

A comparative evaluation of the effects on postoperative pain of systemic and topical forms of benzydamine hydrochloride after periodontal flap surgery: A randomized controlled clinical trial

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Abstract

Objective: The aim of this study was to evaluate comparatively the topical and systemic forms in the postoperative pain control periodontal flap surgery in spite of the daily dose of benzydamine hydrochloride spray form about one in twenty of the oral dose,.

Materials and Methods: In this randomized trial, the 48 systemic healthy individuals in need double-blind study with periodontal flap surgery were evaluated. Consent, demographic information and periodontal clinical parameters were obtained before surgery and periodontal flap surgery was performed with local anesthesia. The patients who underwent surgery were randomly assigned to two groups. One of the groups was prescribed tablet form of postoperative benzydamine hydrochloride and for the other was spray form as topical application. Postoperative pain was assessed by visual analog scale at 2, 6, 8, 12, 24 and 48 hours.

Results: There was no difference between systemic and topical drug groups in terms of demographic characteristics and periodontal clinical parameters. A statistically significant difference was found between 2 and 6 hours in favor of topical application. ($p < 0.05$), but there was no significant difference in pain intensity at the 8th, 12th, 24th and 48th hours.

Conclusion: Although the topical form of benzydamine hydrochloride was 1/20 lower in postoperative pain control after periodontal flap surgery, it was found to be more effective in the early period compared to the systemic form, but equally effective in the late period. We premierly recommend that topical application should be preferred primarily in the prevention of overdose and toxicity in postoperative pain control after periodontal flap operation.

Keywords: Benzydamine hydrochloride, periodontal surgery, postoperative analgesia

Introduction

The basis of successful periodontal treatment is not only the appropriate surgical technique, but also the prevention and management of postoperative complications. Pain is one of the most common symptoms after periodontal surgery. Therefore, surgeons strive for an analgesic method that provides deep analgesia and is best tolerated by the patient, thereby ensuring patient compliance.

Postoperative pain is affected by surgical site, age, sex, premedication, anesthetic agent, administration of analgesia, patient psychology and environmental factors. In addition, each analgesic method has advantages-disadvantages, the area in which it is effective and the type of pain varies. The most pain is in the first 48 hours and different combinations can be used in this period (1).

Nonsteroidal antiinflammatory drugs (NSAIDs) are often sufficient to provide effective analgesia after minor and

major surgery. It can be administered in various ways including surgery, oral, parenteral, inhalation and transdermal (2,3).

Benzydamine hydrochloride (HCl) is an analgesic and NS antiinflammatory drug that can be used systemically and topically. The mechanism of antiinflammatory action of benzydamine HCl is achieved by blocking the biosynthesis of prostaglandins produced as an early response to tissue trauma by inhibition of arachidonic acid and cyclooxygenase enzyme. In addition, anti-inflammatory activity is achieved by mild inhibition of prostaglandin synthesis and strong inhibition of proinflammatory cytokines. Thus, TNF- α , IL-1 β and MCP-1 (such as monocyte chemoattractant protein) cytokines can be classified as a suppressive anti-inflammatory (4). As a result of these effects, it stabilizes the cell membrane and reduces vascular permeability. resolves edema (5).



As a result of these mechanisms, primarily antiinflammatory, as well as anti-edema, antipyretic, antitussive and muscle relaxant effects are revealed benzydamine HCl is effective in the symptomatic treatment of local acute (primary) inflammation as a result of soft tissue injury and many oral disorders such as aphthous ulcers and gingivitis (6,7).

Benzydamine HCl has gel preparations applied to the skin in soft tissues, skin and joints; dragee form in systemic doses, mouthwash form used for the treatment of inflammatory diseases of the mouth and throat region and oral spray form. It is completely and rapidly absorbed from the gastrointestinal tract. (7-9). The recommended single dose of the dragee form is benzydamine 0.7-1 mg / kg or one or two tablets. Each tablet is 50 mg.1

Benzydamine HCl Drageen contains 50 mg of active ingredient per dragee. One oral dose is 0.7-1 mg per kg. Patients are recommended to take 1 dragee on full stomach on average 3 times a day. The recommended daily dose is 150-200 mg. The course of treatment is three to five days.

Benzydamine HCl Spray contains 45 mg benzydamine HCl in 30 ml spray solution. One spray is 0.18 ml and contains 0.27 mg benzydamine HCl. Patients are advised to use an average of 4 sprayings at a time, 6 times in a day. The topical form (4 sprayings at a time: 1.08 mg; 6 times daily: 6.48 mg) is approximately one-twentieth of the oral dose. Therefore, it is envisaged that there is no systemic overdose and toxicity of the spray form.

In this study, it was aimed to determine which is more effective on postoperative pain comparatively after periodontal flap surgery that benzydamine hydrochloride, can be used either systemically or topically.

Material and Methods

This study is a randomized controlled study performed in the periodontology clinic of Karabük Dental and Oral Health Hospital. The study was explained to the patients, and informed consent was obtained. The study protocol was approved by the Institutional Ethical Committee of Karabük University, Turkey with date 08/12/2019, number 2019/54. Following the completion of Phase 1 therapy consisting of oral hygiene instructions and scaling and root planing, re-evaluation was performed after 4 weeks, after which forty-eight patients were enrolled in the study and were randomly assigned to systemic group and topical group by lottery method.

Study population

Forty patients who needed periodontal flap surgery in at least two interproximal regions on at least one side of the maxillary or mandibular arch were included in the study.

Inclusion criteria

- Patients aged between 23 and 64 years with moderate-to-severe chronic periodontitis
- Periodontal pockets >5 mm

- Systemically healthy patients fit for periodontal surgery
- Patients with good oral hygiene maintenance.
- Accepted to participate in the study,
- Has not received surgical or non-surgical periodontal treatment in the last 6 months,
- Individuals with sufficient mental health to read and understand questions

Exclusion criteria

- Patients with present or past systemic illnesses known to affect the outcomes of periodontal therapy
- Immunocompromised patients
- Patients taking medications that may interfere with periodontal therapy
- Pregnant patients
- Smokers.

Measurement of clinical parameters

The periodontal clinical parameters were evaluated to determine whether there was a clinical difference between the study groups.

Periodontal clinical parameters providing clinical evaluation of pathological changes in dental plaque deposition and periodontal soft tissues such as; Silness-Lee plaque index (PI), Lee-Silness gingival index (GI), pocket depth (CD), clinical attachment level (KAS) were used.

The PI, GI, CD, CAS were measured from 6 regions of the teeth (mesial, middle and distal regions of buccal / labial and lingual / palatal surfaces). According to PI defined by Silness and Loe, 0: no plaque; 1: the presence of plaque to be caught by the probe; 2: the presence of visible plaque; 3: excessive plaque deposition (14).

In the evaluation of GI also defined by Loe and Silness, 0: healthy gingiva; 1: mild inflammation and discoloration, no bleeding at probing; 2: moderate inflammation, hyperemia, bleeding at probing; 3: severe inflammation, hyperemia, ulceration, edema, spontaneous bleeding have been evaluated as present (15).

The CD measurement was recorded in millimeters by recording the distance between the gingival / mucosal edge and the periodontal pocket base; The measurement of AS was made by recording the distance between the enamel-cementum and the periodontal pocket base in millimeters.

CD and AS measurements, automatic periodontal catheter (Florida Probe®, version FP 32 / 7.2.2, diameter 0.45 mm, applying standard force (15 g) and measuring with 0.1 mm accuracy, Florida Probe Corporation, Gainesville, USA). The highest score was obtained from PI, GI, CD and CAS measurements in 6 regions. All measurements were performed by a single clinician.

Surgical procedure

Periodontal flap surgery was performed under local anesthesia. After surgery, patients were prescribed analgesic and antimicrobial agents. One group was prescribed tablet form (TANTUM® dragee, Santa Farma Ilac, Istanbul) for the systemic use of benzydamine hydrochloride as the analgesic and topical application of the spray form (TANTUM VERDE® spray, Santa Farma Ilac, Istanbul). The patients were randomly assigned to the groups.

Postoperative care

Postoperatively, all patients were prescribed with topical form (4 sprayings at a time, 6 times a day for 7 days) and systemic tablets (three times in a day for 5 days). The sutures were removed 1 week postoperatively. The surgical sites were gently cleansed with normal saline.

Measurement of pain intensity

Visual pain analog scale was used to evaluate postoperative pain. Visual Analogue Scale (VAS) is the most commonly used method for the evaluation of postoperative pain severity (16). According to this assessment, the meaning of the marked points from 0 to 10

(0 points no pain, 1-4 points mild pain, 5-6 points moderate pain, and 7 points severe pain) on a 10 centimeter line was explained to the patients. Patients were asked to record the severity of pain according to VAS at 2, 6, 8, 12, 24 and 48 hours postoperatively.

Statistical analysis

All statistical analyzes were performed using SPSS 22.0 statistical program in Windows software. The normality distribution of the data was evaluated using the Shapiro Wilk test. Variable relationships between the two groups were compared by Mann Whitney U test. Significance level was calculated as $p < 0.05$.

Results

Demographic and clinical parameters of the patients included in the study is given in Table 1. Of the 24 patients receiving systemic drugs, 41.7% (10/24) were males, 58.3% (14/20) were females. furthermore, 24.2% (24/24) men receiving topical drugs were male, 70.8% (17/24). / 20) women. While the mean age of the patients in the systemic drug group was 42.04 ± 9.48 , the topical group was 45.67 ± 9.43 . There was no statistically significant difference between the two groups in terms of gender and mean age.

According to Table 1, the mean PI value in the periodontal clinical parameters of the patients included in the study was 0.46 ± 0.059 mm, while in the systemic drug group and 0.50 ± 0.51 mm in the topical drug group. The mean GI value was 0.67 ± 0.70 , while in the systemic drug group and 0.46 ± 0.059 in the topical drug group. The mean CD value was 6.30 ± 1.08 , while in the systemic drug group and 6.46 ± 1.18 in the topical drug group. The mean value of CAS was 4.71 ± 0.73 , while in the systemic drug group and 5.52 ± 1.32 in the topical drug group. The mean values of PI, GI, CD and CAS were not statistically significant ($p > 0.05$).

Table 2 shows the distribution of the pain intensity of the patients in the topical and systemic groups according to the results of the time and scoring.

According to hours of pain intensity scores of the topical and systemic groups of benzydamine hydrochloride postoperatively results with Mann-Whitney U test are given in Table 3. When both groups were compared; The mean pain severity at the 2nd and 6th hours were lower in the topical group than the systemic group and the difference was statistically significant ($p < 0.05$). on the other hand, 8, 12, 24, 48. there was no statistically significant difference in pain sensation scores at postoperative hours ($p > 0.05$).

Table 1. Comparison of periodontal clinical parameters of study groups

Parameters	Groups	n(F/M)	Mean \pm standard deviation	p
Sex	Topical	24(14/10)		
	Systemic	24(17/7)		
Age	Topical	24	45.67 ± 9.43	.364
	Systemic	24	42.04 ± 9.48	
PI	Topical	24	0.50 ± 0.51	.670
	Systemic	24	0.46 ± 0.059	
GI	Topical	24	1.80 ± 4.15	.101
	Systemic	24	0.67 ± 0.70	
PD	Topical	24	6.46 ± 1.18	.690
	Systemic	24	6.30 ± 1.08	
CAL	Topical	24	5.52 ± 1.32	.890
	Systemic	24	4.71 ± 0.73	

Table 2. Table of distribution of pain intensity of study groups

Postop hours	Groups	Pain severity values on VAS											n
		0	1	2	3	4	5	6	7	8	9	10	
2nd hour	Topical	9	4	6	0	1	2	1	1	0	0	0	24
	Systemic	5	2	2	8	2	0	1	0	2	0	2	24
6th hour	Topical	11	6	0	1	3	0	1	0	2	0	0	24
	Systemic	5	2	5	4	2	1	1	0	0	2	2	24
8th hour	Topical	14	3	1	1	2	1	0	1	1	0	0	24
	Systemic	5	5	7	2	2	2	0	1	0	0	0	24
12th hour	Topical	15	2	4	1	1	0	1	0	0	0	0	24
	Systemic	8	6	6	0	1	2	0	1	0	0	0	24
24th hour	Topical	15	5	3	0	0	0	1	0	0	0	0	24
	Systemic	12	6	2	1	2	0	1	0	0	0	0	24
48th hour	Topical	17	2	3	2	0	0	0	0	0	0	0	24
	Systemic	15	3	3	2	0	1	0	0	0	0	0	24

Table 3. Comparison of the mean pain intensity of the study groups according to hours with Mann-Whitney U test table

Postop hours	Groups	n	Mean pain intensity \pm Standard deviation	P
2nd hour	Topical	24	1.80 \pm 2.11	.040
	Systemic	24	3.33 \pm 3.03	
6th hour	Topical	24	1.79 \pm 2.55	.035
	Systemic	24	3.38 \pm 3.23	
8th hour	Topical	24	1.50 \pm 2.40	.055
	Systemic	24	2.08 \pm 1.84	
12th hour	Topical	24	0.70 \pm 1.57	.101
	Systemic	24	1.63 \pm 1.88	
24th hour	Topical	24	0.96 \pm 1.33	.324
	Systemic	24	1.17 \pm 1.76	
48th hour	Topical	24	0.58 \pm 1.02	.538
	Systemic	24	0.83 \pm 1.34	

Discussion

In this study, we aimed to compare the effect of local and systemic use of benzydamine HCl on postoperative pain after periodontal flap surgery. Benzydamine hydrochloride, a molecule whose analgesic effect is proven in many studies, topical and systemic forms were used. Subjects were divided into two groups. Comparison of clinical characteristics of both groups with periodontal clinical parameters, postoperative pain was assessed by visual pain scale.

In the study results, when the periodontal clinical parameters were compared before surgery, there was no difference between the groups and the groups had similar characteristics (Table 1 for $p > 0.05$).

Benzydamine HCl was found to be effective in postoperative pain control after periodontal flap surgery, when topically used form and systemic effective tablet form compared to the effectiveness of pain, it was found to be more effective in the postoperative 2nd and 6th hours, ie in the early postoperative period. They were equally effective on postoperative pain in both forms at 8th, 12th, 24th, 48th hours, ie in the late postoperative period (Table 3 for $p < 0.05$).

Postoperative pain not only causes stress on the patient, but also prolongs the recovery period of the disease. Therefore, postoperative pain control is a subject that is continuously studied. Many agents have been used for postoperative pain control. Most of them have limited clinical use due to their potential serious side effects. The agent used for postoperative pain control in the clinic; It is expected to be effective, effect in a short time, not have side effects and be inexpensive (13,14).

Benzydamine hydrochloride is a nonsteroidal antiinflammatory drug that is antiinflammatory, local anesthetic, antipyretic, analgesic effect and can be used systemically and topically (15-18). Peeva et al. according to the results of their study, the use of local benzyadmin is effective in reducing local inflammation and pain by reducing especially prostaglandin and cytokine activity, in the postoperative period. and its postoperative use was recommended (17).

In their study of Cigerim and Eroglu, the analgesic-anti-inflammatory effect used after extraction of the patient's lower third molar was compared and it was shown that benzydamine hydrochloride had a similar effect with

diclofenac potassium and could be used as a non-steroidal anti-inflammatory analgesic drug (16). In a study by Peeva et al. reported that local benzydamine HCl used in tissue trauma after surgery in oral soft and bone tissues is effective in reducing postoperative pain and local inflammation (17). However, in the study of Goswami, stated that oral use of benzydamine hydrochloride does not reduce pain and is insufficient to alleviate pain in on pain after mandibular third molar extraction (18). In our study, in all patients using benzydamine HCl, 81.3% at the 2nd and 6th hours, 87.5% at the 8th hour and at the 12th hour, 91.7% of the patients had mild pain (pain level (1-4 points mild pain, 5-6 points moderate pain). There was no statistical difference between the two forms in achieving mild pain. As a result of this study, we can say that benzydamine HCl is highly effective in relieving postoperative pain after periodontal flap operation.

In postoperative care after periodontal flap surgery, antibiotic, analgesic and antimicrobial agents are needed. Benzydamine hydrochloride is effective in reducing pain and inflammation after surgical procedures in dentistry due to its antiinflammatory and analgesic effect at low doses and it has been reported to have some degree of antibacterial and antifungal activity (7).

The importance of rational drug use is spreading all over the world. In this context, it described as medicines appropriate to the clinical needs of patients, doses that meet personal requirements, for a sufficient period of time, use them with minimum cost to themselves and the society" (19-22). For this reason, medicines in sufficient quantities and in suitable dosage forms at any time should be preferred. In the literature, after periodontal flap surgery, benzydamine HCl has been reported that the capacity of condensation in inflamed tissues is good and potential systemic side effects are limited (20). In a study published in Allergy Journal, benzydamine HCl is a tolerable NSAID and has been demonstrated to be tolerable, and is a viable alternative in patients who are adversely affected by other NSAIDs (23).

In our study, we aimed to provide antiinflammatory, analgesic and antibacterial effects after periodontal surgery, as well as to reduce the number of drugs used and the daily dose taken. In the study results, benzydamine HCl is an effective agent on pain after periodontal flap surgery. Although the daily dose of topical spray form was 1/20, it was found to be more effective on early postoperative pain and equally effective on late pain.

Conclusion

In conclusion, the results of this study both topical and tablet form of benzydamine HCl are effective in reducing postoperative pain. In postoperative administration, the spray form provides better pain control than the tablet form. In the light of these data, topical form of benzydamine HCl may be a better alternative for pain after periodontal flap surgery.

Conflict of interest statement: The authors declare that there is no actual or potential conflict of interest.

Author's contrirbutions: **GK;** Design of research, data collection and Patient examinations, **GK;** preparation of article and revisions

Ethical issues: Author declare, originality and ethical approval of research. The study was conducted under defined rules by the Local Ethics Commission guidelines and audits.

References

1. Tramer MR, Williams JE, Carroll D, Wiffen PJ, Moore RA, McQuay HJ. Comparing analgesic efficacy of non-steroidal anti-inflammatory drugs given by different routes in acute and chronic pain: A qualitative systematic review.
2. Rosenow DE, Albrechtsen M, Stolke D. A comparison of patient-controlled analgesia with lornoxicam versus morphine in patients undergoing lumbar disk surgery. *Anesth Analg* 1998;86:1045-50. (PMID: 9585294)
3. Schug SA, Merry AF, Acland RH. Treatment principles for the use of opioids in pain of nonmalignant origin. *Drugs* 1991;42:228-39. (PMID: 1717222)
4. Griswold DE, Hillegass LM, Breton JJ, Esser KM, Adams JL. "Differentiation in vivo of classical non-steroidal antiinflammatory drugs from cytokine suppressive antiinflammatory drugs and other pharmacological classes using mouse tumour necrosis factor alpha production". *Drugs Exp Clin Res.* 1993; 19(6): 243-8
5. Nuutinen LS, Laitinen JO, Salomaki TE. A risk-benefit appraisal of injectable NSAIDs in the management of postoperative pain. *Drug Safety* 1993;9:380-93. (PMID: 8280405)
6. Moote C. Efficacy of NSAIDs in the management of postoperative pain. *Drugs* 1992; 44 Suppl 5:14-29. (PMID: 1284558)
7. Fanaki NH, El-Nakeeb MA, "Antimicrobial activity of benzydamine, a non-steroid antiinflammatory agent", *J. Chemother.*, 4, 1992, 347-352
8. Landry RG, Turnbull RJ, Howley T. Effectiveness of benzydamine HCl in the treatment of periodontal post-surgical patients. *Res Clin Forum* 1988; 10:105-117.
9. Mazzarella B, Macarone Palmieri A, Mastronardi P, Spatola R, Lamarca S, De Rosa G, et al. Benzydamine for the prevention of pharyngolaryngeal pathology following tracheal intubation. *Int J Tissue React* 1987; 9:121-129.
10. Silness J, L  e H. Periodontal Disease in Pregnancy II. Correlation Between Oral Hygiene and Periodontal Condition. *Acta Odontol Scand* 1964; 22(1): 121-135.
11. L  e H, Silness J. Periodontal Disease in Pregnancy I. Prevalence and Severity. *Acta Odontol Scand* 1963; 21(6): 533-551.
12. Chapman CR, Casey KL, Dubner R, et al. Pain measurement; an overview. *Pain* 1985;22:1-31.
13. Hempel V. Pyrazolones in the treatment of postoperative pain. *Agents Actions Suppl* 1986; 19:331-7. (PMID: 3463186)
14. Acar K, Acar H, Demir F, Eti Aslan F. Determining the incidence of postsurgical pain and amount of analgesic use postsurgical pain and analgesic. *ACU Saėlık Bil Derg* 2016;(2):85-91
15. Alalwani A, Buhara O, T  z  m M  . Oral health-related quality of life and the use of oral and topical nonsteroidal anti-inflammatory drugs for pericoronitis. *Med Sci Monit.* 2019;3;25:9200-9206. doi: 10.12659/MSM.918085.

16. Cigerim L, Eroglu CN. Comparison of clinical efficacies of preoperatively initiated naproxen sodium-codeine phosphate in combination, diclofenac potassium, and benzydamine hydrochloride for pain, edema, and trismus after extraction of impacted lower third molar: a randomized double-blind study. *J Oral Maxillofac Surg.* 2018 Mar;76(3):495-502. doi: 10.1016/j.joms.2017.08.041.
17. Peeva PM, Veleska DS, Apostolova G, Velickovski B, Koneski F. Local effects of using benzydamine in oral surgery. *Apolonia.* 2016.
18. Goswami D, Jain G, Mohod M, Baidya DK, Bhutia O, Roychoudhury A. Randomized controlled trial to compare oral analgesic requirements and patient satisfaction in using oral non-steroidal anti-inflammatory drugs versus benzydamine hydrochloride oral rinses after mandibular third molar extraction: a pilot study *J Dent Anesth Pain Med.* 2018 Feb;18(1):19-25. doi: 10.17245/jdpm.2018.18.1.19.
19. World Health Organization. The rational use of drugs. Report of the conference of experts. Nairobi, 25-29 November 1985. Geneva 1987.
20. World Health Organization. Revised procedures for updating the WHO Model List of Essential Drugs: a summary of proposals and process, May 2001; EB108/ INF.DOC./2.
21. World Health Organization. Model List of Essential Medicines. Seventeenth list, Mar 2011.
22. Maxwell S. Rational prescribing: the principles of drug selection. *Clinical Medicine* 2009; 9:481-485.
23. Nettis E, Di Paola R, Napoli G, Ferrannini A, Tursi A. Benzydamine: an alternative nonsteroidal anti-inflammatory drug in patients with nimesulide-induced urticaria. *Allergy.* 2002; 57(5), 442-445.