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Original article

CANDIDA SPECIES AND POSTEXTRACTION ALVEOLAR SOCKET HEALING

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Abstract

Introduction: The oral microbiome plays a pivotal role in maintaining tissue homeostasis and regulating wound healing after tooth extraction.

Objective: To evaluate the association between preoperative oral *Candida* colonization and post-extraction wound healing, and to assess the effect of a regenerative oropharyngeal mouthwash.

Materials and methods: Thirty patients requiring routine tooth extraction were prospectively enrolled and allocated into two equal groups: a control group without perioperative mouthwash and an intervention group using Perio Plus Regenerate Mouthwash. Preoperative oral swabs were cultured on CHROMagar Candida for identification and quantification of *Candida* species. Postoperative outcomes included pain (VAS), edema, infection, hematoma, trismus, and clinical wound healing. Statistical analyses were performed using non-parametric and categorical tests with statistical significance set at $p<0.05$.

Results: Preoperative *Candida* colonization was detected in 63.3% of participants, with *Candida albicans* representing the predominant isolate. Patients with preoperative *Candida albicans* demonstrated significantly higher postoperative pain compared to patients without fungal colonization ($p=0.0459$). The perioperative use of the regenerative mouthwash was associated with a significant reduction in postoperative pain ($p=0.0052$), complete absence of postoperative edema among *Candida*-positive patients, and significantly greater vestibulo-oral wound closure three days after extraction ($p=0.0026$). In patients with preoperative *Candida* colonization, vestibulo-oral healing remained significantly improved in the mouthwash group ($p=0.011$). Postoperative infection, hematoma, and trismus occurred infrequently.

Conclusion: Preoperative oral colonization with *Candida*, particularly *Candida albicans*, appears to adversely influence early post-extraction healing and postoperative discomfort.

Keywords: oral microbiome, *Candida albicans*, extraction socket healing, oral candidiasis, biofilm, oral microbiology

Introduction

Tooth extraction is one of the most frequently performed invasive procedures in global dental surgery, necessitated by advanced caries, periodontal disease, and trauma. In developing nations, extraction rates represent a significant portion of daily clinical activity, reaching up to 33.40%[1,2].

Although a routine procedure, it entails a profound disruption of the oral mucosal barrier, transforming a stable environment into a high-risk surgical site. Under these conditions, the commensal microflora of the oral cavity-specifically opportunistic fungi-can transition into aggressive pathogens, leading to postoperative complications that jeopardize healing[3].

The healing of an extraction socket is a complex physiological process involving inflammatory, proliferative, and remodeling phases. Following the extraction of a tooth, the alveolar socket undergoes a series of coordinated events: clot formation, granulation tissue development, and eventually, osteogenesis[4].

Critically, the risk of post-extraction candidiasis is intrinsically linked to the host's systemic predisposition. While the baseline infection risk in healthy patients is approximately 10%, this figure escalates to 25% in immunocompromised individuals[6]. Systemic variables, including uncontrolled diabetes mellitus, HIV-AIDS, autoimmune disorders like Grave's disease, and even substance abuse, impair the innate immune response, allowing *Candida* to establish a foothold that leads to chronic wound stagnation or severe complications like mandibular osteomyelitis[5-8].

Unlike systemic health, local factors often play a more immediate role in dictating the speed and quality of tissue regeneration. Among these factors, the presence of fungal pathogens, specifically *Candida* species, has emerged as a significant variable that can stall secondary intention healing and contribute to complications such as alveolar osteitis[9,10].

However, the oral cavity is a non-sterile environment. The oral microbiome functions as a highly regulated ecological niche where eubiosis is maintained by a diverse consortium of commensal microorganisms. Under physiological conditions, beneficial bacteria (e.g., *Streptococcus mitis and Streptococcus sanguinis*) produce inhibitory molecules like hydrogen peroxide to suppress pathogens and maintain a neutral pH. The oral microbiome acts as a protective barrier, preventing the colonization of harmful pathogens and potential infections in the oral cavity[11,12].

While bacterial pathogens (like *Treponema denticola*) are frequently blamed for "dry socket," the fungal component-most notably *Candida albicans*-is often overlooked. Although *Candida albicans* is naturally present in 40-60% of the healthy adult population, it is highly opportunistic, causing infection when the host's defenses are compromised. Among the opportunistic agents, *Candida albicans* represents a primary clinical threat.

The transformation into a pathogenic state, or dysbiotic shift, is genetically regulated by the ROB1 allele and driven by environmental stressors (acid stress, inflammatory stress) rather than the mere presence of new "germs". This shift is not merely structural; the filamentous form secretes potent hydrolytic enzymes, such as secreted aspartyl proteinases, which degrade host tissues and facilitate deep invasion into the extraction socket. In conditions like gingivitis, the host's inflammatory response increases the flow of gingival crevicular fluid (GCF), providing a nutrient-dense substrate for proteolytic anaerobes[13,14].

The healing process of an extraction socket can be significantly impaired by the formation of a biofilm within the wound. This microbial community creates a physical barrier that reduces oxygenation and lowers the redox potential of the local environment. Such hypoxic conditions facilitate the colonization of obligate anaerobes, which harbor numerous virulence factors. These pathogens can disrupt the formation of the blood clot and trigger a prolonged inflammatory response, ultimately delaying tissue regeneration and increasing the risk of localized alveolar osteitis[15,16].

The pathogenicity of *Candida* is further amplified through its role as a "universal substrate" in biofilms. By consuming localized oxygen, *C. albicans* creates protected anaerobic niches that facilitate the proliferation of virulent bacteria such as *Porphyromonas gingivalis* and *Fusobacterium nucleatum*. These multispecies biofilms exhibit a structural resilience that renders them up to 50% more tolerant to conventional antimicrobial therapies compared to monomicrobial colonies[17].

The transition of *Candida* from a commensal yeast to a virulent hyphal form is driven by sophisticated cross-kingdom signaling, where bacterial quorum-sensing molecules and metabolic byproducts like lactic acid act as catalysts for fungal invasion. By providing a structural scaffold for bacteria, *Candida* facilitates the formation of highly resilient, multi-layered biofilms that exhibit enhanced antimicrobial resistance and accelerated tissue destruction within the oral cavity[18-21].

Successful healing of oral extraction sites depends heavily on maintaining microbial homeostasis. The development of microbial dysbiosis - specifically the proliferation of *Candida* species - represents a major impediment to physiological regeneration. Consequently, managing the oral microbiome is critical for preventing pathological outcomes. Given their prevalence, *Candida*-dominant biofilms are now considered central to the pathogenesis of impaired socket healing[22].

Aim

-To determine the possible influence of *Candida spp*. in the oral microbiome on the healing of extraction wounds, as well as the impact on postoperative morbidity and discomfort in patients.

- To determine the possible influence of the perioperative application of regenerative oropharyngeal solutions Perio Plus Regenerate Mouthwash (sodium hyaluronate 0.15%, chlorhexidine digluconate 0.09%) on the healing of extraction wounds and the reduction of the fungal load (microbial load).

Material and methods

The study sample included 30 patients in whom oral surgical intervention (routine tooth extraction) was indicated. All patients completed an anamnestic questionnaire: gender, age, medical status and comorbidities, reason/diagnosis for extraction and the location of the tooth. All participants provided signed informed consent prior to enrollment. Ethical Committee approval confirmation was obtained from the Faculty of Dentistry Teaching and Scientific Council (02-1859/1, 3.7.2023).

Participants were randomly allocated into group I and group II. Preoperative screening was performed–swabs were collected for *Candida* detection and inoculated on a chromogenic medium (Figure 1 and Figure 2).

Group I consisted of 15 patients, in whom extractions were performed without perioperative application of regenerative oropharyngeal solution (ORS).

Group II consisted of15 patients, in whom extractions were performed with perioperative application of regenerative oropharyngeal solution.

Patients in whom ORS was used for rinsing the oral cavity were trained to implement the protocol (10 ml solution, duration 60 sec, twice daily) preoperatively on the day of the intervention, 2 hours after the intervention and seven days postoperatively.



Fig. 1. Preoperative screening for *Candida spp.*

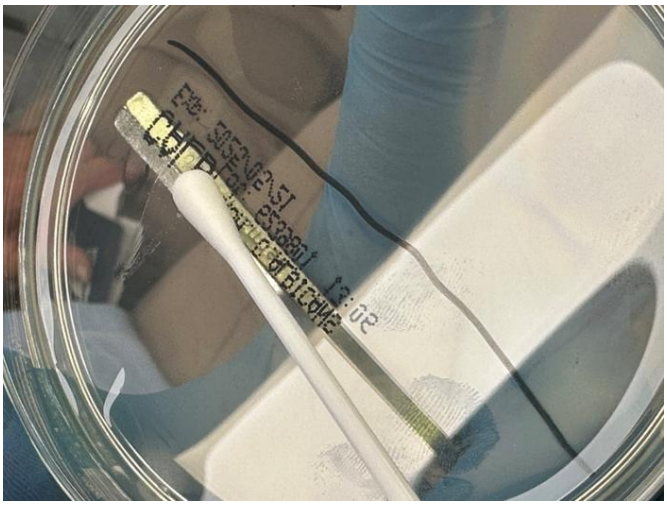

Fig. 2. CHROMagar Candida inoculation

The following clinical parameters were used to determine the postoperative course in patients and were noted postoperatively:

a) Pain

Pain was assessed using a visual analog pain scale (VAS). Patients themselves indicated their pain intensity, ranging from no pain to very severe pain by placing a perpendicular mark (dash) on a 10 cm (100 mm) horizontal or vertical line. Patients did no see the numerical scores that were used exclusively by the therapist (researcher) to numerically quantify the subjective assessment of the patients. Pain intensity was classified as follows: no pain (0-4 mm), mild pain (5-44 mm), moderate pain (45-74 mm) and very severe pain (75-100 mm).

b) Presence of infection, hematoma and edema

Postoperative edema in patients who underwent routine tooth extraction was classified into 3 categories: absence of edema, minor edema, moderate edema and severe edema.

Postoperative edema was determined by analyzing the area located between the line starting from the corner of the mouth and the tragus and the intersection with the line between the outer corner of the eye and the angle of the lower jaw: 0 (absence); + (weak up to 1 cm); ++ (moderate up to 2 cm); +++ (larger than 2 cm);

c) Presence of postoperative trismus according to Ngyene *et al*.

The distance between maxillary and mandibular incisors was measured, with the following grades noted:

0 - >40 mm – no trismus

1 - <40 mm – trismus is present

d) no presence of alveolar osteitis (alveolitis sicca, alveolitis humida).

e) The quality and intensity of clinical healing of post-extraction wounds were assessed by monitoring the dynamics of tissue epithelialization (partial/complete) with a Hy-Friedy periodontal probe in two directions: mesio-distal and vestibulo-oral interepithelial distance at two time points: at zero time after the intervention and 3 days after the intervention (Fig. 3 and Fig. 4).

Laboratory microbiological examinations were performed in the laboratory of the Faculty of Dentistry in Skopje and the mycological laboratory at the Institute of Microbiology and Parasitology at the Faculty of Medicine in Skopje.

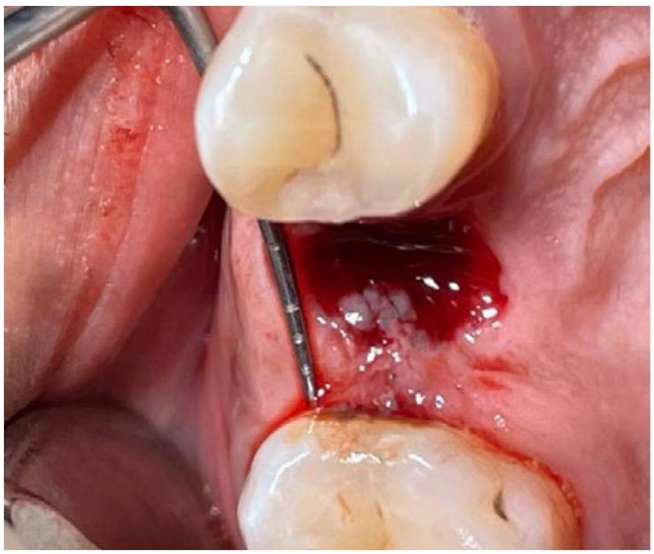

Fig. 3. Mesio-distal interepithelial distance



Fig. 4. Vestibulo-oral interepithelial distance

Laboratory - Microbiological tests

For the analysis of the composition of the fungal microbiome, oral swabs were collected from each patient before extractions using a sterile cotton swab, inoculated on a chromogenic medium (CHROMagar Candida) and incubated at a temperature of 37°C within a period of 48 hours (Biobase Constant-Temperature Incubator, BJPX-H30II), in the biochemical laboratory at the Faculty of Dentistry in Skopje. After the incubation period of 48 hours, the culture media were examined (color and morphology analysis, i.e. the macroscopic appearance of the colonies) and the corresponding results were interpreted. The growth of *Candida albicans* was manifested by the presence of medium-sized protruding colonies with a smooth surface, with flat edges, with a dark green to metallic green or turquoise color, while the growth of non-albicans *Candida* species was determined by the finding of medium-sized colonies that can vary in color from light to light pink or light cream, with a rougher consistency, and uneven edges, most often with a flattened surface of the colonies. Positive samples with yeast growth were further analyzed in the mycology laboratory at the Institute of Microbiology and Parasitology, Faculty of Medicine, Skopje. The macromorphological and biochemical properties were analyzed and the number of colonies of the yeasts grown on the nutrient media was quantitatively determined. For this purpose, a sample taken with a swab was suspended in a universal sterile container, with 10 ml of sterile physiological solution. All samples were concentrated (10-fold) by centrifugation at 1700 g for 10 min. The precipitate was resuspended in 1 ml of sterile physiological solution and centrifuged for 30 seconds to obtain a concentrated sample. One full layer of this sample was inoculated onto the surface of the chromogenic yeast medium, which was incubated under aerobic conditions at 37°C for 48 hours. The number of yeast colonies was categorized as 0-absent, 1-very sparse (<10 CFU/ml), 2-sparse (10-100 CFU/ml), 3-moderate (100-1000 CFU/ml), 4-rich (>1000 CFU/ml).

Statistical analysis

SPSS software package, version 26.0 for Windows was used for data processing. Pearson Chi square test, Fisher Freeman Halton Exact test and Fisher exact test were used to determine the association between certain qualitative nominal and ordinal parameters. Risk factors were quantified using Odd ratio (OR) and confidence intervals (CI). The difference between proportions was tested with Percentage Difference test. For the analysis of quantitative parameters, measures of central tendency (mean, median, minimum and maximum values) and measures of dispersion (standard deviation) were used. The Shapiro-Wilk W test revealed a non-normal frequency distribution for age ($p=0.4929$), mesiodistal distance ($p=0.0470$) and vestibulo-oral distance ($p=0.0084$). Mann Whitney U test was used to test the significance of the difference between quantitative parameters. The Wilcoxon signed rank test was used to compare the groups with/without oropharyngeal regenerative disorder (ORD) in terms of mesiodistal and vestibulooral distance at two time points (zero time before the intervention and 3 days after the intervention). Two-sided analysis of variance was used for statistical significance, with a significance level set at $p<0.05$.

Results

The study included 30 patients with typical tooth extraction. According to the use of oropharyngeal regenerative mouthwash (Perio Plus Regenerate Mouthwash), the patient sample was divided into 2 groups, each one comprising 15 patients.

Sample characteristics

From all 30 patients, 16(53.33%) were male and 14(46.67%) were femalepatients. The group that did not receive ORS included 7(46.67%) male and 8(53.33%) female patients, with a gender ratio of 0.87:1. In the group receiving ORS, the distribution of males and females was

9 (60%) *vs*. 6 (40%) respectively, with a gender ratio of 1.5:1. No significant association was found between gender and the group allocation (Pearson Chi Square test: X^2=0.535; df=1; p=0.4642) (Table 1).

The average age of patients was 54.00±19.09 years with a min/max age of 20 to 83 years, and 50% of patients were aged ≤56.5; the median age was IQR=56.5 (40-71). The average age of patients in the group without ORS was 58.93±14.52 years, and 50% of them were aged ≤62; the median age was IQR=62 (48-71). In the group that did not receive ORS, the average age was 49.07±22.18 years, and 50% of patients were aged ≤50; the mMedian age IQR=50 (26-72). There was no significant difference in age between the two groups of patients (Mann-Whitney U Test: Z=1.078; p=0.2808). Additionally, no significant difference was found in age between genders (Mann-Whitney U Test: Z=0.977; p=0.3286) (Table 1).

In the entire sample, 20(66.67%) maxillary and 10(33.33%) mandibular teeth underwent routine extraction, and the distribution was identical in the groups without/with ORS -10(66.67%) *vs*. 5(33.33%) (Table 1).

Regarding comorbidities, hypertension was present in 4(26.66%) *vs*. 3(20%) patients without/with ORS, respectively. Diabetes was present in only 3(20%) patients in the group with ORS (Table 1).

Table 1. Sample characteristics by groups and selected parameters

Parameters	Groups Without oropharyngeal solution[1] N (%)	Groups With oropharyngeal solution[1] N (%)	Total N (%)
Gender			
Male	7(46.67%)	9(60%)	16(53.33%)
Female	8(53.33%)	6(40%)	14(46.67%)
p	p=0.4642		
Age			
Mean±SD	58.93±14.52	49.07±22.18	54.00±19.09
Min/Max	32/82	20/83	20/83
Median (IQR)	62(48-71)	50(26-72)	56.5(40-71)
p	p=0.3286		
Position			
Maxilla	10(66.67%)	10(66.67%)	20(66.67%)
Mandible	5(33.33%)	5(33.33%)	10(33.33%)
Comorbidities			
Hypertension	4(26.66%)	3(20%)	7(23.33%)
Diabetes	0(0%)	2(13.33%)	2(6.67%)

[1]oropharyngeal solution Perio Plus Regenerate Mouthwash, *significant for p<0.05

Preoperative microbiological finding of Candida

Preoperative microbiological analysis indicated a negative finding of *Candida* in 11 (36.67%) patients. A positive preoperative finding was found in 19(63.33%) patients, out of which *Candida albicans* was isolated in 11(57.89%) and *Candida* species in 8(41.11%), with no significant percentage difference in the presence of the two isolates (Difference test: p=0.3071) (Table 2).

The distribution of preoperative *Candida* findings in the group without/with oropharyngeal mouthwash was 11(73.33%) *vs*. 8(53.33%), respectively, with no significant association between group allocation and the presence of *Candida* (Pearson Chi Square test: X^2=1.291; df=1; p=0.2557) (Table 2).

Table 2. Sample characteristics by groups without/with oropharyngeal solution and preoperative microbiological finding of *Candida*

Preoperative microbiological findings	Groups Without oropharyngeal solution[1] N (%)	Groups With oropharyngeal solution[1] N (%)	Total N (%)
Microbiological finding of Candida			
Negative	4(26.67%)	7(46.67%)	11(36.67%)
Candida - positive	11(73.33%)	8(53.33%)	19(63.33%)
Total	15(50%)	15(50%)	30(100%)
p	p=0.2557		
Microbiological findings of Candida species			
Negative	4(26.67%)	7(46.67%)	11(36.67%)
Candida albicans	9(60%)	2(13.33%)	11(36.67%)
Candida species	2(13.33%)	6(40%)	8(26.66%)
Number of Candida colonies			
No	4(26.67%)	7(46.67%)	11(36.67%)
Very low (<10 CFU/ml)	1(6.67%)	2(13.33%)	3(10%)
Low (10-100 CFU/ml)	8(53.33%)	6(40%)	14(46.67%)
Moderate (>100-1000 CFU/ml)	2(13.33%)	0(0%)	2(6.67%)

[1]oropharyngeal solution Perio Plus Regenerate Mouthwash, *significant for p<0.05

Preoperative *Candida* findings were present in 10(62.10%) male patients *vs*. 9(64.29%) female patients, with no significant association between gender and the presence of *Candida* (Pearson Chi Square test: X^2=0.011; df=1; p=0.9193).

Additional analysis indicated that in the groups without/with ORS, 9(60%) *vs*. 2 (13.33%) patients had a positive preoperative finding of *Candida albicans*. Other *Candida* species were preoperatively detected in 2(13.33%) and 6 (40%) patients, respectively (Table 2). Three (33.33%) patients with hypertension in the group without ORS and 1(50%) in the group with ORS had a positive preoperative finding of *Candida albicans.* In addition, among patients with a positive preoperative finding of *Candida* species, 1(50%) patient *vs*. 2(33.33%) patients had hypertension in the group without/with ORS, respectively. One of the patients with a positive preoperative finding of *Candida* species in the ORS group had diabetes.

Preoperative microbiological findings of Candida colonies and species

Of the 11 preoperative isolates for *Candida albicans*, 3(27.27%) had a very low number of colonies (<10 CFU/ml), 6(54.55%) had a low number of colonies (10-100 CFU/ml), and 2(18.18%) had a moderate number of colonies (100-1000 CFU/ml). In all 8(100%) patients

Table 3. Sample characteristics according to preoperative microbiological findings and number of *Candida* colonies

Parameters	Preoperative microbiological findings		
	Negative	*Candida albicans*	*Candida* species
Number of Candida colonies			
No	11 (100%)	0 (0%)	0 (0%)
Very low (<10 CFU/ml)	0 (0%)	3 (27.27%)	0 (0%)
Low (10 – 100 CFU/ml)	0 (0%)	6 (54.55%)	8 (100%)
Moderate (>100 – 1000 CFU/ml)	0 (0%)	2 (18.18%)	0 (0%)
Total	11 (36.67%)	11 (36.67%)	8 (26.66%)

*significant for p<0.05

with preoperatively isolated *Candida* species, the number of colonies count was low (10-100 CFU/ml). Preoperative microbiological screening detected no patients with a high number of *Candida* isolates (>1000 CFU/ml) (Table 3).

Clinical manifestations

In the postoperative period of patients who underwent routine tooth extraction, 5 selected clinical parameters were monitored: pain, edema, trismus, hematoma, and infection.

TRISMUS-Trismus as a potential clinical manifestation in the postoperative period was not registered in any of the patients in the sample.

INFECTION-The presence of infection was registered in only 1 patient with routine tooth extraction. A 71-year-old woman with a maxillary tooth location, with a preoperative finding of *Candida albicans* with a very low number of colonies (10-100 CFU/ml), who was in the group without ORS, had postoperative mild pain, no trismus, no edema and no comorbidities.

HEMATOMA-The presence of a hematoma was observed in only 1 patient with routine tooth extraction. A 72-year-old woman with a mandibular tooth position, with a preoperative finding of *Candida albicans* with a moderate number of colonies (>100-1000 CFU/ml), who was in the group without ORS, had postoperative mild pain, moderate edema, no trismus, no infection and no present comorbidities.

EDEMA – Postoperative edema in patients with routine tooth extraction was classified into 4 categories: no edema, minor edema, moderate edema, and severe edema. None of the patients had severe edema postoperatively. The analysis was performed according to selected parameters for the entire sample as well as according to the application of ORS.

PAIN-Postoperative pain in patients undergoing routine tooth extraction was determined on a VAS scale and classified into 4 categories: no pain, mild pain, moderately strong pain, and very severe pain. The analysis was performed according to selected parameters for the entire sample as well as according to the application of ORS (Table 4).

Pain/gender-No postoperative pain was observed in 12(75%) men and 8(57%) women, and mild pain was experienced by 4(25%) men and 4(28.58%) women. Moderately strong and very severe pain was experienced by 1(7.14%) woman, whereas no men reported such pain. Overall, 3(10%) patients who declared mild pain were with hypertension and 1(3.33%) with diabetes. There was no significant association between patient gender and the presence/absence of pain using the Fisher exact test: p=0.4421 (Table 4).

Pain/position of extracted tooth-Among patients with a maxillary position of the extracted tooth, 14(70%) were pain-free, in 5(25%) patients the pain was mild, and 1(5%) patient reported very severe pain. Among patients with a mandibular position of the extracted tooth, 6(60%) had no pain, 3(30%) had mild pain, 1(10%) had moderately strong pain, and none of the patients experienced very severe pain. No significant association was found between the location of the extracted tooth (maxilla/mandible) and the presence/absence of pain (Fisher exact test: p=0.6904) (Table 4).

Pain/oropharyngeal regenerative solution-In the group of patients receiving ORS, 14 (93.33%) reported no pain in comparison with 6(40%) patients in the group without this solution. Only 1(6.67%) patient receiving ORS reported mild pain, while in the group without this solution, 7(46.67%) patients had mild pain, and 1(6.67%) patient had moderately strong or very severe pain. A significant association was found between the postoperative use of ORS and the absence of pain (Fisher exact test: p=0.0052) (Table 4).

Pain/preoperative microbiological finding for *Candida*-None of the patients with extracted teeth who had a negative preoperative microbiological finding-11(100%) had postoperative pain. Among patients with a positive *Candida* finding, 9(47.37%) had no

postoperative pain, 8(42.11%) had mild pain, and 1(5.26%) had moderately strong or very severe pain (Table 4).

Pain/preoperative microbial types of *Candida*-Among patients with preoperatively isolated *Candida albicans*, 3(27.27%) patients reported no postoperative pain, 5(54.55%) had mild pain, and 1(9.09%) patient was with moderately strong or very severe pain. Among patients with preoperatively isolated *Candida* species, 6(75%) patients had postoperative pain, and 2(25%) had mild pain. In this group, none of the patients had moderately strong or very severe postoperative pain (Table). There was a significant association of preoperative finding of *Candida albicans* with the presence of postoperative pain (Fisher exact test: p=0.0459) (Table 4).

Pain/preoperative microbiological finding of *Candida* colonies-Among patients with preoperatively very low number of *Candida* colonies (<10 CFU/ml), 2(66.67%) had no postoperative pain and 1(33.33%) had mild pain. Among patients with preoperatively low number of *Candida* colonies (10-100 CFU/ml), 7 (50%) had no pain, 6 (42.86%) had mild pain, and 1(7.14%) had moderately strong pain. None of the patients with a low number of *Candida* colonies had very severe pain. Among patients with preoperatively moderate number of *Candida* colonies (100-1000 CFU/ml), 1(50%) patient reported mild postoperative pain, while another patient (50%) reported very severe pain (Table 4).

Table 4. Postoperative pain intensity according to selected parameters in patients with typical tooth extraction

Parameters	Pain intensity			
	No	Mild	Moderate strong	Very severe
Gender				
Male (N=16)	12(75%)	4(25%)	0(0%)	0(0%)
Female (N=14)	8(57.14%)	4(28.58%)	1(7.14%)	1(7.14%)
p	no/yes: p=0.4421			
Position				
Maxilla (N=20)	14(70%)	5(25%)	0(0%)	1(5%)
Mandible (N=10)	6(60%)	3(30%)	1(10%)	0(0%)
p	no/yes: p=0.6904			
Group				
Without ORS[2] (N=15)	6(40%)	7(46.67%)	1(6.67%)	1(6.67%)
With ORS[2] (N=15)	14(93.33%)	1(6.67%)	0(0%)	0(0%)
p	no/yes: p=0.0052*			
Preoperative microbiological finding of Candida[1]				
Negative (N=11)	11(100%)	0(0%)	0(0%)	0(0%)
Positive (N=19)	9(47.37%)	8(42.11%)	1(5.26%)	1(5.26%)
Preoperative microbiological findings of Candida types[1]				
Negative (N=11)	11(100%)	0(0%)	0(0%)	0(0%)
Candida albicans (N=11)	3(27.27%)	6(54.55%)	1(9.09%)	1(9.09%)
Candida species (N=8)	6(75%)	2(25%)	0(0%)	0(0%)
p	[1]no/yes: p=0.0459*			
Number of Candida colonies [1]				
No (N=11)	11(100%)	0(0%)	0(0%)	0(0%)
Very low (<10 CFU/ml) (N=3)	2(66.67%)	1(33.33%)	0(0%)	0(0%)
Low (10-100 CFU/ml) (N=14)	7(50%)	6(42.86%)	1(7.14%)	0(0%)
Moderate (>100-1000 CFU/ml) (N=2)	0(0%)	1(50%)	0(0%)	1(50%)

[1]*Candida albicans*/ *Candida* species; [2]ORS-oropharyngeal regenerative solution, *significant for p<0.05

EDEMA-Postoperative edema in patients with routine tooth extraction was classified into 3 categories: no edema, minor edema, moderate edema, and severe edema. In the postoperative period, none of the patients had severe edema. The analysis was performed according to selected parameters for the entire sample as well as according to the application of ORS (Table 5).

Preoperative Candida findings and edema size

The intensity of postoperative edema was analyzed in samples with a preoperative positive microbiological finding for *Candida* from both groups without/with ORS administration according to selected parameters (Table 5).

Table 5. Postoperative edema size in typical tooth extraction with preoperative *Candida* findings according to selected parameters

Parameters	Size of edema[3]		
	None	Minor	Moderate
Candida[1] & ORS			
Without ORS[2] (N=11)	8(72.7%)	2(18.2%)	1(9.1%)
With ORS[2] (N=8)	8(100%)	0(0%)	0(0%)
Candida[1] & Position Maxilla			
Without ORS[2] (N=6)	5(83.3%)	1(16.7%)	0(0%)
With ORS[2] (N=5)	5(100%)	0(0%)	0(0%)
Candida[1] & Position Mandible			
Without ORS[2] (N=5)	3(60%)	1(20%)	1(20%)
With ORS[2] (N=3)	3(100%)	0(0%)	0(0%)
Candida[1] & Male			
Without ORS[2] (N=5)	5(100%)	0(0%)	0(0%)
With ORS[2] (N=5)	5(100%)	0(0%)	0(0%)
Candida[1] & Female			
Without ORS[2] (N=6)	3(50%)	2(33.3%)	1(16.7%)
With ORS[2] (N=3)	3(100%)	0(0%)	0(0%)

[1]Preoperative finding of *Candida albicans*/ *Candida* species, [2]ORS-oropharyngeal regenerative solution, *significant for $p<0.05$

Candida/ORS-Among patients with a preoperative *Candida* finding, 8(72.7%) patients from the group without ORS and 8(100%) from the group receiving ORS had no edema in the postoperative period. Minor or moderate postoperative edema was detected in 2(18.2%) *vs*. 1 (9.1%) patients, respectively in the group without ORS and no postoperative edema in the group with ORS. No patients with a positive preoperative *Candida* finding from both groups (without/with ORS) had severe edema (Table 5).

Candida/maxillary position-Among patients with a preoperative microbiological finding of *Candida* and a maxillary tooth extraction, 5(83.3%) patients in the group without ORS had no edema in the postoperative period, whereas 1(16.7%) patient had minor edemarespectively. All 5(100%) patients with a preoperative finding of *Candida* and a maxillary tooth location in whom ORS was administereddid not have edema in the postoperative period. No patients from both groups had moderate or severe postoperative edema (Table 5).

Candida/ mandibular position-Among patients with preoperative *Candida* findings and mandibular tooth extraction, 3(60%) patients without ORS had no edema in the postoperative period, as well as 3(100%) patients who received ORS. In the group without ORS, 1(20%) patient had minor and 1(20%) patient had moderate edema in the postoperative period (Table 5).

Candida/men-All men with preoperative *Candida* findings who underwent routine tooth extraction without postoperative edema belonged to both groups-with/without ORS, i.e. 5(100%) patients (Table 5).

Candida/ female-Among women with preoperative *Candida* findings who underwent routine tooth extraction, 3(50%) patients had postoperative edema in the group without ORS and 3(100%) patients in the group with ORS. Minor or moderate postoperative edema were detected only in the group without ORS, that is, 2(33.3%) *vs*. 1(16.7%) patients, respectively (Table 5).

Mesio-distal and vestibulo-oral distance at two time points by groups

Among patients with typical tooth extraction from both groups (with/without ORS), an analysis of the change in mesio-distol and vestibulo-oral distance was performed at two time points: at zero time of the intervention and 3 days after the intervention (Table 6 and Figure 1).

Intergroup-Mesio-distal distance: At time zero after the intervention, the mesio-distal distance in the group without ORS was 7.60±3.22 mm and was non-significantly greater compared to that in the group with ORS where it was 7.33±2.16 mm (Mann Whitney U test: Z=-3.111; p=0.7557). Three days after the intervention, the mesio-distal distance in the group without ORS was 5.13±2.92 mm and was non-significantly greater compared to that in the group with ORS where it was 3.93±1.28 mm (Mann Whitney U test: Z=0.829; p=0.4068). The difference in mesio-distal distance between the groups without/with ORS at time zero was 0.27 ±1.06 mm and was smaller compared to that 3 days after the intervention, when it was larger (1.20±1.64 mm) (Table 6 and Figure 1).

Table 6. Mesio-distal and vestibulo-oral distance at two time points

Parameters		Statistics					
		N	Mean± SD	Min/Max	Median (IQR)	Difference	p
Intergroup – Mesio-distal distance (mm)							
Zero	Without ORS	15	7.60±3.22	4/14	6(5-10)	0.27±1.06	Z=(-3.111; p=0.7557
	With ORS	15	7.33±2.16	3/11	8(6-9)		
3 days	Without ORS	15	5.13±2.92	2/12	4(3-6)	1.20±1.64	Z=0.829; p=0.4068
	With ORS	15	3.93±1.28	2/6	4(3-5)		
Intragroup – Mesio-distal distance (mm)							
Without ORS	Zero	15	7.60±3.22	4/14	6(5-10)	2.47±0.30	Z=3.4077; p=0.0006*
	3 days	15	5.13±2.92	2/12	4(3-6)		
With ORS	Zero	15	7.33±2.16	3/11	8(6-9)	3.40±0.88	Z=2.5842; p=0.0097*
	3 days	15	3.93±1.28	2/6	4(3-5)		
Intergroup – Vestibulo-oral distance (mm)							
Zero	Without ORS	15	7.13±2.67	4/14	7(5-9)	0.33±0.66	Z=0.207; p=0.8357
	With ORS	15	6.80±2.01	4/12	7(5-8)		
3 days	Without ORS	15	5.13±1.92	3/9	5(4-6)	2.00±0.51	Z=3.007; p=0.0026*
	With ORS	15	3.13±1.41	1/7	3(2-4)		
Intragroup – Vestibulo-oral distance (mm)							
Without ORS	Zero	15	7.13±2.67	4/14	7(5-9)	2.00±0.75	Z=3.296; p=0.0009*
	3 days	15	5.13±1.92	3/9	5(4-6)		
With ORS	Zero	15	6.80±2.01	4/12	7(5-8)	3.67±0.60	Z=2.072; p=0.0383*
	3 days	15	3.13±1.41	1/7	3(2-4)		

Difference=zero-3 days; Mean-Average, SD-Standard Deviation, IQR-Interquartile Range, ORS-Oropharyngeal Regenerative Solution, Mann Whitney U test, Wilcoxon signed-rank test, *significant for p<0.05

Intragroup-Mesio-distal distance: In both groups, without/with ORS, 3 days after the intervention a significantly smaller mesiodistal distance was found compared to time zero immediately after the intervention (Mann Whitney U test: Z=3.4077; p=0.0006 *vs*. Z=2.5842; p=0.0097, respectively). In the group without ORS, the difference between the mesiodistal distance from time zero to 3 days after the intervention was 2.47±0.30 mm. This value was lower compared to that observed in the group receiving ORS where it was 3.40±0.88 mm (Table 6 and Figure 1).

Intergroup-Vestibulo-oral distance: At time zero after the intervention, the vestibulooral distance in the group without ORS was 7.13±2.67 mm and was non-significantly greater compared to that in the group with ORS, where it was 6.80±2.01mm (Mann Whitney U test: Z=0.207; p=0.8357). Three days after the intervention, the vestibulo-oral distance in the group without ORS was 5.13±1.92 mm and was significantly greater compared to that in the group with ORS, where it was 3.13±1.41 mm (Mann Whitney U test: Z=3.007; p=0.0026). The difference in vestibulooral distance between the groups without/with ORS at zero time was 0.33±0.66 mm and was smaller compared to the value 3 days after the intervention, when it was larger (2.00±0.51 mm) (Table 6 and Figure 1).

Intragroup-Vestibulo-oral distance: In both groups, without/with ORS, 3 days after the intervention a significantly smaller vestibular-oral distance was found compared to that at zero time after the intervention (Mann Whitney U test: Z=3.296; p=0.0009 *vs*. Z=2.072; p=0.0383, respectively). In the group without ORS, the difference between the vestibular-oral distance 3 days after the intervention compared to that at zero time was 2.00±0.75 mm and was smaller compared to the value in the group with ORS, where it was larger (3.67±0.60 mm) (Table 6 and Figure 1).

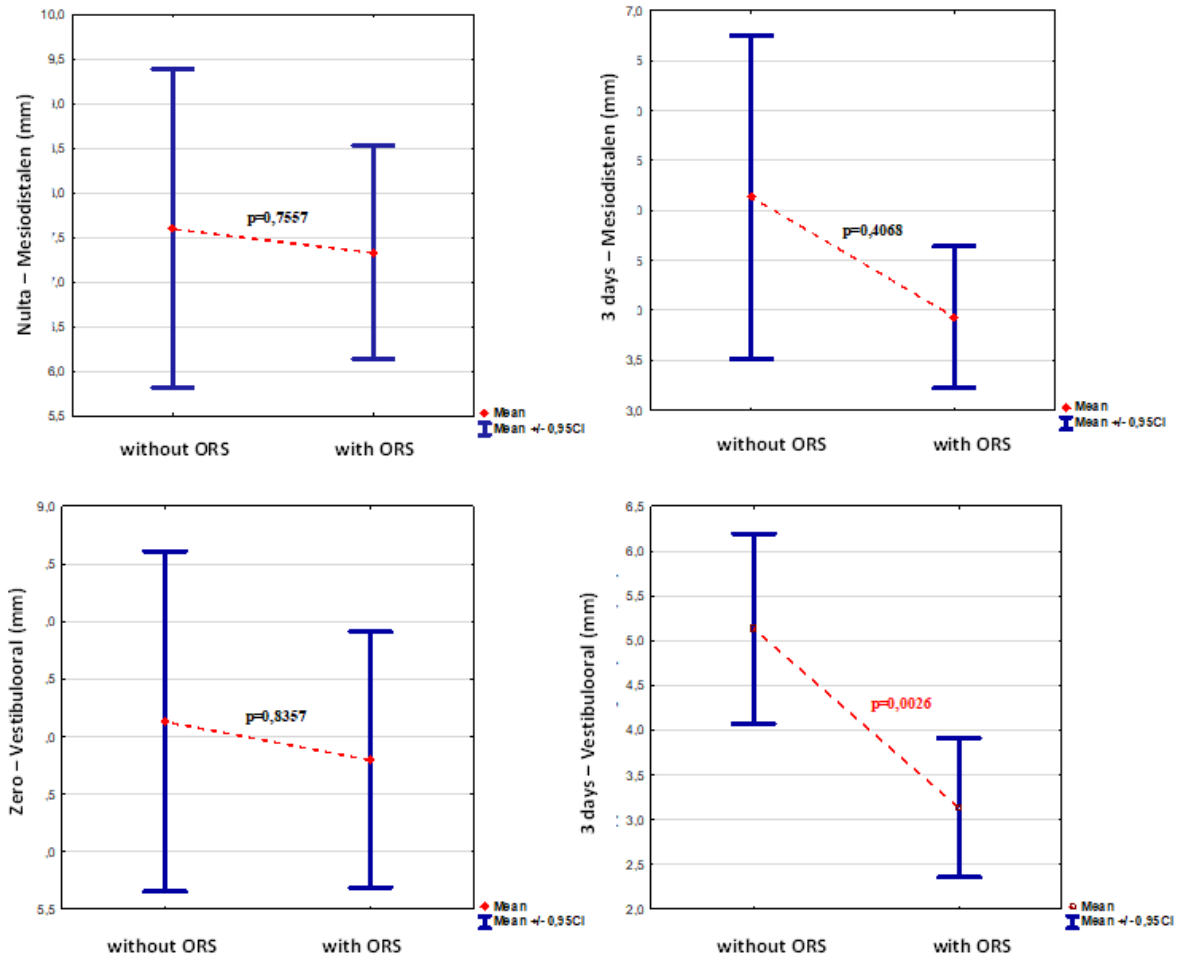

Fig. 1. Intergroup comparison (without/with ORS) of mesio-distal and vestibulo-oral distance at zero and 3 days after the intervention

Mesio-distal and vestibulo-oral distance at two time points according to *Candida* groups: In both groups of patients with preoperative *Candida* findings and typical tooth extraction (with/without ORS), a comparison of the mesio-diastal and vestibulo-oral distances was made at two time points: at zero time of the intervention and 3 days after the intervention (Table 7 and Figure 2).

Table 7. Mesio-distal and vestibulo-oral distance at two time points according to groups with *Candida*

Parameters		Statistics				p
		N	Mean± SD	Min/Max	Median	
Intergroup – Mesio-distal distance (mm)						
Zero	Without ORS & *Candida*	11	7.54±3.26	4/14	6	Z=-0.500; p=0.617
	With ORS & *Candida*	8	6.62±2.67	3/11	6.5	
3 days	Without ORS & *Candida*	11	5.27±3.32	2/12	4.0	Z=-1.179; p=0.238
	With ORS & *Candida*	8	3.50±1.19	2/5	3.5	
Intergroup – Vestibulo-oral distance (mm)						
Zero	Without ORS & *Candida*	11	7.36±2.91	4/14	7	Z=-0.884; p=0.377
	With ORS & *Candida*	8	6.12±1.73	4/9	5.5	
3 days	Without ORS & *Candida*	11	5.54±2.07	3/9	5	Z=-2.532; p=0.011*
	With ORS & *Candida*	8	3.25±0.89	2/4	3.5	

Mean-Average, SD-Standard Deviation, IQR-Interquartile Range, ORS-Oropharyngeal Regenerative Solution, Mann Whitney U test, *significant at p<0.05

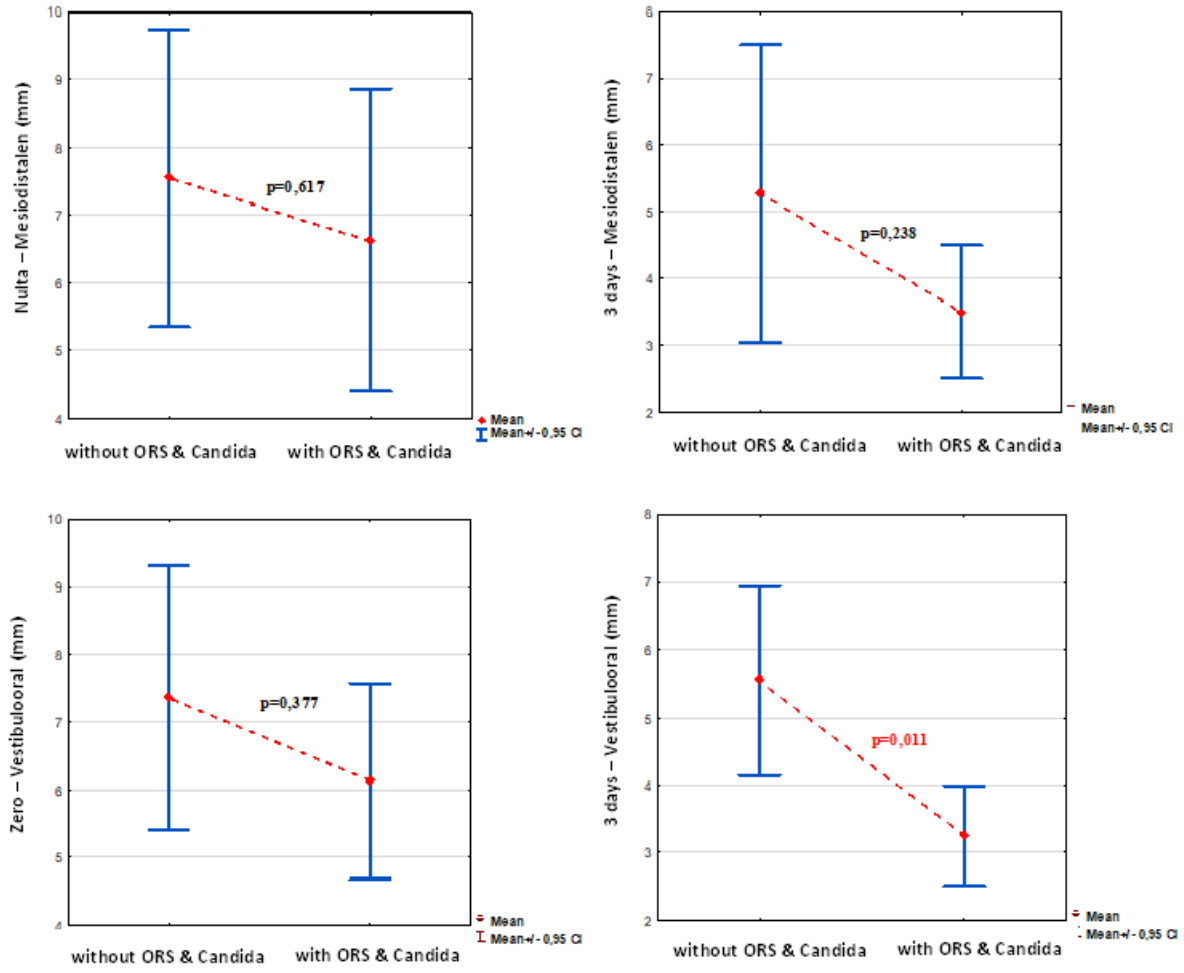

Fig. 2. Intergroup comparison (without/with ORS and *Candida*) of mesio-distal and vestibulo-oral distance at zero and 3 days after the intervention

Intergroup-Mesio-distal distance: At zero time, immediately after routine tooth extraction, the mesiodistal distance in the group without ORS and *Candida* was 7.54±3.26 mm. In the group with ORS and *Candida,* the distance was 6.62±2.67 mm. The difference was not significant (Mann Whitney U test: Z=-0.500; p=0.617). Three days after the intervention, the comparison of the two groups indicated a non-significantly greater mesiodistal distance in the group without ORS and *Candida* compared to ORS and *Candida* for 5.27±3.32 mm *vs*. 3.50± 1.19 mm, respectively (Mann Whitney U test: Z=-1.179; p=0.238). The mesio-distal distance between the two groups, without/with ORS and *Candida*, at zero time was 0.92±0.59 mm and was smaller compared to that 3 days after the interventio-(1.77±2.13 mm) (Table 7 and Figure 2).
Intergroup-Vestibulo-oral distance: At zero time, after routine tooth extraction, the vestibulo-oral distance in the group without ORS and *Candida* was 7.36±2.91 mm, and in the group with ORS and *Candida* it was 6.12±1.7 3 mm. The difference was not statistically significant (Mann Whitney U test: Z=-0.884; p=0.377). Three days after the intervention, the comparison of the two groups indicated a significantly greater vestibulo-oral distance in the group without ORS and *Candida* compared to that in the group with ORS and *Candida* (5.54 ±2.07 mm *vs*. 3.25±0.89 mm, respectively), (Mann Whitney U test: Z=-2.532; p=0.011). The vestibulo-oral distance between the two groups without/with ORS and *Candida* at zero time was 1.24±1.18 mm and was smaller compared to that 3 days after the intervention (2.29±1.18 mm) (Table 7 and Figure 2).

Discussion

The present study demonstrated that preoperative oral colonization with *Candida albicans* was associated with greater postoperative pain and may adversely influence early extraction socket healing. Furthermore, perioperative use of a sodium hyaluronate–chlorhexidine mouthwash significantly reduced postoperative pain, prevented postoperative edema in *Candida*-positive patients, and promoted faster vestibulo-oral epithelial closure. These findings suggest that the fungal component of the oral microbiome should be considered an important factor influencing the early healing response following tooth extraction.

Although *Candida albicans* is a common commensal microorganism of the oral cavity, disruption of microbial homeostasis may promote its transition into a pathogenic phenotype characterized by epithelial invasion, hyphal transformation, biofilm formation and persistent inflammation[9,10]. Recent evidence further emphasizes that oral health depends not only on the bacterial microbiome but also on the oral mycobiome, where *Candida* represents the predominant fungal species and actively interacts with oral bacteria to influence host immune responses and tissue homeostasis[25]. The significantly greater postoperative pain observed among *Candida*-positive patients in the present study supports the hypothesis that fungal dysbiosis may contribute to an exaggerated inflammatory response during early socket healing.

The interaction between *Candida albicans* and bacterial biofilms may further explain the clinical findings. Kilian *et al*., described the oral microbiome as a dynamic ecological community in which microbial imbalance contributes to oral inflammatory diseases[11]. Likewise, Montelongo-Jauregui and Lopez-Ribot demonstrated that *Candida albicans* forms polymicrobial biofilms with oral bacteria, resulting in enhanced microbial virulence, increased antimicrobial tolerance and prolonged inflammatory activity[20]. Although postoperative infection was uncommon in the present study, these polymicrobial interactions may explain the increased postoperative pain observed in patients with preoperative *Candida* colonization.

The beneficial effects of the sodium hyaluronate–chlorhexidine mouthwash observed in this study are consistent with previous reports demonstrating improved postoperative wound healing following oral surgery. Romero-Olid *et al*., reported in a recent systematic review and meta-analysis that chlorhexidine significantly improved oral wound healing and reduced postoperative complications after oral surgical procedures[23]. Similarly, Domic *et al*.,

concluded that hyaluronic acid enhanced soft tissue healing and decreased postoperative pain following tooth extraction through its anti-inflammatory and pro-angiogenic properties[24]. The significant reduction in pain and improved vestibulo-oral epithelial healing observed in the present study are therefore in agreement with current evidence supporting the combined use of antimicrobial and regenerative agents during the early stages of wound healing.

The present study has several limitations, including the relatively small sample size and short follow-up period limited to early soft tissue healing. In addition, fungal identification was performed using culture-based methods without molecular characterization of the oral mycobiome. Nevertheless, this study provides novel clinical evidence suggesting that preoperative *Candida albicans* colonization may represent an overlooked biological factor influencing early extraction socket healing. Future multicenter studies using molecular microbiome analysis are warranted to confirm these findings and determine whether preoperative assessment of the oral mycobiome may contribute to individualized perioperative management and improved healing outcomes following tooth extraction.

Conclusion

The findings of this study suggest that preoperative oral colonization with *Candida* species, particularly *Candida albicans*, may negatively influence early post-extraction wound healing by increasing postoperative pain and delaying soft tissue repair. Perioperative use of a regenerative mouthwash containing sodium hyaluronate and chlorhexidine significantly reduced postoperative pain, minimized edema, and promoted early epithelial healing, particularly among patients with *Candida* colonization. These results highlight the importance of considering the fungal component of the oral microbiome as a potential determinant of extraction socket healing and support microbiome-targeted perioperative management as an adjunctive strategy for improving clinical outcomes. Further randomized controlled studies with larger sample sizes are required to confirm these findings and establish evidence-based clinical protocols.

Conflict of interest statement. None declared.

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