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EVALUATION OF TOPICAL ANALGESIC AND ANESTHETIC EFFICACY OF 0.15% BENZYDAMINE HYDROCHLORIDE MOUTHWASH IN NON-INFLAMED MUCOSA

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ABSTRACT

Benzydamine hydrochloride is a non-steroidal drug which has analgesic, anesthetic, anti-inflammatory, antipyretic and anti-microbial properties. Although many pharmacological effects of benzydamine have been established, the exact mechanism of action of benzydamine hydrochloride is yet unknown. The aim of this study is to evaluate the topical analgesic and anesthetic efficacy of 0.15% benzydamine hydrochloride mouthwash with placebo in non-inflamed mucosa. This study involved 20 volunteers with healthy gingiva who were subjected to two sessions of drug application at an interval of 3 days. The subjects were topically treated with test drug (0.15% benzydamine hydrochloride mouthwash) or placebo in a random manner. At each session, after a total of 3 minutes from drug application, a 26-gauge needle was injected into the test site to a depth of 2-3mm. During and immediately after the needle insertion, each participant quantified the pain perceived using a 10-point visual analog scale (VAS). Analysis

with t-test showed that there was a significant difference between the pain scores with 0.15% benzydamine hydrochloride mouth rinse and normal saline mouth rinse ($P < 0.05$). In conclusion 0.15% Benzydamine hydrochloride Mouthwash produces significant topical analgesia and anesthesia even in non-inflamed mucosa.

Keywords: Benzydamine, Anesthesia, Topical analgesia, Pain, Visual analog scale

INTRODUCTION

Benzydamine hydrochloride is a non-steroidal drug which has analgesic, anesthetic, anti-inflammatory, antipyretic and anti-microbial properties **[1-5]**. Benzydamine is structurally unrelated to corticosteroids and acidic salicylates such as phenylbutazone and indomethacin. The action of benzydamine is believed to be mediated by the prostaglandin system **[3-5]**. The drug is primarily metabolized in the liver and the derivatives of free benzydamine are excreted by the kidney and in the bile **[1, 3, 5]**. The metabolites are inactive. After systemic administration, 50% of the dose is recovered as metabolites and unchanged drug in the urine in 24 hours. A plasma level of approximately 50% of that of a swallowed dose was reported with rinsing **[5]**. Urinary excretion was complete 3 to 4 days after rinsing or swallowing. Repeated administration for 7 days did not result in substantial accumulation of the drug in plasma. Benzydamine has not been associated with major toxicity, and no allergic reactions have been reported **[6-8]**. Benzydamine was formerly available as tablets for systemic usage while it is currently available only for local application. It is available as a mouth gargle, pump spray, gel and ointment preparations. This form of locally acting benzydamine hydrochloride establishes its effect on the soft tissue, skin and joints when applied topically. It is widely used as a topical analgesic agent and has very negligible side effects **[9]**. Although many pharmacological effects of benzydamine have been established, the exact mechanism of action of benzydamine hydrochloride is yet unknown.

Benzydamine is classified under non-steroidal anti-inflammatory drugs (NSAIDs). Unlike common anti-inflammatory drugs which are organic acids or metabolized to acids, benzydamine is a base usually formulated as its hydrochloride salt which is highly lipid soluble in unionized form **[10]**. Benzydamine hydrochloride is identified as a topical non-steroidal anti-inflammatory agent that also has a local anesthetic activity **[11]**.

The recommended dose of benzydamine is 15 ml of a 4-mmol/L solution of hydrochloride salt in water, when administered as a mouthwash **[12]**. This high concentration is transient because when benzydamine solution is used as a mouth rinse the remaining material is diluted by saliva. The level of diffusion of the drug into the tissues is not known but it is probable that the surface concentrations are higher than 100 ktmol/L. The pH of commercially available benzydamine mouthwash is typically 4.5-5.0 but is unbuffered, so it should rise quickly to salivary pH which is about 7. Adjudicating from the uptake of other weakly basic, lipid-soluble drugs into the buccal tissue, only a limited amount should be absorbed into the buccal mucosa during the recommended 30 seconds of mouthwash application [**13, 14]**. Studies on topical anesthetic effect of benzydamine hydrochloride is limited.

The aim of this study is to evaluate the topical analgesic and anesthetic efficacy of 0.15% benzydamine hydrochloride mouthwash with placebo in non-inflamed mucosa.

MATERIALS AND METHODS

This study involved 20 volunteers, 10 women and 10 men from 20-30 years of age.

Inclusion criteria:

1. People who were willing to participate in the study.
2. Volunteers without any systemic disease and not under any medication.
3. Volunteers who had a healthy gingiva.

Exclusion criteria:

1. Volunteers with preexisting systemic disease.
2. Volunteers with known allergies to topical anesthetic agents and NSAIDs.

The study was conducted after obtaining an approval from the Institutional ethical committee of Saveetha Dental College and Hospital, Saveetha Institute of Medical and Technical Sciences, Chennai. Volunteers were informed about the requirements and complications of the study with a patient information sheet following which their informed consent was obtained. They were informed that they would be given drugs and placebo on a double-blind basis. The drugs used were 0.15% benzydamine hydrochloride mouth rinse and normal saline mouth rinse

METHODOLOGY

The volunteers were subjected to two sessions of drug application at an interval of 3 days. The subjects were topically treated with test drug (0.15% benzydamine hydro-chloride mouthwash) or placebo randomly.

The gingival mucosa in relation to the maxillary right central incisor was chosen as the test site in all the subjects. 15 ml of undiluted 0.15% benzydamine hydrochloride mouthwash or normal saline was given to the participants and they were asked to hold the solution in the maxillary anterior vestibular region such that the solution is in direct contact with the anterior mucosa for 1 minute and then to spit the solution. At each session, after a total of 3 minutes from drug application, a 26-gauge needle was injected into the test site to a depth of 2-3mm. During and immediately after the needle insertion, each participant quantified the pain perceived using a 10-point visual analog scale (VAS).

The collected data was subjected to statistical analysis. Statistical analysis of the clinical variables was done using Statistical Package of Social Science (SPSS) version 23 (IBM Corporation, USA, 2012). T test was done to find their statistical significance. Level of significance was set as ≤0.05.

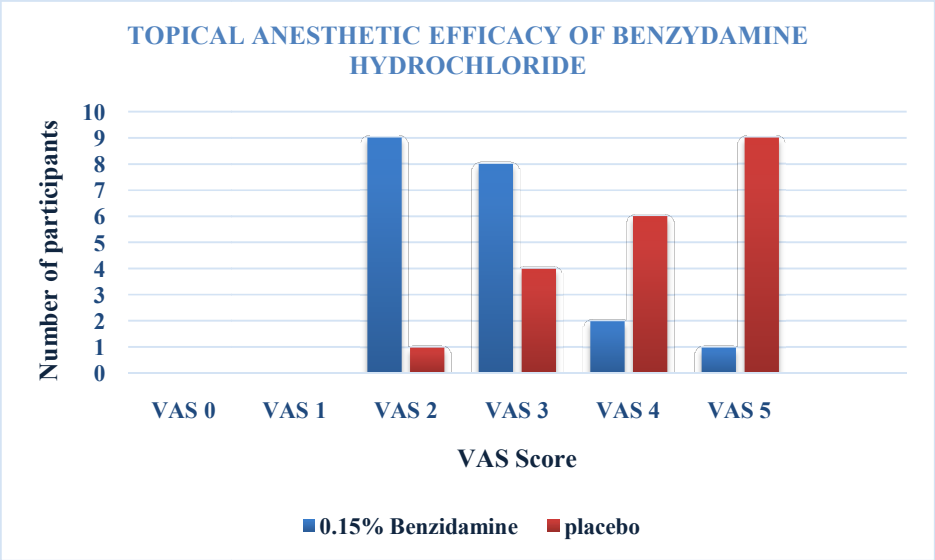
RESULT

The mean values of VAS score after 0.15% benzydamine hydrochloride mouthwash and normal saline mouth rinse application were 2.65 and 4.4 respectively **(Table 1)**. **Graph 1** shows the comparison of visual analog score of Benzydamine hydrochloride mouthwash and normal saline mouth rinse. Analysis with t-test showed that there was a significant difference between the pain scores with 0.15% benzydamine hydrochloride mouth rinse and normal saline mouth rinse ($P < 0.05$).

Table 1: Mean pain score values with 0.15% benzydamine hydrochloride and placebo

PATIENT	0.15% BENZYDAMINE	PLACEBO
Patient 1	2	4
Patient 2	3	5
Patient 3	2	5
Patient 4	3	4
Patient 5	4	4
Patient 6	2	5
Patient 7	4	6
Patient 8	3	5
Patient 9	2	4
Patient 10	3	3
Patient 11	2	4
Patient 12	2	5
Patient 13	3	4
Patient 14	4	5
Patient 15	3	3
Patient 16	2	5
Patient 17	1	3
Patient 18	3	4
Patient 19	2	4
Patient 20	3	6
Mean	53/20=2.65	88/20=4.4

The value of p is < 0.00001. The result is significant at p ≤ 0.05



Graph 1: Visual Analogue Scores with 0.15% benzydamine hydrochloride and placebo

DISCUSSION

The result of this study shows that 0.15% benzydamine hydrochloride mouth rinse has a topical anesthetic potential even on non-inflamed mucosa which was evident from the fact that it showed a higher efficacy in reducing the pain perceived during the needle insertion than placebo.

Many studies were conducted to evaluate the efficacy of benzydamine hydrochloride in relieving the pain perceived from sore throat and many inflammatory conditions such as chemotherapy induced mucositis, stomatitis, pharyngitis, tonsillitis and aphthous ulcers. These studies on topical oral application of benzydamine hydrochloride have shown that benzydamine mouthwash significantly relieves pain from tonsillitis, pharyngitis, oropharyngeal mucositis and chemotherapy-induced mucositis, where the analgesic activity of benzydamine is independent of its anti-inflammatory action **[15-18]**.

Some studies also have shown that topical benzydamine had no pain-relieving effect on tonsillectomy and a very little pain-relieving effect on recurrent aphthous stomatitis because of the topical anesthetic effect of benzydamine **[19, 20]**.

The topical application of benzydamine may usefully decrease the pain and inflammation following dental surgery. A study demonstrated that the oral administration of 50 mg benzydamine had no effect on pain and trismus following impacted molar extraction **[2]**. Although another study showed that administration of a 1.5% oral spray produced analgesia

following third molar extraction **[21]**. In another study done by Simard-Savoie S *et al* **[22]** a significant anesthetic effect of topically applied benzydamine on normal mucosa has been reported.

Thus, this study has shown that topical form of benzydamine as 0.15% benzydamine hydrochloride mouthwash, significantly produces an analgesic and anesthetic effect over a non-inflamed mucosa. Further studies on other potentials of benzydamine, with a larger sample size can produce a more definitive evidence for the efficacy of the drug to diminish pain perception. Knowledge of the concentrations of the drug in tissues is required to put the drug in use at various non-inflammatory conditions as a topical agent to alleviate pain and produce significant analgesia.

CONCLUSION

Within the limitations of this study it can be concluded that

1. Topical anesthetic efficacy of benzydamine hydrochloride mouthwash was better than placebo.
2. 0.15% Benzydamine hydrochloride Mouthwash produces significant topical analgesia and anesthesia even in non-inflamed mucosa.

CONFLICTS OF INTEREST: The authors have no conflicts of interest.

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