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Published in:
PAIN Reports

DOI:
[10.1097/PR9.0000000000000619](https://doi.org/10.1097/PR9.0000000000000619)

Publication date:
2017

Document Version
Publisher's PDF, also known as Version of record

Citation for published version (APA):
Mogensen, S., Tredal, C., Kristensen, C. A., Bentzen, J., Lawson-Smith, L., Petersen, J., & Andersen, O. (2017). Effect of bupivacaine lozenges on oral mucositis pain: a randomized controlled multicenter phase II study. *PAIN Reports*, 2(5), 1-8. [e619]. <https://doi.org/10.1097/PR9.0000000000000619>



Effect of bupivacaine lozenges on oral mucositis pain: a randomized controlled multicenter phase II study

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Abstract

Introduction: A nonblinded parallel-group randomized controlled study investigated the efficacy and tolerability of repeated administration of a bupivacaine lozenge (25 mg) as pain management for oral mucositis pain in head and neck cancer patients as add-on to standard systemic pain management.

Objective: The primary end point was the difference between the intervention group (Lozenge group) and the Control group in daily mean pain scores in the oral cavity or pharynx (whichever was higher).

Method: Fifty patients from 2 hospitals in Denmark were randomized 1:1 to 7 days of treatment with bupivacaine lozenges (taken up to every 2 hours) plus standard pain treatment minus topical lidocaine (Lozenge group) or standard pain treatment including topical lidocaine (Control group). The efficacy analysis included 38 patients, as 12 patients were excluded because of changes in study design and missing data.

Results: Mean pain in the oral cavity or pharynx (whichever was higher) was significantly lower 60 minutes after taking lozenges (35 mm [n = 22]) than for the Control group (51 mm [n = 16]) (difference between groups -16 mm, 95% confidence interval: -26 to -6, $P = 0.0032$). Pain in the oral cavity was also significantly lower in the Lozenge group (18 mm) vs the Control group (36 mm, $P = 0.0002$). Pharyngeal mucositis pain did not differ significantly (37 mm [Lozenge group] vs 48 mm [Control group], $P = 0.0630$). No serious adverse events were reported.

Conclusion: These results show that the bupivacaine lozenge as an add-on to standard pain treatment had a clinically significant pain-relieving effect in patients with oral mucositis.

ClinicalTrials.gov: NCT02252926.

Keywords: Pain management, Local anesthetic, Lozenge, Bupivacaine, Head and neck cancer, Oral mucositis

1. Introduction

Eighty to 100% of adult patients who undergo radiotherapy with or without concurrent chemotherapy for head and neck cancer will experience oral mucositis as a painful side effect of their

cancer treatment.^{1,4,9,16} Oral mucositis is painful damage to the mucosa in the oral cavity and the pharynx and is associated with vital oral dysfunction such as swallowing problems.³ It has been identified by patients as the most severe side effect associated with cancer treatment in head and neck cancer patients as it induces severe problems with eating, drinking, and speaking.^{1,3}

For patients with mild to moderate oral or pharyngeal mucositis pain, it would be advantageous to be able to manage pain locally rather than systemically, as local treatments have fewer side effects.¹⁵ Various lidocaine preparations, in the form of sprays or viscous solutions, are currently used for local anesthesia of the oral cavity and pharynx,¹⁵ but the effect is short lasting and the formulations are not very patient friendly because of unpleasant taste and texture. Such preparations are understood to be of limited, if any, effect in management of pain in patients with oral mucositis.¹⁶ Paracetamol, opioids, and gamma-aminobutyric acid analogs are currently the most frequently used systemic analgesic treatments, but a few data on the most beneficial analgesic therapy are available.¹ At present, no effective pain treatment without substantial side effects exists for patients with severe oral mucositis pain, and in many patients treated with high-dose opioids there is a lack of sufficient pain relief.⁸

Sponsorships or competing interests that may be relevant to content are disclosed at the end of this article.

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PR9 2 (2017) e619

<http://dx.doi.org/10.1097/PR9.0000000000000619>

The lack of adequate pain management for oral mucositis-associated pain has led researchers to conduct numerous studies testing various active compounds in many different formulations in the search for new pain prevention and management options,¹⁵ with limited, if any, success. Two phase I studies, each conducted in 10 healthy subjects and 10 patients with head and neck cancer have investigated the safety of a lozenge containing 25 mg of the local anesthetic bupivacaine. They showed no signs of toxic plasma concentrations or risk of aspiration.^{10,11} Moreover, a pilot study in which a single dose of the lozenge was administered to patients with head and neck cancer showed a strong, long-lasting pain-relieving effect, with a mean duration of maximum pain relief in the oral cavity of 42 minutes and a significant pain relief even after 180 minutes.¹² Lidocaine viscous solution has been reported to have a duration of 15 to 20 minutes.⁶

The aim of this nonblinded parallel-group randomized controlled study was to investigate the efficacy and tolerability of repeated administration of a bupivacaine lozenge (25 mg) as pain management for oral or pharyngeal mucositis pain in patients with head and neck cancer as an add-on to standard systemic pain management. The primary end point was pain in the oral cavity or pharynx (whichever was higher), scored on a 0 to 100 mm visual analog scale (VAS) every 2 hours (Control group) or 60 minutes after taking a lozenge (Lozenge group).

2. Methods

2.1. Ethics

The study protocol and amendments were approved by the National Committee on Health Research Ethics (H-6-2014-034) and the Danish Health and Medicines Authority (EudraCT 2014-002346-42). The study was registered at the Danish Data Protection Agency (AHH-2014-034) and ClinicalTrials.gov (NCT02252926). The study was conducted at 2 sites in Denmark in accordance with the ethical principles that have their origins in the Declaration of Helsinki. The Good Clinical Practice (GCP) unit at Copenhagen University Hospitals monitored the study at both sites. A written declaration of informed consent was obtained from patients before their inclusion in the study.

2.2. Participants

Head and neck cancer outpatients from the Departments of Oncology at Copenhagen University Hospital, Rigshospitalet and

Copenhagen University Hospital, Herlev were included in this randomized controlled study. The inclusion criteria in the original protocol were diagnosis of head and neck cancer, age between 18 and 80 years, ability to speak and read Danish, ability to use electronic devices such as a tablet or smartphone, and ability to provide written informed consent. In an amendment to the original protocol (amendment 2.1) that was introduced after 7 patients had been randomized, oral- or pharyngeal mucositis pain of ≥ 40 mm on a 0 to 100 mm VAS was added as an inclusion criterion to ensure that patients had pain in either the oral cavity or pharynx when they were randomized. In a subsequent amendment (amendment 5), the ability to use electronic devices was removed and a paper diary was introduced instead, because the initial patients had problems registering pain and pain medication intake in the electronic diaries. Five patients (3 in the Lozenge group and 2 in the Control group) used the electronic diary and the remaining patients used the paper diary. The exclusion criteria in the original protocol were need for pain treatment with morphine before the start of radiotherapy, known allergy to bupivacaine or other local anesthetics of the amide type, pregnancy, and breastfeeding. The exclusion criterion related to morphine was removed in amendment 2.1.

2.3. Study medicine

The study medicine was manufactured by direct compression at the Capital Region Pharmacy, Denmark. Each lozenge contained 28.16 mg of bupivacaine hydrochloride, which corresponds to 25 mg of bupivacaine, and licorice powder and aspartame to mask the bitter taste of bupivacaine. The lozenge also contained mannitol, talc, and magnesium stearate as fillers.

2.4. Design

This was a nonblinded parallel-group phase II randomized controlled study. Patients with head and neck cancer who fulfilled the inclusion criteria and none of the exclusion criteria were included in the study by a study nurse or pharmacist and thereafter had daily prerandomization screening visits at the hospital (**Fig. 1**). At these visits, oral mucositis and pain in the oral cavity and pharynx were scored and pain medication use was registered. When their oral mucositis pain could not be relieved by paracetamol treatment (original protocol) or their VAS score for oral- or pharyngeal mucositis pain reached ≥ 40 mm (after amendment 2.1), patients were randomized to either standard pain management plus

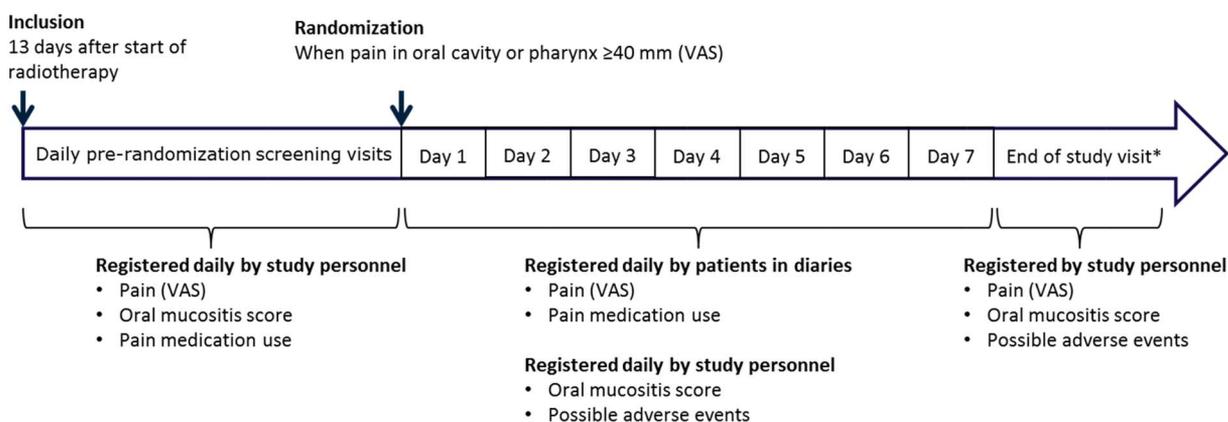


Figure 1. Overview of study visits after implementation of protocol amendment 2.1. *Day 8 or 9. VAS, visual analog scale.

repeated administration of bupivacaine lozenges (Lozenge group) or standard pain treatment plus per need topical lidocaine and benzydamine mouthwash (Control group) for 7 days. Standard pain treatment was systemic analgesics (eg, morphine and paracetamol) as needed. The patients in the Lozenge group did not receive lidocaine or benzydamine during the study; otherwise their standard pain treatment was the same as for the Control group. During the 7-day treatment period, the patients had 6 daily study visits at the hospital in conjunction with their radiotherapy (there was no study visit on the 1 day in the week when they did not receive radiotherapy) (**Fig. 1**). On study day 8 or 9, there was an end of study visit.

2.5. Study procedures

According to the original protocol, patients with head and neck cancer were assessed for pain in the oral cavity and pharynx on a daily basis from their first day of radiotherapy. After amendment 2.1 was introduced, patients were screened daily for oral- and pharyngeal mucositis pain from the first day of their third week of 6 scheduled weeks of radiotherapy.

From their inclusion in the study to the end of study visit, patients scored their oral- and pharyngeal mucositis pain separately from 0 mm (no pain) to 100 mm (worst conceivable pain) on a VAS. During the prerandomization screening period, patients scored oral- and pharyngeal mucositis pain at each hospital visit. After randomization, the patients in the Lozenge group assessed pain in the oral cavity and the pharynx before and 60 minutes after administration of a lozenge and recorded their values in their patient diary (electronic or paper); patients in the Control group assessed pain in the oral cavity and the pharynx separately on the VAS every 2 hours when awake. Pain assessments were performed at home on each of the 7 days of the treatment period and at the hospital at the end of study visit. At each study visit, patients in the Lozenge group were given study medicine for the next day (on the day before their day without radiotherapy, study medicine for 2 days was supplied). Patients were informed to take lozenges every 2 hours during waking hours up to a maximum of 8 lozenges per day. Each time a patient entered a pain score in the electronic diary, the time of the scoring was recorded automatically. In the paper diary, the patient noted both the time of administration of lozenges as well as the time of pain scoring. Pain scores were also entered in the diaries by the patients in both groups each morning (before they took a bupivacaine lozenge, in the case of the Lozenge group). Pain scores were recorded separately for the oral cavity and for the pharynx in both groups.

Along with pain scores and the time of scoring, the patients in both groups were asked to record their use of pain therapeutic drugs during the 7-day treatment period. For all pain therapeutic drugs, including the lozenges, the name and dose of the drug and time of administration were recorded. Pain medication use during the prerandomization screening period was registered by a study nurse or pharmacist.

Oral mucositis was assessed using the World Health Organization scale for oral mucositis, which is based on subjective and objective symptoms,¹⁴ where 0 = no symptoms; 1 = erythema and/or soreness, no ulcers; 2 = erythema and ulcers, the patient can swallow solid food; 3 = ulcers and marked erythema, the patient cannot swallow solid food; and 4 = oral mucositis to a degree that makes normal nutrition impossible. Scoring was performed by a study nurse or pharmacist who was trained in assessing mucositis. The assessment was conducted during each visit from inclusion to the end of study visit.

Adverse events (AEs) were registered at study visits on days 1 to 7 and at the end of study visit. Blood samples were drawn from 10 patients in the Lozenge group to assess whether the bupivacaine concentrations in plasma would accumulate after multiple administrations of the lozenges over 7 days. Method and results of these data on the 10 patients are reported in the study by Mogensen et al., 2017.¹⁰

2.6. Randomization

Patients were randomized to either the Lozenge group or the Control group at a ratio of 1:1. The randomization was performed by an independent statistician at PCG Clinical Services AB, who created a computer-generated randomization schedule with randomly varying block sizes to avoid predictability in the assignment of therapy. The randomization schedule was uploaded to the web-based electronic database system Viedoc, supplied by the Contract Research Organization PCG Solutions AB, which assigned the patients to either the Lozenge group or the Control group.

2.7. Outcomes

2.7.1. Primary end point

The primary end point was the difference between the 2 groups in daily mean pain scores measured on a VAS. For the Lozenge group, the mean daily pain score for each patient was calculated as the mean of the pain scores recorded 60 minutes after administration of each bupivacaine lozenge. The window for pain registration 60 minutes after taking a lozenge was ± 15 minutes. For the Control group, the mean daily pain score for each patient was calculated as the mean of the pain scores recorded every 2 hours. For each assessment (time point), the highest of the scores for the oral cavity and pharynx was used in the calculation of the mean daily pain score for each patient in both groups.

2.7.2. Secondary end points

The secondary end points included mean pain (VAS) for the oral cavity and the pharynx, scored separately 60 minutes after administration of a bupivacaine lozenge (Lozenge group) or every 2 hours (Control group); and mean pain (VAS) for the oral cavity and the pharynx, scored separately and as the highest of the values for these 2 anatomical sites immediately before administration of a bupivacaine lozenge (with the exception of the first lozenge of the day) (Lozenge group) or every 2 hours (Control group). For the Lozenge group, the difference between the first pain score (VAS) in the morning (before administration of the first bupivacaine lozenge of the day) and the pain score (VAS) 60 minutes after the first bupivacaine lozenge of the day was separately assessed for the oral cavity and pharynx. The patients registered their use of concomitant pain medication daily from randomization.

2.8. Statistical methods

2.8.1. Determination of sample size

The power calculation was based on pain scores (VAS) from 10 patients with head and neck cancer from a previous study¹² and was based on a paired *t* test. With a minimum clinically relevant difference in pain between the 2 groups of 15 mm, a mean baseline pain of 57 mm, an SD of 15 mm, 80% power, and a significance level of 0.05; it resulted in a sample size of 32 patients completing the study. Approximately 40 patients were

scheduled to be randomized to take account of an estimated dropout rate of 20%.

2.8.2. Efficacy evaluation

The objective of the statistical analysis of the primary end point was to determine whether there was a difference in mean pain scores between the 2 groups. This was performed by estimating a mixed model for repeated measures. Treatment day was regarded as the time variable. The response variable was mean daily pain (VAS) for each patient. For each time point with a pain recording, the higher of the recorded pain scores for the oral cavity and pharynx was used. Treatment group and oral mucositis scores were included as categorical independent variables. Baseline pain score (the last VAS score before randomization, recorded on day 1 of the treatment period) was included as a continuous independent variable. In the analysis of the primary end point, the higher of the baseline pain scores for the oral cavity and pharynx was used as the baseline for each patient. An interaction effect between treatment day and treatment group was also included in the model. Mixed model for repeated measures models were also calculated for the secondary end points. These models had the same correlation structure as that used in the analysis of the primary end point. Data for percentage of patients using opioids were analyzed by χ^2 test. Results are given as estimate of parameters as a mean difference with a 95% confidence interval (CI).

All statistical analyses, except for the analysis of percentage of patients using opioids, were performed using SAS (Version 9.4, SAS Institute Inc, Cary, NC). All tests were 2 sided and were performed at the 5% significance level.

3. Results

3.1. Subjects

A total of 70 patients with head and neck cancer were screened from October 2014 to November 2015 at the Departments of

Oncology at 2 Danish university hospitals. The last patient completed the study in December 2015. Seven patients were randomized under the original protocol, and 43 patients were randomized after approval of amendment 2.1. Twenty-six patients were randomized to the Lozenge group and 24 to the Control group. The 7 patients included under the original protocol were excluded from the efficacy analysis as their baseline pain scores were <40 mm.

A total of 38 patients were included in the efficacy analysis (Fig. 2). Of these, 22 were from the Lozenge group and 16 were from the Control group. The median number of pain registrations (VAS scores) per day from baseline to day 7 was 7.5 (range: 0–14) in the Lozenge group and 6 (range: 0–8) in the Control group. Demographic data, cancer diagnosis, and baseline pain scores for the patients are shown in Table 1. There were no major differences in baseline data between the 2 groups, although there was a slight majority of ex-smokers, patients with oral cancer, and patients with oral mucositis score 0 at baseline in the lozenge group.

3.2. Primary end point

Mean pain in the oral cavity or pharynx (whichever was higher), scored 60 minutes after administration of a bupivacaine lozenge in the Lozenge group and every 2 hours in the Control group, showed a significant difference between groups in favor of the lozenge. Mean pain was 35 mm in patients in the Lozenge group and 51 mm in patients in the Control group (difference between groups – 16 mm, 95% CI: –26 to –6, $P = 0.0032$) (Table 2 and Fig. 3).

3.3. Secondary end points

When pain scores for the oral cavity and pharynx were analyzed separately, the Lozenge group showed superior results compared with the Control group (Table 2, Fig. 4, and Fig. 5). When pain for the Lozenge group was measured as the mean pain score 60 minutes after lozenge administration, the intensity of oral cavity pain was significantly lower in the Lozenge group than in the Control group (mean difference: –18 mm, 95% CI: –27 to –10, $P = 0.0002$).

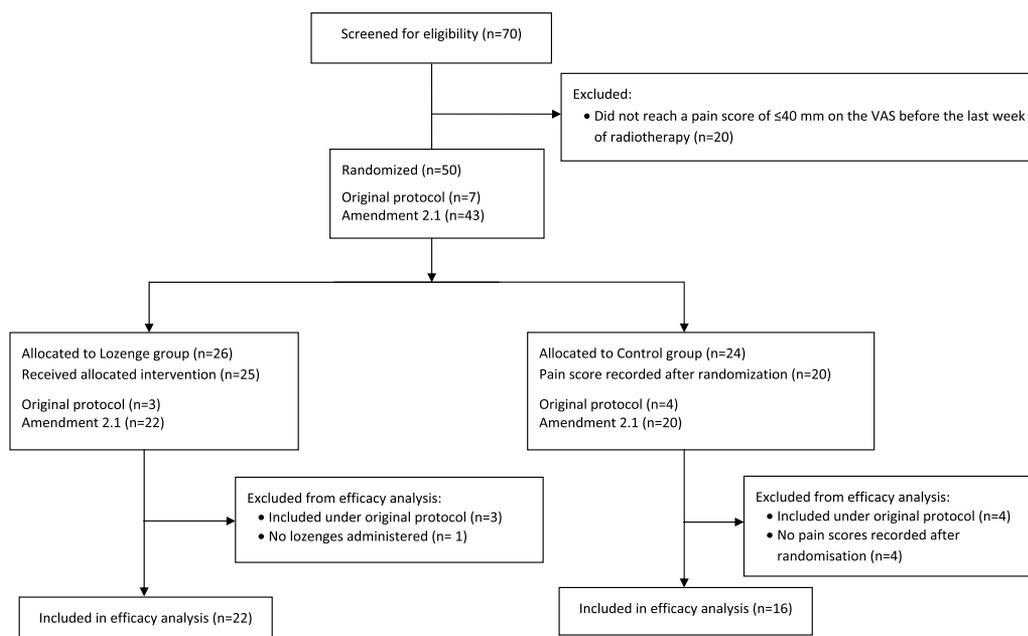


Figure 2. Study flow chart. VAS, visual analog scale.

Table 1
Demographics and baseline characteristics.

	Lozenge group, n = 22	Control group, n = 16
Age, median (range), y	63.0 (50–79)	57.5 (51–72)
Weight, median (range), kg	77 (57–107)	80 (64–123)
Sex, male	21 (95.5%)	13 (81.3%)
Smoking history		
Current smoker	6 (27.3%)	1 (6.3%)
Ex-smoker	12 (54.5%)	13 (81.3%)
Never smoked	4 (18.2%)	2 (12.5%)
Cancer diagnosis		
Oral cancer	4 (18.2%)	0 (0.0%)
Pharyngeal cancer*	14 (63.6%)	13 (81.3%)
Laryngeal cancer	4 (18.2%)	2 (12.5%)
Unknown primary tumor	0 (0.0%)	1 (6.3%)
Cancer treatment		
Radiotherapy	22 (100.0%)	16 (100.0%)
Concurrent chemotherapy	13 (59.1%)	9 (56.3%)
Oral mucositis score at baseline		
0	9 (40.9%)	4 (25.0%)
1–2	11 (50.0%)	10 (62.5%)
3	2 (9.1%)	2 (12.5%)
4	0 (0.0%)	0 (0.0%)
Baseline pain (mm, VAS)		
Higher of the pain scores for the oral cavity and pharynx, mean (SD, range)	58 (17.5, 40–99)	50 (9.8, 40–74)
Oral cavity, mean (SD, range)	35 (23.6, 0–76)	31 (20.8, 0–66)
Pharynx, mean (SD, range)	55 (21.8, 6–99)	48 (11.5, 25–74)

Data are presented as n (%), unless otherwise indicated.

* Pharyngeal cancer, oropharyngeal cancer, hypopharyngeal cancer, or nasopharyngeal cancer.

VAS, visual analog scale.

Pharyngeal mucositis pain did not show a significant difference between groups ($P = 0.0630$) (Table 2, Fig. 4).

When pain for the Lozenge group was measured as the mean pain score immediately before the next lozenge, pain was significantly lower in the Lozenge group than in the Control group for both the oral cavity (mean difference: -15 mm, 95% CI: -23 to -7 , $P = 0.0004$) and the pharynx (mean difference: -11 mm, 95% CI: -22 to 0 , $P = 0.0452$) (Table 2, Fig. 5).

3.4. Patient-reported pain medication use

Pain medications used by patients, in both groups, during the 7-day treatment period included paracetamol, ibuprofen, and opioids. Of the 23 patients assigned to the Lozenge group after

amendment 2.1, 22 used the lozenges, and the median number of bupivacaine lozenges consumed per day was 4 (range: 0–7); 1 patient did not take any lozenges and was excluded from the efficacy analysis (Fig. 2). Eight patients in the Control group (50%) used topical lidocaine after randomization.

3.5. Adverse events

In total, 5 AEs were reported in 3 of the 25 patients (12.0%) who consumed at least 1 bupivacaine lozenge. All AEs were assessed as mild and were categorized as follows: dysphagia (1), odynophagia (1), hyperalgesia (2), and salivary hypersecretion (1). The 2 cases of hyperalgesia were assessed as related to the bupivacaine lozenge; the other 3 AEs were assessed as possibly related to the bupivacaine lozenge. The 2 patients with hyperalgesia in the Lozenge group withdrew because of AEs. One AE (malaise) was reported in the control group. No serious AEs were reported in the study.

4. Discussion

Our aim of this nonblinded parallel-group randomized controlled study to test the efficacy and tolerability of repeated administration of a bupivacaine lozenge (25 mg), as an add-on to standard systemic pain management was fulfilled. The results showed that the pain in the Lozenge group 60 minutes after intake of a 25 mg bupivacaine lozenge was significantly lower than that experienced by the Control group. Moreover, the pain-relieving effect of the lozenge was sustained during a relevant period because there was a statistically and clinically significant reduction in pain in the Lozenge group compared with the Control group immediately before intake of the next lozenge.

Pain scores for the oral cavity were significantly lower 60 minutes after lozenge administration in the Lozenge group than they were in the Control group. Many patients had pain in both the oral cavity and pharynx, but pain was often lower or absent in 1 of these 2 sites. The fact that all randomized patients included in the efficacy analysis had a minimum baseline pain score of 40 mm in the oral cavity and/or pharynx indicates inadequate standard pain management, as all patients were medicated with one or more systemic drugs at randomization. It was therefore surprising that patients in the Lozenge group only consumed a median of 4 of the 8 bupivacaine lozenges they were permitted to take each day. Possible explanations for the lower than anticipated consumption include that the lozenges may have had a prolonged pain-relieving effect, as shown previously.¹² There is an immediate

Table 2
Pain measurements.

	Lozenge group, n = 22	Control group, n = 16	Difference	P
60 min after lozenge administration*				
Worst pain on VAS†, mean (95% CI)	35 mm (28–43)	51 mm (43–84)	-16 mm (-26 to -6)	0.0032
Oral mucositis pain on VAS, mean (95% CI)	18 mm (12–24)	36 mm (30–43)	-18 mm (-27 to -10)	0.0002
Pharyngeal mucositis pain on VAS, mean (95% CI)	37 mm (28–45)	48 mm (39–57)	-12 mm‡ (-24 to 1)	0.0630
Immediately before lozenge administration*				
Worst pain on VAS†, mean (95% CI)	39 mm (31–46)	50 mm (42–58)	-11 mm (-22 to -1)	0.0339
Oral mucositis pain on VAS, mean (95% CI)	21 mm (15–27)	36 mm (30–42)	-15 mm (-23 to -7)	0.0004
Pharyngeal mucositis pain on VAS (95% CI)	37 mm (29–45)	48 mm (40–56)	-11 mm (-22 to 0)	0.0452

* In the Lozenge group (values from the control group are derived from scoring done every 2 hours).

† In oral cavity or pharynx (whichever was higher).

‡ To the nearest whole number (-11.63 to 2 decimal places).

CI, confidence interval; VAS, visual analog scale.

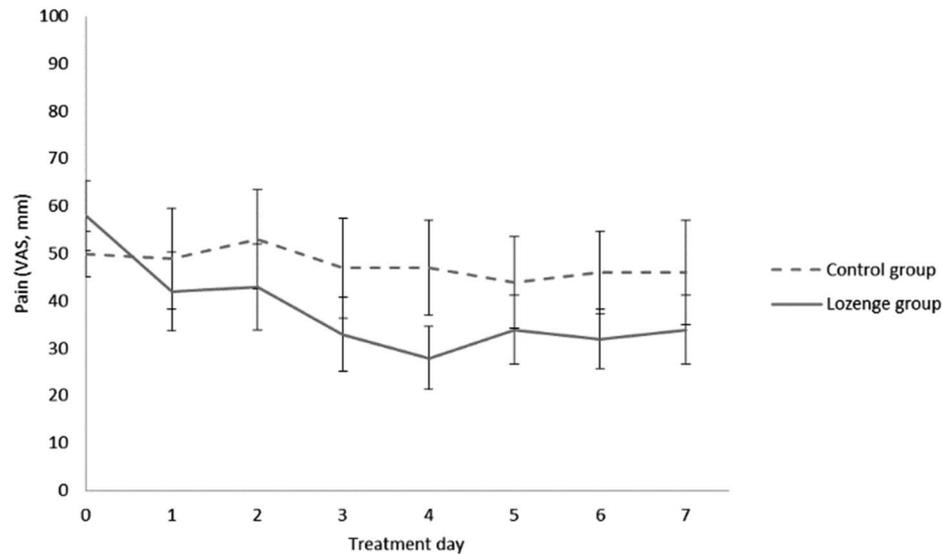


Figure 3. Mean pain in the oral cavity or pharynx (whichever was higher), scored on a visual analog scale (VAS) 60 minutes after administration of a lozenge in the Lozenge group (n=22) and every 2 hours in the Control group (n=16). The error bars show 95 confidence intervals.

need for improved pain management in patients with head and neck cancer with oral mucositis.

A randomized double-blind placebo-controlled study on 59 patients with oral mucosal trauma or minor aphthous ulcers found that a 1% topical lidocaine solution significantly reduced oral pain. The efficacy of the topical lidocaine solution was not related to the type of lesion. Although similar results might be expected in patients with pain due to oral mucositis, while all patients in the Control group in the present study were offered topical lidocaine to use after randomization, only 50% of them did so.

Ketamine has been tested in different studies as a topical analgesic administered as an oral mouthwash. In one study, 8 patients with oral mucositis were treated with ketamine mouthwash plus intravenously administered opioids. Five of the 8 patients experienced relief of their mucositis pain, but 4 patients experienced side effects which were probably related to the ketamine mouthwash. The side effects included mild confusion, hallucinations, nausea, and dizziness.¹⁷ The theory that inflammation causes increased expression of peripheral opioid receptors has led to studies of the effect of morphine-containing

mouthwashes on oral mucositis pain, but the results are not consistent.^{13,18} A systematic review concluded that a 0.2% morphine mouthwash could be effective in the treatment of oral mucositis pain in patients with head and neck cancer.¹⁸

Tricyclic antidepressants, such as doxepin, have also been investigated as pain relief, and the above-mentioned systematic review concluded that a 0.5% doxepin mouthwash could be used to treat oral mucositis.¹⁸ In a study on 51 patients with oral mucositis due to radiotherapy, pain decreased after pain management with an oral rinse containing doxepin.⁵ However, both morphine and doxepin have systemic effects and some patients find the mouthwashes unpleasant, as they feel thick and sticky in the mouth and can cause nausea.⁷ The above-described studies on systemic drugs show various effects of different kinds of pain management. However, the tested systemic drugs have disadvantages in terms of efficacy, tolerability, and/or patient friendliness. By contrast, topical formulations, such as lozenges, used as local anesthetics in the oral cavity may possess the advantages that the concentration of the anesthetic agent will be high in the oral cavity.²

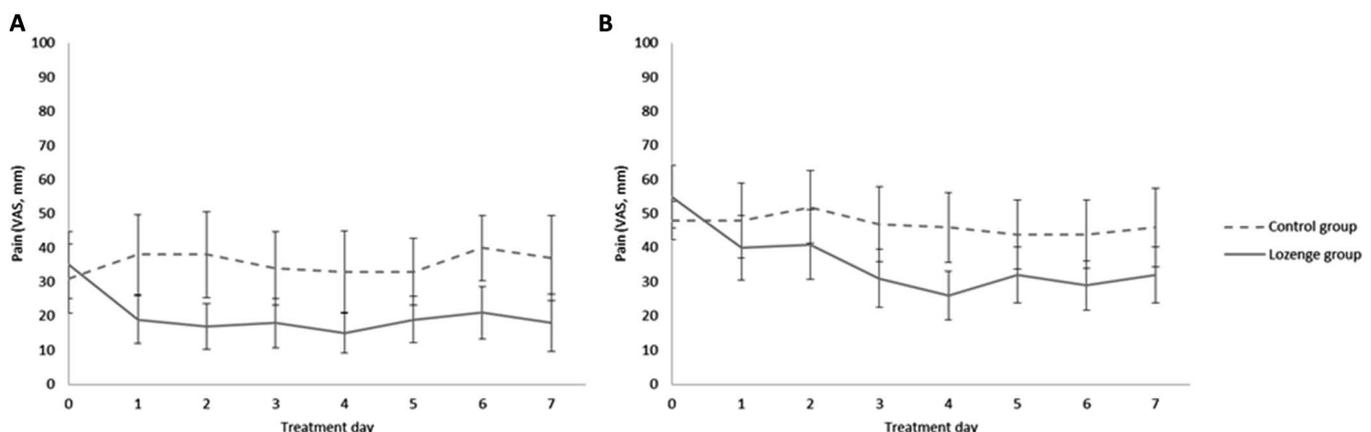


Figure 4. Mean pain in (A) the oral cavity and (B) the pharynx, scored on a visual analog scale (VAS) 60 minutes after administration of a lozenge in the Lozenge group (n=22) and every 2 hours in the Control group (n=16). The error bars show 95% confidence intervals.

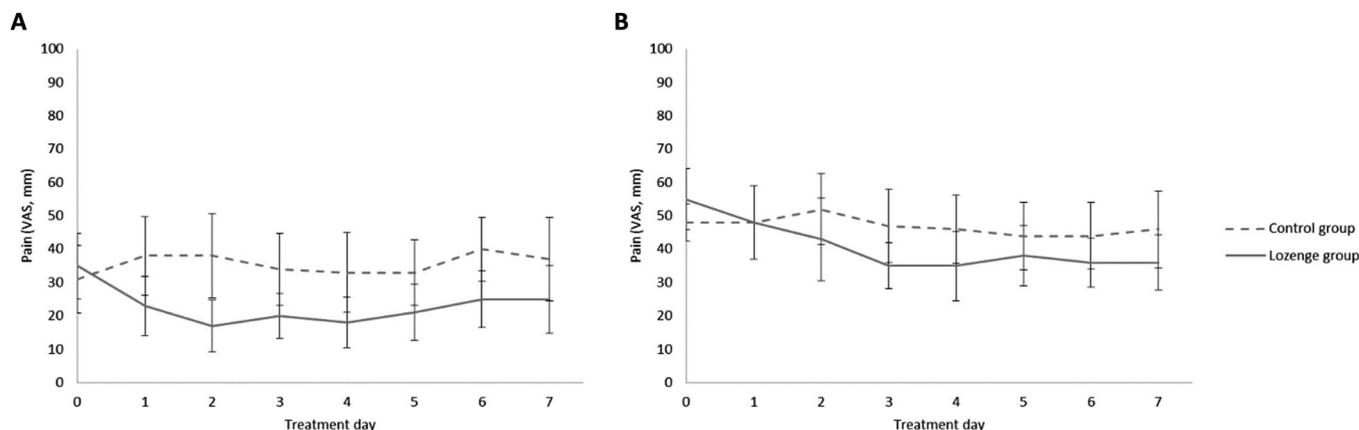


Figure 5. Mean pain in (A) the oral cavity and (B) the pharynx, assessed on a visual analog scale (VAS) immediately before administration of the next lozenge in the Lozenge group (n=22) and every 2 hours in the Control group (n=16). The error bars show 95% confidence intervals.

From a safety perspective, the AEs assessed as related to the bupivacaine lozenge in the present study were few and mild. Two patients withdrew because of hyperalgesia. Study personnel were instructed to be alert to any symptoms indicating systemic toxicity of bupivacaine, and no such symptoms were reported. The reporting of AEs focused on possible side effects of the treatment and did not focus on medical conditions that are common in the studied patient population, such as nausea and somnolence. Patients undergoing radiotherapy often experience dry mouth because of reduced saliva production. In the present study, this may give rise to a prolonged dissolution of the lozenge and reduce the effect of bupivacaine by delaying its transport to the oral cavity and pharynx. The fact that the patients were not hospitalized but instead used a patient diary at home to register pain scores as outpatients made it difficult to ensure that they registered all the required pain scores. However, compliance was judged to be satisfactory as there were enough pain registrations to analyze the data. The severity of oral mucositis was assessed using the World Health Organization scale for oral mucositis. Unfortunately, the study personnel who did the assessments focused solely on visible changes in the oral mucosa; they failed to appreciate that pain, by definition, renders a score of at least 1. This explains why some patients had a mucositis score of 0 at randomization despite a baseline pain score of ≥ 40 mm.

The pain-relieving effect of bupivacaine lozenges has not been tested in a blinded placebo-controlled study. It is difficult to design a blinded placebo-controlled study for several reasons, not least that it would be difficult to blind patients because the local anesthetic effect of bupivacaine has been found to be instant and strong. Therefore, not only is there a risk of unintended bias in favor of the local anesthetic lozenge, but also patients will know whether or not they are receiving the active drug, which makes it very difficult to use a placebo-controlled design. For these reasons, a placebo group was not considered appropriate for this study and the most relevant control was considered to be standard pain treatment.

In conclusion, the tested bupivacaine lozenge was found to be an effective and safe treatment to reduce pain due to oral mucositis in patients with head and neck cancer. Further clinical investigations are warranted to investigate whether the bupivacaine lozenge may improve pain relief in this difficult-to-treat condition. Indeed, a multicountry phase III trial is planned. Furthermore, the effect of the bupivacaine lozenge on other important outcomes should also be investigated. Such outcomes might include quality

of life, patient nutrition, and the risk of an intermission in cancer treatment due to inadequate patient nutrition. Finally, because the bupivacaine lozenge is a noninvasive and patient-friendly way to alleviate oral mucositis pain, it should be investigated in patients with other cancer diagnoses who also have oral mucositis, such as patients with bone marrow transplant.

Disclosures

S. Mogensen, C. Trelldal, and O. Andersen are inventors on a patent grant (EP2701681B1) published October 19, 2016. Proprietor Moberg Pharma AB, Bromma (Sweden). S. Mogensen, C. Trelldal, and O. Andersen are stockholders in Oracain II Aps and have a European patent (Grant EP2701681B1) for the bupivacaine lozenge. The clinical development of the bupivacaine lozenge was supported by SEED capital in the period 2010 to 2014. In 2014, the IP rights for the lozenge were licensed to Moberg Pharma AB, Sweden, which is now in charge of further development of the bupivacaine lozenge. In 2014, Moberg Pharma awarded the Clinical Research Centre at Amager and Hvidovre Hospital, Denmark an unrestricted grant for pain research in the amount of 131.800 euros. The remaining authors have no conflicts of interest to declare.

Acknowledgments

The authors show our gratitude to all patients included in this study as well as to the project nurse Christina Dahl and all the nurses and doctors at the 2 Departments of Oncology for their contribution to the data collection.

Article history:

Received 11 January 2017

Received in revised form 18 July 2017

Accepted 20 July 2017

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