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Original Article

Investigation of the effect of fibrin glue as a sealant in the unilateral alveolar bone grafting successes

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ABSTRACT

Background: Bone grafting is the primary treatment for the alveolar cleft. Due to the reduced complications by the sealant materials, this study aimed to evaluate fibrin glue's effect on the success rate of unilateral alveolar bone grafting.

Materials and Methods: This study was a single-blind clinical trial performed on 20 patients with a unilateral alveolar cleft. Patients were randomly divided into groups: group A patients as a control group underwent bone grafting without fibrin glue, and in Group B, patients were grafted using fibrin glue. The subject was followed up through routine examination and the cone-beam computed tomography systems technique for up to 4 months. Paired t-test and Chi-square tests were used to analyze the data and the $P < 0.05$ was considered the significance threshold.

Results: The mean age, gender, and cleft side distribution did not represent significant differences. Before surgery, the average alveolar cleft volume in Group A and B patients was 0.95 ± 0.25 cm^3 and 0.99 ± 0.22 cm^3, respectively, which was not statistically different. After the surgery procedure, the alveolar cleft volume in Group A and B patients was determined to be 0.31 ± 0.10 cm^3 and 0.23 ± 0.11 cm^3, which represented 66.7% ± 8.9% cm^3 and 76.2 ± 11.4 cm^3 bone formation, respectively, with no remarkable difference. Our examination did not reveal any necrosis and infection in both groups. However, despite no dehiscence observation in fibrin glue treatment patients, one subject showed dehiscence complication in the control group.

Conclusion: According to results, fibrin glue may increase the percentage of bone volume formed and prevent dehiscence.

Key Words: Alveolar bone grafting, cleft lip, cleft palate, fibrin tissue adhesive

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INTRODUCTION

Anatomically, the maxilla horizontal portion is ascribed as the alveolar process, a cribriform compact bone of the primary palate responsible for holding the tooth roots and dentition support. Fibers, nerves, cells, blood vessels, intercellular substances, and lymphatics are the main component of the alveolar bone.[1-3] As an essential medical condition, the alveolar cleft results from frontonasal prominence maldevelopment due to the failure in the fuse of the premaxilla with the upper jaw. Several factors are responsible for its cause, including the environmental factors involved

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in the etiology of facial clefting disorders, such as drugs, chemicals, maternal metabolic imbalances, and maternal infections. According to the World Health Organization, 69 participants indicated a cleft malfunction in every 10,000 live borns. On the other hand, the alveolar cleft causes various limitations for patients, including problems in speech, feeding, oral health, and the behavioral burden that finally affects psychosocial well-being.[4-6] Nevertheless, to restore normal function, the patient should undergo surgical closure.

Studies show that surgical closure alone cannot wholly restore functional and esthetic recovery in patients with an alveolar cleft. Therefore, in addition to routine surgery, other materials are used to improve the results, including bone grafts and other alternative materials. The most common type of bone graft is autograft and allograft. Essential criteria should be considered, such as the immune system, graft rejection, and the possibility of infection. According to the mentioned criteria, autograft transplantation appears suitable for this operation.[6-8] Among the various bone sources for graft in patients with an alveolar cleft, the iliac crest bone has many advantages, including easy harvesting, providing a large amount of spongy bone. However, some limitations can be encountered in this procedure, including infection, scarring, and bleeding from the donor area, along with dehiscence, tissue necrosis, and inflammation after surgery.[6,9,10]

A significant complication in 30%–75% of cases of alveolar cleft surgery is bone resorption. One alternative way is to use fibrin glue to integrate the bond.[11,12] Fibrin glue is a biodegradable material widely used in abdominal surgery to close wounds, reduce leakage and bleeding, heal wounds, and prevent tissue adhesions. Today, fibrin glue prepared from fibrinogen concentrates as a biological glue has various medical applications. The hemostatic properties of this glue lead to blood loss reduction and secure the graft in place. Such a process causes reduced hematoma formation and graft mobility, both of which increase graft survival. Another advantage of fibrin glue is its antibacterial function. Bacterial growth in fibrin glue clots is slower than physiological clots. Therefore, this biological material is highly regarded as a sealant in surgery due to its properties.[13-15]

Due to the importance of alveolar cleft manifestations that, in addition to the patient's physiology, also affect the mental health and behavior of patients, treatment management of this complication is very crucial; therefore, this study aimed to investigate the effect of fibrin glue on autologous iliac bone graft in patients with a unilateral alveolar cleft.

MATERIALS AND METHODS

Study population

The present study was a single-blind clinical trial. The study population was selected from the patient with a unilateral alveolar cleft between 8 and 12-year-old referred to Al-Zahra Hospital in Isfahan, Iran. Patients with a bilateral alveolar cleft, presence of systemic diseases or pathological disorders, history of chemotherapy or radiotherapy, and patients with a history of unsuccessful alveolar bone graft in the past were excluded from the study. According to Formula 1, a total of 20 patients were selected. The Iran National Committee for Ethics in Biomedical Research has confirmed the present study with an ethics code of IR. MUI. RESEARCH. REC.1400.002.

$$N = \frac{(Z_1 + Z_2)^2 \left(2S^2\right)}{d^2}$$

Formula 1. the sample size calculation.

- In which: N was the number of patients per group
  Z_1 is referred to a 95% confidence interval that was obtained 1.96
  Z_2 was the 80% test power factor that was equal to 84%
  S was an estimate of the mean, the standard deviation of changes in bone volume between the two groups
  d was the minimum difference between the mean changes in bone volume between the two groups, which shows a significant difference and is considered 0.9

Randomization

In this study, patients were selected based on the inclusion and exclusion criteria of two-digit codes from 10 to 30 and randomization was performed based on the lottery method. Assignment codes were written on paper and placed inside an envelope. One of the researchers picked up the written code without looking inside the envelope and was assigned to the control Group (A) or intervention Group (B) alternatively. After removing each code, to equalize the chances of all people, read code was replaced in

the envelope, and in case of re-picking up an assigned code, it was considered an empty option. It should be noted that all interventions in both Groups A and B except fibrin glue were quite similar. This study was registered under the code IRCT20210501051143N1 in the Iranian Registry of Clinical Trials system.

Presurgical examination

All patients in both groups were examined according to the mentioned criteria before entering the study. In addition, patients' information such as age, gender, medical and pharmacological history, allergies, sensitivities, and alveolar cleft side were assessed using a preprepared checklist.

Patients were also evaluated using the cone-beam computed tomography (CBCT) (Planmega, Helsinki, Finland) technique to determine the cleft volume before surgery. Before surgery, CBCT images were taken from patients' maxilla in axial and coronal views with a scan thickness of 0.5 mm in slices. Romexis software version 5.2.0 (Planmeca Romexis®) displayed and analyzed the data. A radiologist, unaware of the treatment type (blind), determined the size of the cleft volume before surgery and the amount of bone formation after surgery. To calculate the intra-observer error, each CBCT image was evaluated twice with an interval of 4 months. Defect volume was measured according to formula 2 (thickness 0.5 mm for axial sections):

$$\text{Volume} = \frac{\text{Sm of the area on axial plane}\left(\text{mm}^2\right) \times \text{defect vertical dimension on coronal plane}(\text{mm}^2)}{\text{the number of scan cuts}}$$

Formula 2. Cleft volume determination.

Surgery procedure

To perform surgery, all patients underwent general anesthesia and nasotracheal intubation. Topical injection of 2% lidocaine with epinephrine: 1: 100,000 was used to induce hemostasis and reduce intraoperative bleeding. The defect area was prepared intraorally utilizing a method called gingival flap adjuvant. The mucosa of the defect area was divided into nasal and oral parts. The nasal mucosa flaps were detached from the bony walls and sutured together to reconstruct the nasal floor. Then, the palatal mucous flaps were sutured, and the recipient substrate was prepared.

The iliac crest has been obtained from each patient for autologous graft through a standard incision [Figure 1a]. A cortico-cancellous bone fragment was removed from the iliac crest by an osteotome and a hammer according to approximate alveolar cleft size. After washing, the donor area was sutured in several layers [Figure 1b]. For Group A, the extracted bone fragment was divided into smaller pieces, placed inside the alveolar cleft, and closed. A cortical wall was placed under the nasal mucosa. On the other hand, the exact procedure has performed for Group B and fibrin glue (Evicel® [Quixil®/ Crosseal™] was sutured on the nasal mucosa and palatal mucosa, to prevent bacteria leakage.

Patients follow up

One week, 1 month, and 4 months after surgery, all patients were examined and re-evaluated. The sutures in the iliac region were removed 7–10 days after surgery in all patients. CBCT was taken 4 months after treatment. Then, the blind radiologist to treatment type determined the formation of the bone bridge and the volume of new bone formation (cm^3). The patient was followed up for the possibility of dehiscence, necrosis, and infection. The presence of an oronasal fistula at the trimester examination was considered a treatment defect. Criteria for treatment success were no cleft pus, no oronasal fistula, and stable bone grafting.

Statistical analysis

Data were analyzed using the SPSS software (IBM version 90, SPSS, Statistics, Chicago, IL, USA). Data distribution was measured using the Kolmogorov − Smirnov test. If it was normal, parametric tests and, otherwise, nonparametric equivalents were used. Paired *t*-test and Chi-square tests were used to analyze the data. Intraclass correlation coefficient and Pearson test were used to calculate the observer error. $P < 0.05$ was considered statistically significant thresholds.

RESULTS

Demographic and routine examination

According to obtained data, the control group consisted of six males and four females with a mean age of 10.2 ± 1.6 years old, and the fibrin glue group consisted of five males and five females with an average of 9.6 ± 1.34 years [Table 1]. No significant changes were observed regarding gender and age between the two groups ($P > 0.05$).

According to the results, tissue necrosis and infection rates after surgery were not observed in both Groups A and B. However, despite no dehiscence complications in patients treated with fibrin glue, one

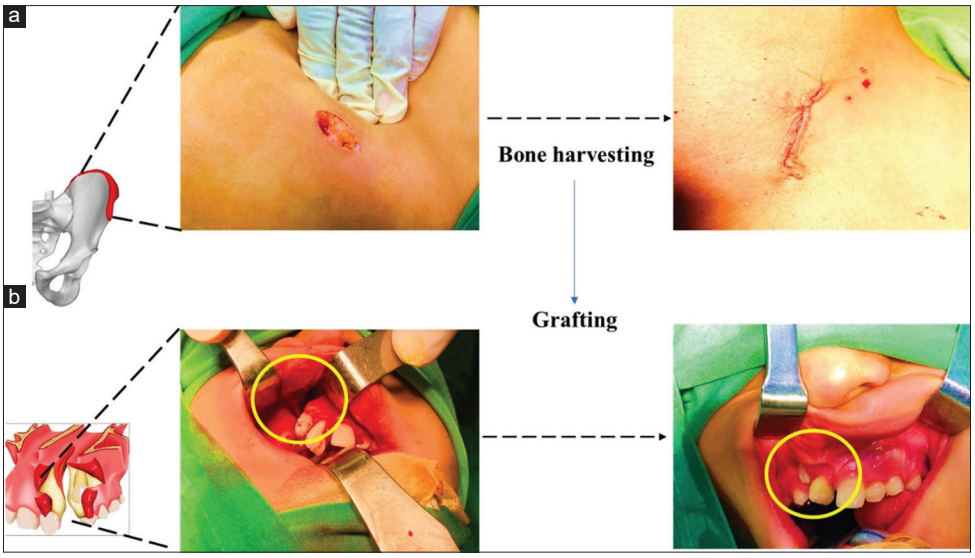

Figure 1: (a) Iliac crest harvesting and (b) cleft preparation and bone grafting of a 10 years male patient.

patient resembled dehiscence manifestation in the control group. Further follow-up revealed that it was repaired secondarily after 10 days.

Alveolar cleft volume evaluation

After the initial examination and using the CBCT technique, the volume of the alveolar cleft was evaluated. Figure 2 represents the CBCT images of the alveolar cleft in a 10-year male patient before and 4 months after surgery using fibrin glue groups. As shown in Table 2, the mean volume of the preoperative alveolar cleft in patients in the control Group (A) was 0.95 ± 0.25 cm^3, and in the fibrin glue (B) was 0.99 ± 0.22 cm^3 which was not significantly different ($P > 0.852$).

The mean alveolar cleft volume after surgery was 0.31 ± 0.10 cm^3 and 0.23 ± 0.11 cm^3 for the Group (A) and (B), respectively, which did not provide a significant difference ($P = 0.429$). The mean percentage of the bone formed was 66.7% ± 8.9% and 76.2% ± 11.4% of the initial cleft for Groups (A) and (B). Although these data were not statistically significant, they had boundary conditions ($P = 0.055$).

Linear regression analysis to evaluate the effect of fibrin glue on alveolar bone grafting showed that there was no significant difference between the two groups considering the initial volume of the alveolar cleft, surgical site position, and patient gender ($P = 0.07$).

DISCUSSION

A unilateral alveolar cleft may appear only as a small incision at the edge of the lip or extend into the nose

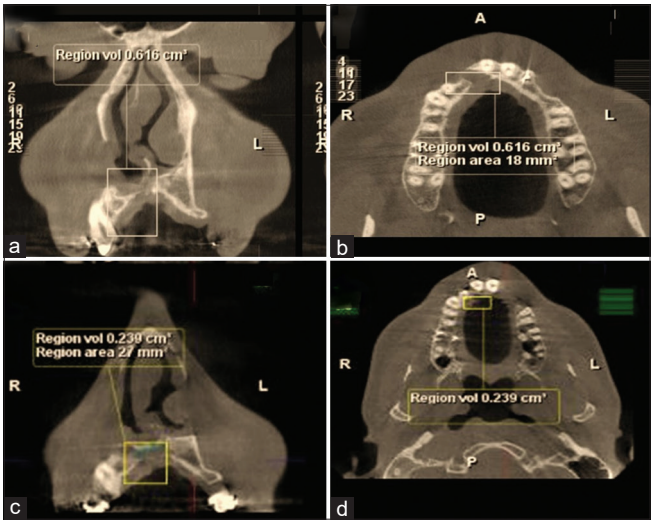

Figure 2: Cone beam computed tomography images of a 10-year-old male patient who underwent unilateral alveolar cleft surgery using fibrin glue. (a and b) the coronal and axial cuts before surgery and (c and d) the coronal and axial cuts after surgery, respectively.

or gums. It can also be associated with environmental factors such as women's use of certain medications, exposure to smoking, or deficiency of specific vitamins during pregnancy. However, the cause is unclear in most cases. In addition, this condition may lead to other problems, including nutritional issues, fluid retention in the middle ear and hearing loss, dental malformations, and speech problems. Therefore, predominant treatment of this complication seems very important, and in some cases, vital.[16-18] The present study aimed to evaluate the effect of fibrin adhesive on survival and clinical manifestations in patients with unilateral alveolar cleft after surgery.

Currently, the primary treatment for this complication is surgery and reconstruction of the area by bone grafting. In this procedure, the patient's bone is removed from various bone sources, mainly the iliac crest, and grafted to the alveolar fissure. Autogenous bone grafting in the alveolar cleft provides different benefits, including bone support for nonerupted teeth and adjacent cleft teeth, forming a continuous alveolar ridge to facilitate orthodontic treatment and supporting the nasal cavity floor and alar base to improve the beauty of the nose.[19] The results of bone grafts in patients with alveolar clefts can range from a very successful graft with partial reabsorption to a poor outcome with a small amount/lack of bone bridges. The results of our study showed that the formed bone filled about 66% and 74% of the initial cleft in the control and fibrin glue patients, respectively. Although the percentage of bone formation among the patients in the intervention group seemed higher than the control group, it was not statistically significant and had borderline conditions. Feichtinger *et al*.[20] assessed the volume changes of 24 patients with alveolar clefts over 3 years. Grafted bone was 49.5% absorbed in the 1st year and 52% in 3 years. An 8% increase in bone volume was reported. Therefore, it is reasonable to expect the grafted bone volume to change slightly over time due to the resorption process.[21] Based on our results, it can be concluded that fibrin glue may be effective in bone formation after the graft, although the differences were not significant.

In another study, Tan *et al*.[22] evaluated the effect of fibrin glue on reducing bone resorption. The researchers concluded that fibrin glue significantly reduces bone resorption and improves fusion and bond quality. The difference in their results with our results can be explained by differences in the method of fibrin glue, the number of samples, the differences in follow-up duration, and the examination method.

Fibrin glue is a particular biological material providing attractive properties for clinics, especially to improve bone grafting conditions. Fibrin glue mimics the final stages of coagulation and offers multiple advantages in alveolar cleft surgery, including adequate sealing of the sutures, declining possible wound infection, dehiscence, and tissue necrosis. In the present study, no complications, including dehiscence, tissue necrosis, and postoperative infection, were observed in the fibrin glue treatment patients. Mahmoodzadeh *et al*. showed the possible role of fibrin glue in reducing postoperative lymph leakage gastrectomy.[23] Tofuku *et al*. also investigated the effect of antibiotic-impregnated fibrin sealant (AFS) on preventing surgical site infections in the spinal cord. Their results showed that AFS has appropriate clinical outcomes in terms of the prevention of postoperative spinal infections. According to Wu *et al*., fibrin glue can promote cleft healing through enhance hemostasis and adhere tissues as a tissue sealant.[24] Fibrin glue also has excellent antibacterial effects. Numerous articles have reported the antibacterial effect of this substance against microorganisms. Therefore, according to these studies, it can be concluded that fibrin glue with its antibacterial effect to a large extent prevents infection at the surgical site.[25] This study also showed that patients treated with fibrin glue did not show any infection in subsequent follow-ups.[26] Compared to our research, it can be deduced that fibrin glue can prevent disease after surgery by.

On the other hand, complete nasal floor closure may be a fundamental challenge in surgery due to the maxilla anatomy and the lack of proper access to the surgical area during suturing. In this regard, fibrin sealant is widely used in neurosurgery to close the suture line, seal the suture site and prevent

Table 1: The demographic data of patients

Groups	Gender	Patients (number)	Cleft side		Age (year) (mean±SD)
			Right	Left	
Control (A)	Male	6	2	4	10.83±1.16
	Female	4	1	3	9.25±1.98
Fibrin glue (B)	Male	5	2	3	10.00±1.58
	Female	5	4	1	9.20±1.09

SD: Standard deviation

Table 2: The alveolar cleft volume before and after surgery

Evaluation time	Groups	Cleft volume (cm^3) (Mean±SD)	*P*	Bone formation (%)		*P*
				Control	Fibrin glue	
Before surgery	Control (A)	0.948±0.249	0.852	66.72±8.9	76.2±11.4	0.055
	Fibrin glue (B)	0.99±0.225				
After surgery	Control (A)	0.313±0.099	0.429			
	Fibrin glue (B)	0.228±0.112				

SD: Standard deviation

cerebrospinal fluid leakage.[14] Man *et al*. investigated the effect of autologous platelets and autologous fibrin glue in stopping capillary bleeding in the surgical flaps of patients undergoing cosmetic surgery. This group showed that despite the capillary bleeding in all cases, within 3 min after using platelet gel and fibrin glue, bleeding was effectively inhibited, and the so-called sealing occurred.[27] These results are entirely consistent with our study because our data showed that we did not have any significant bleeding or even bone resorption in patients treated with fibrin glue.

CONCLUSION

The present study results showed no significant difference in postoperative bone volume between the study and control groups. Furthermore, the percentage of bone formation compared to the initial failure was examined in both groups. The results showed an increase in the rate of bone formation in the fibrin glue group, although it was not statistically significant.

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Conflicts of interest

The authors of this manuscript declare that they have no conflicts of interest, real or perceived, financial or nonfinancial in this article.

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