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THE EFFECTIVENESS OF BENZYDAMINE HYDROCHLORIDE GARGLE VERSUS THROAT SPRAY IN POST-TONSILLECTOMY PATIENT: A RANDOMIZED CONTROLLED TRIAL

Siti Asmat Md Arepen[1], Nor Eyzawiyah Hassan[1], Norhafiza Mat Lazim[2], Shahrul Hitam[3], Irfan Mohamad[2*]

Unit of Otorhinolaryngology-Head and Neck Surgery, Department of Surgical-Based, Faculty of Medicine and Health Sciences, Universiti Sains Islam Malaysia, Persiaran Ilmu, Putera Nilai,71800 Nilai, Negeri Sembilan, Malaysia[1]
Department of Otorhinolaryngology-Head & Neck Surgery, School of Medical Sciences, Universiti Sains Malaysia, 16150 Kota Bharu, Kelantan, Malaysia[2]
Department of Otorhinolaryngology, Hospital Ampang, Jalan Mewah Utara, Pandan Mewah, 68000, Ampang, Selangor, Malaysia[3]

Corresponding author: 2*

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ABSTRACT

Post-tonsillectomy pain is an undesirable complication that can affect a patient's emotion and daily activity. There have been many studies on different surgical techniques and medications to find the best treatment to alleviate pain in post-tonsillectomy patients. This study aims to compare the effectiveness of oral gargle and throat spray as different modes of delivery of benzydamine hydrochloride in post-tonsillectomy pain control. We focused on local analgesia using different methods of delivery. A total of 92 patients aged between 13 and 40 who underwent tonsillectomy with or without adenotonsillectomy, were included. They were randomly divided into two groups: gargle group and spray group, with 46 patients in each group. Pain score using Visual Analogue Score (VAS) was assessed for both groups at least six hours post operation as the baseline pain score, followed by assessments at days 1, 4 and 7. There was a significant difference in the VAS pain scores between the two modes of benzydamine hydrochloride delivery. The gargle group reported higher pain scores compared to the throat spray group ($p < 0.001$). In conclusion, using throat spray as a method to deliver local analgesia provides greater benefit in pain control for post-tonsillectomy patients, to the use of oral gargle. So, we can consider prescribing throat spray for treating the post-tonsillectomy pain perhaps it can prevent further complications such as dehydration, infection and bleeding.

1. INTRODUCTION

Tonsillectomy is a common procedure done by otorhinolaryngologists. The operation results in an open wound therefore can cause significant post-operative pain. The pain may impair the swallowing process and cause the patients to refuse to eat, resulting in a delay of return to a normal diet, dehydration and post-tonsillectomy haemorrhage [1]. The reported morbidity rate caused by post-operative pain and secondary post-tonsillectomy haemorrhage was about 1 in 35,000 tonsillectomy cases [2], [3].

There have been many studies introducing different surgical techniques and medications to find the best treatment to alleviate pain in post-tonsillectomy patients. In this study, we focus on the use of local analgesic by comparing different modes of delivery using same contents of medication, benzydamine hydrochloride (BHCL). BHCL has analgesic, anti-inflammatory, anti-pyretic, anti-microbial and anti-fungal properties [4]. BHCL mouthwash or throat spray in concentration of 0.15% is commonly used for relief of inflammatory conditions of the mouth and throat, such as in the case of oral ulcer, mucositis, pharyngitis and laryngitis [5]. BHCL action is exclusively based on a patient's perception of pain through local anaesthetic properties [3].

From a physiology point of view, when there is a presence of fluid in the oral cavity, palatopharyngeus and palatoglossus will lower the soft palate until it reaches the base of the tongue as a protective mechanism. Thus, most of the solution will be confined in the oral cavity and minimal amount will goes to the oropharynx area. This physiology mechanism also applies during gargling. [6] in their study found that spray is more effective at reaching the tonsils and posterior pharyngeal wall compared with rinse and gargle. Other studies showed that using a throat spray method for analgesia such as fusafungine spray or lidocaine spray in post-tonsillectomy gives a significant effective result [8], [9].

However, there is no reports of studies that compare the two methods of delivery for local anesthesia in post-tonsillectomy patients. There is an assumption that the use of direct sprays will directly deliver the medication to the targeted area, prolonging contact with the mucosa. This, in turn, it would result in more tissue absorption and the effect of medication will become more effective. This study was therefore conducted to compare the effectiveness of BHCL gargle versus throat spray in pain control among post-tonsillectomy patients.

2. METHODOLOGY

2.1 Subjects

This study is an interventional open-labelled prospective randomized controlled trial. A total of 92 patients who underwent tonsillectomy and fulfilled the inclusion and exclusion criteria were recruited. These are patients who attended ORL clinics in two tertiary hospitals. They were randomly divided into two groups (group A- gargle, group B- throat spray) using the Research Randomizer software. The inclusion criteria were that all patients were indicated for tonsillectomy/adenotonsillectomy operation with a history of recurrent or chronic tonsillitis/adenotonsillitis, and those aged between 13 and 40 years old. Patients who underwent tonsillectomy/adenotonsillectomy with other procedures in the same setting such as nasal operation or Cauterization Assisted Palatal Stiffening Operation (CAPSO), who were allergic to BHCL and those unable to follow instructions were excluded.

2.2 Surgical procedures and intervention

For all patients who agreed to participate in the study signed a prepared written consent. For those who were minors, parental consent was obtained. All selected patients underwent operations conducted by surgeons with at least two years' experience in tonsillectomy operations. This was to avoid the possibility of additional pain imposed on to patients due to unnecessary injury if an inexperienced surgeon did the operation.

Intraoperatively, all patients received the same analgesia (one dose Intravenous Parecoxib Sodium 40 mg and Intravenous Morphine 0.1 mg/kg) administered by an anaesthetist. Surgeons also used the same procedure, which was the cold dissection technique, on all patients involved in this study. This was to standardize the method of surgery so that the pain is not influenced by the technique or instrument used.

Post-operation patients received the medications as randomized. Patient in the gargle group applied 15 mls per gargle for 30 seconds each, while patients in the throat spray group applied the medication directly to tonsillar fossa with two puffs on each side every three hours, except during sleep, for seven days. If patients from either group still developed pain after using the medications, they would take Cap Celecoxib 200 mg upon need, at the maximum two times per day, as a rescue medication. If upon using extra analgesia, the pain was still not controlled, the patients would go to the emergency department or contact the primary investigator for further treatment. Both groups used the medication for one-week.

The first pain score was assessed at least six hours post operation and when patients were fully conscious from the general anaesthesia effect before starting pain medication. This first pain score was used as the baseline pain score. Pain scores were then assessed again on Days 1, 4 and 7 during post operation follow up using the Visual Analogue Score (VAS). We assessed the improvement of pain scores between the two groups of medications for Days 1, 4 and 7. Besides the pain score, patient oral intake, other co-morbidities related to post-tonsillectomy pain such as bleeding and otalgia, and compliance to administering the medication were also assessed.

2.3 Statistical analysis

Statistical analysis was done using SPSS for Windows 22. Pain score differences between groups at several occasions (Days 1, 4 and 7) were evaluated using repeated measure ANOVA test, as we measured a variable on several occasions for each subject. This was consistent with a previous study done to compare the effectiveness of two medications used on several occasions [9].

3. RESULTS

A total of 92 patients were recruited in this prospective randomized controlled study and all were included for further analysis. They were divided into two groups, with 46 patients in the gargle group and another 46 patients in the throat spray group.

3.1 Demographics

Out of the 92 enrolled patients, 51 (55.4%) patients were female and 41 (44.6%) were male. The patients' age ranged from 13 to 30 years old with a mean age of 23 years. The majority, 88, were Malay (95.7%). The indications for tonsillectomy were mostly recurrent tonsillitis, as seen in 72 (78.3%) patients. Sixty-six (71.7%) patients had tonsillitis Grade 3, followed by 20 (21.7%) patients with Grade 2 and six (6.5%) Grade 4.

3.2 Treatment efficacy

In the analysis of within-group difference, it was found that among the gargle group, there was no significant difference of pain scores between Day 1 and Day 4 post operation ($p = 0.060$). However, there were significant difference of pain scores between Day 1 and Day 7 ($p < 0.001$) and between Day 4 and Day 7 ($p < 0.001$).

However, for the throat spray group, significant difference in the pain scores were found for all comparisons (Day 1 and Day 4, Day 1 and Day 7, Day 4 and Day 7) (Table 2). In the analysis of between-group difference, VAS pain scores showed a significant difference between gargle and throat spray ($p < 0.001$) (Table 3).

Comparisons between different time groups (Day 1, Day 4, Day 7) for pain scores were statistically significant for Day 4 and Day 7 but not for Day 1 (Table 4). The mean pain score was lower in the spray group compared to the gargle group and the mean difference was higher during Day 4. Thus, we concluded that pain scores were lower in the spray group compared to the gargle group.

Table 1: Demographics and characteristics of both study groups

Demographic characteristics	**BHCL [*n* (%)]**	
	Gargle (*n*=46)	**Throat Spray (*n*=46)**
Age[a]	23	22
Sex		
Male	23 (25.0%)	18 (20.0%)
Female	23 (25.0%)	28 (30.0%)
Race		
Malay	44 (47.8%)	44 (47.8%)
Chinese	1 (1.1%)	2 (2.2%)
Indian	0 (0.0%)	0 (0.0%)
Others	1 (1.1%)	0 (0.0%)
Indications		
Recurrent Tonsillitis	35 (38.0%)	37 (40.2%)
Chronic Tonsillitis	4 (4.3%)	3 (3.3%)
Obstructive Symptoms	7 (7.6%)	3 (3.3%)
Others	0 (0.0%)	3 (3.3%)
Tonsil Size		
Grade 1	0 (0.0%)	0(0.0%)
Grade 2	7 (7.6%)	13 (14.1%)
Grade 3	36 (39.1%)	30 (32.6%)
Grade 4	3 (3.3%)	3 (3.3%)

[a] Mean (SD)

Table 2: Comparison of pain score (VAS) within each BHCL group with time

Comparison	**BHCL Gargle**		**BHCL Throat Spray**	
	Mean difference (95% CI)	***p*-value**	**Mean difference (95% CI)**	***p*-value**
Day 1 – Day 4	0.48 (-0.02, 0.97)	0.060	1.37 (0.91, 1.82)	< 0.001
Day 1 – Day 7	2.04 (1.49, 2.60)	<0.001	2.67 (2.19, 3.16)	<0.001
Day 4 – Day 7	1.57 (1.10, 2.03)	<0.001	1.30 (0.90, 1.71)	<0.001

Repeated measure ANOVA within group analysis was applied followed by pairwise comparison with 95% confidence interval adjustment by Bonferroni correction.

Table 3: Overall mean differences of pain score between gargle and spray methods.

BHCL group	**Mean (95% CI)**	**Mean difference (95% CI)**	**F-stats (df)**[a]	***p*-value**
Gargle	4.18 (3.80, 4.56)	0.96 (0.43, 1.50)	12.65 (1)	< 0.001
Spray	3.22 (2.84, 3.60)			

[a]Post-hoc test not applicable for two treatment groups

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Table 4: Comparison of pain scores between two treatment groups based on time

Time	BHCL group	Mean Pain Score	Mean difference (95% CI)	*p*-value
Day 1	Gargle	5.02	0.46	0.132
	Spray	4.57	(-0.14, 1.05)	
Day 4	Gargle	4.54	1.35	< 0.001
	Spray	3.20	(0.67, 2.03)	
Day 7	Gargle	2.98	1.09	< 0.001
	Spray	1.89	(0.50, 1.68)	

Repeated measures ANOVA between group analysis with regard to time was applied. Assumption of normality, homogeneity of variances and compound symmetry were checked and fulfilled.

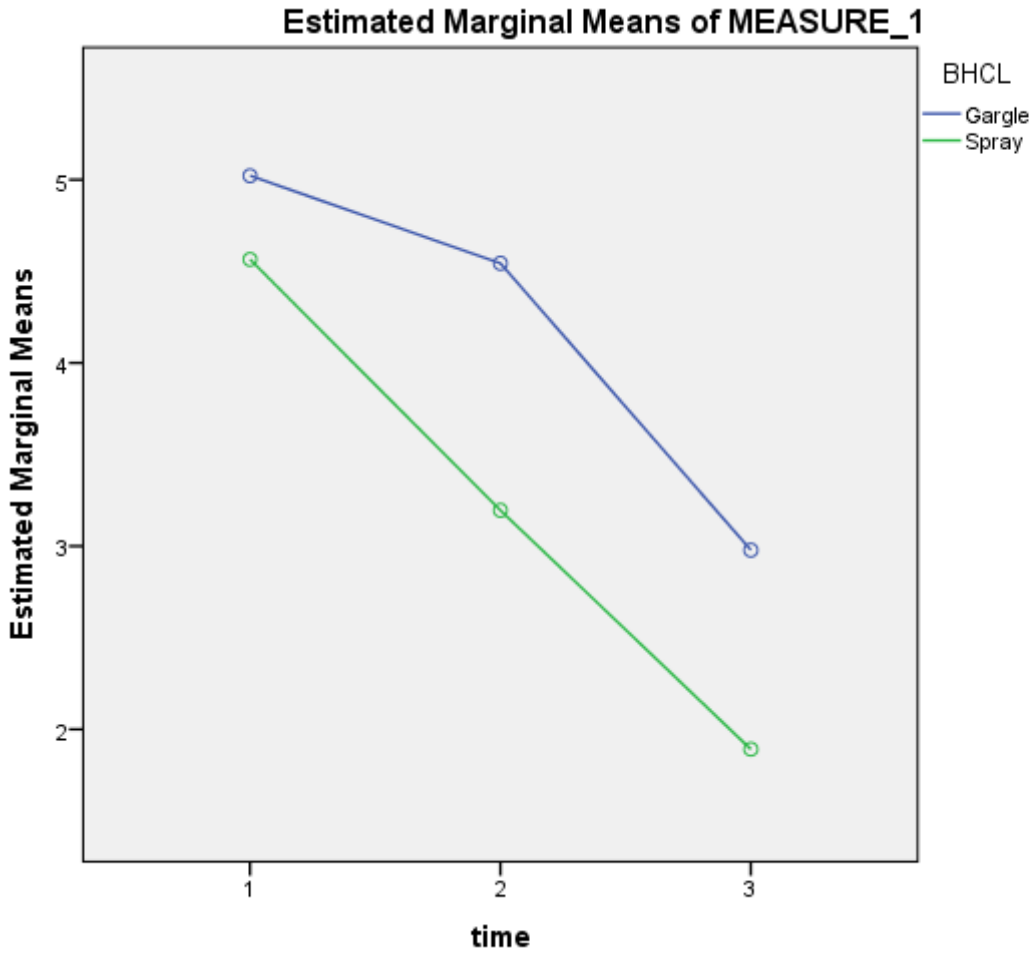

Fig 1. Pain score (VAS) comparison between BHCL gargle group and BHCL throat spray group. Time points 1- Day 1 post operation, 2- Day 4 post operation, 3- Day 7 post operation.

Throughout the study, three (3.2%) patients, all from the gargle group, developed bleeding. One of the bleeding cases occurred on day 1 after surgery that was most probably due to the surgical technique applied. The case required examination under general anaesthesia to stop the bleeding. In another two patients, bleeding occurred at Day 4 post operation and required re-hospitalization and both patients were treated conservatively. Forty (43.5%) patients had otalgia, and they were from both groups and most occurred on Day 1 and Day 4 post operation. In the gargle group, 17 (18.5%) occurred at Day 1, nine (9.8%) at Day 4 and four (4.3%) at Day 7. In the spray group, six (6.5%) had otalgia that occurred at Day 1, three (3.2%) occurred

at Day 4 and one (1.1%) at Day 7. Thirty-two (34.8%) patients needed to take rescue analgesia due to uncontrolled pain. In the gargle group, 11 (12.0%) patients needed rescue analgesia at Day 1, seven (7.6%) at Day 4 and five (5.4%) at Day 7. While in the spray group, four (4.3%) patients required rescue analgesia at Day 1, three (3.3%) Day 4 and two (2.2%) at Day 7. For oral intake, the majority of patients in both groups had moderate to good intake at Days 4 and 7.

4. DISCUSSION

This study was designed to compare the effectiveness of two methods of BHCL application for post-tonsillectomy pain control. We have demonstrated that BHCL throat spray is superior to BHCL gargle in reducing post-tonsillectomy pain and the difference between the two methods is statistically significant. To our knowledge, this is the first study conducted to compare different methods of delivery of local analgesia using BHCL in post-tonsillectomy pain control.

Local analgesia was used in this study as it plays a major role in controlling post-tonsillectomy pain. [10] had suggested that post-tonsillectomy pain developed due to an inflammation process, irritation of nerve ending and cyclical spasm of the exposed pharyngeal muscles after removal of tonsil. There have been many studies on local anaesthesia either using pharmacological or non-pharmacological techniques applied before, during or after a tonsillectomy operation. [11] found that early postoperative pain was relieved slightly faster in Tualang honey plus antibiotic group. [12] conducted a study regarding efficacy of TachoComb® (a fibrinogen/thrombin-based collagen fleece) that also showed significant results in reducing pain and risk of bleeding. [9] used clindamycin with the assumption that using antibiotics would reduce bacteria colonization and cause less pain. However, this study did not show a significant result.

Systemic analgesia also gives effective result in reducing pain, however studies have showed that they are associated with other side effects. In the NSAIDs group (e.g. Salicylate, Ibuprofen), these have been associated with increased incidence of haemorrhage due to their effect as an inhibitor for prostaglandin and platelet while the opioids group, which are widely used, have known side effects such as vomiting, over sedation and risk of respiratory depression [13]. In this study, no patients reported any medication adverse effects, either from gargle or throat spray group. BHCL has alkaline pH which becomes more concentrated in inflamed tissue but not in normal tissue that can reduce systemic absorption [14], and reduced risk of systemic adverse reaction.

This study also supports our hypothesis by using throat spray, the medication will directly reach the operation site, compared to the gargle. In addition, for throat spray, there is a prolonged contact time of the medications at the targeted area compare to the gargle. As for the gargle, physiologically with the presence of fluid in the oral cavity, the palatoglossal and palatopharyngeus muscles come in contact with the base of the tongue as a protective mechanism to protect aspiration. As a result, the solution is mainly confined in the oral cavity and minimal amount end up reaching the tonsillar fossa or operation site. However, there are no proper tools yet to objectively measure how far the medication solution can reach the oropharynx region by gargling and no previous study has been performed to test this hypothesis.

[15] compared the effectiveness of Ketoprofen Lysin Salt mouthwash versus BCHL mouthwash in treating acute pharyngeal inflammation. From this study, only 25% of BHCL and 32% of KLS experienced improvement in pain more than 50% after six hours using the medication. It showed that both mouthwashes used as a gargle gave minimal effect in pain control. However, a study done by [7] using fusafungine throat spray showed significant pain improvement in post tonsillectomy patient from Day 7 to Day 14 post operation. Another study done by [8] used lidocaine spray and gave significant pain score results compared to a placebo,

on Day 1 and Day 3. In this study 4 mg/kg of 10% lidocaine HCl was sprayed onto the tonsillectomy fossa four times a day compared with placebo using 9% NaCl. It was showed that throat spray gave positive results compare to the gargle. However, there are no reported study comparing both methods of delivery using same medications.

BHCL was chosen in this study due to it availability in both gargle and throat spray preparation. It has anti-inflammatory, analgesic and antimicrobial properties which can help in reducing pain and promote healing and the recovery process. It also has anti-TNF alpha effects that may help in the management of mucosal ulcerations [16]. Its use is recommended for relief of inflammation occurring over the oral cavity, soft tissue and skin. Action of BHCL is mainly via the patient's perception of pain through local anesthetic properties [15].

In this study, we tried to avoid other factors that can influence post-tonsillectomy pain such as surgeon factors, instruments factors and anaesthetic drugs by standardizing it in the protocol. All the surgeons operating on the patients in this study have at least two years of experience in doing the operation. We were unable to limit the procedures to be performed by one surgeon only as this study was conducted at two centres and involved a university hospital. The instrument used during the procedure was also standardized to cold instrument only as it is available at both centres. Some newer surgical instruments such as Harmonic Scalpel and Coblator which theoretically operated at lower temperatures cause less thermal tissue injury and less pain. [17] reported from their study comparing coblator and electrocautery showed that using coblator result in decreasing post-operative pain compared to electrocautery.

In this study, we assessed pain levels by directly asking the patients using Visual Analogue Score (VAS) as all our patients were aged thirteen and above and were able to give their own pain score. We did not include children less than 12 years old as most of the children would need help from their parents to provide a score and this would create a bias in the assessment. However, although the VAS is a good scale and are widely used and all our subjects give their own pain score, the accuracy of the pain score is still questionable as pain itself is a subjective measurement. The pain threshold also depends on the personal and private experience of each patient. Thus, we also need to evaluate other elements that may be associated with poor control of pain such as development of other morbidity (otalgia and bleeding), extra analgesia consumption and oral intake. Otalgia may have a strong association with poor pain control in view of referred pain from the same nerve supply. In this study we did assess the development of otalgia post-operatively, however no further analysis was done to look for an association between pain score and otalgia.

Throughout the study, no major complications from medications were reported except several patients reported a stinging sensation during spraying or gargling. However, the sensation was tolerable and the patients were still able to continue the medication. There were also some minor complications from surgery such as injury to the lips and tongue due to instruments handling which did not affect the pain levels of the patient.

5. CONCLUSION

Throat spray is a more effective method to deliver local analgesia in post-tonsillectomy patients due to the direct application of medication into the tonsillar fossa compared to the gargle. Effective local analgesia will help to control post-tonsillectomy pain which can encourage patients to have good oral intake and prevent further complications such as dehydration, infection and bleeding.

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