# Hyaluronic Acid and Chlorine Dioxide on Post-odontectomy Swelling and Pain: A Randomised Controlled Trial

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#### Abstract

Gels containing hyaluronic acid (HA) and chlorine dioxide (ClO2) can be used to treat postodontectomy swelling and pain. There is minimal study comparing the outcome of these preparations.

This study aims to compare swelling and pain in post-odontectomy patients treated with HA and CIO2 gels. Material and methods: A RCT with three parallel arms were designed for this study. 165 patients with impacted third molar were included and allocated into HA-treated, CIO2-treated, and control group (n=55). The measurement is using Gabka and Matsumara technique and numeric rating scale. Data was collected during the same day, 2-days, and 7-days after surgery.

Median pain scores on HA, CIO2 were lower than the control group on the same day (HA=6, CIO2=7, control=8; p<0.001) and on the second collection (HA=1, CIO2=2, control=3; p<0.001) and in the third collection were 0 in all groups (p<0.001). The median value of swelling was measured at 14.6 cm in all groups before surgery. On the second and third measurement, the median value of swelling on HA and CIO2 groups were minimally reduced compared to the control group (p>0.05).

HA and CIO2 treatment reduces post-odontectomy pain score, and minimal effects on swelling were observed.

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#### Introduction

discomfort Post-odontectomy often occurs in the first week after third molar surgery with various manifestations. Pain, swelling, and restricted mouth opening are most frequently reported amongst other post-operative discomfort following an odontectomy.<sup>1</sup> To reduce postoperative discomfort, most clinicians prescribe medications, such as analgesics, antibiotics, or even corticosteroids, including prednisolone.<sup>2,3</sup> However, side effects such as nausea, upset stomach, and potential toxicity needs to be considered when prescribing post-operative medications.<sup>2</sup> Not to mention the risk of drug abuse in opioid group prescription and patients'

\*Corresponding author: Yudy Ardilla Utomo, Department of Oral and Maxillofacial Surgery, Faculty of Dentistry, Universitas Indonesia. Jalan Salemba Raya 4, Jakarta Pusat, Jakarta 10430, Indonesia. E-mail: yudyardillautomo@gmail.com systemic diseases that needs to be considered.<sup>2</sup> Therefore, numerous topical post-operative treatment have been developed to alleviate discomforts after third molar surgery.

Hyaluronic acid (HA) and chlorine dioxide (CIO<sub>2</sub>) are two novel agents in dentistry, currently gaining attention to be used in third molar surgeries. HA has been widely used as gingivitis periodontitis treatment and reducing and postoperative pain and discomfort in sinus lifting procedure. In a study published by Akshar et al., patients using of CIO<sub>2</sub> mouthwashes after odontectomy have 8% lower dry socket incidence.<sup>4</sup> However, studies about the effects of these agents on post-odontectomy two discomfort are limited.

The objective of this study is to compare swelling and pain in post-odontectomy patients treated with hyaluronic acid and chlorine dioxide gels.

## Materials and methods

This study was design as randomised controlled clinical trial with 3-arm parallel group. The ethical approval was provided by the ethical

review board of Faculty of Dentistry Universitas Indonesia (18/Ethical Approval/FKGUIVIII/2021) dan the study was in line with the Helsinki Declaration. Written informed consent was provided for every subject participating in this study.

# Sample Size & Study Population

Sample sizes were predetermined and calculated using G\*Power 3.1 program (v.3.1.9.3, 2017, Institut für Experimentelle Psychologie, Heinrich-Heine-Universität, Düsseldorf, Germany). 55 cases per group were the minimum sample size to get expected effect size of 0.25 with an alpha level of 0.05 and a power of 80% at the 1:1:1 distribution ratio.

The 165 patients included in this study was presented at the Universitas Indonesia Dental Hospital for a third molar surgery. All patients were male or female aged 18-59 years old with class I and position A or B impacted molar, according to the Pell & Gregory classification. All patients have no history of coagulation disorder and do not have any uncontrolled systemic disease. Pregnant and lactating women, patients with uncontrolled systemic disease, and patients allergic to HA and  $ClO_2$  were excluded from this study.

**Surgical Procedure** 

Odontectomy were performed to remove impacted third molars by oral and the maxillofacial surgery residents in Universitas Indonesia Dental Hospital. All surgeries were performed by under local anesthesia without sedation (lidocaine 2% 1:80 000 adrenaline). The technique used were mandibular block for posterior mandibular molars and superior alveolar nerve block and palatal infiltration for maxillary molars. The third molar surgery were then done by making a triangular flap, and bone is reduced as needed. Tooth separations were performed if needed and removed by using bein. Figure of eight or interrupted sutures were made based on the flap size after the surgery and patient were given post-operative instructions.

Randomisation and Intervention

The patients were randomly assigned into 3 groups with 1:1:1 ratio, using online randomisator, random.org, by a researcher (JA). Then, the code will be given to the practitioner (DA or YU) to prescribe post-operative medication based on treatment groups. All groups were treated with amoxicillin 500 mg orally for 5-days and etoricoxib 120 mg orally once a day for 3-days after odontectomy. The first and second group respectively received additional post-operative topical treatments of 0,2% HA bioadhesive gel (Gengigel<sup>®</sup> Gel, Ricefarma, Italy) and ClO<sub>2</sub> bioadhesive gel (Pro Relief, Oxyfresh, USA), while the third group received no additional treatment as the control group. Patients were instructed to apply 0,2 mL gel around the surgical site using q-tip 3 times a day for 7-days. Food and water were restricted 1-hour after application and patients were instructed to maintain oral hygiene.

**Outcome Measurement** 

Pain and swelling were two main outcomes assessed in this study. Pain intensity were measured using the numerical rating scale, a scale from 0 to 10, with 0 representing absent of pain, and 10 representing the most intense pain imaginable. Measurement of pain intensity were followed-up after the anesthesia wear off in the day of surgery (8-10 hours), 2-days after surgery, and 7-days after surgery. The presence of swelling were measured using the Gabka and Matsumara technique with 5 reference point: (1) lateral eye corner, (2) mandible angle, (3) tragus, (4) labial commissure, and (5) pogonion (Figure 1).<sup>5</sup> The distance between 1-2, 3-4, and 3-5 were measured before odontectomy (preoperative), 2days, and 7-days after the procedure, on the region where the teeth were removed.



Figure 1. Gabka and Matsumara Technique.

5 References point were used: (1) lateral eye corner, (2) mandible angle, (3) tragus, (4)

labial commissure, and (5) pogonion. Then, the distance between 1-2, 3-4, and 3-5 were measured.

# Statistical Analysis

Statistical analysis was performed using IBM SPSS Statistics 25 software (IBM Corporation, New York, NY, USA). Following data collection, descriptive statistic was retrieved and comparative statistic were performed using (1) (2) One-wav ANOVA or Kruskal-Wallis, depending on the normality of data distribution, tested using Kolmogorov-Smirnov. All data are presented with mean ± standard deviation for normally distributed data or median (minimum value-maximum value) non-normally distributed data

# Results

**Patients Characteristics** 

The 165 participants enrolled in this study have a mean age of  $27.22 \pm 6.213$  years with 32.7% to 67.3% male to female proportion. The mean age of the HA, ClO<sub>2</sub>, and control group were, respectively,  $27.05 \pm 7.56$  years,  $27.09 \pm$ 5.25 years, and  $27.53 \pm 5.70$  years with no statistically significant difference (p>0.05). All patients have either impacted 38 (48.5%) or 48 (51.5%), and no maxillary third molar surgery was performed for this study. Class IA, IB, IIA, and IIB cases were respectively proportioned 26.1% (n=43), 3.6% (n=6), 53.9% (n=89), and 16.4% (n=27). Separation was performed in 64.2% of all cases.

Variables	HA Group	ClO <sub>2</sub> Group	Control Group	Total
Age (Mean, Years)*	$27.05\pm7.56$	$27.09 \pm 5.25$	$27.53 \pm 5.70$	$27.22\pm 6.213$
Sex*				
Male	32.7% (18)	34.5% (19)	30.9% (17)	32.7% (54)
Female	67.3% (37)	65.5% (36)	69.1% (38)	67.3% (111)
Impacted Teeth*				
38	43.6% (24)	56.4% (31)	45.5% (25)	48.5% (80)
48	56.4% (31)	43.6% (24)	54.5% (30)	51.5% (85)
Classification*				
ΙA	27.3% (15)	20% (11)	30.9% (17)	26.1% (43)
I B	3.6% (2)	5.5% (3)	1.8% (1)	3.6% (6)
ΠA	56.4% (31)	49.1% (27)	56.4% (31)	53.9% (89)
ΠВ	12.7% (7)	25.5% (14)	10.9% (6)	16.4% (27)
Angulation*				
Mesioangular	36.4% (20)	30.9% (17)	47.3% (26)	38.2% (63)
Horizontal	29.1% (16)	40.0% (22)	21.8% (12)	30.3% (50)
Vertical	34.5% (19)	29.1% (16)	30.9% (17)	31.5% (52)
Separation*				
No	40% (22)	27.3% (15)	40% (22)	35.8% (59)
Yes	60% (33)	72.7% % (40)	60% (33)	64.2% (106)
Surgery Duration	$24.15\pm8.13$	$28.15\pm9.44$	$25.49 \pm 8.33$	$25.93{\pm}\ 8.76$
(Minutes)*				
*p>0.05 in all variables between groups				

**Table 1.** Characteristics of Enrolled Participants.

The mean duration of the surgery was 25.93± 8.76 minutes. All variables have no

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statistically significant difference (p>0.05), and the full descriptive characteristics of study participants are presented on Table 1.

Post-odontectomy Pain Were Lower on HA-treated and CIO<sub>2</sub>-treated Groups

Pain scores were collected on the same day after the anesthesia wears off, 2-days after surgery, and 7-days after surgery (Table 2). Pain scores measured in each intervention group were statistically compared using Kruskal-Wallis test because of non-normal distribution. On the same day collection, the mean scores of HA, ClO<sub>2</sub>, and control group were 6 (2-9), 7, and 8 (p < 0.001) respectively. The scores significantly reduced on 2-days postoperative and 7-days postoperative collection. On the second collection, the HAtreated group had a mean pain score of 1, CIO<sub>2</sub>treated group had a mean pain score of 2, and the control group had a mean pain score of 3 (p < 0.001). The mean pain value was 0 in all groups on the third collection. The difference between HA-treated and CIO<sub>2</sub>-treated groups were statistically significant (p<0.05) as showed in the modified kernel density plot in Figure 2.

	1 <sup>st</sup> Measurement	2 <sup>nd</sup> Measurement	3 <sup>rd</sup> Measurement
Pain			
HA-treated	6 (2-9)	1 (0-4)	0 (0-2)
ClO <sub>2</sub> -treated	7 (3-9)	2 (0-5)	0 (0-2)
Control	8 (4-10)	3 (1-7)	0 (0-2)
	p<0.001	p<0.001	p<0.001
Swelling			
HA-treated	14.6 (12.6-17) cm	15.3 (13.1-18) cm	15 (13-17) cm
ClO <sub>2</sub> -treated	14.6 (13-17) cm	15.6 (13.1-18) cm	15 (13.6-17.10) cm
Control	14.6 (12.6-17) cm	15.8 (14-18) cm	15.3 (12.6-17.3) cm
	p>0.05	p>0.05	p>0.05





**Figure 2.** Modified Kernel Density Plot Pain Score.

Swelling Showed No Statistically Significant Reduction in Treated Groups (Fig. 3).

Swelling was measured 3 times, on the same day of odontectomy (preoperative), 2-days after surgery, and 7-days after surgery. The mean size measured using the Gabka and Matsumara technique were 14.6 cm in all groups (p>0.05). On the second measurement, the mean size for HA-treated group,  $CIO_2$ -treated group, and control group were 15.3 cm, 15.6 cm, and 15.8 cm (p>0.05). Seven days after surgery, the mean was 15 cm for HA-treated and  $CIO_2$ -treated group, and 15.3 cm in the control group (p>0.05).



**Figure 3.** Swelling Before, 2-days, and 7-days After Surgery.

Swelling showed no difference on first, second, and third measurement in all treatments.

## Discussion

This randomized controlled trial was conducted to assess the effectiveness of HA and ClO<sub>2</sub> in reducing pain and swelling after odontectomy. Numerical rating scale and Gabka & Matsumara technique were used to assess pain and swelling after surgical removal of third molars in 0-day, 2-days, and 7-days after odontectomy. This study showed some potential effects of HA and ClO<sub>2</sub> application as a postoperative treatment of odontectomy.

Several factors are associated with postoperative morbidity of third molar surgery, including but not limited to swelling, pain, and trismus. Patient's characteristics, such as age, gender, and body mass index are most influential factors in post-odontectomy pain, swelling, and trismus.<sup>6,7</sup> Moreover, intraoperative factors such as surgical difficulty, duration, and whether or not separation were performed also contribute to post-odontectomy morbidity.<sup>8</sup> Author used Pell and Gregory classification and surgical difficulty in all

cases. The present study showed similar characteristics between groups with p values larger than 0.05 in all comparative statistics. However, BMI was not calculated in this study as a baseline characteristic of the participants.

Based on the results, the application of HA and  $ClO_2$  reduces pain in both treatment groups compared to control group on the same day after surgery and 2-days after surgery. The median score was 6 (2-9) and 7 (3-9) on the same day of surgery of respectively HA and  $ClO_2$  treatment, while the median score was 8 (4-10) in the control group (p<0.001). The score were reduced in all groups on 2-days after surgery, 1 (0-4) in HA-treated group, 2 (0-5) in ClO2-treated group, and 3 (1-7) in control group (p<0.001). The median score was 0 (0-2) in all groups 7-days after the surgery (p<0.001). The results indicate lower pain experienced in both treatment groups.

The finding of the effect of HA on postodontectomy pain in this study is similar to some previously reported studies but is also still up for debate. On two studies published by Yilmaz et al (2017) and Nariman et al (2021), patients receiving odontectomy and postoperative HA experience lower levels of pain in the span of 7days after the procedure compared to control group.<sup>9,10</sup> A systematic review including 5 studies by Souza et al. (2020) showed similar results on third and seventh postoperative days.<sup>11</sup> However, Koray et al (2014) in their respective study observed no difference in post-odontectomy pain levels treated with HA compared to control group.<sup>12</sup>

HA is a key element which has a lot of structural and physiological functions in and hard periodontal soft tissues. This characteristic, along with its' antioxidant effect, drew interests of researchers for further research on the therapeutic and regenerative potential of HA on tissues of the oral cavity. Wound and epithelial healing were found to be faster in the HA-treated palatal donor site of free gingival graft and post-tonsilectomy wound.<sup>13,14</sup> Gocmen et al (2015) in their study also suggest that HA may have wound healing and antiinflammation effects on post-odontectomy patients, however pain level reduction were not found to be statistically significant.<sup>15</sup> This wound healing effect may play a role in reducing postoperative pain, but the pain relieving mode of action of HA on postodontectomy pain still need further research.

CIO<sub>2</sub> is an antimicrobial agent currently gaining attention as a potential alternative for commonly used chlorhexidine.<sup>16</sup> Antimicrobial prescription, such as chlorhexidine, is common after an odontectomy with the potential of reducing duration of disability after third molar removal.<sup>6</sup> Hare et al. (2018) in their study suggest that the use of CIO<sub>2</sub> is effective in reducing the risk of alveolar osteitis (dry socket) and reduce post-odontectomy pain. Lower pain level may be possible by providing a favourable environment for the wound to heal, due to its' effectivity on anaerobic and aerobic pathogens. However, due to this study self-reported assessment of pain, placebo control can be applied in future studies.

Swelling measurements were reduced in all 7-days post-odontectomy measurement compared to the 2-days post-odontectomy measurement, while the baseline median were all measured at 14.6 cm. HA-treated group experienced lower overall swelling on the second, 15.3 (13.1-18) cm, and third, 15 (13-17) cm, measurements. CIO<sub>2</sub>-treated group also experienced the same phenomenon with 0.6 cm reduction between the second and third measurement (15.6 cm vs. 15 cm). However, all outcome on swelling were tested statistically not significant (p>0.05).

The effects of HA on post-odontectomy swelling in previous studies are variables. Yilmaz et al. (2017) and Deleme et al. (2019) in their studies showed no statistically significant post-odontectomy difference on HA-treated swelling on 1<sup>st</sup>, 3<sup>rd</sup> and 7<sup>th</sup> day.<sup>10,17</sup> In contrast, Koray et al. (2014) and Marouf and Rejab (2020) in their studies presented statistically significant reduction in swelling with HA post-odontectomy treatment on the 3rd day, with no statistically significant difference on the 7<sup>th</sup> day.<sup>12,18</sup> No study recorded the effect of CIO<sub>2</sub> on swelling of any this further kind. Therefore. vlami no antiinflammation effects from HA and ClO<sub>2</sub> that needs to be further investigated.

## Conclusions

The results of our clinical study showed significantly greater reduction of pain scores in HA-treated and ClO<sub>2</sub>-treated groups. Although wound healing may be one of the explanatory mode of actions of these two agents, no histological comparison was made to assess

healing processes. However, this study suggests that HA and  $CIO_2$  have minimal effects on swelling reduction with no statistical significance. No studies recorded the effects of  $CIO_2$  in postodontectomy swelling before; therefore, further confirmation is needed. HA and  $CIO_2$  have some benefits in reducing post-odontectomy discomfort.

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#### **Declaration of Interest**

The authors report no conflict of interest.

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