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EFFECTS OF HYALURONIC ACID GEL APPLICATION IN REDUCTION OF POST-SURGICAL COMPLICATIONS AFTER LOWER WISDOM TEETH REMOVAL–A PROSPECTIVE STUDY

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Abstract

The aim of this study was to evaluate the efficacy of hyaluronic acid gel (Afta Med®) in reducing the post-surgical complications such as pain, swelling and trismus after lower wisdom teeth removal. This prospective clinical study included 46 patients with bilaterally impacted mandibular third molars of similar surgical difficulty classification. Hyaluronic acid gel was placed into the extraction socket after surgical extraction of impacted tooth on one side and the socket was left empty after extraction on opposite side. Post-operative complications of pain, trismus and swelling was evaluated on 1st, 2nd and 7th days. Statistically significant differences were detected for all the parameters measured ($p<0.05$) on all the post-operative days evaluated. Placement of hyaluronic acid gel was effective in reducing the post-surgical complications of pain, trismus and swelling after lower wisdom teeth removal. Hyaluronic acid gel application appears to offer a beneficial effect in managing pain, trismus and swelling during the post-operative period following wisdom tooth removal.

***Keywords*:** Impacted third molar, Surgical extraction, Hyaluronic acid, Pain, Trismus, Swelling.

Introduction

The surgical removal of impacted teeth is one of the most common procedures performed in oral surgery. Post-surgical complications such as pain, swelling and trismus are expected as response to surgical trauma (Üstün *et al.*, 2003; Dahiya and Kamal, 2013). Apart from these, other post-operative sequelae like dry socket and infections can make the post-operative period difficult for the patient and negatively affect the psyche of the surgeon (Blum, 2002; Ren and Malmstrom, 2007). Numerous studies were done to find an effective pharmacological means to reduce these post-operative complications following third molar surgery including use of local or systemic corticosteroid, nonsteroidal anti-inflammatory drugs and antibiotic prophylaxis (Üstün *et al.*, 2003; Ren and Malmstrom, 2007; Kim *et al.*, 2009). Corticosteroids have shown relatively good effectiveness in reducing the oedema and trismus relating to the surgical extraction (Üstün *et al.*, 2003; Piecuch, 2012). But the potential side-effects of perioperative steroid administration like increased susceptibility to infection, delayed wound healing and sometimes adrenal suppression are problematic (Kim *et al.*, 2009).

Hyaluronan or hyaluronic acid (HA) based biomaterial has been introduced as an alternative approach to enhance wound healing (Dahiya and Kamal, 2013). HA is a naturally occurring glycosaminoglycan consisting of polyanionic disaccharide units of glucuronic acid and N-acetyl. It is a polysaccharide component of the extracellular matrix of various tissues and organs such as synovial fluid, embryonic mesenchyme, vitreous humor, skin, connective tissue etc (Ialenti and Di Rosa, 1994). In the oral cavity, HA forms many structural components of periodontal ligament, gingiva, cementum and the alveolar bone (Dahiya and Kamal, 2013). Apart from the structural role, HA plays important physiological role in regulation of inflammatory response in the oral cavity. High-molecular-weight HA synthesized by hyaluronan synthase enzymes in the oral tissues can undergo degradation in the presence of chronic inflammation into low molecular weight HA (Bartold and Page, 1986; Ijuin *et al.*, 2001). These low molecular weight HA predominate in the gingival tissues of patients during the initial stages of tissue inflammation that may be seen in oral infection or any oral surgical procedures, functioning to signal tissue damage and mobilize immune response (Manzanares *et al.*, 2007). It also supports the homeostatic integrity of tissues regulating osmotic pressure and tissue lubrication (Balazs and Laurent, 1998).

As HA is one of the most hygroscopic polysaccharide in nature, it can retain water and maintain conformational stiffness. HA also has a unique viscoelastic properties that prevents the penetration of viruses and bacteria into the tissue (Sutherland, 1998). It is also an important component associated with the wound-healing process in both mineralized and non-mineralized tissues including granulation tissue formation, epithelium formation, bone formation and tissue remodelling (Bertolami and Messadi, 1994; Chen and Abatangelo, 1999).

As a result of the various properties and functions of HA, HA-based biomaterials have been developed and applied in the treatment of various inflammatory conditions as well as healing of the mineralized and non-mineralized tissues of the oral cavity (Bertolami and Messadi, 1994; Balazs and Laurent, 1998; Chen and Abatangelo, 1999).

The aim of this study was to explore the efficacies of HA based gel in the treatment of post-surgical complications after lower wisdom teeth removal.

Materials and Methods

This clinical study included 46 healthy patients visited the Department of Oral and Maxillofacial Surgery, Tishk International University, Erbil, Iraqi Kurdistan from October 2018 until December 2019 for surgical extraction of impacted asymptomatic lower third molars. Out of the total 46 patients, 32 were males and 14 were females with age ranging from 18 to 35 years. All the patients fulfilled the set inclusion and exclusion criteria as follows

Inclusion criteria are:

1. Age is between 18 to 35 years

2. Have bilateral impacted lower third molars with similar difficulty level according to Pell–Gregory and Winter classification
3. Do not have any systemic disease

Exclusion criteria are:

1. Any history of allergy or adverse effects to antibiotics, analgesics, or local anesthetics.
2. Acute infection such as pericoronitis and/or complication or pain on the impaction area before extraction
3. Any physical or mental disability.
4. Pregnant woman and any use of contraceptives or corticosteroids which can affect the postsurgical complication of healing and amount of swelling on the face
5. Tobacco use in any form
6. Any patient taking antibiotics and analgesics for 15 days before operation
7. Uncooperative patient

Same patients were classified as group A (HA group), where all right-side impacted tooth was included and group B (control group), where all left side impacted tooth were included. A gap of 4 – 6 weeks was given between every operation performed for each side to assess objective evaluation.

Surgical Technique:

The surgical procedure was performed according to classical surgical impacted third molar extraction technique. Using 2% lidocaine with 1:100,000 epinephrine conventional inferior alveolar, lingual and long buccal nerve blocks were given. Two-sided mucoperiosteal flap was reflected and tooth extraction was performed following adequate bone removal and tooth sectioning if required, using straight surgical hand piece with external cooling system.

Finally, the extracted socket was irrigated, debrided, and the flap was repositioned. In group A, HA gel (Afta Med®) was inserted into the socket before suture placement. In group B, the mucoperiosteal flap was sutured back conventionally without any treatment. Aseptic, atraumatic and coolant techniques were used for all patients to minimize both soft and hard tissues trauma.

Postoperative instruction were given and patients was prescribed antibiotics (oral Amoclan 1000 mg twice daily for 5 days) and analgesic medication (Ibuprofen 500 mg) as necessary.

Postoperative Evaluation

Visual analog scale (VAS) with a 10 units' number line marked by degrees was used for evaluating postoperative pain. According to this scale, score (0) indicated "absence of pain" and score (10) indicated "excessive pain." And the intermediate scores indicated "moderate pain." The standard question asked of all patients was "On the scale, how much pain are you having for today?" In addition, the scale contains facial expression illustrations to direct the patients. Brokelman *et al.* (2012) reported VAS scale is simple instrument to evaluate postsurgical pain and satisfaction of the patient with the intra class coefficient of 0.95. In this study measuring postoperative pain was recorded by using VAS in the immediate postoperative 1st, 2rd, and 7th days.

Preoperative and postoperative maximal mouth openings were recorded as a measure of the degree of trismus. using a calliper, the inter incisal distance between the upper and lower central incisors was measured for the purpose (Kumar *et al.*, 2012).

In our study, the assessment of facial swelling was determined by using modification of Gabka and Matsumara method (Gabka and Matsumura, 1971). The measurement points included tragus (T), soft tissue pogonion (P), lateral border of alaeque nasi (AN), lateral corner of the eye (CE), angle of the mandible (AM), and the corner of the mouth (CM). Seven different measurements (D1 to D7) were recorded between each case respectively; D1: T-AN; D2: T-CM; D3 T-P; D4: AM-CE; D5: AM-AN; D6: AM-CM and D7: AM-P. All measurements were taken before surgery and on the 1st, 2nd, and 7th days after surgery from both sides for all cases.

Results

A total of 46 patients with age ranging from 18 to 34years were included in this study, out of which 32 were males and 14 were females. The surgical difficulty levels as per Pell-Gregory and Winter classification (Almendros-Marqués *et al.*, 2008) were similar in each group. In all patients, the asymptomatic impacted lower third molars were extracted surgically without any intraoperative and postoperative complications. Follow up review was done on 1st, 2nd, and 7th postoperative days to evaluate the pain, maximal mouth opening and gross facial swelling at the surgical site.

Mean VAS scores denoting the postoperative pain intensity is displayed in table 1. There was a statistically significant difference in VAS score between the control group and HA group during the 1st and 2nd postoperative day($P<0.05$) denoting pain intensity was less in HA group than in control group.

Mean maximal interincisal opening scores for control and HA group are denoted in table 2. Maximum interincisal opening was recorded in preoperative period as a base value for assessing trismus. There was a statistically significant difference ($P<0.05$) in the interincisal measurements between the preoperative and the postoperative period especially during the 1st and 2nd postoperative day. This clearly indicated that the degree of mouth opening is significantly reduced during early postoperative period following surgery. When comparing the mouth opening between the control group and HA group, significant difference ($P<0.05$) was seen during the 1st and 2nd postoperative day.

Mean facial swelling measurements (D1–D7) for both groups are denoted in table 3. Significant amount of facial swelling was present during the early postoperative period as compared to the preoperative period in both groups. Degree of facial swelling was significantly less ($p<0.05$) in the HA group than the control group for both 1st, 2nd and 7th postoperative days.

Discussion

Post-operative complications such as pain, swelling, and trismus are commonly seen inflammatory response following surgical removal of impacted lower wisdom teeth despite all the precautions taken to prevent them. Many studies have been performed aiming to relieve the postoperative discomfort following wisdom tooth impaction surgery (Üstün *et al.*, 2003; Ren and Malmstrom, 2007; Kim *et al.*, 2009; Piecuch, 2012). It is generally understood that the maximal inflammatory response is seen during the initial

post-operative days following surgery reaching a peak level 2-3 days after surgery and gradual reduction in about 1-week time. This makes the first post-operative week crucial in terms of the patient's quality of life being affected by the inflammatory response to surgery. Thus, the 1st week after surgery has a strong effect on patients' quality of life, and it is critical to eliminate associated factors affecting the initial phases of wound healing (van Wijk *et al.*, 2009; Yilmaz *et al.*, 2017).

The current study was aimed at increasing postoperative comfort of wisdom tooth surgery patients by use of an alternative anti-inflammatory option with minimal adverse drug effects. The results with the application of HA into the extraction socket indicated a reduction in the post-operative pain and swelling as well as an improvement in the mouth opening ability during the initial post-operative period. Several studies in the literature reported that HA reduces the symptom of pain, swelling and reduced mouth opening during the initial post-operative period (van Wijk *et al.*, 2009; Koray *et al.*, 2014; Yilmaz *et al.*, 2017). Gotoh *et al.* (1993) had reported that HA has an analgesic effect due to the ability to cover bradykinin receptors relieving pain generation. In a study by Gocmen *et al.* (2015), it was found that HA application after third molar extraction would result in less leucocytic infiltration and more degree of angiogenesis. Nelson *et al.* (2015) studied the effect of oral administration of HA (Oralvisc®) using spectral analyses of serum and joint synovial fluid found a notable decrease in the majority of inflammatory cytokines such as interferon, interleukin-1α (IL), IL-1β, IL-6, tumor necrosis factor and bradykinin. They concluded that HA reduces not only pain but also local and systemic inflammation. In addition, HA in gel form has been found to be effective in new bone formation in critical sized calvarial defects in rats and rabbits (de Brito Bezerra *et al.*, 2012; Bae *et al.*, 2014).

Koray *et al.* (2014) assessed the efficacy of HA spray after third molar extraction and reported a statistically significant reduction in the degree of swelling and trismus, but no statistically significant reduction in pain. In contrast, study performed by Yilmaz *et al.* (2017), concluded that there was a statistically significant reduction of pain but no difference in swelling and trismus parameters postoperatively. On the contrary, in the present study, there was statistically significant difference in all the parameters assess i.e., pain, swelling and trismus. The possible reason for this could be the delivery method used for applying HA in gel form rather than as a spray, enhancing its physical properties and local availability (Sutherland, 1998). Efficacy of HA gel seems to be good in the initial phase of healing during the 1st and 2nd postoperative days and by 7th post-operative day negligible difference is noticed as confirmed by other studies as well (van Wijk *et al.*, 2009; Yilmaz *et al.*, 2017). The possible limitations of this study may be inaccuracy in measuring pain scale as it is subjective and there may be individual variations in pain threshold.

Table 1 : Comparison of Pain scores on VAS for postoperative 1st, 2nd, and 7th days among HA group and control group

		1st Day	2nd Day	7 Day
Control group	N	46	46	46
	Mean	6.74	6.24	0.74
	Std. Deviation	1.307	1.099	0.773
	Median	7	6	1
	Minimum	4	4	0
	Maximum	9	8	2
Test group	N	46	46	46
	Mean	4.48	3.35	0.41
	Std. Deviation	1.225	0.924	0.652
	Median	4	3	0
	Minimum	2	2	0
	Maximum	7	5	2
Test statistics		-5.207c	-5.876c	-1.925c
p value		**<0.001****	**<0.001****	0.054

**statistically significant

Table 2: Comparison of maximum interincisal opening for preoperative, postoperative 1st, 2nd, and 7th days among HA group and control group.

		Pre op	1st Day	2nd Day	7 Day
Control group	N	46	46	46	46
	Mean	45.39	34.52	33.74	44.76
	Std. Deviation	2.285	1.986	2.005	2.068
	Median	46	34	34	45
	Minimum	40	31	30	40
	Maximum	49	39	38	49
Test group	N	46	46	46	46
	Mean	45.57	39.85	40.2	45.07
	Std. Deviation	2.146	1.92	2.197	1.914
	Median	46	40	41	45.5
	Minimum	41	35	36	41
	Maximum	49	43	43	48
test statistics		-1.178b	-5.816b	-5.920c	-1.725b
p value		0.239	**<0.001****	**<0.001****	0.085

**Statistically significant

Table 3: Comparison of swelling measured from seven different drawings between groups

			1 Day		2 Day		7 Day	
		Pre OP	**control group**	**test group**	**control group**	**test group**	**control group**	**test group**
D1	Mean	11.82739	13.09478	12.09674	13.12326	12.38913	12.08174	11.86087
	Std. Deviation	0.178941	0.354249	0.541697	0.393926	0.688595	0.530242	0.224795
D2	Mean	11.38239	11.95174	11.68239	12.06783	11.43783	11.4663	11.42478
	Std. Deviation	0.222413	0.427693	0.395593	0.395856	0.192757	0.186754	0.220088
D3	Mean	14.59544	14.88544	14.845	14.86544	14.70739	14.61348	14.61109
	Std. Deviation	0.295633	0.408992	0.40454	0.394325	0.376796	0.303683	0.321284
D4	Mean	11.165	11.73435	11.465	11.85044	11.22044	11.24891	11.20739
	Std. Deviation	0.473755	0.716974	0.50588	0.661214	0.504966	0.456597	0.480312
D5	Mean	11.98435	13.22935	12.22522	13.25109	12.57217	12.24304	12.01783
	Std. Deviation	0.362078	0.374323	0.529393	0.365892	0.609101	0.545079	0.389221
D6	Mean	10.0263	11.1187	10.21978	10.8863	10.44761	10.17478	9.968043
	Std. Deviation	0.525781	1.148084	0.693274	1.520243	0.884723	0.651994	0.479007
D7	Mean	11.87413	13.14044	12.15457	13.14717	12.42587	12.1313	11.90283
	Std. Deviation	0.265962	0.402636	0.566693	0.448195	0.712063	0.61394	0.309039
test statistics			-11.155b		-10.079b		-4.058b	
p value			**<0.001****		**<0.001****		**<0.001****	

**statistically significant

Conclusion

HA gel seems to be an effective alternative to corticosteroids and other anti-inflammatory medications in reducing postoperative pain, swelling and trismus with no adverse effects. Further clinical and long-term studies on the usage of HA gel for reducing post-surgical complications after lower wisdom teeth removal are required to draw any further clinical conclusions.

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