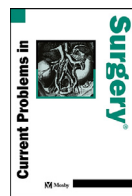




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Clinical and radiographical evaluation of the effects of two different flap designs in third molar surgery: A single blind randomized clinical trial



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Introduction

Impacted third molar tooth extraction is 1 of the most commonly performed procedures in oral and maxillofacial surgery because of the high prevalence of third molar impaction (90%).¹ The surgical extraction stage includes flap reflection and bone removal (according to the bone retention condition), extraction of the tooth from the socket and subsequent suturing of the removed flap.² Many complications can occur, such as pain, swelling, trismus, dry socket, compromised periodontal status of the adjacent second molar, and neurological complications.^{3,4} Since these complications may be directly related to surgical manipulation, surgeons have developed various alternative surgical flap designs to minimize the risks of these complications.⁵

The primary purpose of flap design is to create incisions with minimal tissue damage and adequate blood supply that allows visualization of the surgical field and easy access and use of surgical instruments.⁵ Flap design is important not only for the angle of view but also for the ease of surgical access. It is known that it also closely affects postoperative recovery. It is known that the flap type has an effect on parameters such as the feasibility of primary closure in the tissue, wound healing time, pain, trismus, alveolar osteitis and soft tissue/bone healing.⁶ Therefore, many modified flap types and their success levels in impacted dental surgery have been the subject of studies in the literature.^{5,7,8}

Flaps used for impacted third molar surgery are generally classified as triangular or envelope flaps. Various modifications have been developed for these headings, and their use has been

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attempted for impacted third molar surgery, such as the use of envelope flaps, Ward incisions, modified Ward incisions, Berwick's Tongue Flap incisions, Henry incisions, Killey and Kay incisions, Nageshwar incisions, Bayonet Flap, Mead Flap, Cogswell Flap, Avellanal Flap, Berzaghi Flap, Saurez Flap and Heitz flaps.⁵

The triangular flap type is one of the most commonly used flap types in mandibular impacted third molar surgery. The incision is made in the retromolar region, from the distal of the 2nd molar tooth toward the ramus and up to the distal gingival sulcus of the 2nd molar, and includes a vertical releasing incision added from the distobuccal sulcus of the 2nd molar tooth. The auxiliary vertical incision made in this flap allows the wound to be closed without tension.⁴

Berwick described a type of flap whose base is in the distolingual direction of the second molar tooth, in which the tongue-shaped vestibular wing extends to the buccal part of the mandible. In this modification, the incision line is not over the bone defect created by the extraction.⁹

The purpose of this study was to evaluate the clinical and radiological results of the use of modified Triangular and Berwick flap incisions in mandibular third molar surgery.

Materials and methods

The study was submitted and approved by the Ethical Committee under approval number 2019/04 (dated 19.02.2019) and registered on the Clinical Trials PRS System under approval number NCT06266052. This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

This study adhered to the principles of the Helsinki Declaration; all patients provided both verbal and written consent for the use of their photos and clinical information. This study included patients who had mandibular impacted third molar teeth with bone retention in the vertical/mesioangular position and who were referred to Recep Tayyip Erdoğan University, Department of Oral and Maxillofacial Surgery for impacted third molar surgery after January 2019. Patients aged 18-45 years who underwent impacted third molar surgery and who volunteered to complete the follow-up period were selected. Patients who were pregnant, had drug allergies, had diabetes, smoked or had poor oral hygiene were excluded from the study.

The study was performed as a single-blind study, and the investigators and patients were unannounced about the flap type used. Surgical procedures for all 38 patients were performed by a single surgeon, and the patients were randomly and equally divided into 2 groups. All follow-up measurements were performed by another surgeon.

Incision types applied in groups;

Group 1: Buccal-based triangular flap

A vertical incision was made in the distobuccal gingiva of the mandibular second molar. The incision was then made along the sulcus of the gingiva and extended distal to the mandibular second molar at 45 degrees along the distobuccal line angle to the ramus of the mandible [Fig. 1](#).

Group 2: Berwick flap

The Berwick flap is a tongue-shaped flap whose base extends at the distolingual aspect of the second molar to spare the periodontal ligament of the adjacent tooth. The incision line does not lie over the bony defect created by the removal of the impacted tooth and its base at the distolingual aspect of the second molar. This flap extends to the buccal shelf of the mandible [\(Fig. 2\)](#).¹⁰

Medication and follow-up protocol

Patients were prescribed Flurbiprofen twice daily (Majezik, 100 mg; Sanovel, Istanbul, Turkey), Amoxicillin twice daily (Largopen 1000 mg; Bilim, Istanbul, Turkey) and Chlorhexidine Gluconate-Benzylamine HCl antiseptic mouthwash (Kloroben; Drogosan, Istanbul, Turkey).



Fig. 1. Modified triangular flap incision borders.



Fig. 2. Berwick flap incision borders.

Patients were called for controls on the 3rd and 7th postoperative days. Sutures were taken on the 7th control day.

Parameters evaluated in the study

Edema

Five preoperative lengths were measured using a flexible ruler to evaluate edema in patients;

- Tragus-Commissura Labiorum (TR-CL)

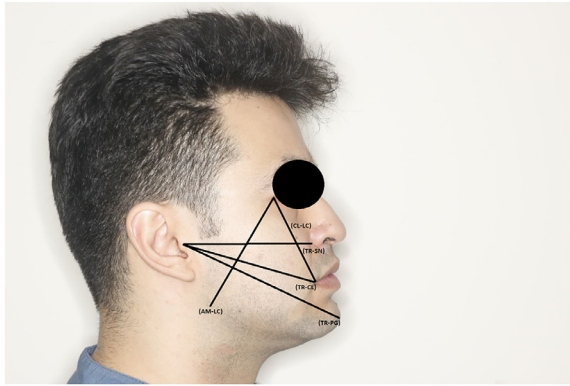


Fig. 3. Five length measurements for edema evaluation.

- > Tragus-Sulcus Nasolabialis (TR-SN)
- > Tragus-Pogonion (TR-PG)
- > Angulus Mandibule-Lateral Canthus (AM-LC)
- > Commissure Labiorum-Lateral Canthus (CL-LC)

On the 3rd and 7th day follow-up session, patients were asked to score the edema on their faces according to a scale, numbered from 0 to 10, and the numerical values were recorded on the follow-up forms. The changes in five different length measurements and a total of 5 length values were recorded preoperatively and on the 3rd and 7th follow-up sessions (Fig. 3).

Trismus

The maximum mouth opening (MMO) (mm) (the distance between the lower and upper central incisors while the maximum mouth opening) was measured preoperatively and 3 and 7 days postoperatively and was measured and recorded on the follow-up form.

Pain

The Visual Analog Scale (VAS), which was a subjective evaluation (calibrated between 0 and 10) was used to assess postoperative pain at 3rd and 7th days follow-up.^{11,12}

Number of analgesics taken

The number of analgesics the patient needed per day after the procedure was recorded at the 3rd and 7th days follow-up.

Granulation tissue

The data were recorded at the forms at 3rd and 7th days follow-up as present/absent.

Erythema in the extraction socket

The forms were recorded at the 3rd and 7th days follow-up as present/absent.

Operation time

The operation time was recorded on the forms (the time from the beginning of the first incision to the last suturing).

Radiographical evaluation

Panoramic radiographs in jpeg format with a size of 288×1435 pixels were used in the study. The fractal dimension was calculated by determining the region of interest (RoI) on 3 different areas of each third molar extraction site on panoramic radiographs. All radiographs were taken in the same position and with the same parameters before and 6 months after impacted third molar extraction. The region of interest (ROI) was determined to be

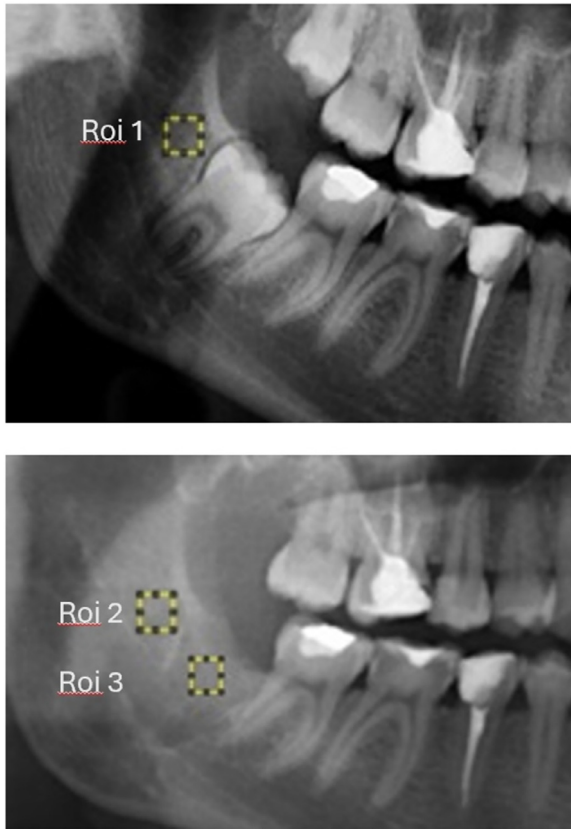


Fig. 4. Representative areas of Roi' s; Roi 1: Distal area of extracted third molar tooth in preop panoramic radiograph; Roi 2: Distal area of extracted third molar tooth in postop panoramic radiograph; Roi 3: Area of alveolar tooth extraction socket.

Roi 1: On the panoramic radiograph taken before tooth extraction (T0), on the trabecular bone with a size of 50×50 pixels, just distal to the extracted wisdom tooth

Roi 2: On the panoramic radiograph taken 3 months after tooth extraction (T1), on the trabecular bone in the same location as Roi 1, just distal to the extracted third molar tooth, with a size of 50×50 pixels

Roi 3: On the panoramic radiograph taken 3 months after tooth extraction (T1), there is a 50×50 pixel sized image in the extraction socket of the extracted wisdom tooth (Fig. 4).

The selected ROIs were duplicated via the ImageJ program, and Gaussian blurr filters were applied. This blurred image was subtracted from the original image, and 128 gray values were added. With the 'threshold' option, the image was converted to black and white, and noise was reduced with the erode-dilate option. By the 'invert' option, black regions were transformed to white regions, and white regions were transformed to black regions. By the 'skeletonize' option, the trabecular structure was prepared for fractal analysis; after the skeletonize option, the trabecular structure was prepared for fractal analysis, and the fractal dimension was calculated by the 'analyze' option (Fig. 5).

These measurements were performed by a single observer for all mandibular third molar teeth patients who met the preoperative and postoperative study criteria.

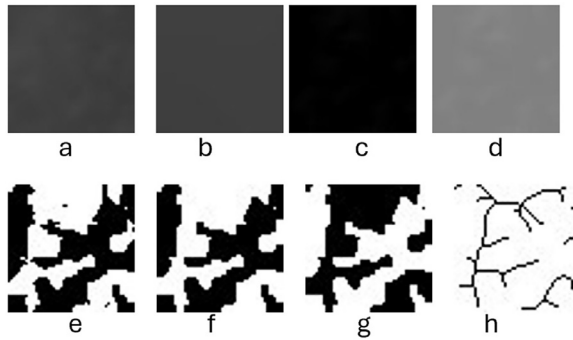


Fig. 5. Steps of fractal analysis; (A) Region of interest (Roi); (B) blurred image; (C) subtracted blurred image from the original image; (D) added 128 gray value; (E) threshold; (F) eroded -dilated; (G) inverted; (H) skeletonized.

Statistical analysis

The Statistical Package for Social Science (SPSS 23.0) was used for the data analysis phase. In the analysis of qualitative data, the chi-square test was used to compare independent groups, and the McNemar test was used to compare dependent groups.

The Kolmogorov–Smirnov test was used to evaluate the normality of the data. Comparisons of numerical variables between 2 independent groups were evaluated with Student's t test when the data were normally distributed and with the Mann–Whitney U test when the data were not normally distributed. Comparisons of numerical variables between 2 dependent groups were performed with paired t tests when the data were normally distributed and with Wilcoxon tests when the data were not normally distributed. In the analysis of measurements repeated more than twice in dependent groups, repeated-measures ANOVA was used when normally distributed conditions were met, and Freidman analysis was used when not. The Bonferroni correction, one of the posthoc tests, was used to determine the source of a significant difference between more than 2 measurements. The level of statistical significance was accepted as $P < 0.05$.

Results

A total of 38 patients whose impacted third molars were extracted were included in the study: 19 patients in the triangular flap group (Group 1) (17 women, 2 men) and 19 patients in the Modifiye Berwick flap group (Group 2) (13 women, 6 men). The average age of all participants was 22.4 ± 3.6 years. The descriptive statistics of the participants are shown in [Table 1](#). According to the descriptive statistics, there was no difference between the groups in terms of average age or sex ([Table 1](#))

Edema

However, there was no significant difference between the groups in terms of the TR-CL, TR-SN, TR-PG, or CL-LC measurements on the 3rd and 7th days, and only the AM-LC value in Group

Table 1
Descriptive statistics of the participants.

		Group 1 (N/%)	Group 2 (N/%)	P
Age (Mean \pm SD)	22,3 \pm 4,4	22,6 \pm 2,7	0,758	
Gender	Female	17 (89,5)	13 (68,4)	0.232
	Male	2 (10,5)	6 (31,6)	

Table 2

Edema measurement analysis.

	Group 1 (Mean±SD)	Group 2 (Mean±SD)	P
Preop. TR-CL	109,5±8,6	110,9±6,7	0.573
3th day TR-CL	112,5±8,3	112,7±7,5	0.470
7th day TR-CL	109,7±8,6	110,9±5,4	0.608
Preop. AM-LC	95,7±8,0	101,4±9,4	0.052
3th day AM-LC	98,1±9,3	101,5±6,9	0.198
7th day AM-LC	96,2±8,8	102,0±7,4	0.032
Preop. CL-LC	74,7±3,6	73,7±6,0	0.539
3th day CL-LC	76,9±4,1	75,4±5,7	0.350
7th day CL-LC	75,0±3,9	73,1±5,6	0.222
Preop. TR-SN	114,8±6,2	115,7±4,8	0.713
3th day TR-SN	116,0±7,5	114,9±8,7	0.693
7th day TR-SN	114,1±6,2	113,2±6,1	0.906
Preop. TR-PG	145,6±6,1	145,2±10,0	0.861
3th day TR-PG	148,7±6,8	147,5±9,6	0.656
7th day TR-PG	145,6±7,1	140,9±11,4	0.134
Preop (Sum of five length)	540,4±23,8	546,9±23,7	0.402
3th day (Sum of five length)	552,2±28,8	552,1±25,1	0.990
7th day (Sum of five length)	540,6±26,8	540,1±25,0	0.955

Table 3

Preoperative and postoperative MMO evaluation between groups.

	Group 1 (Mean±SD)	Group 2 (Mean±SD)	P
Preop. MMO	40,9±5,3	43,6±6,2	0.158
3th day MMO	31,1±7,4	27,4±8,9	0.181
7th day MMO	37,5±5,0	38,2±6,8	0.726

2 was found to be greater than that in Group 1 on the 7th day ($P=0.032$). There was no significant difference between preoperative, 3rd and 7th day values in terms of total edema length (TE) between Groups 1 and 2 ($P > 0.05$). (Table 2) No significant difference was detected between the 2 groups on the 3rd and 7th days in terms of the patients' own edema (OE) assessment scores ($P > 0.05$).

MMO

In both Group 1 and Group 2, the MMO values on the 3rd day decreased significantly compared to the preoperative values, and a significant increase was detected on the 7th day follow-up compared to the 3rd days follow-up. In the comparison between groups, no significant difference was observed between Group 1 and Group 2 in terms of MMO values ($P > 0.05$) (Table 3).

Pain

Although the VAS score was greater in Group 2 than in Group 1 on the 3rd and 7th days follow-up, this difference was not found to be statistically significant (Table 4).

Analgesic taken

On the 3rd day of follow-up, 9 patients reported needing 1 analgesic a day, 8 patients 2 times a day, and 2 patients 3 times a day. In the modified group, 1 patient reported using 0 analgesics

Table 4

Preoperative and postoperative pain value (VAS) evaluation between groups.

	Group 1 (Mean±SD)	Group 2 (Mean±SD)	P
3th day (VAS)	2,8±2,6	3,6±2,7	0.236
7th day (VAS)	0,6±0,8	1,3±1,5	0.153

Table 5

Comparison of postoperative analgesic intake between groups.

		Group 1 (Mean±SD)	Group 2 (Mean±SD)	P
Analgesic taken (3th day)	2 or less More than 2	17 (89,5) 2 (10,5)	15 (78,9) 4 (21,1)	0.660
Analgesic taken (7th day)	2 or less More than 2	17 (89,5) 2 (10,5)	17 (89,5) 2 (10,5)	1.000

Table 6

Comparison of the presence of granulation tissue at 3th and 7th day between groups.

	Granulation tissue at 3 th days		P	Granulation tissue at 7 th days		P
	Absent (N)	Present (N)		Absent (N)	Present (N)	
Group 1	16	3	0.230	0	0	-
Group 2	19	0		0	0	
Total	35	3		0	0	

per day, 4 patients reported using 1 analgesic per day, 10 patients reported using 2 analgesics per day, 3 patients reported using 3 analgesics per day, and 1 patient reported using 4 analgesics per day.

At the 7th day follow-up, 11 patients reported no need for analgesics, 3 patients needed 1 analgesic per day, 3 patients needed 2 analgesics per day, and 2 patients needed 3 analgesics per day in Group 1. In Group 2, 8 patients reported no need for analgesics, 3 patients reported using 1 analgesic per day, 6 patients reported using 2 analgesics per day, and 2 patients reported using 3 analgesics per day.

Analgesic intake amounts were grouped as 2 and less and more than 2, and no statistically significant difference was detected between the groups in terms of analgesic intake amounts on the 3rd and 7th days follow-up. (Table 5) ($P > 0.05$).

Granulation tissue

Any difference was not detected between the groups in terms of the presence of granulation tissue on the 3rd day. Granulation tissue was detected in 3 patients (15.8%) (1 patient with a yellow-gray color and 1 patient with a red color), and no granulation tissue was detected in 16 patients in the triangular flap group on the 3rd day. Any granulation tissue was not observed in the modified flep group on the 3rd day. Any statistically significant difference was not observed between the two groups in terms of granulation tissue on the 3rd day follow-up. ($P > 0.05$). Any granulation tissue was not observed on the 7th day follow-up in either group (Table 6).

Erythema in the extraction socket

On the 3rd day follow-up, erythema was observed in 5 patients (26.3%) in Group 1 and in 4 patients (21.1%) in Group 2. Any significant difference was not detected between the groups

Table 7

Erythema comparison in 3th and 7th days between groups.

	3 th day erythema		P	7 th day eythema		P
	Absent (N)	Present (N)		Absent (N)	Present (N)	
Group 1	14	5	1.000	17	2	0.486
Group 2	15	4		19	0	
Total	29	9		36	2	

Table 8

Operation time between groups.

	Group 1 (Mean±SD)	Group 2 (Mean±SD)	P
Operation time	7,6±2,9	9,1±2,7	0.028

Table 9

Bone trabeculation evaluation between groups.

	Group 1 (Mean±SD)	Group 2 (Mean±SD)	P
T0 alveol bone	1456,4±111,8	1462,7±90,0	0.859
T1 alveol bone	1522,2±113,0	1506,4±92,5	0.665
T1 (extraction socket)	1486,9±120,0	1503,3±96,2	0,670

on the 3rd day follow-up ($P=1.000$). (Table 7). On the 7th day follow-up, erythema was observed in 2 patients in Group 1 (10.5%), while no erythema was noted in Group 2. On the 7th day follow-up, this difference between the groups was not statistically significant ($P=0.486$). (Table 8).

Operation time

The average operation time was 7.6 ± 2.9 in Group 1 and 9.1 ± 2.7 in Group 2. The operation time in Group 2 was found to be significantly longer than that in Group 1. (Table 9).

Radiographic evaluation

When the T0 and T1 changes were compared, the T1 value in the socket in Group 2 was greater than that in Group 1, but this difference was not statistically significant (Table 9).

Discussion

Surgical extraction of impacted lower third molars is one of the most common procedures in oral and maxillofacial surgery. Impacted third molar surgery carries the risk of many complications such as pain, swelling, trismus, dry socket, impaired periodontal status of the adjacent second molar and neurological complications. These postoperative complications may occur depending on many factors such as the difficulty of the surgery (depth of the teeth, its angulation in relation to the second molar, the density of the bone), osteotomy type used for the surgery, irrigation procedure, the type of surgical flap used and etc. Trauma during the surgical procedure causes damage to the capillary vessel, promote the release of inflammatory cytokines and results in increased permeability of vessels causing accumulation of exudate. Additionally, surgery-associated trauma initiates an inflammatory cascade, impairs the patient's quality of life.¹³ Since

postoperative complications are related to quality of life and wound healing, it is necessary to perform surgical procedures with as little trauma as possible.^{2,17} Therefore, clinicians have tried many different methods to minimize these complications and presented their results in the literature. Even though they tried to reduce complications and determine the ideal method by testing osteotomy, irrigation, using surgical drains and flap variations, there is still no consensus on this issue today.¹³⁻¹⁶

Mucoperiosteal flap removal during the surgical procedure can cause trauma, and this trauma affects the wound and bone healing processes during the postoperative period. Therefore, the design and boundaries of the flap used play a key role in third molar surgery.¹⁸ It is recommended that the flap borders used in impacted third molar surgery be planned on intact bone. In this way, the possibility of wound dehiscence and alveolar osteitis may be reduced, and intact bone support may be provided to the flap.¹⁹ However, contrary to this rule, there are also flap types located on bone defects in the literature. Among these types of flaps, flap types generally collapse into the wound, dehiscence occurs, and the possibility of bacterial invasion into the wound increases during the postoperative period.²⁰ In the present study, the postoperative clinical and radiographical results of the buccal-based triangular flap, whose borders were planned on the extraction socket, and the lingual-based Berwick flap, whose borders were planned outside the extraction defect, were comparatively evaluated.

The triangular flap type is one of the most commonly used flap types in impacted mandibular third molar surgery. It is a type of flap that is made in the retromolar region, from the distal of the 2nd molar tooth toward the ramus and up to the distal gingival sulcus of the 2nd molar, and includes a vertical releasing incision from the distobuccal sulcus of the 2nd molar tooth. The auxiliary vertical incision made in this flap allows the wound to be closed without tension.⁴ The modified triangular flap is a more conservative version of the triangular flap. In this type of incision, there is less tissue reflection, there is no tissue reflection in the buccal region of the 2nd molar, and tissue closure can be achieved more easily; however, it is also difficult to readily expand the flap.^{20,21} Berwick described a type of flap whose base is in the distolingual direction of the second molar tooth, in which the tongue-shaped vestibular wing extends to the buccal part of the mandible. In this modification, the incision line is not over the bone defect created by the extraction.²²

Any significant differences was not detected in terms of edema, pain, MMO or the presence of granulation tissue between the 2 groups in this study. The density of the newly formed bone in the socket, revealed that the amount of trabeculation of the bone formed in the extraction socket in the modified group was higher than that in the triangular group, but this difference was not found statistically significant. Only the operation time was higher in the modified flap group than in the modified triangular flap group.

In the literature, the effects of different types of flap use in terms of postoperative comfort parameters for impacted third molar surgery have been studied many times.^{2,3,7,8,18} According to the study results, although there are studies stating that the flap type is individually effective for postoperative complications such as pain, swelling, mouth opening, and wound healing, there are also meta-analysis studies reporting the opposite.²³ Although the effect of flap design on postoperative comfort has been the subject of many studies, there is no consensus. In addition, no study has reported the effect of flap design on postoperative discomfort and bone healing. In this study, the authors investigated the effect of 2 different flap designs (a buccal-based modified triangular flap and a lingual-based Berwick flap) on postoperative morbidity, including postoperative comfort parameters and soft/hard tissue healing parameters. It is thought that this study will provide new information to the literature in terms of examining the effects of different flap types on bone healing as well as postoperative comfort parameters.

In their split-mouth study, Yolcu et al.¹⁹ compared the effects of buccal-based triangular flaps and lingual-based modified flaps on postoperative comfort in 22 patients, and as a result, they found no differences in terms of swelling, trismus or wound dehiscence. In terms of pain, they reported that there was more pain in the area where the buccal-based triangular flap was applied. The present study results support the results of Yolcu et al.¹⁹ in terms of swelling, tris-

mus and wound dehiscence. Our results, in terms of pain, did not reveal a significant difference, unlike the study of Yolcu et al.¹⁹ This difference can be attributed to the fact that in the split-mouth study, the patient had the opportunity to score pain by comparing it with the other side, whereas in the current study, the patient only received individual single scores. When the density of the newly formed bone in the extraction socket was examined, the number of trabeculation of the bone formed in the modified group was greater than that in the triangular group, but this difference was not statistically significant. This result is one of the rare and valuable data in the literature that presents the effect of flap type on bone healing. In this sense, this result also radiographically supports the clinical data of Yolcu et al.¹⁹

As a result of their study comparing the envelope and triangular flap, Erdogan et al.²⁴ reported that there was no difference between the 2 flap types in terms of trismus, operation time or the number of painkillers taken, and on the other hand, they reported less inflammation in the envelope flap group. Many studies in the literature have reported that postoperative pain, trismus, gingival margin, periodontal probing depth, and periodontal attachment loss are not related to the incision type. Therefore, they reported that flap type does not significantly improve postoperative quality of life.^{3,25-27}

Saures Conqueiro et al.²⁸ reported better wound healing with the marginal flap type than with the paramarginal flap type. They also reported that the marginal flap type was sufficient in terms of tissue exposure and bone support. In contrast, Rabi et al.²⁹ compared triangular and envelope flaps in their study and reported that the triangular flap showed better postoperative results than the envelope flap in terms of mouth opening.

A mucoperiosteal flap incision and elevation is a kind of trauma, and this trauma causes increased osteoclastic activity in the alveolar bone, resulting in bone resorption. The sulcular incision applied to impacted third molar teeth also causes trauma to the periodontal ligament of the second molar. This trauma induces periodontal tissue damage around the adjacent molar tissue. For this reason, in the literature, alternative lingual-based buccal tongue flap incisions have been used to minimize damage to periodontal tissue.^{5,9,30} It is known that protecting the periodontal ligament distal to the second molar reduces attachment loss, facilitates socket closure, supports clot formation and promotes wound healing. In light of this information in the literature, the clinical and radiographic results of the use of the modified triangular flap and Berwick tongue flap in impacted mandibular third molar surgery were compared in this study.

The study was performed under sterile conditions by a single surgeon using the same surgical instruments, and all surgical procedures were performed by the same surgeon. Patients were randomly included in the study groups. The 3rd- and 7th-day controls were subjected to surgery by another surgeon. Radiographic analyses were also evaluated by a radiologist blinded to the incision type. The study was conducted in such a way that all surgical conditions were standardized, and the only difference between the study groups was the flap type. There was no significant difference between our study groups in terms of postoperative edema, pain, number of analgesics taken, tissue redness, granulation tissue or bone quality in the socket. Among our groups, only the operation time was significantly greater in group 2 than in group 1. This result can be attributed to reasons such as the atypical design of the lingual-based Berwick flap type and the difficulty of retraction of the flap compared to the triangular flap.

Conclusion

Based on these results, it can be concluded that postoperative complications and quality of life parameters are independent of the flap type used, and possible complication parameters may depend on the technical sensitivity of the surgeon. As a result, the bone trabeculation fractal analysis value in the modified group was greater than that in the triangular group, but the difference was not found to be statistically significant. This radiographic analysis may provide new information supporting the clinical parameter analysis results in the literature. These results will be improved with comprehensive clinical studies.

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CRedit authorship contribution statement

Zeynep Gümürkçü: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing. **Seval Bayrak:** Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization. **Emre Balaban:** Supervision, Validation, Visualization.

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