Journal of Cranio-Maxillo-Facial Surgery xxx (2015) 1–5

Contents lists available at ScienceDirect

Journal of Cranio-Maxillo-Facial Surgery

journal homepage: www.jcmfs.com

The antioxidant and anti-inflammatory efficiency of hyaluronic acid after third molar extraction

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ARTICLE INFO

Article history:
Paper received 2 December 2014
Accepted 23 April 2015
Available online xxx

Keywords:
Hyaluronic acid
Third molar extraction
Wound healing

ABSTRACT

Purpose: Hyaluronic acid (HA) has a number of clinical applications in current practice. Therefore, correlation of HA with free radicals and inflammatory cells is clinically important. The purpose of this study is to measure the efficacy of high molecular weight HA on the oxidative stress of oral wounds (glutathione (GSH) and lipid peroxidation (LPO) levels), the inflammatory reaction (leucocytes, collagen and angiogenesis content), pain (visual analogue scale (VAS) records) and trismus (maximum interincisal opening (MIO) records) after third molar (M3) extraction.

Patients and methods: 40 patients were included in this study. 0.2 ml 0.8% HA was applied immediately after surgery within the HA group ($n = 20$). Nothing was applied to the control group ($n = 20$). The primary outcome variables were the changes in the inflammatory reaction (leucocyte, angiogenesis and collagen content), oxidative stress (GSH, LPO) and clinical parameters (VAS, MIO). Results were compared immediately after extraction (T0) and 1 week after surgery (T1). Bivariate analyses were used to assess the differences between the HA and control groups for each study variable.

Results: There was a statistically significant difference of leucocyte infiltration and angiogenesis between the groups at T1. The HA group showed less leucocyte infiltration and more angiogenesis than the control group. There was no statistically significant difference in oxidative stress, VAS or MIO levels between the groups.

Conclusion: Our results confirm the hypothesis that HA has an anti-inflammatory effect following M3 extraction. However, the oxidative stress levels and clinical outcomes were similar after one week. Further studies examining these parameters at different times are necessary.

1. Introduction

Hyaluronic acid (HA) is a high molecular weight glycosaminoglycan. It is one of the major components of the extracellular matrix. It has various functions including: maintenance of the elastoviscosity of joint synovial fluid; control of tissue hydration; and many receptor-mediated roles in cell detachment, such as mitosis, migration, tumour metastasis and inflammation (Chen and Abatangelo, 1999; Teh et al., 2012).

The unique viscoelastic nature of exogenous HA along with its biocompatibility and non-immunogenicity has led to its use in a number of clinical applications including: supplementation of joint fluid, assisting wound regeneration and dermal filling (Price et al., 2005; Bannuru et al., 2011). However, there is insufficient evidence about its application for oral wound healing.

Wound healing consists of highly integrated and overlapping phases (Jiang et al., 2007). HA, can be involved at any stage of these phases or be indirectly associated with accompanying processes including: migration of inflammatory cells, interaction with remaining inflammatory elements, and the scavenging of free radicals (Prosdocimi and Bevilacqua, 2012). These potential interactions raise the question of whether there is a correlation between the presence of HA and the clinical outcomes of inflammatory reaction.

Extraction of mandibular third molars (M3), still the most common oral surgical procedure, often results in swelling, pain and trismus. Therefore, it affects the patient's quality of life (Majid and Mahmood, 2011). Corticosteroids are often used to reduce the inflammatory reaction. Correspondingly, exogenous HA application

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http://dx.doi.org/10.1016/j.jcms.2015.04.022
1010-5182/

may offer similar outcomes; decrease the inflammatory response and prevent oxygen free-radical damage after tooth extraction (Foschi et al., 1990; Brown, 2004).

The purpose of this study is to measure the efficacy of high molecular weight HA on wound healing considering biochemical and histological parameters after M3 extractions. We compared glutathione (GSH) and lipid peroxidation (LPO) levels biochemically; pain and trismus levels clinically; and leucocytes, collagen and angiogenesis content histologically between control and HA groups.

2. Materials and methods

2.1. Study design and sample

We implemented a double blind, randomized, and controlled clinical trial. The tissue samples were obtained from 40 patients (female patients, $n = 20$), who were referred to the Department of Oral and Maxillofacial Surgery at Marmara University, Istanbul, Turkey, for evaluation and management of M3 between January 2011 and January 2012. Patients included in the study had M3s which had erupted, or were half impacted but without bone retention, and were vertically positioned. All patients were healthy and classified as ASA I–II (American Society of Anesthesiologists I–II). The mean age was 26.6 ± 6.3 years. Patients were excluded from the study if they had: signs of pericoronitis or pain before surgery; an extraction time greater than 30 min; antibiotics or any other medication therapies during the preceding 2 weeks; or active carious lesions and/or periodontal diseases.

The extractions, application of 0.8% HA gel (GENGIGEL PROF, Milano, Italy), sampling and follow-up were performed by the same operator. Marmara University Department of Biochemistry implemented the biochemical processing and made the analyses and evaluation. The Department of Histology and Embryology completed the histological evaluation of the fixed samples. The clinical research ethics committee of Marmara University approved the study protocol (Protocol number: 2011-1).

2.2. Variables

The primary predictor variable, HA exposure, was coded as a binary variable: the patients in the HA group ($n = 20$) had HA applied following M3 removal; the patients in the control group ($n = 20$) received no other application following extraction. Inflammatory response, oxidative stress, pain and trismus, as the primary comparisons, were recorded immediately after surgery (T0) and compared with the outcomes after one week (T1). The primary outcome variables of oxidative stress were tissue GSH as an important antioxidant, and LPO levels as an indicator of oxidative damage. The primary outcome variables of inflammatory reaction were leucocyte, angiogenesis and collagen content. A visual analogue scale (VAS) was used to record pain, and maximum interincisal opening (MIO) was noted to evaluate trismus as the primary clinical outcome variables.

2.3. Data collection, management, and analyses

Tissue samples, about 2 mm^3 in volume, were obtained following extraction. All samples were taken from the buccal wound edge of extraction socket. Wound closures were made with 3.0 silk sutures. Subjects were randomly assigned to receive HA application. In the HA group ($n = 20$), 0.2 ml 0.8% HA was applied immediately after M3 removal to the edge of extraction socket. In the control group ($n = 20$), nothing was applied. Tissue samples were taken from the same region after one week. They were divided and stored separately at −24 °C for biochemical and histological evaluation.

Samples were thawed and kept at 4 °C for biochemical evaluation. They were homogenized for determination of LPO and GSH levels. Afterwards, they were centrifuged and supernatants taken for analysis. LPO levels were determined by Ledwozyw's method (Ledwozyw et al., 1986). In brief, this method involves boiling the supernatant with thiobarbituric acid and extracting the adducts formed with n-butanol. Its absorbance at 532 nm was measured in terms of the tissue malonedialdhyde (MDA) content, which is taken as an index of LPO. The result was expressed in nmol MDA/g tissue.

GSH measurements were performed using a modification of the Ellman procedure (*Beutler,* 1975). Briefly, 0.5 ml of supernatant was added to 2 ml of 0.3 M $Na_2HPO_4.2H_2O$ solution after centrifugation at 3000 g for 10 min. Next, 0.2 ml of dithiobisnitrobenzoate solution (0.4 mg/ml 1% sodium citrate) was added and the absorbance at 412 nm was measured immediately after mixing. GSH levels were calculated using an extinction coefficient of 1.36×10^4 $M^{-1}cm^{-1}$. Results are expressed in mg/g in tissue.

The specimens obtained for histological evaluation were embedded in paraffin blocks, sectioned and stained with hematoxylin and eosin and Masson's trichrome stain for examination under light microscope. The grading of the inflammatory infiltration was established by randomly selecting and counting fields for leucocyte infiltration, angiogenesis and fibrosis (collagen deposition) content at ×400 magnification. Scoring was made in the following manner: '0', when none of the fields show parameters; 'slight', when at least five fields contain the parameter that occupy <50% of the field; 'mild', when at least five fields show the parameter that occupy >50% of the field; and 'intense', when all 10 fields evaluated show parameters that occupy >90% of the field.

Trismus was evaluated by measuring the distance between the edges of the upper and lower right central incisors at maximum opening of the jaws preoperatively and 7 days after surgery. Pain intensity was assessed using a 10-point VAS, with the patient placing a mark on the scale to indicate an intensity range from no pain, 0, to severe/unbearable pain, 10. The severity of the pain was evaluated on the operation day and on postoperative day 7.

The results were analysed using the Statistical Package for the Social Sciences (SPSS version 12.0; SPSS, Chicago, IL). Descriptive statistics was computed for all variables. A paired sample *t*-test, chi-square test and Mann–Whitney U test were used to assess the differences between the HA and control groups for each study variable. The level of statistical significance was set at $p < 0.05$.

3. Results

There was no statistically significant difference between groups regarding distribution of the parameters: leucocytes, angiogenesis, collagen content, GSH and LPO at T0; and also GSH, LPO and collagen content were the same at T1 (Tables 1–3), (Figs. 1 and 2). There was a statistically significant difference in leucocyte infiltration and angiogenesis between the groups at T1. Evaluation of leucocyte infiltration in the HA group found fewer cases of 'mild' and 'intensive' and more 'slight' infiltration than the control group (Table 4). Angiogenesis in the control group was found to be more 'mild' and 'slight' with fewer 'intensive' changes then the HA group (Table 5).

There were no statistically significant differences in VAS between the two groups on the day of the operation or on the postoperative 7th day. There was a significant decrease in mean VAS for both groups after 1 week ($p < 0.05$) (Table 6). On the 7th postoperative day, almost all of the patients had regained their preoperative MIO and there was no statistically significant difference between the two groups (Table 7).

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Table 1
Collagen parameters in histological evaluations.

Collagen		Control group	HA group	[a]p
		n (%)	n (%)	
Immediately after extraction	None	0 (0)	0 (0)	0.832
	Slight	1 (5)	2 (10)	
	Mild	15 (75)	14 (70)	
	Intensive	4 (20)	4 (20)	
After 1 week	None	7 (35)	7 (35)	≅1
	Slight	13 (65)	13 (65)	
	Mild	0 (0)	0 (0)	
	Intensive	0 (0)	0 (0)	

HA: hyaluronic acid.
[a] Chi-square test.

Table 2
Evaluations of glutathione (GSH) (mg/g) in tissue.

GSH	Control group	HA group
	Mean ± SD	Mean ± SD
Immediately after extraction	121.59 ± 88.65	130.24 ± 78.70
After 1 week	138.40 ± 80.77	142.31 ± 48.26
+p	**0.379**	**0.578**

			[a]p
Median (min; max)	24.7 (−70; 564.7)	27 (−64.6; 682.7)	≅**1**

HA: hyaluronic acid.
+paired sample *t*-test.
[a] Mann–Whitney U test.

Table 3
Evaluations of lipid peroxidation (LPO) (nmol MDA/gr) levels in tissue.

MDA	Control group	HA group
	Mean ± SD	Mean ± SD
Immediately after extraction	254.25 ± 177.0	232.88 ± 143.03
After 1 week	271.44 ± 173.23	306.35 ± 192.38
+p	**0.781**	**0.183**

			[a]p
Median (min; max)	10.68 (−76.09; 659.55)	66.44 (−94.41; 668.67)	**0.547**

HA: hyaluronic acid.
+paired sample *t*-test.
[a] Mann–Whitney U test.

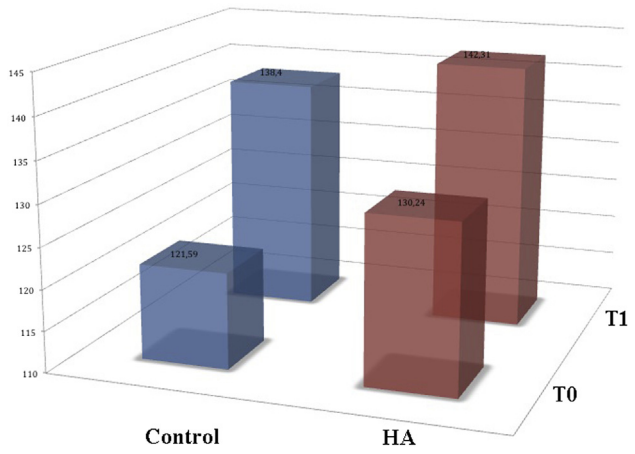

Fig. 1. Mean glutathione (GSH) levels (mg/g) for control and HA groups, at T0 and T1.

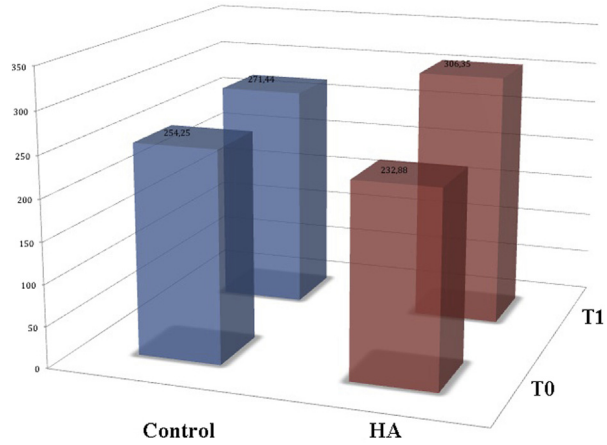

Fig. 2. Mean lipid peroxidation (LPO) (nmol MDA/g tissue) for control and HA groups, at T0 and T1.

4. Discussion

The purpose of this study was to measure the efficacy of high molecular weight HA on the wound after M3 extraction. HA can reduce the acute inflammatory reaction and decrease oxygen free-radical damage after M3 extraction. We aimed to measure the anti-inflammatory and anti-oxidant effects of HA after M3 extraction. The results of this study confirmed just one of the hypotheses, that the application of 0.8% HA following M3 extraction has an anti-inflammatory effect.

Current trends in maxillofacial surgery centre on increased patient comfort and a faster return to social life (van Wijk et al., 2009). Patients generally suffer from swelling, trismus and pain, which are caused by the expected acute inflammatory response (Bienstock et al., 2011). Clinical evidences of postoperative inflammatory reaction reach a maximum level 1–2 days after surgery and generally resolve by the end of the week. Therefore, the first postoperative week is critical when considering associated factors affecting the initial phases of wound healing (Sato et al., 2009).

In our study, we investigated changes after one week to examine the short-term effects of HA on the inflammatory reaction. Several studies investigated systemic or local administration of agents to diminish postoperative oedema. Busti et al. stated that there is no clear consensus on the use of steroidal anti-inflammatory drugs to prevent swelling. These agents, or their biological equivalents, do not normally have a role in wound healing. They interfere with the natural progress of inflammation and local immune responses (Busti et al., 2005). HA has many properties that make it an ideal molecule for assisting wound healing by inducing early granulation tissue formation and inhibiting inflammation. As a natural component of the extra-cellular matrix, the presence of HA provides a structural framework, hydration and a non-immunogenic environment and consequently assists regeneration (Gontiya and Galgali, 2012).

Various mechanisms have been proposed to explain the effect of HA on the inflammatory process. Cortivo et al. (1986) considered that HA produces a physical barrier against bacteria and their products in the extracellular matrix. HA has been shown to be the main ligand of the CD44 receptor and subsequent ligand-receptor interaction is involved in a number of cell-to-cell interactions.

Kobayashi and Terao (1997) showed that cytokine production in human uterine fibroblasts is regulated by CD44 receptors and HA interactions. Tumour necrosis factor-inducible gene 6 protein (TSG-6) plays a major role by moderating pro-inflammatory cytokines in

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Table 4
Leucocyte parameters in histological evaluations.

Leucocyte		Control group	HA group	[a]p
		n (%)	n (%)	
Immediately after extraction	None	2 (10)	2 (10)	≅1
	Slight	12 (60)	12 (60)	
	Mild	6 (30)	6 (30)	
	Intensive	0 (0)	0 (0)	
After 1 week	None	0 (0)	0 (0)	0.005
	Slight	0 (0)	8 (40)	
	Mild	12 (60)	9 (45)	
	Intensive	8 (40)	3 (15)	

HA: hyaluronic acid.
[a] Chi-square test.

Table 5
Angiogenesis parameters in histological evaluations.

Angiogenesis		Control group	HA group	[a]p
		n (%)	n (%)	
Immediately after extraction	None	0 (0)	0 (0)	≅1
	Slight	15 (75)	14 (70)	
	Mild	5 (25)	6 (30)	
	Intensive	0 (0)	0 (0)	
After 1 week	None	0 (0)	0 (0)	0.042
	Slight	9 (45)	3 (15)	
	Mild	11 (55)	14 (70)	
	Intensive	0 (0)	3 (15)	

HA: hyaluronic acid.
[a] Chi-square test.

Table 6
Comparison of visual analogue scale (VAS) scores.

VAS	Control group	HA group	
	Mean ± SD	Mean ± SD	
Operation day	7.15 ± 1.18	7.05 ± 1.37	**p**[a]
After 1 week	1.45 ± 0.7	1.3 ± 0.56	**>0.05**
+p	**<0.05**	**<0.05**	

+paired sample *t*-test.
HA: hyaluronic acid.
[a] Mann–Whitney U test.

Table 7
Comparison of maximum interincisal opening (MIO) scores.

	Control group	HA group	p
Preoperative	32.26 ± 3.97	32.3 ± 4.12	
After 1 week	31.12 ± 4.1	31.97 ± 3.8	***<0.05***
p	***<0.05***	***<0.05***	

Paired sample *t*-test.
HA: hyaluronic acid.

a negative feedback control mechanism (Wisniewski and Vilcek, 1997). Baranova et al. (2013) reported that TSG-6 is a potent HA cross-linking agent. Consequently, the presence of HA can moderate the inflammatory reaction in many different ways: leucocyte infiltration, angiogenesis and collagen content. Abdalla et al. reported an increase in new vessel formation and a decrease in collagen deposition in hyaluronic acid based hydrogel-injected groups using haematoxylin and eosin and vascular endothelial growth factor (VEGF) staining (Park et al., 2012; Abdalla et al., 2013). In our study, the histological outcomes for the HA group, when considering leucocyte infiltration and angiogenesis, are consistent with the literature. It caused less leucocyte infiltration and more angiogenesis. However, the effect on collagen content was not statistically significant between the groups. Collagen deposition starts within the first 3–4 days and reaches its maximum at about 14th day (Brown, 2004). Therefore, the effect of HA on collagen deposition should be examined after at least 2 weeks.

Since removal of mandibular third molars is one of the most common oral surgical procedures performed in the outpatient setting, applications which reduce the expected postoperative sequelae increase in importance, and this is correlated with the consequential social cost and economic outcome (Majid and Mahmood, 2011). HA application, with an average cost for application of less than 30 euros per patient, offers a low-cost solution for the typical patient, reducing the discomfort associated with the surgical extraction of lower third molars. It produces an effective therapeutic strategy for limiting trismus, pain and reducing the postoperative sequelae with its anti-inflammatory effects. In addition to its clinical benefits, a shorter postoperative recovery time benefits the patients with a lower burden of care to themselves, which means better quality of life, and fewer work days lost, and thus a reduction in loss of income. Therefore, in terms of economic considerations, the use of HA might achieve fewer days of absence from work with its cost-effective application.

In our study, histological outcomes of HA application showed less inflammatory response, and that might lead to less VAS and MIO after 2–3 days. However, the clinical outcomes after one week showed no significant difference between the groups, this is because postoperative sequelae generally resolve within one week. To assess the clinical benefits of this application, patients would need daily assessment of pain and trismus for the first week after surgery, such a study would be difficult to carry out. Nevertheless, these outcomes do not support that the application does not reduce pain and trismus. The hypothesis that 'HA application might reduce pain and trismus after 2–3 days' might be supported by the one week histological outcomes with the signs and clues of less inflammatory response in our study.

HA can counter the reactive oxygen intermediates. It has a moderating affect by free radical scavenging (Presti and Scott, 1994). Mendoza et al. (2009) reviewed all available data on the features and clinical profile of HA and claimed that it can scavenge free radicals. Ye et al. (2012) reported that high molecular weight HA was an effective protective agent that had antioxidant properties. However, in our study, there was no statistically significant difference in oxidative stress parameters. We suggest that inconsistency with the literature is due to timing of calculation for the parameters (GSH and LPO). Our clinical study examined the outcomes after 1 week, which might be too late to test the oxidative stress and too early to see collagen deposition. Ethical considerations and patient follow-up difficulties generally limit the design of patient-oriented studies. Untimely or redundant interventions are unethical. Tissue sampling is only possible during required interventions. In our study, we could only take tissue samples from patients who asked for local anaesthesia administration during over-buried or deep stitch removal. Therefore, we could only present one-week outcomes.

5. Conclusion

Our results confirm the hypothesis that HA has an anti-inflammatory effect following M3 removal; however, at 1 week there was no difference in the oxidative stress and the clinical outcomes between groups. Further studies examining parameters at more appropriate times are necessary to present more useful outcomes.

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Acknowledgements

The project (No: SAG-C-DRP-080212-0019) was funded by The Commission of Scientific Research Projects of Marmara University.

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