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Comparative Evaluation of Clinical Efficacy of Hyaluronic Acid Spray versus Normal Saline Spray on Swelling, Pain, and Trimus after Surgical Extraction of Impacted Mandibular Third Molar - A Randomized Controlled Split Mouth Study

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Abstract: ***Aim and objective: The aim of this study was compare the efficacies of two oral sprays in reducing swelling, pain, and trismus after the extraction of impacted mandibular third molars. Materials and method: This prospective double-blind, randomized, crossover clinical trial included 30 patients with bilateral symmetrically impacted mandibular third molars of similar surgical difficulty. Hyaluronic acid or Normal saline spray was applied (two pumps) to the extraction area, three times daily for 7 days. Swelling was evaluated using a tape measure method, pain with a visual analogue scale (VAS), and trismus by measuring the maximum inter-incisal opening. Assessments were made on the day of surgery and on days 2 and 7 after surgery. Result: Statistically significant differences were detected for the swelling and trismus values between the two treatment groups on the second postoperative day (P = 0.000 and P = 0.024, respectively). However, there was no statistically significant difference in VAS scores between the two groups. The administration of hyaluronic acid spray was more effective than Normal saline spray in reducing swelling and trismus. Conclusion: Although no evidence of a reduction in pain levels was detected, hyaluronic acid appears to offer a beneficial effect in the management of swelling and trismus during the immediate postoperative period following impacted third molar surgery.***

Keywords: Hyaluronic Acid, Swelling, Trismus, Impacted, Mandibular third molar

1. Introduction

The surgical extraction of impacted third molars is one of the most common procedures in oral and maxillofacial surgery. Patients following the surgery complainsof the postoperative swelling, pain, and trismus associated with the inflammatory response to surgical trauma.[1-3]In order to prevent these post -operative complaints adequate anti-inflammatory therapy is required. Corticosteroids are used widely to decrease the edema and trismus related to third molar surgery.[4,5] However the potential side-effects of perioperative corticosteroid use are delayed wound healing, increased susceptibility to infection and adrenal suppression .[6]

Hyaluronan or hyaluronic acid (HA) is a biomaterial that has been introduced as an alternative approach to enhance wound healing.[7]Hyaluronic acid is a major carbohydrate component of the extracellular matrix and can be found in many tissues.[8]It has multifaceted roles in biology, utilizing both its physicochemical and biological properties, and also has many properties that make it a potentially ideal molecule for assisting wound healing by inducing beneficial early granulation tissue formation, inhibiting destructive inflammation during the healing phase, and promoting re-epithelialization and also angiogenesis.[7,8]

In 2016 Koray et al conducted a study to evaluate the efficacy of topical hyaluronic acid gel (HA) and compared with triamcinolone acetonide pomad (TA) in the treatment of recurrent aphthous stomatitis[56]. They concluded that hyaluronic acid rapidly reduces the pain and discomfort caused by the ulcers, accelerated the healing process, and significantly reduce the risk of recurrence of the disorder. It also controls the inflammatory process and rehydrates the tissues.[9,10]

Thus the present study was planned to evaluate the clinical efficacy of hyaluronic acid spray versus normal saline spray on swelling, pain, and trismus after surgical extraction of impacted mandibular third molars.

Aim: To evaluate the efficacy of hyaluronic acid spray to reduce post-operative swelling, pain, and trismus compared to a normal saline.

Objectives:

1) To evaluate the efficacy of hyaluronic acid spray after mandibular 3rd molar surgery to reduce post-operative swelling, pain, and trismus.
2) To evaluate the efficacy of normal saline after mandibular 3rd molar surgery to reduce post-operative swelling, pain, and trismus.
3) To compare the efficacy of hyaluronic acid and normal saline after mandibular 3rd molar surgery to reduce post-operative swelling, pain, and trismus.

2. Materials and Methods

Patient selection

This study was a prospective double-blind, randomized, crossover clinical trial. The study received approval from the institutional ethics committee. Thirty patients were enrolled in the study and provided a signed statement of informed consent. All patients had bilateral symmetrically impacted mandibular third molars. Out of thirty patients 15 male, 15 female; mean age 23.35_ 3.89 years completed the study. Patients with no systemic disease, his-tory of allergy, or bleeding problems, those who co-operated with the study

and with postoperative follow-up, and those who had bilateral symmetrically impacted mandibular third molars with total or partial bone cover and of comparable surgical difficulty and those with absence of pain, trismus and swelling at the time of extraction were included in the study.

The following patients were excluded from the study: those with signs of pericoronitis and/or pain before surgery, those who were pregnant or nursing a baby, those who had undergone antibiotic or other medication therapies during the pre-ceding 2 weeks, those who had active carious lesions and/or periodontal dis-eases, and those who had contraindications to the drugs or anesthetics used in the surgical protocol.

3. Study Design

All of the patients included in the study were operated on by the same experienced oral and maxillofacial surgeon and assistant in order to minimize differences due to operator variability. Each patient underwent two surgical operations, separated by 2-4 weeks. In the first operation, the site of third molar extracted was decided by the patient. The patients were divided randomly into two groups "A" and "B", after the operation the patient was given either Normal saline spray (30 ml, 0.9% w/v sodium chloride; Fresenius Kabi Pharmaceutical Company, Germany) or HA spray (30 ml, 0.5% HA; Kojimax Cosderma) and instructed to apply the spray, two puff to the extraction area/suture line three times a day, for 7 days. In the second operation, the side of third molar which remained was extracted and the other spray was given to the patient. Both the surgeon and the patient were blinded to the spray given. The patients were instructed not to eat or drink for one hour after the use of both sprays. Patient were provided with a chart (fig 1) and were ask to tick on the chart whenever they use the spray and were ask to carry the chart whenever they come for follow-ups. All necessary patient consents were taken pre-operatively.

Surgical Protocol

All patients had undergone the procedure under inferior alveolar, lingual and buccal nerve blocks using lignocaine with 1:2,00,000 epinephrine. A three-cornered flap was raised to gain access to the third molar and buccal osteotomy and sectioning was carried out if necessary. Once the tooth extracted, the alveolus was irrigated with sterile saline solution at room temperature to eliminate debris and the bone edges were smoothened. The flap was then repositioned and the closure was done with 3–0 silk. Then two puff of the spray was applied on the sutured area and patients were educated about the spray and how to apply it. All patients were receiving prophylactic antimicrobial and non-steroidal anti-inflammatory/analgesic drugs, and postoperative instructions. The postoperative medication for both groups were, capsule amoxicillin 500mg three times a day and tablets Paracetamol 500 or tab tramadol 50mg two times a day for 5 days. The degrees of surgical difficulty were rated before the extractions by a single investigator, who performed the preoperative patient selection. The Pederson scales were used for this purpose.The extractions were classified as easy, moderate, or difficult (Table 1). The degree of facial swelling was determined by a modification[11] of the tape measure method described by Gabkaand Matsumara[10] (fig 2). Three measurements were made between five reference points, the distance between the lateral corner of the eye and angle of the mandible, the distance between the tragus and soft tissue pogonion, and the distance between the tragus and outer corner of the mouth. The mean of these three measurements were calculated. Measurements were taken pre-operatively and on postoperative days 2, 5 and 7.

Pain intensity were assessed using a 10-point visual analogue scale (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 were evaluated on the operation day and on postoperative days 2^{nd}, 5^{th} and 7^{th}.

Trismus was evaluated by measuring the distance between the edges of the Upper and lower right central incisors at maximum opening of the jaws using Vernier caliper, preoperatively and on days 2^{nd}, 5^{th} and 7^{th} day after surgery. All of the data obtained were evaluated using SPSS 14.0 package program. Data were analyzed as the frequency and percentage rate, and as the mean and standard deviation. The Student t-test and repeated measures tests were performed for parametric continuous data. A significance level of $P < 0.05$ for the 95% confidence interval was chosen to define statistical significance.

4. Results

Thirty patients 15 male and 15 female (graph 1),the mean age of the patients was 25.80±4.708 years with a median age of 25.0 years (graph 2)completed the present study (table 2). The impacted mandibular third molars on the left and right sides of the patients were comparable with respect to the degree of surgical difficulty. There was no significant difference in the difficulty score for mandibular third molar impaction between the sides and there mean difficulty score for the Hyaluronic acid group 4.73_ 0.22 and for the Normal saline group 4.86_ 0.21 (table 2). The test showed that there was no significant differencein the difficulty level for both groups (p=0.668). On the second postoperative day, facial swelling was significantly increased in both groups when compared to preoperative measurements; however, the facial swelling in the HA group was lower than that in the Normal saline group and the difference between the two groups was statistically significant (P 0.000). There was no significant difference in swelling between hyaluronic acid and saline in the Pre-op period (p = 0.286). There was a significant difference in swelling between hyaluronic acid and saline on the 2^{nd} post-op Day (p = 0.000). The swelling was significantly less (graph 3) in Hyaluronic Acid Group (123.9±1.53) than in Saline group (125.6±1.46). There was a significant difference in swelling between hyaluronic acid and saline on the 5^{th} post-op Day (p = 0.003). The swelling was significantly less in Hyaluronic Acid Group (122.2±1.56) than in Saline group (123.4±1.32). By the seventh postoperative day, facial swelling in both groups was minimal and there was no statistically significant difference between the two groups (Table 4). With regard to the mean VAS scores, They are compared and p-values for each time interval are given pain was highest on the

operation day and decreased gradually in both groups on postoperative days 2 and 7.There was no significant difference in pain between hyaluronic acid and saline (graph 4) in the Immediate post-op period (p = 0.794). There was no significant difference in pain between hyaluronic acid and saline on the 2nd post-op Day (p = 1.000). There was no significant difference in pain between hyaluronic acid and saline on the 5th post-op Day (p = 0.921). There was no significant difference in pain between hyaluronic acid and saline on the 7th post-op Day (p = 0.708).The maximum pain was seen in Saline group on immediate post op which was 8.433. The minimum pain was seen in on 7th Day in saline group which was 4.833. The table 5 shows the average values of Pain on each day in each group. Maximal mouth opening levels were similar preoperatively in the two groups. The means of mouth opening at (table 6) each time interval were compared and the results were as follows, there was no significant difference in mouth opening between hyaluronic acid and saline in the Pre-op period (p = 1.000). There was a significant difference in mouth opening between hyaluronic acid and saline on the 2nd post-op Day (p=0.011) (Graph-5). The mouth opening was significantly greater in Hyaluronic Acid Group (28.83±3.19) than in Saline group (26.6±3.19). There was a significant difference in mouth opening between hyaluronic acid and saline on the 5th post-op Day (p = 0.024). The mouth opening was significantly greater in Hyaluronic Acid Group (34.5±2.62) than in Saline group (32.8±2.84). There was no significant difference in the mouth opening between hyaluronic acid and saline on the 7th post-op Day (p = 0.577). None of the patients displayed alveolar osteitis, postoperative infection, or an allergic reaction to any of the drugs.

Case Report:

A 25 years old female patientstudent by occupation, residing at kalamboli, reported to our OPD with a chief complain of food lodgment in left posterior most teeth region since three months Patient gave no history of pain, swelling or discharge form the site of complaint.

Patient's medical history was non-contributory as was her dental and family history. Patient gave history of brushing teeth twice daily with paste and brush. Patient denied any addiction of tobacco or alcohol. On general examination, he presented with no anemia, cyanosis, clubbing, icterus, edema or lymphadenopathy. Her CVS, CNS, RS, abdomen, GCS and pupillary response al appeared to be normal. On extra oral examination, there was no gross facial asymmetry; her moth opening was 31 mm preoperatively. On intraoral examination, she had bilateral angles class 1 molar relation, partially erupted 38. Patient was advised for an OPG, which suggestive of bilateral impacted mandibular molars. She was considered in the study, coin was tossed, left side in group "A", hyaluronic acid spray and right side in group "B" which was normal saline. She was treated with bilateral surgical extraction of third molar and medicament spray was given and postoperative pain, swelling and trismus were evaluated.

On postoperative day 2 and 5 in group "A" had less swelling and trismus then in group "B". However, VAS score was 8in both the group with more on post operatively day 1, patient was given tramadol 50 mg twice daily. Post-operative swelling measured using tape measure method described by Gabka and Matsumara in HA group on day 2 was 124 , 126 on day 5 and 123 on day 7 and in Saline group it was 128 on post-operative day 2, 125 on day 5 and 124 on day 7. Post-operative mouth opening measured using vernier caliper in HA group on day 2 was 33, 38 on day 5 and 40 on day 7 and in Saline group it was 31 on post-operative day 2, 36 on day 5 and 39 on day 7 (fig 3 to 6).

5. Discussion

This study was designed to evaluate the efficacy of HA, in comparison to that of Normal saline, on the control of swelling, pain, and trismus following impacted mandibular third molar surgery. The results of the present study showed both facial swelling and trismus to be significantly decreased in the HA group when compared with normal saline group on the second and fifth postoperative day.

This procedure was done on thirty patients with bilateral impacted mandibular third molar with similar criteria and scores of the Pederson scale (Table 1).

In the present study, with regard to age and gender, controls were taken as double blind randomized study, thus eliminating bias in data collection.

The age of the patients included in this study were between 17 years to 40 years of age. Out of 30 patients in our study, fifteen patients (50%) were male and fifteen patients (50%) were female. The mean age of the patients was 25.80±4.708 years with a median age of 25.0 years.(Table .2).

In a study by Samir Mansuri et al[14], concluded that the postoperative complication like pain, swelling and trismus varies with the difficulty index of the impacted mandibular 3rd molar, however the degrees of difficulty of the surgical interventions were found to be similar (p=0.668) in the both hyaluronic and saline groups in the present study. (Table .3)

After the surgical procedure the pain from the site of the mandibular third molar extraction reaches to its maximum intensity 2-3 hour after the end of surgery. As stated by Esteller-Martı´nez et al in a study[15], considering that the surgical extraction implies a certain degree of osteotomy due to the existing molar inclusion, it is to be assumed that none of the patients will be without postoperative pain, which increases with increasing difficulty of the surgery. Lago-MendinezL et al study in 2007 concluded that pain after extraction of mandibular third molar decreases with increased surgical difficulty.[16]

In our study we found that patient in both the groups complained of pain following the third molar surgery, however there was no significant difference in post-operative pain levels between patients given hyaluronic acid and saline group at all-time intervals (F(1.868) = 1.058, p = 0.350).(Table 4)

In the present study ,the maximum pain was on the postoperative day one, hence, tramadol was provided on

ethical grounds, although the ideal design of a study evaluating pain intensity would involve the elimination of postoperative analgesics.However ,the present study showed that as time progressed there was a significant decrease in pain in both groups (F(2.342) = 128.509, p= 0.000). (Table 4). Chethan-Ramamuthy et all concluded in a study[17] that 50mg tramadol provides pain relief but has no clinical benefit in terms of reducing edema during the post-operative period following removal of impacted mandibular third molars[17] ,thus concluding that the administration of tramadol did not interfere with our findings regarding swelling and trismus and also that hyaluronic has no added analgesic properties.

Most surgical procedures result in a certain amount of swelling or edema, which often leads to trismus or difficulties in mouth opening. It has been noted that the swelling, reaches its maximum at 1–2 days after the surgical procedure and it begins to subside on the third or fourth day and resolves by the end of the first week.

In this study of 30 patient with bilateral impacted third molar with similar Pederson difficulties were provided with two spray to use locally at the suture line intraorally after surgical extraction of third molar. On post op day 2,5 and 7, the swelling was evaluated using Gabka and Matsumara method (figure 2). The test showed that there was a significant difference in the swelling levels between patients given saline and hyaluronic acid. (F(2.090) = 59.154, p = 0.000). The swelling in the saline group was comparatively more than in the hyaluronic acid spray group on post-operative day 2 ,5 and 7.(Table 5). M. Koray et al[18], conducted a study in 2014,to compare the efficacies of two oral sprays, Hyaluronic acid or benzydamine hydrochloride spray in reducing swelling, pain, and trismus after the extraction of impacted mandibular third molar and concluded that the administration of hyaluronic acid spray was more effective than benzydamine hydrochloride spray in reducing swelling[18].

In our study, we found that the mouth opening was significantly greater in Hyaluronic Acid Group (28.83±3.19) than in Saline group (26.6±3.19) on post op day 2 and also on day 5in Hyaluronic Acid Group (34.5±2.62) than in Saline group (32.8±2.84).There was no significant difference in the mouth opening between hyaluronic acid and saline on the 7th post-op Day (F(58) = 0.315, p = 0.577). This result may be related to the prevention of excessive inflammation and subsequent exacerbations by the high molecular weight HA employed in the present study thus suggesting that 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..

Robert Stern[19] in 2004 also concluded that the the osmotic buffering capacity of HA may be responsible for antiedematous effect as observed in the present study. The study shows that Hyaluronic acid acts by scavenging reactive oxygen species, such as superoxide radical (O2 _) and hydroxyl radical (OH) species, and inhibiting inflammatory cell-derived serine proteinases which are responsible for initiation of inflammation, thus inhibiting tissue destruction and accelerates healing.[9,10]Many clinicians[20] have stressed the importance of identifying the best treatment approaches to limit or avoid trismus and swelling in patients who undergo third molar surgery and to improve patient management.

As increased swelling after the third day may be an indication of infection rather than postsurgical oedema,[10] so the prophylactic antibiotic regimen used in the present study was also a further attempt to balance the groups with respect to post-operative infection control,[20] and to minimize the bias in the collection of pain, trismus, and swelling data, which might have been altered in the case of an infection.The routine use of systemic pre-and/or postoperative antibacterial that is cap Amoxicillin 500mg thrice in a day was given prophylactically, however uses of prophylactic antibiotic is highly disputed.[5] In the present study no patient had Alveolar osteitis or postoperative infection.

Many agents have been investigated in the quest for the one that reduces postoperative symptoms and complications and promotes oral wound healing and to improve patient management.[16] HA is reported to be a very promising for the mediation of periodontal tissue regeneration and wound healing.[22] Topically applied high molecular weight HA has been shown to induce oral tissue healing after gingival therapy[22] and significantly improves oral wound healing at the clinical level in an animal study. Gontiya and Galgali[23] showed that sub-gingival placement of 0.2% HA gel along with scaling and root planning provided a significant improvement in gingival parameters and reduced inflammatory infiltrate at experimental sites evaluated histologically.

Koray M[10] et al in 2016 conducted study to evaluate the efficacy of topical hyaluronic acid gel (HA) and compared with triamcinolone acetonide (TA) in the treatment and pain control of recurrent aphthous stomatitis (RAS). They concluded that HA gel can be effectively used for pain control in RAS treatment.

6. Conclusion

- The study results indicate that the efficacy of hyaluronic acid spray in term of swelling and trismus is significant when compare to that of normal saline spray after surgical extraction of mandibular third molar.
- In line with these studies, there are no significant reduction in pain levels as identified in both the group, HA spray appears to offer a beneficial effect on the management of swelling and trismus in the immediate postoperative period following impacted third molar surgery and can be recommended for the patient's postoperative comfort.
- Further larger randomized placebo-controlled trials are needed to confirm the efficacy of HA in this clinical setting.

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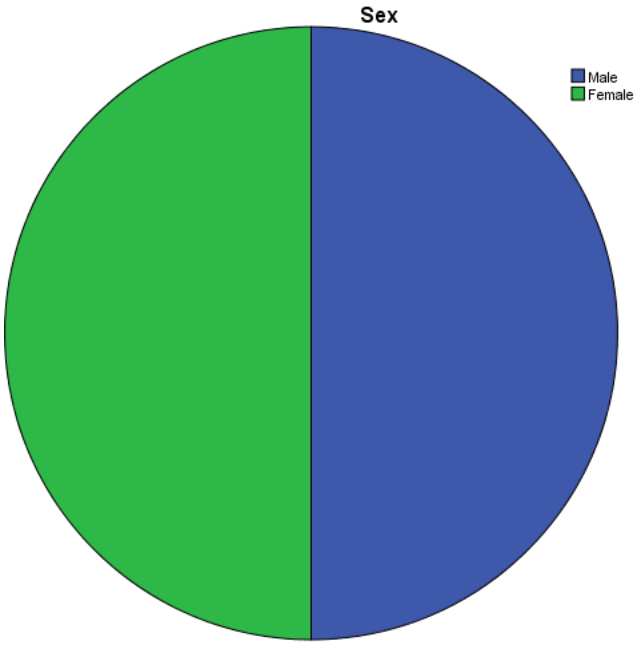
Graphs and Tables

Table 1: Criteria and scores of the Pederson scale.

Criteria	Scores
1. Spatial relationship	
Mesioangular	**1**
Horizontal/transverse	**2**
Vertica	**3**
Distoangular	**4**
2. Ramus relationship	
Class 1: sufficient space	**1**
Class 2: reduced space	**2**
Class 3: no space	**3**

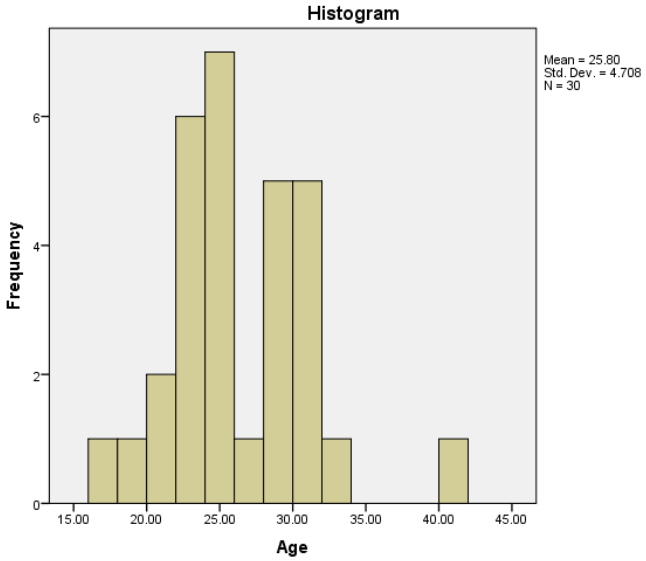
3. Depth	
Level A: high occlusal level	**1**
Level B: medium occlusal level	**2**
Level C: low occlusal level	**3**
Difficulty score	
Difficult	**7-10**
Moderate	**5-6**
Easy	**3-4**



Graph 1: Demographic data of Sex

Table 2: Distribution of Age

N	Valid	30
	Missing	0
Mean		25.8000
Median		25.0000
Std. Deviation		4.70803
Range		23.00
Minimum		17.00
Maximum		40.00
Percentiles	25	22.7500
	50	25.0000
	75	29.2500



Graph 2: Demographic data of age.

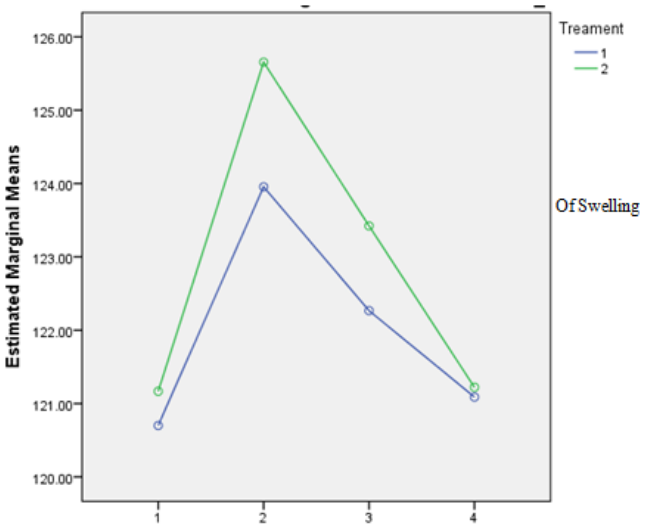
Table 3: Group Statistics for Pederson scale

	Group	N	Mean	Std. Deviation	Std. Error Mean
Pederson Scale	Group A Hyaluronic	30	4.7333	1.22990	.22455
	Group B Saline	30	4.8667	1.16658	.21299

HA=Hyaluronic Acid, Sal=Saline

Table 4: Descriptive Statistics hyaluronic acid and saline spray with respect to swelling

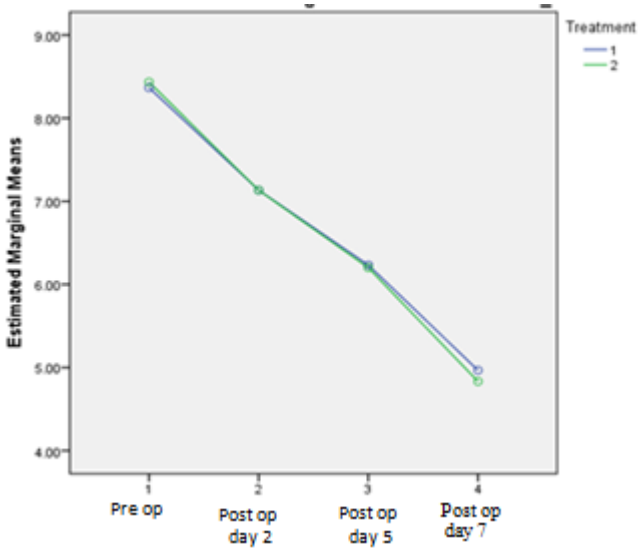
	Mean	Std. Deviation	N
HA Preop	120.7000	1.74494	30
HA Swelling 2nd Day	123.9556	1.53062	30
HA Swelling 5th Day	122.2667	1.56445	30
HA Swelling 7th Day	121.0889	1.68821	30
Sal Swelling Preop	121.1667	1.61114	30
Sal Swelling 2nd Day	125.6556	1.46081	30
Sal Swelling 5th Day	123.4222	1.32738	30
Sal Swelling 7th Day	121.2222	1.52460	30



Graph 3: Estimated marginal mean of measure for Swelling in Hyaluronic Acid vs Normal Saline spray

Table 5: Details descriptive of Comparison for Individual Sets for VAS scale in Hyaluronic Acid vs Saline

		Sum of Squares	df	Mean Square	F	Sig.
VAS Immediate	Between Groups	.067	1	.067	.069	.794
	Within Groups	56.333	58	.971		
	Total	56.400	59			
VAS2nd Day	Between Groups	.000	1	.000	.000	1.000
	Within Groups	40.933	58	.706		
	Total	40.933	59			
VAS5th Day	Between Groups	.017	1	.017	.010	.921
	Within Groups	98.167	58	1.693		
	Total	98.183	59			
VAS7th Day	Between Groups	.267	1	.267	.142	.708
	Within Groups	109.133	58	1.882		
	Total	109.400	59			

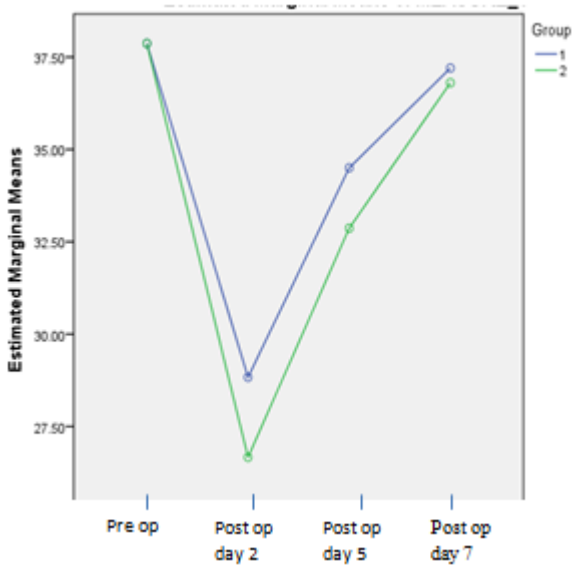


Graph 4: Estimated marginal mean of measure for VAS scale in Hyaluronic Acid vs Normal Saline spray.

Table 6: Descriptive Statistics hyaluronic acid and saline spray with respect to mouth opening

	Mean	Std. Deviation	N
Ha Mouth Op Preop	37.8667	2.84948	30
Ha Mouth Op 2nd Day	28.8333	3.19572	30
Ha Mouth Op 5th Day	34.5000	2.62284	30
Ha Mouth Op 7th Day	37.2000	2.75931	30
Sal Mouth Op Pre op	37.8667	2.84948	30
Sal Mouth Op 2nd Day	26.6667	3.19842	30
Sal Mouth Op 5th Day	32.8667	2.84948	30
Sal Mouth Op 7th Day	36.8000	2.75931	30

HA=Hyaluronic Acid, Sal=Saline



Graph 5: Estimated marginal mean of measure for trismus in Hyaluronic Acid vs Normal Saline spray.

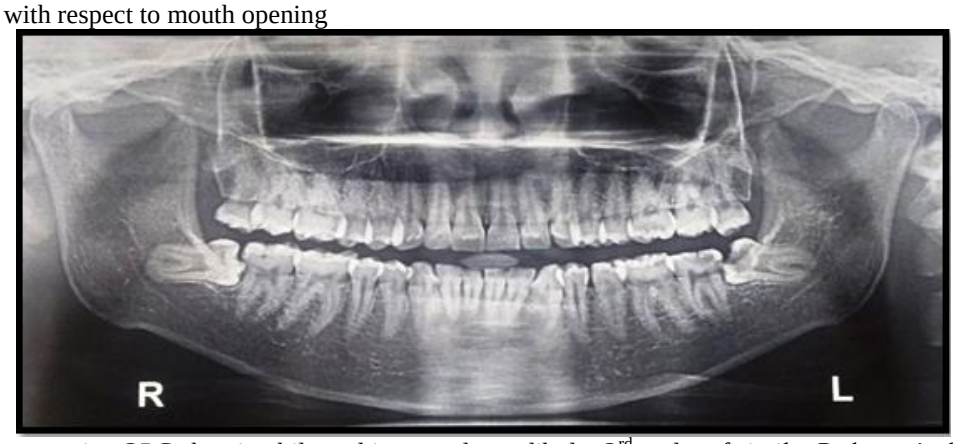


Figure 3: Pre-operative OPG showing bilateral impacted mandibular 3rd molar of similar Pederson's difficulty index

Figure 4: Pre-operative extra oral photo showing no gross facial asymmetry and pre-op mouth opening 32mm.

Figure 5: Showing picture of post-operative swelling on day 2 in group "A" (HA) measured from point A to point C (tragus to corner of mouth) according to Gabka and Matsumara mean of all Point is 124 mm & showing post-operative mouth opening on day 2 in group "A" (HA) 18 mm on vernier caliper.

Figure 6: Showing gross facial asymmetry on right side on post-operative day 2 after surgical extraction of 3rd molar in group "B" (normal saline) and Showing picture of post-operative swelling on day 5 in group "B" (normal saline) measured from point A to point D (tragus to corner of mouth) according to Gabka and Matsumara mean of all Point is 125 mm and Showing post-operative mouth opening on day 2 in group "B" (normal saline) 12 mm on vernier caliper.