in and around the extraction area, which increases from the first to the third post-extraction day, and is combined with partial or total destruction of a blood clot in the alveolus [1]. AO develops after 3–4% of all extractions, and even more often after surgical extraction of impacted lower third molars, up to around 30%. The incidence of AO is five times higher in women than in men and much higher in the lower jaw (10 times more often after the extraction of the lower molars than of the upper ones) [2–4]. AO is probably caused by excessive fibrinolytic activity in the post-extraction coagulum that leads to destruction of the fibrin matrix and blood clot degradation [5].

The first symptoms of AO usually appear 1–3 days after extraction [6, 7] in the form of severe pain, taste disorder and bad breath. All reported cases were diagnosed in up to 7 days following extraction. The symptoms of AO are present, depending on the aggressiveness of the disease, usually 5–10 days [1]. In the alveolus, there are either remains of a decomposed coagulum or the alveolus is empty, with exposed bone. The alveolus can be filled with food remains and the surrounding gingiva can be edematous and erythematous. Regional lymphadenopathy can be present [8].

There were various approaches to the treatment of AO that involved the use of a wide range of resources, rinsing solutions and procedures [2]. These procedures were proposed for suppressing the symptoms of AO. On the average, it takes 7–10 days for the exposed bone to become covered with young granulated tissue. During this time it is necessary to make efforts in order to reduce subjective discomforts of the patient [9]. Most commonly used for that purpose is Alvogyl® (Septodont, France), an anesthetic and antiseptic paste.

Hyaluronic acid has anti-inflammatory and anti-edematous potential which helps wound healing and increases the tissue elasticity [10–14]. A pilot study conducted on rats showed that treatment of a dry socket with a preparation that contains 1% of hyaluronic acid resulted in rapid formation of coagulum and accelerated healing of post-extraction wound [15].

Aminocaproic acid (epsilon-aminocaproic acid) is a potent antifibrinolytic agent. It competitively blocks high affinity lysine receptors on the plasminogen proenzyme and thus prevents formation of a ternary complex with tissue plasminogen activator (t-PA) and fibrin [16]. For many years, the aminocaproic acid has been used in various fields of surgery (oral surgery, cardiac surgery) [17].

The aim of this clinical study was to explore if hyaluronic and aminocaproic acid can be used successfully in the treatment of AO.

Methods

This prospective randomized clinical study was carried out in the period from 2011 to 2014 at the Department of Oral Surgery of the Faculty of Medicine, University of Priš-tina, Kosovska Mitrovica, Serbia. All check-ups as well as surgical procedures were performed by one oral surgeon. The patients voluntarily participated in the study and were thoroughly familiarized with the principles of performing clinical research. The study was approved by the Ethic Committee of the Faculty of Medicine, University of Priš-tina, Kosovska Mitrovica.

The study included 60 patients of both sexes and of different age who, based on the anamnesis and clinical examination, were diagnosed with AO. The study included patients who had undergone tooth extraction and who came to check-up because of an onset of pain in and around the extraction region. The AO diagnosis was made in accordance with Blum's [1] definition, based on the following clinical signs and symptoms: onset of pain from the first to the third post-extraction day, the presence of a decomposed coagulum in the post-extraction alveolus or a bare alveolar bone. The study excluded patients who used antibiotics or analgesics after extraction, patients who previously received radiotherapy or chemotherapy, patients on anticoagulant therapy and patients with systemic diseases that influence the processes of healing of the post extraction wound (*eg*. diabetes mellitus, vascular or hematological disorders and other serious pathological lesions in the mouth).

All the patients were randomly divided into two groups *per* 30 patients each according to the applied non-pharmacological measure: irrigation – irrigation and medicament; curettage – curettage and medicament. Dry sockets of the patients from the irrigation group were irrigated with 20 mL of sterile saline (0.09% NaCl), which was enough to completely remove debris from the alveolus. Dry sockets of the patients from the curettage group were carefully curetted and a remotely healthy coagulum was preserved. Before curettage, local infiltration anesthesia, articaine with adrenaline (UbistesinTM forte, 3M ESPE AG, Germany), was administered to patients.

Furthermore, each of these two large groups was divided into three subgroups with 10 patients each regarding the used medicament: hyaluronic acid – irrigation (HA-I), hyaluronic acid + aminocaproic acid – irrigation (HA+AA-I) and Alvogyl® – irrigation (Alvogyl®-I); hyaluronic acid – curettage (HA-C), hyaluronic acid + aminocaproic acid – curettage (HA+AA-C) and Alvogyl® – curettage (Alvogyl®-C). Dry sockets of the patients from the subgroups were then treated according to the following protocol: HA-I and HA-C: 0.2 mL of hyaluronic acid in the form of a 0.8% gel (Gengigel® prof. - 0.8% hyaluronic acid, Ricerfarma SRL, Milan, Italy); HA+AA-I and HA+AA-C: 2 ml of aminocaproic acid (Amicar®, XANODYNE PHARMACEUTICALS, INC, USA, ampoule 250 mg/ml) and hyaluronic acid; Alvogyl®-I and Alvogyl®-C: Alvogyl® (Septodont, France). The patients were not given any other types of medicaments.

The patients had scheduled control visits for every two days until complete absence of painful sensations. At every control visit, the patients had the therapeutic method repeated as at the first examination.

During each control visit the number of present symptoms and signs of AO was recorded for every patient. Marked as the

symptoms and signs of AO were: pain, pain irradiation, swelling of the regional lymph nodes, redness of the gingiva around the extraction wound and halitosis. The presence of symptoms and signs was recorded in the "present" / "not present" manner. The level of pain was determined (measured with a visual analogue scale – VAS, graded in centimetres from 0 to 10, where 0 was the lowest notch marking the "absence of pain" while notch 10 marked "unbearable pain"). The total number of examinations was also recorded, to a complete cessation of painful sensations, for each individual patient.

The data primarily obtained were analyzed with descriptive statistical methods and methods for testing statistical hypotheses. From descriptive methods, measures of central tendency ($\bar{x}$; median), measures of variability (SD, variation interval) and the relative numbers (structure indicators) were used. For testing the hypotheses, the methods used were: χ^2 test for testing the difference in frequency among the groups; Kruskal-Wallis and Mann-Whitney test for testing the differences in value of the characteristics among the groups, Friedman and Wilcoxon test for testing the changes in the value of the characteristics in time. The statistical hypotheses were tested at a significance level of 0.05.

Results

Of the total number of patients, 60% were male and 40% female. There was no significant difference in the frequency of gender in the groups examined ($\chi 2 = 0.278$; SS = 1; $p = 0.598$). The mean age of patients in the groups was 37.72 ± 10.91 (Table 1).

At the first visit following tooth extraction, of all the determined symptoms and sings of AO, only pain was present in all the patients. There was no difference in the average number of present symptoms and signs of AO between the examined groups at the first and the second visit ($p > 0.05$). A statistical significance existed among the subgroups of the Curettage group, where hyaluronic acid was applied, during the third, fourth and fifth visit in relation to the group Alvogyl-C (Tables 2 and 3).

Regardless of the treatment, the scores on the VAS of pain decreased during the follow-up period but there was a statistical difference in pain levels among the groups (Table 4). Among the subgroups where hyaluronic acid was applied, with or without aminocaproic one, in relation to the subgroups that were treated with Alvogyl®, a statistical difference

Table 1

Age and gender distribution of the patients with alveolar osteitis

Age (years)	Gender, n (%)		Treatment, n (%)		Total n (%)
	male	female	irrigation	curettage	
> 30	8 (22.2)	7 (29.2)	7 (23.3)	8 (26.7)	15 (25)
30–39	14 (38.9)	9 (37.5)	8 (26.7)	15 (50)	23 (38.3)
40–49	8 (22.2)	5 (20.8)	9 (30)	4 (13.3)	13 (21.7)
50–59	4 (11.1)	2 (8.3)	3 (10)	3 (10)	6 (10)
≥ 60	2 (5.6)	1 (4.2)	3 (10)	0 (0)	3 (5)
Total	36 (100)	24 (100)	30 (100)	30 (100)	60 (100)

Table 2

Clinical symptoms and signs of the study groups that underwent irrigation (I) during follow-up

Visit	Patients' group	Symptoms and signs of alveolar osteitis (AO)					
		n	Pain*	Pain irradiation	Swelling of the regional lymph nodes	Redness of the gingiva	Halitosis
1	HA-I	3.3	10	8	5	4	6
	HA+AA-I	3	10	7	4	5	4
	Alvogyl®-I	3.4	10	6	7	6	5
2	HA-I	2.6	10	5	4	3	4
	HA+AA-I	2.7	10	6	5	4	2
	Alvogyl®-I	3.4	10	6	7	6	5
3	HA-I	1.7	7	4	2	2	2
	HA+AA-I	1.1	7	1	1	2	0
	Alvogyl®-I	2	9	3	3	4	1
4	HA-I	0.7	4	2	0	1	0
	HA+AA-I	0.6	4	0	0	2	0
	Alvogyl®-I	1.3	7	2	1	3	0
5	HA-I	0.1	1	0	0	0	0
	HA+AA-I	0.2	2	0	0	0	0
	Alvogyl®-I	0.5	4	0	0	1	0

HA – hyaluronic acid; AA – aminocaproic acid; n – average number of patients with symptoms and signs of AO.
***Pain was estimated by visual analog scale (VAS): 0 – no pain; 10 – unbearable pain.**

Table 3

Clinical symtoms and signs of the study groups that underwent curretage (C) during follow-up

Visit	Patients' group	Symptoms and signs of alveolar osteitis (AO)					
		n	Pain*	Pain irradiation	Swelling of the regional lymph nodes	Redness of the gingiva	Halitosis
1	HA-C	3.4	10	8	6	5	5
	HA+AA-C	3.2	10	8	4	5	5
	Alvogyl-C	3.4	10	7	6	7	4
2	HA-C	2	8	4	4	2	2
	HA+AA-C	2.1	8	5	2	3	3
	Alvogyl-C	2.9	9	6	5	6	3
3	HA-C	0.9†	6	1	0	2	0
	HA+AA-C	0.9†	7	0	0	0	2
	Alvogyl-C	2.3	9	5	4	3	2
4	HA-C	0.3†	2	0	1	0	0
	HA+AA-C	0.4	3	0	1	0	0
	Alvogyl-C	1.1	7	2	1	1	0
5	HA-C	0†	0	0	0	0	0
	HA+AA-C	0†	0	0	0	0	0
	Alvogyl-C	0.3	3	0	0	0	0

† – statistical significance compared to the Alvogyl® - C group ($p = 0.05$). For abbrevations see under Table 2.
***Pain was estimated by visual analog scale (VAS): 0 – no pain; 10 – unbearable pain.**

Table 4

Average level of pain estimated by visual analog scale (VAS)* in the patients with alveolar osteitis by the groups during follow-up visits

Visit	Irrigation ($\bar{x} \pm SD$)			Curettage ($\bar{x} \pm SD$)		
	HA-I	HA+AA-I	Alvogyl®-I	HA-C	HA+AA-C	Alvogyl®-C
1	7.3 ± 2.06	7.9 ± 1.66	7.4 ± 1.43	7.7 ± 1.49	7.9 ± 1.59	7.4 ± 1.65
2	5.1 ± 2.51	5.1 ± 2.51	7.2 ± 1.34	3.8 ± 2.7	3.5 ± 2.32	6.1 ± 2.6
3	2.4 ± 2.12†	2.4 ± 2.12†	5.1 ± 1.91	1.6 ± 1.5†	1.8 ± 1.8†	4.3 ± 2.5
4	0.7 ± 1.1†	0.7 ± 1.1†	2.9 ± 1.9	0.3 ± 0.68†	0.6 ± 1.1†	2.1 ± 1.91
5	0.2 ± 0.63	0.4 ± 0.84	0.8 ± 0.92	0†	0†	0.5 ± 0.85

***VAS: 0 – no pain; 10 – unbearable pain; † – statistical significance compared to Alvogyl® group ($p = 0.05$); $\bar{x}$ – mean; SD – standard deviation.**

was noticed during the third, fourth and fifth visit. The pain levels were the same between the groups where hyaluronic acid was used and those treated with aminocaproic acid, as well.

Comparison of the groups in relation to the average number of visits, up to a complete cessation of painful sensations, demonstrated similar results (Table 5). In the irrigation group, there was a statistically significant difference in the number of visits between the treatment subgroups HA-I and HA+AA-I compared to Alvogyl®-I, while in the curettage group, statistical significance existed between the treatment subgroups HA-C and HA+AA-C compared to Alvogyl®-C.

Discussion

The therapy of AO is symptomatic. It includes irrigation or curettage of the dry socket and topical use of different pharmacological and non-pharmacological packaging [18]. By irrigation with saline, food debris and remains of decomposed blood cloth are eliminated and the number of bacteria from the

Table 5

Average number of visits up to the complete cessation of painful sensations by the groups during follow-up

Group of patients	$\bar{x}$	SD	Med	Min	Max
HA-I	3.2†	1.03	3	2	5
HA+AA-I	3.3†	0.95	3	2	5
Alvogyl®-I	4.3	0.82	4.5	3	5
HA-C	2.6†	1.07	3	1	4
HA+AA-C	2.8†	1.13	3	1	4
Alvogyl®-C	3.9	1.1	4	1	5

† – statistical significance compared to the Alvogyl® group ($p = 0.05$); $\bar{x}$ – mean; SD – standard deviation; Med – median; Min-max – minimal-maximal value. For abbrevations see under Tables 2 and 3.

socket reduced. A similar effect is achieved with curettage, but it is possible to provoke bleeding from the alveolar bone, which could enable the creation of a new, healthy blood clot. After the irrigation, *ie* curettage, topical packaging should suppress subjective discomfort of patients, up to the moment when the bare bone is covered with young granulated tissue. The idea to use hyaluronic acid in the treatment of AO stemmed from its proven qualities: analgesic, reparative and regenerative potential, high elasticity, biocompatibility, biodegradability and low immunogenicity [11, 19].

The results of this study are consistent with the results obtained by McGregor [20] who states that AO usually occurs in the third and fourth decade of life. The results show that AO often occurs in the fifth decade of life, which coincides with the claims of some other authors [1]. While the study was being conducted, there were no any patients of younger age (< 20 years old), so it can be concluded that in this age AO occurs only exceptionally.

Even though some authors [21] state that AO occurs more frequently in the female population, no such results were obtained in this study.

Although the main goal in the treatment of AO is pain relief, it is very important to evaluate other, more objective, clinical parameters that will provide an unbiased comparison between the examined treatment methods. It is obvious that the promotion of wound healing will lead to the reduction of painful sensations [22]. The data obtained in this study indicate that hyaluronic acid significantly faster reduces the number of symptoms and signs of AO compared to relatively frequent use of Alvogyl®. The best results were gained within the group with curettage performed and followed by the use of hyaluronic acid.

The main and most discomforting symptom of AO is severe pain. All the treatment methods investigated in this study decreased the level of pain, but there was a statistically significant difference in pain level throughout the examination period between the patients treated with hyaluronic acid and those treated with Alvogyl®. In all the groups of patients treated with hyaluronic acid a faster reduction of pain level was achieved comparing to Alvogyl® groups.

With the introduction of aminocaproic acid, followed by hyaluronic acid in the treatment of AO in this study, the expected positive results were not obtained. There was no statistically significant difference in terms of the reduction of subjective discomfort of patients whose painful alveoli were, besides with hyaluronic acid, treated with aminocaproic acid, as well. This coincides with some previous studies in which there were attempts to reduce the incidence of AO with local application of tranexamic acid (TXA), a potent antifibrinolytic, but with little or no sucsess [23, 24].

All the results gained in this study prove that hyaluronic acid has a positive influence on the healing process of dry socket, but the exact mechanism of its actual role is yet to be investigated. Based on the results of this study and the available literature, it might be possible to suppose the following: when the dry socket is curetted and bleeding is provoked, a new blood clot may be created; hyaluronic acid placed into this new wound will act as a coagulum stabilizer, preventing its uneven and excessive degradation; during the first phase of wound healing, the fibrin threads form a web that represents a matrix for the platelet clot formation, followed by a production of hyaluronic acid (by simulating different inflammatory mediators, especially interleukin –β and platelet-derived growth factor); the molecules of hyaluronic acid penetrate the fibrin matrix and stimulate cell migration, particularly the fibroblast from the surrounding tissue, and the production of new collagen; [25–29] additional amount of hyaluronic acid in this way probably stabilizes coagulum and has a positive effect on the wound healing.

If the alveolus affected with AO is rinsed with saline until the complete removal of debris, and then hyaluronic acid is applied to it, other positive qualities of hyaluronic acid will come to the fore. Namely, anti-inflammatory, antiedematous and analgesic potential of hyaluronic acid will contribute to wound healing and, consequently, lower pain sensations. One of the advantages of local application of hyaluronic acid is reflected in its adhesive properties which allow its positive qualities to establish healthy coagulum for a longer period of time [30]. Covering completely the bare alveolar bone, hyaluronic acid represents a barrier to irritant influences of external substances.

Conclusion

The obtained results confirm the hypothesis that hyaluronic acid can be successfully used in the treatment of alveolar osteitis in the manner in this study described. Hyaluronic acid application accelerates the reduction of painful sensations, and also reduces the number of symptoms and signs of alveolar osteitis compared to the use of Alvogyl® alone.

REFERENCES

1. *Blum IR.* Contemporary views on dry socket (alveolar osteitis): A clinical appraisal of standardization, aetiopathogenesis and management: A critical review. Int J Oral Maxillofac Surg 2002; 31(3): 309−17.
2. *Noroozi A, Philbert RF.* Modern concepts in understanding and management of the "dry socket" syndrome: Comprehensive review of the literature. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2009; 107(1): 30−5.
3. *Tjernberg A.* Influence of oral hygiene measures on the development of alveolitis sicca dolorosa after surgical removal of mandibular third molars. Int J Oral Surg 1979; 8(6): 430−4.
4. *Rubio-Palau J, Garcia-Linares J, Hueto-Madrid JA, González-Lagunas J, Raspall-Martin G,*et al. Effect of intra-alveolar placement of 0.2% chlorhexidine bioadhesive gel on the incidence of alveolar osteitis following the extraction of mandibular third molars: A double-blind randomized clinical trial. Med Oral Patol Oral Cir Bucal 2015; 20(1): 117−22.
5. *Birn H.* Etiology and pathogenesis in fibrinolytic alveolitis (dry socket). Int J Oral Surg 1973; 2: 211−63.
6. *Fridrich KL, Olson RA.* Alveolar osteitis following removal of mandibular third molars. Anaesth Prog 1990; 37(1): 32−41.

7. *Nitzan DW*. On the genesis of "dry socket". J Oral Maxillofac Surg 1983; 41(11): 706−10. 41(11): 706-10.
8. *Fazakerley M, Field EA*. Dry socket: A painful post-extraction complication (a review). Dent Update 1991; 18(1): 31−4.
9. *Trieger N, Schlagel GD*. Preventing dry socket: A simple procedure that works. J Am Dent Assoc 1991; 122(2): 67−8.
10. *Demarosi F, Sardella A, Lodi G, Carassi A*. Acido ialuronico: effetti biologici e applicazioni cliniche. Dent Clin 2007; I(2): 7−13.
11. *Rodgers KE, Johns DB, Girgis W, Campeau JD, diZerega GS*. Reduction of adhesion formation with hyaluronic acid after peritoneal surgery in rabbits. Fertil Steril 1997; 67(3): 553−8.
12. *Beck DE*. The role of Seprafilm registreted bioresorbable membrane in adhesion prevention. Eur J Surg Suppl. 1997; (577): 49−55.
13. *Burns JW, Colt MJ, Burgess LS, Skinner KC*. Preclinical evaluation of Seprafilm registreted bioresorbable membrane. Eur J Surg 1997; 163(Suppl 577): 40−8.
14. *Liguori V, Guillemin C, Pesce GF, Mirimanoff RO, Bernier J*. Double-blind, randomized clinical study comparing hyaluronic acid cream to placebo in patients treated with radiotherapy. Radiother Oncol 1997; 42(2): 155−61.
15. *Mendes RM, Silva GA, Lima MF, Calliari MV, Almeida AP, Alves JB,* et al. Sodium hyaluronate accelerates the healing process in tooth sockets of rats. Arch Oral Biol 2008; 53(12): 1155−62.
16. *Ozier Y, Bellamy* L. Pharmacological agents: Antifibrinolytics and desmopressin. Best Pract Res Clin Anaesthesiol 2010; 24(1): 107−19.
17. *Verstraete M*. Clinical application of inhibitors of fibrinolysis. Drugs 1985; 29(3): 236−61.
18. *Betts NJ, Makowski G, Shen YH, Hersh EV*. Evaluation of topical viscous 2% lidocaine jelly as an adjunct during the management of alveolar osteitis. J Oral Maxillofac Surg 1995; 53(10): 1140−4.
19. *King SR, Hickerson WL, Proctor KG*. Beneficial actions of exogenous hyaluronic acid on wound healing. Surgery 1991; 109(1): 76−84.
20. *MacGregor AJ*. Aetiology of dry socket: A clinical investigation. Br J Oral Surg 1968; 6(1): 49−58.
21. *Sweet JB, Butler DP*. Predisposing and operative factors: Effect on the incidence of localized osteitis in mandibular third molar surgery. Oral Surg Oral Med Oral Pathol 1978; 46(2): 206−15.
22. *Kaya GŞ, Yapici G, Savaş Z, Güngörmüş M*. Comparison of alvogyl, SaliCept patch, and low-level laser therapy in the management of alveolar osteitis. J Oral Maxillofac Surg 2011; 69(6): 1571−7.
23. *Ritzau M*. The prophylactic use of tranexamic acid (Cyklokapron®) on alveolitis sicca dolorosa. Int J Oral Surg 1973; 2(5): 196−9.
24. *Gersel-Pedersen N*. Tranexamic acid in alveolar sockets in the prevention of alveolitis sicca dolorosa. Int J Oral Surg 1979; 8(6): 421−9.
25. *Weigel PH, Fuller GM, Leboeuf R*. A model for the role of hyaluronic acid and fibrin in the early events during the inflammatory response and wound healing. J Theor Biol 1986; 119(2): 219−34.
26. *Bartold MP*. The effect of interleukin-1 beta on hyaluronic acid synthesized by adult human gingival fibroblasts in vitro. J Periodont Res 1988; 23(2): 139−47.
27. *Oksala O, Salo T, Tammi* R, *Häkkinen L, Jalkanen M, Inki P,* et al. Expression of proteoglycans and hyaluronan during wound healing. J Histochem Cytochem 1995; 43(2): 125−35.
28. *Bartold PM*. Platelet-derived growth factor stimulates hyaluronate but not proteoglycan synthesis by human fibroblasts in vitro. J Dental Res 1993;72:1473−80.
29. *Irwin CR, Schor SL, Ferguson MW*. Effects of cytokines on gingival fibroblasts in vitro are modulated by the extracellular matrix. J Periodont Res 1994; 29(5): 309−17.
30. *Rabasseda X*. The role of hyaluronic acid in the management of periodontal disease. Drugs Today (Barc) 2000; 36(Suppl C): 1−20.

Received on March 4, 2015.
Revised on July 9, 2015.
Accepted on July 21, 2015.
Online First May, 2016.