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Original Article

Lidocaine lozenges for pharyngeal anesthesia during upper gastrointestinal endoscopy: A randomized controlled trial

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Abstract

Background and Objectives: A novel lozenge formulation with advantages of ease of drug administration, palatable taste and improved patient compliance could be the preferred mode of topical pharyngeal anesthesia during upper gastrointestinal endoscopy (UGE). This randomized, open-label, active-controlled study was conducted to evaluate the efficacy and safety of lidocaine lozenges versus lidocaine spray in the diagnostic gastroduodenal endoscopy in Indian patients. **Subjects and Methods:** Two hundred and forty-seven patients of either sex (18-80 years) undergoing diagnostic gastroduodenal endoscopy were randomized either to; lidocaine lozenge 200 mg or lidocaine spray 200 mg to be applied as a single dose before gastroduodenal endoscopy. Ease of procedure, level of gag reflex, ease of application of the local anesthetic, and investigators global assessment were the primary efficacy endpoints. Need for rescue medication and patient's global assessment were secondary efficacy endpoints. The incidence of any adverse event was the safety endpoint. Between groups, comparison was done by using appropriate statistical test. **Results:** Investigator reported significantly lesser procedural difficulty ($P = 0.0007$) and suppressed gag reflex ($P < 0.0001$) during UGE with lidocaine lozenge compared to spray. Ease of application of local anesthetic was reported easy in significantly more patients as compared with lidocaine spray ($P = 0.001$). Global assessment by patient and physician was favorable toward lozenge. Incidences of adverse events were similar in both the groups. **Conclusions:** The study suggests that lidocaine lozenges are an easier way of applying local oropharyngeal anesthesia, produces better suppression of gag reflex and makes the procedure easier when compared with lidocaine spray.

Key words

Gastroduodenal endoscopy, lidocaine lozenge, lidocaine spray, upper gastrointestinal endoscopy

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Introduction

Esophagogastroduodenoscopy or upper gastrointestinal endoscopy (UGE) is a valuable screening, diagnostic, and therapeutic procedure for the upper gastrointestinal tract. However, nearly 40% of patients poorly tolerate unsedated UGE, and 10% of patients experience severe discomfort despite the use of an ultrathin endoscope. Patient's discomfort can

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interfere with the endoscopist's examination and can evoke cardiopulmonary complications, including cardiac arrhythmia, myocardial ischemia, aspiration, and hypoxemia.[1]

Local anesthetic agents during UGE are widely used as a single method or in combination with intravenous anesthetic agents.[2] There is compelling evidence for the use of topical pharyngeal anesthesia during UGE, and it is reported to improve ease of the procedure, as well as patient tolerance.[3-5] Local anesthesia in UGE is also useful and beneficial in reducing the gag reflex. Number of gag events are reported to decrease in patients anaesthetized with pharyngeal lidocaine.[6]

Lidocaine-induced pharyngeal anesthesia is known to decrease cough, gag reflex and overall airway hyper-reactivity, enhancing patient compliance and practitioner satisfaction.[7] As a topical pharyngeal anesthesia, lidocaine is the primary choice of drug, often applied as either a spray, gargle or a viscous solution.

Spray of lidocaine has been reported to produce gag reflex by itself and also has a bitter taste[8] while lidocaine solution for gargles are viscous in nature, and they also have a bitter taste. Use of viscous gargle solutions requires accurate dispensing, failure of which may lead to variable dosing and level of anesthesia. Improper gargle technique may also lead to inadequate pharyngeal anesthesia. The bitter taste of lidocaine can decrease patient's acceptance of UGE.[9] Laryngotracheal lidocaine spray before intubation is also reported to be associated with an increased risk of postoperative throat problems. Additives in lidocaine spray, not lidocaine itself, are reported to contribute to sore throat, hoarseness, dysphagia, and bitter taste.[10]

Lozenge is a solid, single-dose preparation designed to be sucked to obtain a local effect in the oral cavity and the throat. The lozenge dissolves over 5-10 min in the mouth and releases the drug dissolved in the saliva.[11] It can deliver drug multi-directionally into the oral cavity and to the pharyngeal mucosa,[12] and extends the time of contact of drug in the oral cavity to elicit significant pharyngeal anesthesia secondary to swallowing of saliva mixed with lidocaine. Lidocaine lozenges have been approved by the Drugs Controller General of India, and are made available in Indian market by Troikaa Pharmaceuticals Ltd. under the brand name of Xynova Lozenges since November 2009.

Advantages like ease of drug administration, palatable taste and improved patient compliance would make lidocaine lozenge a preferred mode of topical pharyngeal anesthesia. This study was conducted to evaluate the efficacy and safety of Lidocaine Lozenges versus lidocaine spray as a pharyngeal anesthetic during UGE.

Subjects and Methods

This randomized, open-label, parallel group, active controlled study was conducted at five centers in India. The study was initiated at each center after getting ethics committee approval from respective centers and after registration in clinical trial registry-India (CTRI Reg: No CTRI/2010/091/001217). Study was conducted as per ethical guidelines for biomedical research on human participants from Indian Council of Medical Research (India), good clinical practice guideline and schedule Y from Central Drugs Standard Control Organization (India), and International Conference on Harmonization guideline for good clinical practice. Before subjecting to the screening procedure, a written informed consent was taken from all the patients after explaining the study procedures and other necessary information as per ethics committee approved informed consent document.

The patients of either sex, aged between 18 and 80 years, advised for a diagnostic gastroduodenal endoscopy were screened for eligibility. During screening, medical history was obtained, and physical examination and laboratory tests were performed. Patients with medical history of significant impairment of hepatic, renal or cardiac functions and respiratory disease such as asthma, bronchitis or chronic obstructive pulmonary disease were excluded. Patients with a history of hypersensitivity to amide type of local anesthetics or undergone emergency surgery or surgery needing hospitalizations were excluded from the study. Women of childbearing age underwent the urine pregnancy test. Pregnant and lactating women were excluded from the study.

Two hundred and forty-seven enrolled patients were randomized to receive one of the two study treatments as per computer generated randomization sheet to receive either lidocaine lozenge 200 mg (Xynova 200, manufactured by Troikaa Pharmaceuticals Ltd, India) or lidocaine 10% spray (LOX 10%, manufactured by Neon Labs) in amount equivalent to 200 mg of lidocaine. One unit of lidocaine lozenge (equivalent to 200 mg lidocaine) was placed in the mouth given 15 min prior to procedure and patient was instructed to suck (one unit) by rolling it side to side till it dissolves. In lidocaine spray group, total 20 sprays of 10% lidocaine (equivalent to 200 mg lidocaine) were administered 15 min before the procedure in 2 consecutive 1 min interval (each interval consisted of 10 sprays [10 mg/spray]).

Investigator assessed the efficacy and safety of local anesthesia in both the treatment groups after completion of the procedure. Immediately after the procedure, investigator filled the questionnaire evaluating (1) Ease of the endoscopy procedure: Recorded on an ascending scale from 0 (easy) to 5 (difficult). The criteria used to evaluate the procedural difficulty were presence of excessive gag reflex, retching, restlessness, and combativeness. (2) Level of Gag reflex: Assessed during the procedure and recorded on a scale of 0-5 (0 being strong gag reflex and five being absence of gag reflex) and (3) Ease of application of local anesthetic: Measured as easy, adequate or difficult.

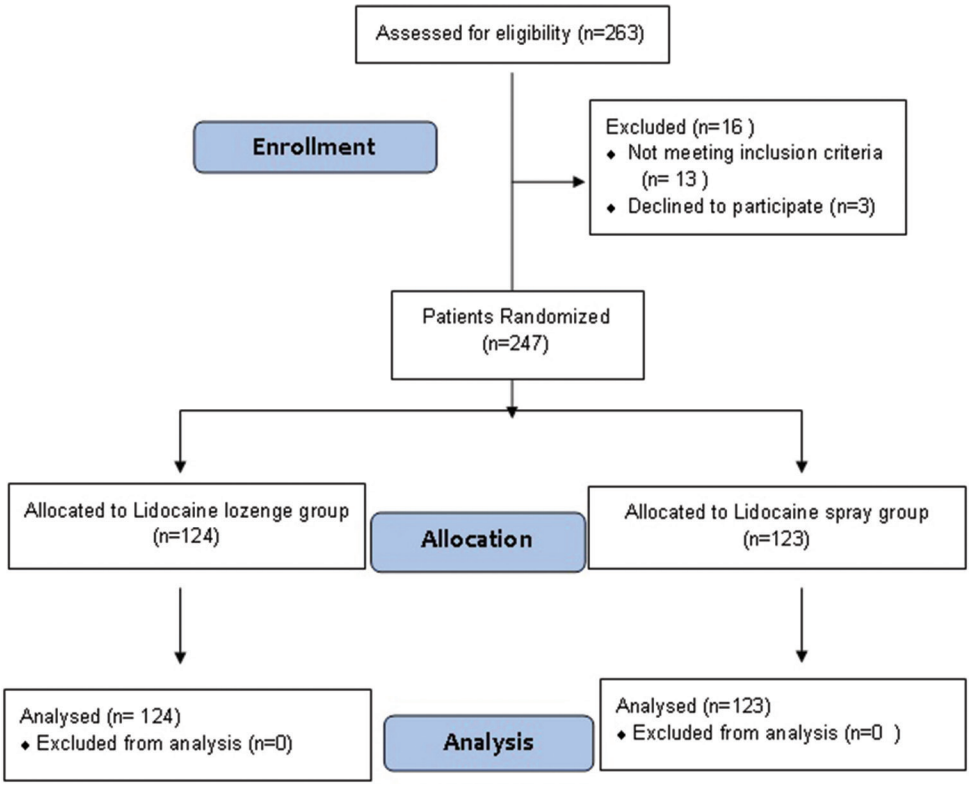

Figure 1: Patient disposition chart (*n* = number of patients)

Measurement of vital parameters and physical examination was performed before and after procedure to assess the safety. Any adverse events observed or reported during the study period were noted in the case record form. At the end of the study, overall efficacy and safety of the study treatments were rated by patients and physician on a global assessment scale.

Injection midazolam (dose titrated to each patient) for sedation was given if required as rescue medication according to investigator's assessment in patients having discomfort (excessive gag, retching, restlessness, combativeness) during the procedure.

Primary efficacy endpoints were efficacy of topical analgesia as determined by ease of the procedure, level of gag reflex, ease of application of local anesthetic and investigators global assessment. Need for sedation and patient's global assessment were the secondary efficacy endpoints. Incidence of any adverse event was included as a safety endpoint.

Statistical analysis

The sample size was calculated to detect difference of 0.46 in ease of procedure measured on scale 0 (easy) to 5 (difficult), with standard deviation of 1.1[8] to achieve 90% power at significance level of 0.05. This gave required sample size of 121 patients in each group.

For continuous variables, values are expressed as mean ± standard deviation and comparisons between treatments were made using unpaired Student's *t*-test. Between groups comparison was done by using appropriate parametric or nonparametric tests, depending on the type and distribution of data. For categorical outcomes, between groups comparison were performed using Chi-square test or fisher's exact test depending on data. All statistical analysis were performed using Statistica (data analysis software system), version 11, StatSoft, Inc., Oklahoma, USA (2012). A $P < 0.05$ was regarded as "statistical significant difference" between the two treatment groups.

Results

Total 263 patients were screened, 247 patients were enrolled and randomized, with 124 patients in lozenge group and 123 patients in a spray group. All 247 patients completed the study, and their data were included for statistical analysis [Figure 1]. A brief description of demographic data for both the study groups is presented in Table 1.

Ease of endoscopic procedure, as evaluated by investigator on a scale of 0 (easy) to 5 (difficult), was reported easier with the use of lidocaine lozenge (0.97 ± 0.84) when compared to lidocaine spray [1.30 ± 0.89; Figure 2]. The difference was statistically significant between the two groups ($P = 0.0007$).

The level of gag reflex during the UGE, assessed by the investigator on a scale of 0 (strong) to 5 (absent), also was found to be significantly suppressed in patients of lidocaine

lozenge group (3.79 ± 1.15) when compared to lidocaine spray group [3.21 ± 1.25; Figure 3]. The difference between the two groups was statistically significant ($P < 0.0001$).

The ease of application of local anesthetic, assessed by the investigator at the end of the procedure, in lozenge and spray group was found to be easy in 110 patients (88.71%) versus 86 patients ([69.22%]; [Figure 4]), respectively. The difference was statistically significant between the two groups ($P = 0.001$).

Requirement of rescue medication was similar in both study groups. 5 out of 124 patients (4.03%) in lozenge group and 2 out of 123 patients (1.62%) in spray group required rescue medication ($P > 0.05$).

Table 1: Demographic characteristics

Parameters	Lidocaine lozenge (*n*=124)	Lidocaine spray (*n*=123)
Age (years)	44.48±15.37	44.82±14.41
Weight (kg)	61.32±11.22	63.15±11.17
Height (cm)	160.38±7.78	160.79±8.06
Gender (male/female)	73/51	77/46

Values are expressed in mean±SD for age, weight, height and absolute numbers for gender. *n*=Number of patients in each treatment groups, SD=Standard deviation

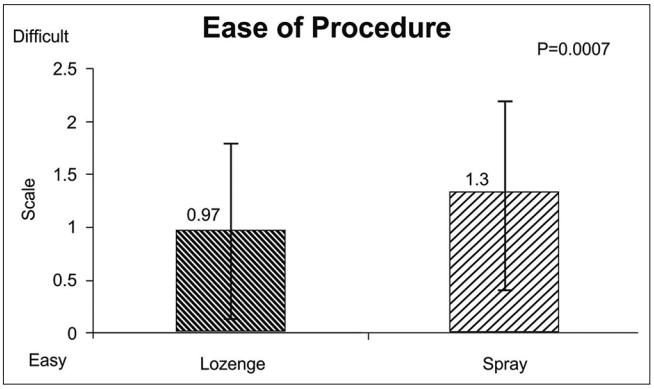

Figure 2: Ease of procedure evaluated by the investigator on a scale of 0 (easy) to 5 (difficult)

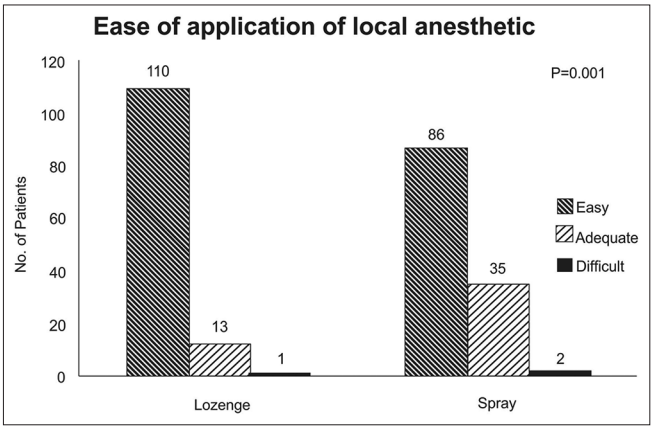

Figure 4: Ease of application of local anaesthetic evaluated by investigator as easy, adequate or difficult

Global assessment by the patients for lozenge and spray group was found to be excellent to good in 102 patients versus 89 patients respectively, and fair in 21 patients versus 32 patients respectively. Investigators global assessment was found to be excellent to good in 111 patients versus 108 patients respectively for the lozenge and spray group. The difference between both the groups was not statistically significant [Figure 5].

Incidence of adverse events like cough, nausea, vomiting and mild throat irritation, reported during the study in lozenge group (9 patients out of 124) and spray group (9 patients out of 123) was similar. No case of any other unexpected or serious adverse event was reported during study period.

Discussion

This is the first comparative study evaluating the efficacy and safety of lidocaine lozenge versus spray formulation during UGE in Indian population. The dose of lidocaine used for induction of local anesthesia was 200 mg for both spray and lozenges. Lidocaine lozenges are available in the market in only single strength of 200 mg/lozenge unit. Hence, the strength of the lidocaine lozenges used was 200 mg and to standardize the treatment dose, spray was also used in 200 mg dose. It has been reported in the literature that 200 mg of lidocaine spray

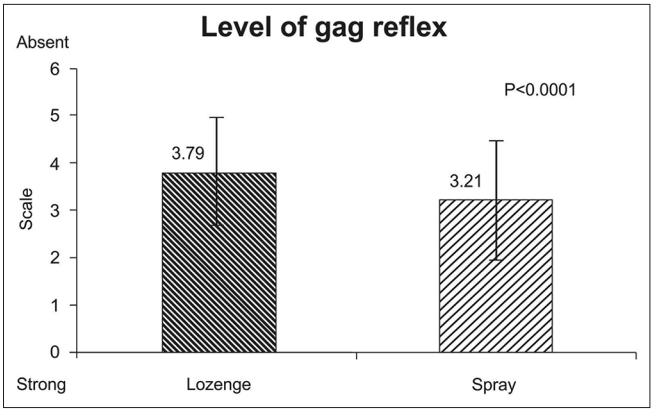

Figure 3: Level of gag reflex during the upper gastrointestinal endoscopy evaluated by the investigator on a scale of 0 (strong) to 5 (absent)

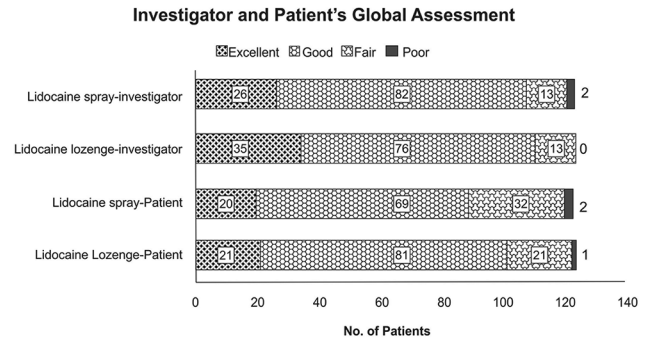

Figure 5: Patients and investigators global assessment of the study drugs

provides safe and effective local anesthesia for diagnostic endoscopic procedures.[13]

The results of the study established that both lozenge and spray formulations were effective as topical anesthesia during UGE. Endoscopic procedure was reported by investigator as easy in significantly more number of patients (P = 0.0007) in the lozenge group when compared to the spray group. Similar results were also reported by Ayoub *et al*.[14] in patients undergoing elective UGE. The reported ease of the procedure with lozenges, may be attributed to the suppressed gag reflex, retching, restlessness and combativeness experienced by the patients during the diagnostic procedure.

A strong gag reflex during the UGE is a major concern associated with endoscopic procedures. In the present study, it was reported that, gag reflexes were significantly suppressed ($P < 0.0001$) in lozenge group as compared to the spray group. Reduced gag reflex in the lozenge group could be due to the mechanism of drug delivery by which the lozenge formulation dissolves, mixes with saliva and spreads to produce a local anesthetic effect. Moreover, lozenge formulation releases the drug steadily for a prolonged period in the oral mucosa and hence form a coat of the anesthetic mixed with mucus on wider surface of the pharyngeal mucosa providing an improved local anesthetic effect. It is also reported by Mogensen *et al*.[9] that the lozenge formulation provides its local anesthetic effect on the soft palate and posterior third of the tongue (in addition to the pharyngeal mucosa), which contains deep pressure receptors for the gag reflex.

Ease of application of local anesthetic assessed by the investigator was reported to be easy in greater number of patients in lozenge group as compared to the spray group ($P = 0.001$). This could also be related to the formulation difference between the lozenge and spray. The spray formulation has to be administered at precise area of the throat and cannot be self-administered. There is also a factor of inconvenience as the patient has to hold mouth wide open until an assistant could apply the lidocaine spray. The lozenge formulation with appropriate instructions can be readily self-administered without any assistance or supervision. The lozenge formulation of a local anesthetic is easier and convenient method to deliver a topical anesthetic as the patient has to simply suck the lozenge for 15-20 min prior to the procedure. The sweet and flavored lozenge helps to mask the bitter taste of lidocaine as well as makes the formulation more palatable and acceptable for the patients, which is unlikely in spray formulation.

Global assessment of local anesthetic by the patient as well as the investigator was favorable for lozenge mainly because of ease of procedure and ease of application of the lozenge for the investigator and due to suppression of gag reflex, pleasant flavor of lozenge and improved acceptance of the procedure for the patients.

Requirement of rescue medication (IV sedative agent-midazolam) was similar in both groups. Sedation of patients did not affect the assessment of gag reflex during the UGE because sedation was administered after initiation of the diagnostic procedure, if required.

The incidence of adverse events reported during the procedure was found to be similar for both the groups in our study. The adverse events reported were cough, nausea, vomiting and mild throat irritation. These adverse events could be due to procedure related experiences as it is reported that many patients experience minor throat discomfort after the upper gastroduodenal endoscopy.[15]

Cost difference between the spray and lozenge used for each patient is not significantly different, in spite of the fact that lidocaine lozenges are unit dosage forms. Lidocaine sprays are available in multiple dosage spray bottles. Using a spray bottle for a single patient causes a lot of wastage, and reusing the remaining spray bottle for different patients, poses a risk of cross contamination by repeated use of the same spray nozzle. Since lozenges are unit dosage form and are used for a single patient, they do not pose any risk of cross contamination. This makes the lozenge hygienic and cost-effective as compared to sprays.

Kacker *et al*. conducted a study to evaluate the efficacy of lidocaine lozenges in awake diagnostic direct laryngoscopy. Their study reported similar results to current findings like significantly lesser procedural difficulty and suppressed gag reflex during the procedure with lidocaine lozenges compared to spray. The study concluded that lidocaine lozenges given before direct awake laryngoscopy provide a significant benefit by offering a more effective, safe, and convenient anesthesia compared to spray.[16]

A limitation of this study was that the study was open-labeled due to the formulation difference between the test and the reference treatment; hence, the results may be affected by patient or observer bias.

Conclusion

The study suggests that lidocaine lozenges are an easier way of applying local oropharyngeal anesthesia, produces better suppression of gag reflex and makes the procedure easier when compared to lidocaine spray.

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