CURRENT THERAPEUTIC RESEARCH®
VOLUME 65, NO. 4, JULY/AUGUST 2004

Comparison of Benzydamine Hydrochloride and *Salvia officinalis* as an Adjuvant Local Treatment to Systemic Nonsteroidal Anti-Inflammatory Drug in Controlling Pain After Tonsillectomy, Adenoidectomy, or Both: An Open-Label, Single-Blind, Randomized Clinical Trial

Siniša Lalićević, MD, and Ivan Djordjević, MD

Department of Otorhinolaryngology, Clinical Hospital Center "Dr. Dragiša Mišović—Dedinje," Belgrade, Serbia and Montenegro

ABSTRACT

Background: Benzydamine hydrochloride (BNZD) is a nonsteroidal anti-inflammatory drug (NSAID) used in an oral rinse formulation as an adjuvant to other NSAIDs in controlling postoperative pain after tonsillectomy, adenoidectomy, or both. *Salvia officinalis* (SO) is a topically applied herbal preparation frequently used for the same indication. Pain, bleeding, and infection are the most common postoperative complications of tonsillectomy.

Objective: The aim of this study was to compare the efficacy and tolerability of BNDZ with those of SO as adjuvant treatments in controlling postoperative pain.

Methods: This open-label, single-blind, randomized clinical trial was conducted at the Department of Otorhinolaryngology, Clinical Hospital Center "Dr. Dragiša Mišović—Dedinje" (Belgrade, Serbia and Montenegro). Pediatric and adult patients undergoing tonsillectomy, adenoidectomy, or both were enrolled. Patients were randomized to receive BNZD or SO, in addition to ibuprofen 20 mg/kg·d (children) or diclofenac 100 mg/d (adults). The primary end point was the proportion of patients with mild or no pain on postoperative days 1, 2, 4, and 7. Secondary end points were the incidences of infection, hemorrhage, and other adverse events.

Results: A total of 420 patients were enrolled (217 females, 203 males; 278 children, 142 adults; mean [SD] age, 6.2 [2.1] years [children] and 24.1 [9.8] years [adults] [range, 3–45 years]). One hundred thirty-eight children received BNZD; 140 received SO (both in addition to ibuprofen 20 mg/kg·d). Seventy-two adults received BNZD; 70 received SO (both in addition to diclofenac 100 mg/d). A significantly lower proportion of children treated with adjuvant BNZD experienced moderate or severe pain than those treated with SO at each

Accepted for publication May 24, 2004.
doi:10.1016/j.curtheres.2004.07.002
0011-393X/04/$19.00

time point ($P < 0.01$ at days 1 and 4; $P < 0.001$ at days 2 and 7). In children, the risk for postoperative infection was similar between BNZD and SO (absolute risk reduction [ARR], 6.9%; 95% CI, 6.4%–7.6%); however, the risk was reduced in adults (ARR, 19.0%; 95% CI, 16.5%–21.9%; $P = 0.008$).

Conclusions: In this clinical trial of children and adults who underwent tonsillectomy, adenoidectomy, or both, BNZD, as an adjuvant to an NSAID, was more effective than SO in controlling postoperative pain and infection. The pain-reducing effect of BNZD was of quick onset and persisted for 1 week after surgery. The safety profile of BNZD was comparable to that of SO, with the exception of postoperative infection in adults, for which BNZD was more efficacious. In particular, the use of BNZD was not associated with a high risk for early postoperative hemorrhage. (*Curr Ther Res Clin Exp.* 2004;65:360–372)

Key words: benzydamine hydrochloride, *Salvia officinalis,* tonsillectomy, clinical trial, efficacy, safety.

INTRODUCTION

Diseases of the tonsils and adenoids are common conditions that are frequently treated surgically. Tonsillectomy is 1 of the 10 most commonly performed procedures in outpatient centers.[1]

Postoperative pain is the most common complication of the surgical procedure, followed by respiratory distress and airway obstruction, postoperative hemorrhage, and changes in speech that are usually temporary.[2,3] Infection following tonsillectomy is uncommon,[4] and nasopharyngeal stenosis, atlantoaxial subluxation, meningitis, depression, and death are extremely rare.[5–7]

Postoperative pain can be treated with systemic analgesic therapy in combination with local infiltration of anesthetics or local application of analgesics, although some investigators have been unable to show the effect of locally applied therapy.[8–11] Nonsteroidal anti-inflammatory drugs (NSAIDs) are used for pain relief following tonsillectomy[12] and may also reduce postoperative nausea and vomiting.[13] Most of the effects of NSAIDs may result from inhibition of prostaglandin synthesis. Prostaglandins appear to sensitize pain receptors to mechanical stimulation or other chemical mediators and to mediate inflammatory effects and the effect of endogenous pyrogen in the hypothalamus.[14] However, NSAIDs reversibly inhibit thromboxane A_2 production and therefore inhibit platelet aggregation and prolong bleeding time.[15] The Royal College of Anaesthetists' Guidelines for the Use of Non-steroidal Anti-Inflammatory Drugs in the Perioperative Period[16] recommend that systemic administration of NSAIDs be avoided for tonsillectomy in patients for whom increased blood loss or reduced platelet function poses particular risks.

Salvia officinalis (SO) is widely used in herbal medicinal products. A number of components have been isolated from SO, including diterpenoids, flavonoids, triterpenoids, phenolic glycosides, and phenolic acid derivates.[17] SO is be-

lieved to be effective in a number of medical conditions requiring topical treatment, including herpes labialis,[18] mostly because of its anti-inflammatory properties.[19]

Benzydamine hydrochloride (BNZD) is the first NSAID for topical application. Following topical application, the systemic concentration of the drug is minimal, and bioavailability is ~87%, which shows that the drug is well absorbed at the site of application.[20,21]

BNZD has been used in clinical practice in some European countries for >20 years,[22] and in the United States, it was added to the US Food and Drug Administration's Orphan Drug list in May 1998. Due to the drug's prolonged use in Europe, substantial data are available on its efficacy and tolerability. Its efficacy as adjuvant therapy in reducing pain, hyperemia, and edema compared with that of placebo has been shown in numerous clinical trials.[20,21,23–26] However, in those studies, the efficacy and tolerability of BNZD were rarely[23,25,26] compared with those of other frequently used treatments following tonsillectomy. An overview of published studies found on MEDLINE (key terms: *benzydamine* and *Salvia officinalis*) revealed that none compared BNZD with SO, which is, in Serbia, widely used as a folk medicine adjuvant to treatment with systemic NSAIDs in controlling postoperative pain following tonsillectomy and tonsilloadenoidectomy.

The objective of this trial was to compare the efficacy and tolerability of BNZD with those of SO as adjuvant therapy in the postoperative treatment of pain after tonsillectomy, adenoidectomy, or both.

PATIENTS AND METHODS

Study Design

This open-label, single-blind, randomized clinical study was conducted at the Department for Otorhinolaryngology, Clinical Hospital Center "Dr. Dragiša Mišović—Dedinje" (Belgrade, Serbia and Montenegro) from January 2002 to July 2002. Institutional review board approval was obtained prior to the start of the study.

Patients

Patients eligible for the trial were children (aged 3–12 years) and adults (aged 13–45 years) in whom tonsillectomy, adenoidectomy, or both were performed. Before the screening procedures took place, the purpose of the study and the requirements for the study were explained to the patients, and their written informed consent to participate in the study was obtained. For pediatric patients, patients' parents or legal guardians were informed in detail about study drug and procedures and provided written informed consent.

Preoperative preparation required obtaining a detailed medical history, which included the presence of different types of recurring infection, upper respiratory tract obstruction, obstructive sleep apnea, impaired hearing, and recurrent otitis or sinusitis. Patients who were otherwise not in good general

health or who had any other comorbidity, particularly reduced platelet function, were excluded from the trial. General health was assessed using a thorough physical examination performed by a physician (pediatrician or internist) and laboratory tests, including complete blood count, erythrocyte sedimentation rate, bleeding time, platelet aggregation time, serum electrolyte (Fe^{2+}, Na^{+}, K^{+}, and Ca^{2+}) levels, liver enzyme (aminotransferases, phosphatase) activities, serum bilirubin concentration, and serum lipid profile, as well as concentrations of blood glucose, blood urea nitrogen, and serum creatinine. Pregnant, possibly pregnant, or breastfeeding women were excluded from the study.

Methods

In children, the conventional technique for the removal of tonsils and/or adenoids was performed with the patient under general anesthesia; the children were intubated and placed in the Rose position, with the head and neck retroflexed.[27,28] Exploration was performed using a Crowe-Davis mouth gag, the soft palate was palpated for occlusion abnormalities, and a mirror or endotracheal tube was used to visualize the adenoids. Tonsillectomy was performed using a combination of sharp and blunt dissection; adenoidectomy was performed using an adenotome, and in cases of residual nasopharyngeal tissue, forceps could be used. Intraoperative bleeding was controlled using tamponade, aspiration, fibrin glue, bipolar cautery, or sutures.

In adults, the conventional technique was performed with the patient receiving local anesthesia. Patients were sitting and were required to assist during the exploration with a mouth gag. Surgery and bleeding control were performed as in children.

Treatment

Children received ibuprofen suspension 20 mg/kg body weight per day PO, divided into 3 doses. Adults received diclofenac tablets 100 mg/d (50 mg BID) PO. The patients were randomly assigned in blocks of 2, using a computer-generated randomization list, to receive BNZD or SO as adjuvant therapy. In children, BNZD spray was applied 4 to 8 hours following surgery by the surgeon who performed the operation, and then 6 times a day by a parent or guardian, who received application instructions from a trained nurse. In adults, BNZD oral rinse was given 4 to 8 hours following surgery, and then 6 times a day by the patients, who received application instructions from a trained nurse. SO was prepared as an infusion of 3 g herbal preparation per 200 mL hot water and used as an oral rinse by both children and adults 4 to 8 hours following surgery, and then 6 times a day. All treatments were given for 4 weeks. Independent pharmacists dispensed the BNZD and SO.

Efficacy and Tolerability Assessments

We tested the hypothesis that BNZD is at least as effective in reducing postoperative pain and local infection as the SO herbal preparation and of compa-

rable tolerability. The primary outcome measure was patients' self-ratings of pain on a dichotomous scale on days 1, 2, 4, and 7 following surgery. The presence of mild or no pain represented one category, whereas the presence of moderate or severe pain represented the other. Secondary outcome measures were signs of local infection and/or postoperative hemorrhage, clinically assessed by 2 otorhinolaryngologists blinded to treatment assignment, on postoperative days 1, 2, 4, and 7 following surgery. Blinding was possible because medications were issued to patients by a pharmacist. All patients were examined by the investigator (I.D.) for other adverse events (AEs) on days 1, 2, 4, 7, and 14 and week 4 following surgery. AEs were recorded on case-report forms during the study period and were entered on case-report forms by the investigator.

Statistical Analysis

For children, sample size calculation was performed to detect the differences in the proportion of patients experiencing moderate or severe pain on day 2 following surgery. Our pilot study indicated that ~30% of children treated with SO experienced moderate or severe pain on day 2 following surgery. The authors assumed that the incidence of moderate or severe pain experienced with BNZD would be decreased by 15%. It was calculated that group sample sizes of 133 would achieve 80% power to detect a difference of 15% between the null hypothesis that patients experiencing moderate or severe pain is 30% in both groups, and the alternative hypothesis that the proportion of patients experiencing moderate or severe pain in the treatment group is 15% using a 2-sided chi-square test with continuity correction and a significance level of $\alpha = 0.05$. Given an attrition rate of 10%, it was calculated that 293 children should be enrolled in the study.

No formal sample size calculation was performed for adults because the analysis in adults was considered supportive of the pediatric analysis.

All data analyses were performed according to the preestablished analysis plan developed during the pilot study. Proportions were compared using the chi-square test with continuity correction. Two-sided tests were used as defined by the study protocol; the variables were categorized by response.

Reduction in the risk for moderate or severe pain for the intervention compared with the control (SO) group was assessed using relative risk reduction (RRR), absolute risk reduction (ARR), and number needed to treat (NNT). In RRR, ARR, and NNT analyses, 95% CIs were calculated. Statistical analysis was performed using Statistica software version 6.1 (StatSoft, Inc., Tulsa, Oklahoma).

RESULTS

Study Population

In total, 454 patients were assessed for eligibility (**Figure 1**). Of these, 420 patients were eligible and were randomized (217 females, 203 males; 278 chil-

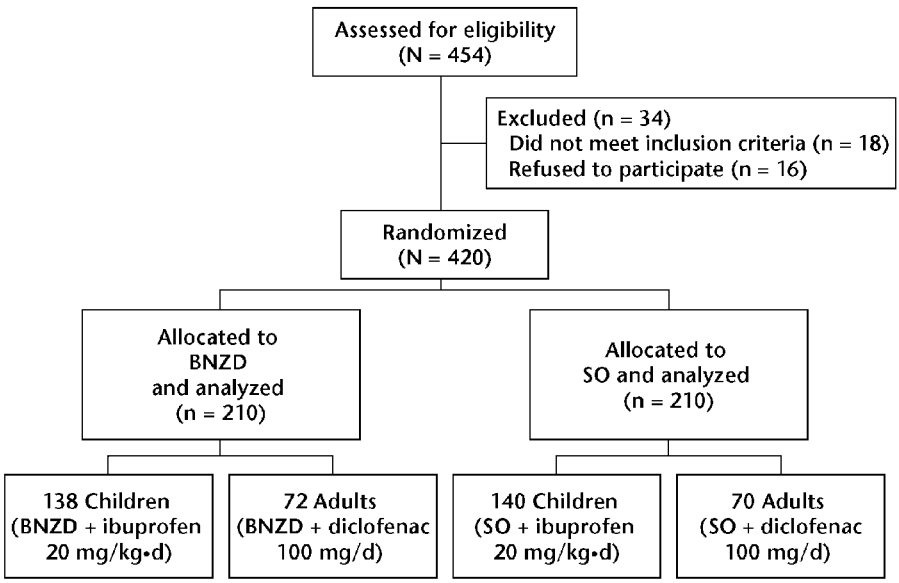

Figure 1. Study design for comparison of the efficacy and tolerability of adjuvant therapy with benzydamine hydrochloride (BNZD) and *Salvia officinalis* (SO).

dren, 142 adults; mean [SD] age, 6.2 [2.1] years [children] and 24.1 [9.8] years [adults] [range, 3–45 years]; 210 patients per treatment group). All 420 patients were included in the efficacy and tolerability analyses. One hundred thirty-eight children received BNZD and 140 children received SO; both groups also received ibuprofen suspension 20 mg/kg body weight per day. Seventy-two adults received BNZD and 70 adults received SO; both groups also received diclofenac 100 mg/d. Patients were not allowed to receive any additional analgesic medication. No protocol violations were observed that required withdrawal from the study. The 2 treatment arms were comparable with regard to baseline demographic characteristics (**Table I**). The primary analysis was intent to treat and involved all 278 children and all 142 adults.

Efficacy

All patients experienced moderate or severe pain on the day of surgery. A significantly lower proportion of children treated with adjuvant BNZD experienced moderate or severe pain at each time point than those treated with SO (all, $P \leq 0.01$; **Table II** and **Figure 2**).

A significantly lower number of adults treated with BNZD reported moderate or severe pain on days 1 and 2 following surgery than those treated with SO ($P < 0.001$ and $P = 0.004$ on days 1 and 2, respectively). Treatment with BNZD was associated with similar pain intensity on days 4 and 7 following surgery.

Table I. Baseline demographic characteristics of study patients (N = 420).*

Characteristic	Benzydamine Hydrochloride		*Salvia officinalis*	
	Children (n = 138)	Adults (n = 72)	Children (n = 140)	Adults (n = 70)
Age, y				
Mean (SD)	6.0 (2.1)	23.0 (6.7)	6.2 (2.5)	24.0 (7.3)
Range	3–12	13–45	3–12	13–45
Sex, no. (%)				
Female	72 (52.2)	34 (47.2)	74 (52.9)	37 (52.9)
Male	66 (47.8)	38 (52.8)	66 (47.1)	33 (47.1)

*No significant between-group differences were found.

Compared with the RRR for moderate or severe pain observed in the SO treatment arm, the RRR on day 1 after surgery was 39.8% (95% CI, 16.6%–56.5%) in children who received BNZD treatment (**Table II**). The RRRs were 56.5% (95% CI, 31.5%–72.4%) on day 2, 67.4% (95% CI, 33.5%–84.0%) on day 4, and 84.0% (95% CI, 47.0%–95.2%) on day 7.

The ARRs for moderate or severe pain in children treated with BNZD were 18.2% (95% CI, 16.3%–20.3%) on postoperative day 1 and 19.8% (95% CI, 17.9%–21.8%) on day 2. The ARRs remained high on days 4 and 7 (13.5% [95% CI, 12.5%–14.6%] and 11.4% [95% CI, 10.7%–12.1%], respectively).

Supportive analysis in adults also displayed a reduced risk for moderate or severe pain when BNZD treatment was applied, the effect being the most pronounced on day 2.

Tolerability

In children, the risk for postoperative infection was similar between BNZD and SO (ARR, 6.9%; 95% CI, 6.4%–7.6%); however, the risk was reduced in adults (ARR, 19.0%; 95% CI, 16.5%–21.9%; $P = 0.008$) (**Table III**). The incidence of postoperative hemorrhage during the study period was similar between the BNZD and SO groups in children (both, 4.3%) and in adults (BNZD, 22.2%; SO, 24.3%).

All other AEs were mild and of similar incidence between the 2 treatments (**Tables III** and **IV**). With BNZD, 4 children (2.9%) and 1 adult (1.4%) experienced ≥1 AE. With SO, 3 children (2.1%) and 2 adults (2.9%) reported AEs. The incidences of AEs other than infection and hemorrhage are shown in **Table IV**. Although rare, the most commonly reported AE in the BNZD group was nausea (1 child [0.7%] and 1 adult [1.4%]), and in the SO group nausea and constipation (each, 1 child [0.7%] and 1 adult [1.4%]). Because these AEs are usually associated with prolonged postoperative inactivity, lack of food intake before the

Table II. Risk for moderate or severe pain during the study period.

Study Day	EER (BNZD) No. (%)	CER (SO) No. (%)	RRR, % (95% CI)	ARR, % (95% CI)	NNT (95% CI)	*P*
1						
Children	38/138 (27.5)	64/140 (45.7)	39.8 (16.6–56.5)	18.2 (16.3–20.3)	5.5 (4.9–6.1)	0.01
Adults	11/72 (15.3)	29/70 (41.4)	63.1 (32.1–80.0)	26.2 (22.7–30.1)	3.8 (3.3, 4.4)	<0.001
2						
Children	21/138 (15.2)	49/140 (35.0)	56.5 (31.5–72.4)	19.8 (17.9–21.8)	5.1 (4.6–5.6)	<0.001
Adults	8/72 (11.1)	21/70 (30.0)	63.0 (22.0–82.4)	18.9 (16.6–21.5)	5.3 (4.7, 6.0)	0.004
4						
Children	9/138 (6.5)	28/140 (20.0)	67.4 (33.5–84.0)	13.5 (12.5–14.6)	7.4 (6.9–8.0)	0.01
Adults	6/72 (8.3)	13/70 (18.6)	55.1 (−11.4 to 81.9)	10.2 (9.2–11.4)	9.8 (8.7–10.9)	0.071
7						
Children	3/138 (2.2)	19/140 (13.6)	84.0 (47.1–95.2)	11.4 (10.7–12.1)	8.8 (8.2–9.3)	<0.001
Adults	4/72 (5.6)	7/70 (10.0)	44.4 (−81.5 to 83.0)	4.4 (4.1–4.9)	22.5 (20.6–24.6)	0.322

EER = experimental event rate; BNZD = benzydamine hydrochloride; CER = control event rate; SO = *Salvia officinalis*; RRR = relative risk reduction; ARR = absolute risk reduction; NNT = number needed to treat.

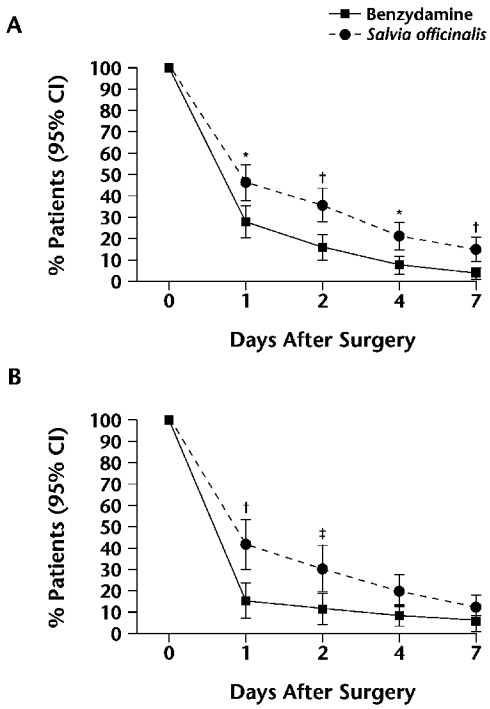

Figure 2. Percentages of (A) children and (B) adults experiencing moderate or severe pain during the study period. *$P < 0.01$; †$P < 0.001$; ‡$P < 0.05$.

operation, or the effect of systemic anesthetics administered immediately before surgery,[29] an association between these AEs and benzydamine was thought to be unlikely.

DISCUSSION

In this study, the risk for severe pain after tonsillectomy, adenoidectomy, or both was reduced when BNZD was used as adjuvant therapy instead of SO. The risk for pain observed with the more commonly used adjuvant treatment SO could be reduced as much as 84% in the week following surgery. The more profound properties of pain reduction with BNZD over SO as adjuvant therapy were observable on the first postoperative day and remained notable for 1 week following surgery. Treatments with BNZD and SO were associated with similarly favorable safety profiles.

One finding of this study was a lower infection risk when BNZD, rather than SO, was applied as adjuvant therapy. Compared with SO, BNZD as adjuvant therapy to diclofenac in adults was associated with a significantly lower infection rate. The magnitude of this effect is best observed when one considers that

Table III. Postoperative infection, hemorrhage, and other adverse events during the study.

Adverse Event	EER (BNZD), No. (%)	CER (SO), No. (%)	RRR, % (95% CI)	ARR, % (95% CI)
Infection				
Children	19/138 (13.8)	29/140 (20.7)	33.5 (−12.8 to 60.8)	6.9 (6.4–7.6)
Adults	12/72 (16.7)	25/70 (35.7)	53.3 (14.6–74.5)	19.0 (16.5–21.9)
Hemorrhage				
Children	6/138 (4.3)	6/140 (4.3)	−1.4 (−206.9 to 66.5)	−0.06 (−0.06 to −0.07)
Adults	16/72 (22.2)	17/70 (24.3)	8.5 (−66.4 to 49.7)	2.1 (1.8–2.4)
Adverse event*				
Children	4/138 (2.9)	3/140 (2.1)	−35.3 (−493.3 to 69.2)	−0.76 (−0.7 to −4.4)
Adults	1/72 (1.4)	2/70 (2.9)	51.4 (−424.1 to 95.5)	1.5 (1.4–1.5)

EER = experimental event rate; BNZD = benzydamine hydrochloride; CER = control event rate; SO = *Salvia officinalis*; RRR = relative risk reduction; ARR = absolute risk reduction.
*For the complete list of adverse events, see Table IV.

Table IV. Incidence (no. [%]) of adverse events with benzydamine hydrochloride and *Salvia officinalis* adjuvant therapy in the postoperative treatment of patients who underwent tonsillectomy, adenoidectomy, or both (N = 420).

	Benzydamine Hydrochloride		*Salvia officinalis*	
Adverse Event	Children (n = 138)	Adults (n = 72)	Children (n = 140)	Adults (n = 70)
Nausea	1 (0.7)	1 (1.4)	1 (0.7)	1 (1.4)
Vomiting	1 (0.7)	0 (0.0)	1 (0.7)	0 (0.0)
Constipation	1 (0.7)	0 (0.0)	1 (0.7)	1 (1.4)
Vertigo	1 (0.7)	0 (0.0)	0 (0.0)	0 (0.0)
Total	4 (2.9)	1 (1.4)	3 (2.1)	2 (2.9)

1 in 5 people treated with SO develops infection postoperatively, which is not the case in those treated with BNZD. BNZD has been found to have antimicrobial activity,[30] to be effective in controlling transitory colonization of the oral cavity by microbes,[31] to exhibit synergistic bactericidal efficacy,[32] and to have fungistatic and fungicidal properties.[33]

Antibacterial properties of diclofenac have been also described,[34] and it seems reasonable to contemplate whether the infection risk reduction found in the present study was due to the synergistic effects of BNZD and diclofenac. However, the risk for infection in children was 6.9% lower with BNZD compared with SO, indicating that the effect also exists when BNZD is used as an adjuvant to ibuprofen, a compound that also possesses some antibacterial activity.[35] Further research could clarify the extent to which topical BNZD contributes to infection risk reduction.

We did not find any significant differences between BNZD and SO in the incidence of postoperative hemorrhage, indicating that concerns[15,16] about prolonged bleeding associated with NSAID use in adults and children[36] may not be clinically relevant in topical treatment.

Systemic administration of NSAIDs might be accompanied by serious AEs (eg, gastrointestinal, hematologic, renal, hepatic, central nervous system, dermatologic, and metabolic changes).[37] However, such AEs appear to be largely avoided by topical NSAID administration.[37] Although we studied topical NSAID as an adjuvant to systemic NSAID therapy, the results of this research warrant further studies assessing the capacity of topical BNZD to reduce the amount of (and/or completely substitute for) systemically administered NSAIDs used to control postoperative pain.

CONCLUSIONS

In this clinical trial of children and adults who underwent tonsillectomy, adenoidectomy, or both, BNZD, as an adjuvant to an NSAID, was more effective than SO in controlling postoperative pain and infection. The pain-reducing effect of

BNZD was of quick onset and persisted during the week after surgery. The safety profile of BNZD was comparable to that of SO. In addition, the use of BNZD was not associated with a high risk for early postoperative hemorrhage.

REFERENCES

1. Richardson MA. Sore throat, tonsillitis, and adenoiditis. *Med Clin North Am.* 1999;83: 75–83.
2. Paradise JL. Tonsillectomy and adenoidectomy. In: Bluestone CD, Stool SE, Kenna MA, eds. *Pediatric Otolaryngology.* 3rd ed. Philadelphia, Pa: WB Saunders; 1996:1054–1065.
3. Wiatrak BJ, Myer CM III, Andrews TM. Complications of adenotonsillectomy in children under 3 years of age. *Am J Otolaryngol.* 1991;12:170–172.
4. Deutsch ES. Tonsillectomy and adenoidectomy. Changing indications. *Pediatr Clin North Am.* 1996;43:1319–1338.
5. Handler SD, Miller L, Richmond KH, Baranak CC. Post-tonsillectomy hemorrhage: Incidence, prevention and management. *Laryngoscope.* 1986;96:1243–1247.
6. Gates GA, Muntz HR, Gaylis B. Adenoidectomy and otitis media. *Ann Otol Rhinol Laryngol Suppl.* 1992;155:24–32.
7. Singer JI. Evaluation of the patient with neck complications following tonsillectomy or adenoidectomy. *Pediatr Emerg Care.* 1992;8:276–279.
8. Goldsher M, Podoshin L, Fradis M, et al. Effects of peritonsillar infiltration on post-tonsillectomy pain. A double-blind study. *Ann Otol Rhinol Laryngol.* 1996;105:868–870.
9. Wong AK, Bissonnette B, Braude BM, et al. Post-tonsillectomy infiltration with bupivacaine reduces immediate postoperative pain in children. *Can J Anaesth.* 1995; 42:770–774.
10. Kountakis SE. Effectiveness of perioperative bupivacaine infiltration in tonsillectomy patients. *Am J Otolaryngol.* 2002;23:76–80.
11. Watters CH, Patterson CC, Matthews HM, Campbell W. Diclofenac sodium for post-tonsillectomy pain in children. *Anaesthesia.* 1988;43:641–643.
12. Dahl JB, Kehlet H. Non-steroidal anti-inflammatory drugs: Rationale for use in severe postoperative pain. *Br J Anaesth.* 1991;66:703–712.
13. Mather LE. Do the pharmacodynamics of the nonsteroidal anti-inflammatory drugs suggest a role in the management of postoperative pain? *Drugs.* 1992;44(Suppl 5): 1–12, discussion 13.
14. American Society of Hospital Pharmacists (ASHP). *Drug Information.* Bethesda, Md: ASHP; 1993.
15. Romsing J, Walther-Larsen S. Peri-operative use of nonsteroidal anti-inflammatory drugs in children: Analgesic efficacy and bleeding. *Anaesthesia.* 1997;52:673–683.
16. Royal College of Anaesthesists. Guidelines for the Use of Non-Steroidal Anti-Inflammatory Drugs in the Perioperative Period; 1998.
17. Miura K, Kikuzaki H, Nakatani N. Apianane terpenoids from *Salvia officinalis*. *Phytochemistry.* 2001;58:1171–1175.
18. Saller R, Buechi S, Meyrat R, Schmidhauser C. Combined herbal preparation for topical treatment of herpes labialis. *Forsch Komplementarmed Klass Naturheilkd.* 2001;8:373–382.
19. Baricevic D, Sosa S, Della Loggia R, et al. Topical anti-inflammatory activity of *Salvia officinalis* L. leaves: The relevance of ursolic acid. *J Ethnopharmacol.* 2001;75:125–132.

20. Giacomelli F. Tantum Verde nebulizer in post-operative management of tonsillectomized patients. *Gaz Med It.* 1983;142.
21. Fior R. Use of benzydamine hydrochloride (nebulized formulation) in patients submitted to adenotonsillectomy. *Otorhinolaryngologia.* 1990;40:1–5.
22. Mahon WA, De Gregorio M. Benzydamine: A critical review of clinical data. *Int J Tiss React.* 1985;7:229–235.
23. Irwin BC, Acharya KB. A comparative study of benzydamine hydrochloride 0.15% w/v ("Difflam" oral rinse) and acetyl salicylic acid as analgesics following tonsillectomy. *J Int Med Res.* 1984;12:216–218.
24. Wethington JF. Double-blind study of benzydamine hydrochloride, a new treatment for sore throat. *Clin Ther.* 1985;7:641–646.
25. Raj TB, Wickham MH. The effect of benzydamine hydrochloride (Difflam) spray on post-tonsillectomy symptoms: A double-blind study. *J Laryngol Otol.* 1986;100:303–306.
26. Young JR. A comparative study of benzydamine hydrochloride ("Difflam" pump spray) and placebo as analgesics following tonsillectomy. *Int J Tissue React.* 1987;9: 131–133.
27. Andrea M. Microsurgical bipolar cautery tonsillectomy. *Laryngoscope.* 1993;103: 1177–1178.
28. Crowe SJ, Watkins SS, Rothholz AS. Relation of tonsillar and nasopharyngeal infections to general systemic disorders. *Bull Johns Hopkins Hosp.* 1917;28:1.
29. Moir MS, Bair E, Shinnick P, Messner A. Acetaminophen versus acetaminophen with codeine after pediatric tonsillectomy. *Laryngoscope.* 2000;110:1824–1827.
30. Fanaki NH, El-Nakeeb MA. Antimicrobial activity of benzydamine, a non-steroid anti-inflammatory agent. *J Chemother.* 1992;4:347–352.
31. Pilloni AP, Buttini G, Giannarelli D, et al. Antimicrobial action of Nitens mouthwash (cetyltrimethylammonium naproxenate) on multiple isolates of pharyngeal microbes: A controlled study against chlorhexidine, benzydamine, hexetidine, amoxicillin, amoxicillin-clavulanate, clarithromycin, and cefaclor. *Chemotherapy.* 2002;48: 168–173.
32. Fanaki NH, El-Nakeeb MA. Antibacterial activity of benzydamine and antibiotic-benzydamine combinations against multifold resistant clinical isolates. *Arzneimittelforschung.* 1996;46:320–323.
33. Pina-Vaz C, Rodrigues AG, Sansonetty F, et al. Antifungal activity of local anesthetics against *Candida* species. *Infect Dis Obstet Gynecol.* 2000;8:124–137.
34. Annadurai S, Guha-Thakurta A, Sa B, et al. Experimental studies on synergism between aminoglycosides and the antimicrobial antiinflammatory agent diclofenac sodium. *J Chemother.* 2002;14:47–53.
35. Elvers KT, Wright SJ. Antibacterial activity of the anti-inflammatory compound ibuprofen. *Lett Appl Microbiol.* 1995;20:82–84.
36. Kokki H. Nonsteroidal anti-inflammatory drugs for postoperative pain: A focus on children. *Paediatr Drugs.* 2003;5:103–123.
37. Vaile JH, Davis P. Topical NSAIDs for musculoskeletal conditions. A review of the literature. *Drugs.* 1998;56:783–799.

Address correspondence to: Ivan Djordjević, MD, Department of Otorhinolaryngology, Clinical Hospital Center "Dr. Dragiša Mišović—Dedinje," 10000 Belgrade, Serbia and Montenegro. E-mail: ivandjor@yahoo.com