Clinical efficacy of hyaluronic acid in post-extraction sockets of impacted mandibular third molar

Sairan Khurshed Nariman*, Reiadh Kamal AL-kamali**

Background and Objectives: Pain and swelling are the most common complications that occur after surgical removal of impacted third molar. Aim of this study to evaluate the effectiveness of local hyaluronic acid (HA) administration to surgically remove impacted third molar sockets to evaluate pain and swelling.

Materials and Methods: A comparative study included 50 healthy patients were subdivided into two equal sub group, aged 18-35 years with impacted lower third molars type of impaction (class II; position B according to Pell–Gregory classification). The procedure has been performed under local anesthesia. In the study group, 0.8% HA (Gengigel®) was applied in the post-extraction sockets of third molars and in the control group nothing was applied to the extraction sockets of third molars. Pain and swelling were evaluated with a visual analogue scale (VAS). Assessments were made on 1st, 2nd, 3th, 4th, 5th, 6th, 7th days after surgery.

Results: Statistically significant difference was detected for the pain values between the two treatment groups in different days of the study ($p < 0.05$). The swelling scores of the hyaluronic acid group were significantly lesser than those of the control group in day 1 ($p = 0.008$), day 3 ($p = 0.006$), and day 4 ($p = 0.036$). In the other days, the scores were less but the differences were not significant.

Conclusion: hyaluronic acid appears to offer a beneficial effect in the management of pain and swelling during the immediate postoperative period following impacted third molar surgery.

Keywords: Hyaluronic Acid, pain, swelling, impacted mandibular third molar.

* Candidate, Erbil Directorate of Health, Erbil, Iraq.

** College of Dentistry, Hawler Medical University, Erbil, Iraq.

Introduction

Mandibular third molar is the most common impaction tooth is due to inadequate space in the dental arch. Impaction may lead several complications and disorders including tooth caries, dental crowding, pericoronitis, root resorption and periodontal diseases. Additionally, serious complications such as osteomyelitis of the mandible and development of cysts and tumors have been reported in relation to impacted third molars [1-3].

The prevalence rates of mandibular third molar teeth varies from one population to another and several authors have reported prevalence rates ranging from 9.5% to 50%, higher in the western region [4]. Impaction of the third molar is occurring in up to 73% of young adults in Europe [5, 6].Mandibular third molar are the most prevalent impacted teeth with no differences reported between genders[3].

One of the most common procedures in oral and maxillofacial surgery is the surgical extraction of wisdom teeth. However, several complications can develop during surgical extraction of wisdom tooth, such as nerve injury, bone fractures, escape of the tooth or the root of the tooth to anatomical site, adjacent tooth damage, delayed healing, inflammation, pain, swelling, and trismus [7-9].

Pain, swelling, and trismus are the most common complications that occur after impacted lower third molar surgery. Surgical swelling start immediately after the removal of third molar and it reaches to peak value 2 to 3 days postoperatively and

resolves by 7 days [8-10]. Pain is also one of the most common postoperative complications after third molar extraction [11] and it might be produced by the release of pain mediators from the injured tissues. Pain initiates after the anesthesia subsides and reaches its maximum levels intensity 6-8 hours following surgery, continues for 2-3 days and decreases towards the seventh day [12, 13].

All these complications have undesirable effects on quality of life for patients. Many previous studies were based on decreasing the complications after impacted tooth surgery by use local or systemic steroid, non-steroidal anti-inflammatory drugs consumption and antibiotic prophylaxis are common medication methods [7]. Hyaluronic acid (HA) biomaterial is a better choice than corticosteroids for relief of post-operative complication after third molar intervention [14, 15]. Hyaluronic acid also play a role in wound healing and prevent or reduce post-operative inflammation [16]. Previous investigations found that HA appears to offer a beneficial effect on the management of swelling and trismus and on the inflammatory reaction following third molar extraction surgery [17]. Pain and swelling are main problems after surgical extraction of impacted mandibular third molar, therefore many material introduced in the market to reduce these complications. Recently use hyaluronic acid to minimize these complications arises after surgical extraction. In addition to that there is limited number of studies done on evaluation of effect hyaluronic acid after surgical extraction of mandibular wisdom tooth.

Materials and methods

Study design, setting and duration of study. Comparative study included fifty patients were treated in the department of oral surgery\ college of dentistry and maxillofacial surgery, at the Rizgary teaching hospital in Erbil city for surgical extraction of impacted mandibular third molar. The patients randomization was done by using Microsoft excel program (software) where simple random sampling was used to choose the management method (code 1) was assigned to HA group and (code 2) was assigned to comparison group. Accordingly patients with an odd number were given HA while patients with even number nothing was given to avoid bias. In this study was received approval from the institutional ethics committee and written inform consent was obtained from all patients that received HA. The patients included in the study were informed about the procedure, importance of oral hygiene maintenance, and follow-up visits before starting the procedure.

Inclusion criteria. Patients aged 18 – 35 years. To have impacted lower third molars with equal surgical difficulty (class II, position B according to Pell–Gregory classification) irrespective of their angulations [18]. Patients with normal mouth opening at the time of extraction. Surgical site free of active infection. Patients free of systemic diseases that may affect healing process. No allergies to local anesthetic agent (lidocaine). No allergies to antibiotic (Amoxicillin) and to analgesic acetaminophen (Paracetamol).

Exclusion criteria. Pregnancy, mental disability patients. Contraceptives or corticosteroids user which can affect the postsurgical healing phase.[19, 20] Non-cooperation patient. Patients with a history of smoking which can affect the postsurgical healing phase. Surgical procedure more than 30 minute was excluded.

Patients who meet the inclusion criteria were randomly divided to the following two groups:

Group I (N=25) patient receive Hyaluronic acid after surgical extraction (study group).

Group II (N=25) No intervention (control group).

Surgical procedure. Routine regional anesthesia procedures were applied including inferior alveolar nerve block together with long buccal nerve infiltration anesthesia by lidocaine 2% with epinephrine 1:80,000, after that two-sided incision (Triangular flap) was performed, and then mucoperiosteal soft tissue flap was reflected. The bone on the occlusal surface of the tooth was removed to expose the crown of the tooth then the buccal bone was removed by using straight hand piece with round bur in under abundant irrigation to prevent heat

generation and bone damage. A straight elevator was inserted into the slot made by the bur and then rotated to split the tooth and tooth extraction was performing by elevator. After extraction the socket was inspected to remove any sharp bone by bone file then socket irrigated with normal saline. In study group (1ml) of 0.8 % HA was inserted in to the socket. In control group nothing was applied, and then the flap was sutured by silk 3.0 [7] . For all patients the sutures were removed after 7 post-operative days. Post-operative medications for both groups were, amoxicillin (500 mg cap three times daily) and paracetamol (acetaminophen) (500 mg tab three times daily) for 5 days [21-23]. Antiseptic mouth wash (0.2% Chlohexidine) was used three time daily for seven days [9].

Postoperative evaluation of pain and swelling. Patients were asked to record the degree of pain and swelling by VAS: Visual Analogic Scale themselves at home as our patients can report back only 7 days after the surgery for suture removal. The pain scale was 5 cm long, subdivided into five equal parts, one end corresponding to no pain, the other to extremely severe pain (Table.1) while the swelling scale was also 5 cm long with no swelling on one end and extremely severe swelling on the other (Table. 2)[18, 24, 25]

Table 1: Table1: VAS for pain.

NO	Pain intensity	Patient experience
0	No pain	The patient feels well
1	Slight pain	If the patient is distracted he or she does not feel the pain
2	Mild pain	The patient feels the pain even if concentrating on some activity
3	Sever pain	The patient is very disturbed but nevertheless can continue with normal activities
4	Very severe pain	The patient is forced to abandon normal activities
5	Extremely severe pain	The patient must abandon every type of activity and feels the need to lie down

Table 2: VAS for swelling

No	Swelling intensity	Patient experience
0	No swelling	The patient does not detect the slightest swelling
1	Slight swelling	The patient detects slight swelling but it is not very noticeable
2	Mild swelling	The swelling is noticeable but does not interfere with normal mastication and swallowing
3	Sever swelling	The swelling is evident and hinders normal mastication
4	Very sever swelling	The swelling is marked. Mastication is hindered but there is no reduction in mouth opening (no trismus)
5	Extremely very severe swelling	The swelling is very evident and mouth opening is reduced (trismus)

Statistical analysis. Data were analyzed using the Statistical Package for Social Sciences (SPSS, version 22). Chi square test of association was used to compare proportions. Fisher's exact test was used when the expected count of more than 20% of the cells of the table was less than 5. The normality of the data was tested by Shapiro-Wilk test. Mann Whitney test was used to compare the mean ranks of two groups. A p value of ≤ 0.05 was considered statistically significant.

Results

Fifty patients underwent surgical extraction of mandibular third molar teeth. They were divided into two groups, 25 in each. Hyaluronic acid was applied on the socket of the extracted tooth for the group I, while nothing was applied for the group II (control). The mean age ± SD of the patients were 25.60 ± 4.52 years, ranging from 18 to 35 years. The median was 25 years. Graph.1 presents the age distribution of the studied sample, where no significant difference was detected between the two groups (p = 0.210). Graph .2 shows that 76% of the hyaluronic acid group were females, while only 40% of the control group were females (p = 0.01).

It is evident in Table 3 that all the pain parameters were significantly lower than those of the control group in different days of the study (p < 0.05).

In table 4 the swelling scores of the hyaluronic acid group were significantly lower than those of the control group in day 1 (p = 0.008), day 3 (p = 0.006), and day 4 (p = 0.036). In the other days, the swelling scores were less than those of control group but the differences were not significant.

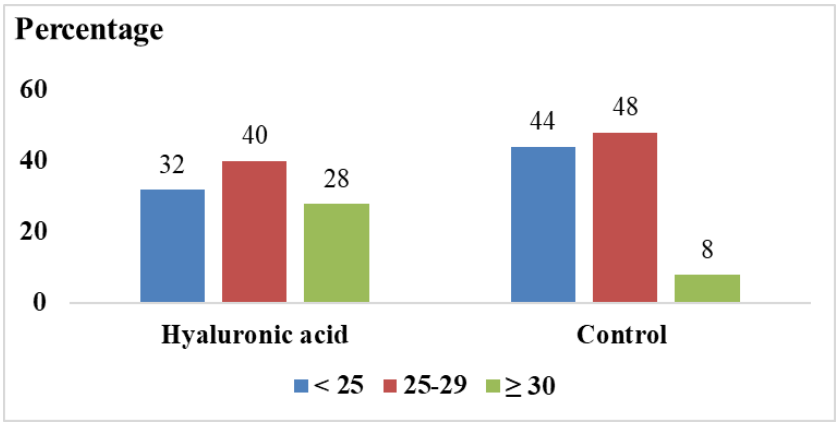

Figure 1: Age distribution.

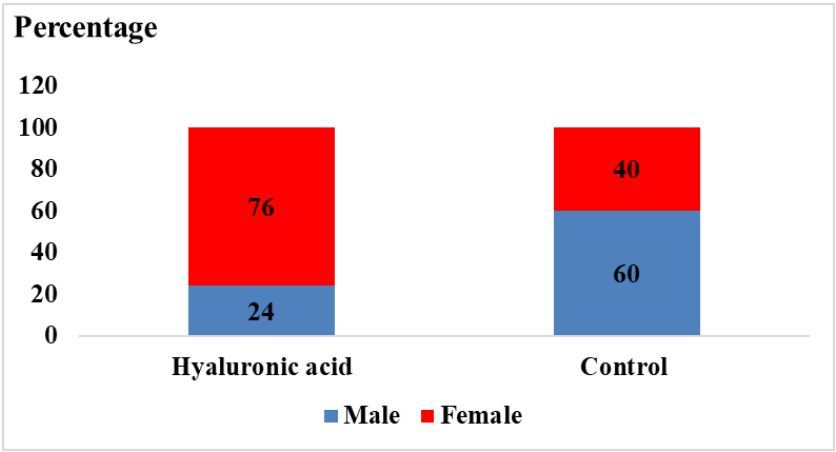

Figure 2: Gender distribution.

Table 3. Pain parameters of the two study groups in different days.

	Hyaluronic acid			Control			
Pain (days)	Mean score†	Median score†	Mean rank	Mean score†	Median score†	Mean rank	p*
P1	2.92	3.00	(18.64)	4.00	4.00	(32.36)	0.001
P2	2.52	2.00	(19.70)	3.40	3.00	(31.30)	0.003
P3	1.88	2.00	(18.36)	2.92	3.00	(32.64)	< 0.001
P4	1.40	1.00	(18.76)	2.48	3.00	(32.24)	0.001
P5	0.80	1.00	(17.40)	1.88	2.00	(33.60)	< 0.001
P6	0.52	0.00	(20.02)	1.20	1.00	(30.98)	0.005
P7	0.12	0.00	(19.14)	0.84	1.00	(31.86)	< 0.001

*Comparing the mean ranks of pain scoresbetween the two groups by Mann Whitney test.
†Pain scores according to visual analogue scale (VAS).

Table 4. Swelling parameters of the two study groups in different days.

	Hyaluronic acid			Control			
Swelling days	Mean score†	Median score†	Mean rank	Mean score	Median score†	Mean rank†	P*
S1	2.40	3.00	(20.20)	3.24	3.00	(30.80)	0.008
S2	3.28	3.00	(21.90)	3.84	4.00	(29.10)	0.069
S3	2.40	2.00	(20.18)	3.12	3.00	(30.82)	0.006
S4	1.72	2.00	(21.42)	2.24	2.00	(29.58)	0.036
S5	1.20	1.00	(22.00)	1.64	2.00	(29.00)	0.066
S6	0.76	1.00	(24.00)	1.04	1.00	(27.00)	0.405
S7	0.28	0.00	(24.58)	0.44	0.00	(26.42)	0.578

*Comparing the mean ranks of swelling scores between the two groups by Mann Whitney test.
†Swelling scores according to visual analogue scale (VAS).

Discussion

Surgical removal of impacted mandibular third molars is one of the most common carried out procedures in oral and maxilla-facial surgery [26-28]. Most third molars surgeries are done without operative difficulties. However, sometimes this common procedure can result in many complications. The most common complications following third molar surgery include: nerve damage, dry socket, infection, hemorrhage and pain. While severe trismus, iatrogenic damage to the adjacent second molar and iatrogenic mandibular fracture are Less common complications after surgical extraction of third molar [27]. It is obviously known that postoperative inflammatory reactions reach a peak level two days after surgery and generally decrease in seven days. Thus, the first week after surgery has a strong effect on patients' quality of life, and it is

important to eliminate associated factors affecting the initial phases of wound healing. [7, 29].

Comparison of Pain between control and study groups. Pain is one of the most common complication after third molar extraction, "Pain is unpleasant sensory and emotional experience" associated with tissue damage[30]. Relief of post-operative pain is an essential criterion in the overall success of tooth extraction. In the present study, the degree of pain was measured using VAS. The result of this study showed statically significant difference between control and study group from 1 day to 7 days. Yilmaz et al evaluated the efficacy of hyaluronic acid in post-extraction sockets of impacted third molar and reported HA decreasing the pain; this study was in agreement with present study [7]. Gotoh et al reported an analgesic effect of HA that involves covering bradykinin receptors in synovial tissues, the data supported a role for HA as a pain medication.[31]. Nelson et al suggested that HA reduces pain and inflammation [32].Gocmen et al stated that HA has anti-inflammatory effect, there were no statistically significant differences in pain between the groups[33], also Koray et al and Merchant et al reported HA that did not effect in reducing the pain, the results of these studies disagreement with present study [23, 34]. Das et al reported that HA can reduce symptoms of osteoarthritis knee pain as effectively as oral non-steroidal anti-inflammatory drugs or steroid injection[35]. Hanci and Altun addressed the value of HA on pain relief following tonsillectomy.[36].

Comparison of swelling between control and hyaluronic acid group. Postsurgical swelling was expected complication after third molar surgery. Swelling is a normal physiologic response of the tissues to manipulation and trauma caused during surgery. Its onset is slow and maximum swelling is present during 48 h after surgery procedure and it begins to diminish on the third or fourth day and resolves by the end of the first week. [37]. As increased swelling after the third day may be related to infection rather than postsurgical swelling[23]. The result of this study in 1st, 3rd and 4th days after extraction, there was statically significant difference between control and study group, while in 2nd, 5th, 6th and 7th days, there was difference in swelling between two groups but statistically not significant. Merchant et al concluded HA appears to offer a beneficial effect on the management of swelling in the immediate postoperative period following impacted third molar surgery and can be recommended for the patient's postoperative comfort. HA is more effective in controlling the postsurgical edema originating from the inflammatory processes which are initiated by the surgical trauma to the underline tissues [23]. The study of Koray et al evaluated the efficacy of HA compared to benzydamine hydrochloride to control pain, swelling, and limited mouth opening after third molar intervention. Postoperatively, limited mouth opening and edema were significantly reduced in the HA group compared to patients who received benzydamine hydrochloride [34]. Longinotti et al and Erickson and Stern also observed the anti-edematous effects of HA [38, 39]. Romeo et al showed that HA accelerated the resolution of facial swelling, with relief realized at 7 days post-intervention.[40]

Conclusion

In this study, it was concluded that HA can be a good choice after third molar surgery to reduce pain and swelling. However, further trials should be designed with larger participants to investigate the efficacy of HA after surgical extraction of impacted third molar.

Conflict of interest

The authors reported no conflict of interests.

References

1. Sun R, Cai Y, Yuan Y, Zhao JH. The characteristics of adjacent anatomy of mandibular third molar germs: a CBCT study to assess the risk of extraction. Scientific reports. 2017;7(1):14154.
2. Bhuju KG, Shrestha S, Kaki R, Aryal S. Effect of age, gender, side and impaction types on surgical difficulty during mandibular third molar extraction. MJSBH. 2018;17(1).

3. Rashid MO, Talabani RM, Baban MT, Gul SS, Salih RO, Abdulkareem BN, et al. Prevalence of impacted mandibular third molars and its association with distal caries in mandibular second molars using cone beam computed tomography. J Oral Res. 2019;8(1):66-73.
4. Muhamad AH, Nezar W. Prevalence of Impacted Mandibular Third Molars in Population of Arab Israeli. IOSR Journal of Dental and Medical Sciences (IOSR-JDMS). 2016;15(1): 00.
5. Juodzbalys G, Daugela P. Mandibular third molar impaction: review of literature and a proposal of a classification. Journal of oral & maxillofacial research. 2013;4(2):e1.
6. Santosh P. Impacted Mandibular Third Molars: Review of Literature and a Proposal of a Combined Clinical and Radiological Classification. Annals of medical and health sciences research. 2015;5(4):229-34.
7. Yilmaz N, Demirtas N, Kazancioglu HO, Bayer S, Acar AH, Mihmanli A. The efficacy of hyaluronic acid in postextraction sockets of impacted third molars: A pilot study. Nigerian journal of clinical practice. 2017;20(12):1626-31.
8. Santhosh Kumar MP, Vimalakshan I. Complications of Impacted Lower Third Molar Surgery and its Management. Int J Pharm Sci Rev Res. 2017;43 (2):8-12.
9. Cigerim L, Kaplan V, Orhan ZD. The Treatment of Complications of Impacted Wisdom Teeth. 2018.
10. Deliverska EG, Petkova M. Complications after Extraction of Impacted Third Molars - Literature Review. Journal of IMAB - Annual Proceeding (Scientific Papers). 2016;22(3):1202-11.
11. de Santana-Santos T, de Souza-Santos a A, Martins-Filho PR, da Silva LC, de Oliveira ESED, Gomes AC. Prediction of postoperative facial swelling, pain and trismus following third molar surgery based on preoperative variables. Medicina oral, patologia oral y cirugia bucal. 2013;18(1):e65-70.
12. Markovic AB, Todorovic L. Postoperative analgesia after lower third molar surgery: contribution of the use of long-acting local anesthetics, low-power laser, and diclofenac. Oral Surgery, Oral Medicine, Oral Pathology, Oral Radiology, and Endodontology. 2006;102(5):e4-e8.
13. Haraji A, Rakhshan V. Chlorhexidine gel and less difficult surgeries might reduce post-operative pain, controlling for dry socket, infection and analgesic consumption: a split-mouth controlled randomised clinical trial. Journal of oral rehabilitation. 2015;42(3):209-19.
14. Migliore A, Granata M. Intra-articular use of hyaluronic acid in the treatment of osteoarthritis. Clinical interventions in aging. 2008;3(2):365.
15. Allegra L, Della Patrona S, Petrigni G. Hyaluronic acid : perspectives in lung diseases. Handbook of experimental pharmacology. 2012(207):385-401.
16. Shuborna NS, Chaiyasamut T, Sakdajeyont W, Vorakulpipat C, Rojvanakarn M, Wongsirichat N. Generation of novel hyaluronic acid biomaterials for study of pain in third molar intervention: a review. Journal of dental anesthesia and pain medicine. 2019;19(1):11-9.
17. Alcantara CEP, Castro MAA, Noronha MS, Martins-Junior PA, Mendes RM, Caliari MV, et al. Hyaluronic acid accelerates bone repair in human dental sockets: a randomized triple-blind clinical trial. Brazilian oral research. 2018;32:e84.
18. Shivpuri A. Effect of Primary VS Secondary Wound Closure Technique after Removal of Impacted Mandibular. Acta Scientific Dental Sciences. 2017;1(3).
19. Tiigimae-Saar J, Leibur E, Tamme T. The effect of prednisolone on reduction of complaints after impacted third molar removal. Stomatologija. 2010;12(1):17-22.
20. Sharma J, Thiboutot D, Zaenglein A. The effects of isotretinoin on wisdom tooth extraction. Journal of the American Academy of Dermatology. 2012;67(4):794-5.
21. Shaban B, Azimi HR, Naderi H, Janani A, Zarrabi MJ, Nejat AH. Effect of 0.2% chlorhexidine gel on frequency of dry socket following mandibular third molar surgery: a double-blind clinical trial clinical trial. Journal of Dental Materials and Techniques. 2014;3(4):175-9.
22. Balakrishnan G, Narendar R, Kavin T, Venkataraman S, Gokulanathan S. Incidence of trismus in transalveolar extraction of lower third molar. Journal of pharmacy & bioallied sciences. 2017;9 (1):222.
23. Merchant R, Khalid I, Natrajan S, Galinde J. Comparative Evaluation of Clinical Efficacy of hyluronic acid spray versus normal saline spray on swelling ,painand trismus after surgical extraction of impacted mandibular third molar-A randomized contolled split mouth. International Journal of Science and Research (IJSR). 2018;7(9).
24. Shahab OI. Pain and swelling after lower 3rd molar surgery. Acomparative study between three methods of wound closure. 2008.
25. Samad AA. Comparison between Flapless and Flap Implant Surgery. Clinical and Radiographic Study. 2012.
26. Woldenberg Y, Gatot I, Bodner L. Iatrogenic mandibular fracture associated with third molar removal: Can it be prevented? Medicina Oral, Patología Oral y Cirugía Bucal 2007;12(1):70-2.
27. Contar C, Kanegusuku K, Berticelli R, Azevedo-Alanis L, Machado M. Complications in third mo-

lar removal: a retrospective study of 588 patients. Medicina oral, patologia oral y cirugia bucal. 2010;15(1):e74-8.
28. Chiapasco M, Flora A, Serioli L, Zaniboni M. The removal of deeply impacted lower third molars by means of the bone lid technique with piezoelectric instruments. Italian Journal of Dental Medicine. 2017;2:13-7.
29. van Wijk A, Kieffer JM, Lindeboom JH. Effect of third molar surgery on oral health-related quality of life in the first postoperative week using Dutch version of Oral Health Impact Profile-14. Journal of oral and maxillofacial surgery : official journal of the American Association of Oral and Maxillofacial Surgeons. 2009;67(5):1026-31.
30. Sakamoto E, Yokoyama T. Pain and Anxiety in Dentistry and Oral and Maxillofacial Surgery Focusing on the Relation between Pain and Anxiety. Remedy Publications LLC. 2018;1(1).
31. Gotoh S, Onaya J, Abe M, Miyazaki K, Hamai A, Horie K, et al. Effects of the molecular weight of hyaluronic acid and its action mechanisms on experimental joint pain in rats. Annals of the rheumatic diseases. 1993;52(11):817-22.
32. Nelson FR, Zvirbulis RA, Zonca B, Li KW, Turner SM, Pasierb M, et al. The effects of an oral preparation containing hyaluronic acid on obese knee osteoarthritis patients determined by pain, function, bradykinin, leptin, inflammatory cytokines, and heavy water analyses. Rheumatology international. 2015;35(1):43-52.
33. Gocmen G, Gonul O, Oktay NS, Yarat A, Goker K. The antioxidant and anti-inflammatory efficiency of hyaluronic acid after third molar extraction. Journal of Cranio-Maxillofacial Surgery. 2015;43 (7):1033-7.
34. Koray M, Ofluoglu D, Onal EA, Ozgul M, Ersev H, Yaltirik M, et al. Efficacy of hyaluronic acid spray on swelling, pain, and trismus after surgical extraction of impacted mandibular third molars. Int J Oral Maxillofac Surg. 2014;43(11):1399-403.
35. Das A, Neher JO, Safranek S. Clinical inquiries. Do hyaluronic acid injections relieve OA knee pain? The Journal of family practice. 2009;58(5):281.
36. Hanci D, Altun H. Effectiveness of hyaluronic acid in post-tonsillectomy pain relief and wound healing: a prospective, double-blind, controlled clinical study. International journal of pediatric otorhinolaryngology. 2015;79(9):1388-92.
37. Darawade DA, Kumar S, Mehta R, Sharma AR, Reddy GS. In search of a better option: dexamethasone versus methylprednisolone in third molar impaction surgery. Journal of international oral health: JIOH. 2014;6(6):14.
38. Longinotti C. The use of hyaluronic acid based dressings to treat burns: A review. Burns & trauma. 2014;2(4):162.
39. Erickson M, Stern R. Chain gangs: new aspects of hyaluronan metabolism. Biochemistry research international. 2012.
40. Romeo U, Libotte F, Palaia G, Galanakis A, Gaimari G, Tenore G, et al. Oral soft tissue wound healing after laser surgery with or without a pool of amino acids and sodium hyaluronate: a randomized clinical study. Photomedicine and laser surgery. 2014;32(1):10-6.