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CLINICAL TRIAL REPORT

Comparison of Lidocaine Spray and Lidocaine Ice Popsicle in Patients Undergoing Unsedated Esophagogastroduodenoscopy: A Single Center Prospective Randomized Controlled Trial

Prasit Mahawongkajit[1]
Nantawat Talalak[1]
Neranchala Soonthornkes[2]

[1]Department of Surgery, Faculty of Medicine, Thammasat University, Pathumthani, 12120, Thailand; [2]Department of Anesthesiology, Faculty of Medicine, Thammasat University, Pathumthani, 12120, Thailand

Purpose: Esophagogastroduodenoscopy (EGD) under topical pharyngeal anesthesia has the advantage of avoiding the unwanted cardiopulmonary adverse events experienced following intravenous sedation. Lidocaine spray is a common anesthetic option and is safe for unsedated EGD. Although several studies have compared different topical anesthetic agents, their formulations, and delivery techniques, questions still remain concerning the optimal mode of administration. We have designed a lidocaine formulation in the form of an ice popsicle and compared its effectiveness and tolerability with lidocaine spray in patients undergoing unsedated EGD.

Methods: This was a single-center prospective randomized controlled trial. Unsedated EGD patients were randomly allocated the lidocaine spray [Group (Gp) A] or lidocaine ice popsicle (Gp B) formulation.

Results: In total, 204 unsedated EGD patients were evaluated. Compared to the spray, the lidocaine ice popsicle group showed better scores for effects in terms of endoscopist satisfaction (Gp A, 7.28±1.44; Gp B, 7.8±0.89; p=0.0022), gag reflex (Gp A, 1.3±0.66; Gp B, 1.02±0.61; p=0.0016), patient satisfaction (Gp A, 7.74±0.82; Gp B, 8.08±0.82; p=0.0039), discomfort (Gp A, 6.54±1.34; Gp B, 5.95±1.21; p=0.0012), and pain (Gp A, 5.38±1.85; Gp B, 4.51±2.01; p=0.0015).

Conclusion: Both the lidocaine spray and ice popsicle formulations are safe, effective options for diagnostic EGD with the ice popsicle exhibiting better performance. We propose the lidocaine ice popsicle formulation for topical pharyngeal anesthesia in patients undergoing unsedated diagnostic EGD and suggest it may be a suitable option during the COVID-19 pandemic.

Clinical Trial Register: Thai Clinical Trials Registry (TCTR) number TCTR20190502001.

Keywords: lidocaine spray, lidocaine ice popsicle, esophagogastroduodenoscopy, upper gastrointestinal endoscopy, topical pharyngeal anesthesia

Introduction

Esophagogastroduodenoscopy (EGD) is an essential and widely used diagnostic and therapeutic procedure in gastroenterology.[1–4] EGD can be performed in association with topical anesthesia of the pharynx,[5,6] intravenous anesthesia,[7–9] or with their combination.[10–13] EGD under topical pharyngeal anesthesia has the advantage of avoiding unwanted cardiopulmonary adverse events from intravenous sedation-like respiratory depression, cardiorespiratory arrest, especially in patients with cardiopulmonary disease, the elderly, and obese.[14–16]

Correspondence: Prasit Mahawongkajit
Department of Surgery, Faculty of Medicine, Thammasat University (Rangsit Campus), 99/209 Moo 18, Paholyothin Road, Amphur Klongluang, Pathumthani, 12120, Thailand
Tel +66 2926 9523
Fax +66 2926 9530
Email prasit_md@yahoo.com

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In Thailand, lidocaine spray is commonly used and is safe and easy in procedures requiring unsedated EGD. Many studies have compared topical anesthetic agents to other formulations and techniques such as viscous, lozenge, lollipop, and nebulized lidocaine administration. However, it is still unclear which technique is optimal in terms of its influence on the gag reflex, patient tolerability, and pain.[17–22] A recent study demonstrated the effectiveness of using ice for topical anesthesia of the oral mucosa compared to lidocaine 5% gel dental injection.[23] The ice popsicle is a famous dessert in Thailand due to the hot weather and led us to the idea of using this for delivering lidocaine. We, therefore, designed the present study to develop and compare the lidocaine ice popsicle and lidocaine spray in patients undergoing unsedated EGD.

Materials and Methods

This study was a single-center, prospective randomized, controlled trial that was registered with the Thai Clinical Trials Registry (TCTR20190502001) (Date of registration 02/05/2019). This study was approved by the Human Ethics Committee of Thammasat University (Faculty of Medicine), reference number MTU-EC-SU-1-253/61.

From May 2019 to January 2020 and May to August 2020, we enrolled consecutive patients with a minimum age of 20 years, eligible for unsedated diagnostic EGD via the oral route by pharyngeal anesthesia at Thammasat University Hospital. The indications of diagnostic endoscopy were cancer screening and work-up for symptomatic patients such as dysphagia, dyspepsia, reflux, abdominal pain, or anemia. Patients with head and neck cancer, upper gastrointestinal cancer, previous surgery of the upper aerodigestive tract, corrosive ingestion, pregnancy, contraindication for EGD, allergy to lidocaine, psychiatric problems, neuromuscular disorders, emergency cases, and unstable vital signs were excluded from the study. All patients were fully informed of the objectives of this study. All procedures were performed in accordance with the declaration of Helsinki. Written informed consent was obtained from each patient before randomization.

The patients were randomly allocated by a research assistant to one of two groups using the opaque sealed envelope technique: (i) lidocaine spray [Group (Gp) A] or (ii) lidocaine popsicle (Gp B). The lidocaine spray was applied as two puffs to the left side, right side, and middle part of the pharynx (10 mg lidocaine/metered dose) and then repeated five minutes apart for a total of 120 mg of lidocaine. The lidocaine ice popsicle consisting of a 6 mL of a viscous lidocaine solution (20 mg/mL) was formed on a silicone mold with a stick inserted in the center. The preparation was stored overnight in a freezer until the day of the endoscopy. The ice popsicle (Figure 1) contained 120 mg of lidocaine and was required to be sucked by the patient until it completely dissolved, which usually required approximately five minutes.

Anxiety was evaluated using a numerical rating scale (NRS) before applying the topical pharyngeal anesthesia (range 0, calm to 10, anxious). Topical pharyngeal anesthesia was applied by the first endoscopy nurse. After 2 to 5 minutes, the EGD was performed by a single operator, having experience with >1000 EGDs, accompanied by a second endoscopy nurse (a registered nurse skilled in assisting endoscopists performing endoscopies). The endoscopist and second endoscopy nurse were blinded to the lidocaine allocation group. All EGDs were performed using one of two models of standard upper endoscopes (GIF-HQ190 and GIF-H290Z; Olympus, Tokyo, Japan).

After completing the endoscopic examination, the research assistant administered a questionnaire. Different NRSs were used to assess: procedural experience (0, no discomfort and 10, the worst discomfort imaginable), pain score (0, no pain and 10, pain as bad as it could be), and patient satisfaction (0, no satisfaction and 10, extreme satisfaction). In addition, the ease of use of esophageal instrumentation (0, very difficult and 10, very easy), satisfaction (0, no satisfaction and 10, extreme satisfaction), and the gag reflex (0, no gag reflex; 1, mild gag reflex; 2, moderate gag reflex sedation not needed; 3, strong gag

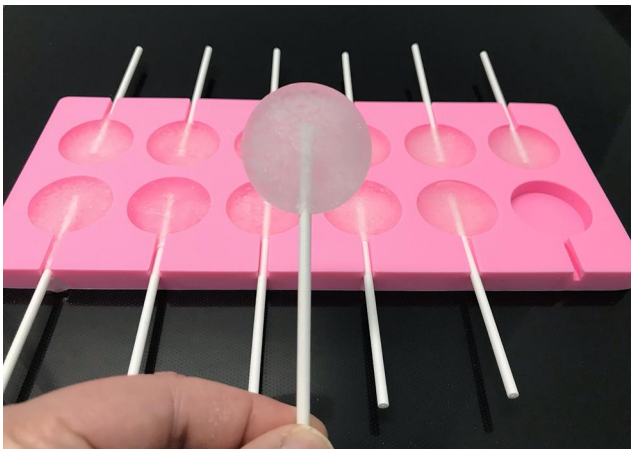

Figure 1 Lidocaine ice popsicle. The lidocaine ice popsicle made by viscous lidocaine solution 20 mg/mL, 6 mL with a stick in the silicone mold. It is stored overnight in the freezer to the day of endoscopy.

reflex sedation needed; 4, strong gag reflex and instrumentation refused). The following data was inserted on the case record forms: patient characteristics, endoscopic examination, and duration. All patient data were analyzed in a blind manner.

Several studies have demonstrated that lidocaine spray is superior to other anesthetic formulations.[17–19,22] We chose to include the endoscopists' satisfaction as a parameter because the study design included an endoscopic procedure performed by a single blinded operator with an overview of the overall procedure, which was evaluated using NRS. A prior study evaluated the endoscopist's satisfaction using a visual analog scale (VAS: 0 (very unsatisfied) to 10). The VAS for the lidocaine spray group (7.54 ± 1.97) was higher than that the lozenge formulation group (6.87 ± 2.35).[19] We estimated that the sample size needed for a two-sample comparison of means (STATA/SE 12.0 for MAC, StataCorp LP, Texas, USA) under the research hypothesis to determine the superiority of the novel formulation of anesthetic agents required a total of 214 interventions for an alpha error 0.05 and beta-error 0.20 (Power 80%) with a ratio of sample size of 1. Thus, a sample size of 107 was needed for each group. The primary outcome was to evaluate the difference in the endoscopists' satisfaction between two groups. The secondary outcome was esophageal endoscopy instruments, gag reflex, patients' satisfaction, anxiety, pain, discomfort, adverse events, need for sedation, procedural duration, and complete endoscopy.

The data are expressed as mean ± standard error of the mean. Statistical analysis was performed using the χ^2 test and Fisher's test for categorical data and the Mann–Whitney *U*-test was used for continuous data. All data were analyzed with SPSS v.22.0 data (Statistical Package

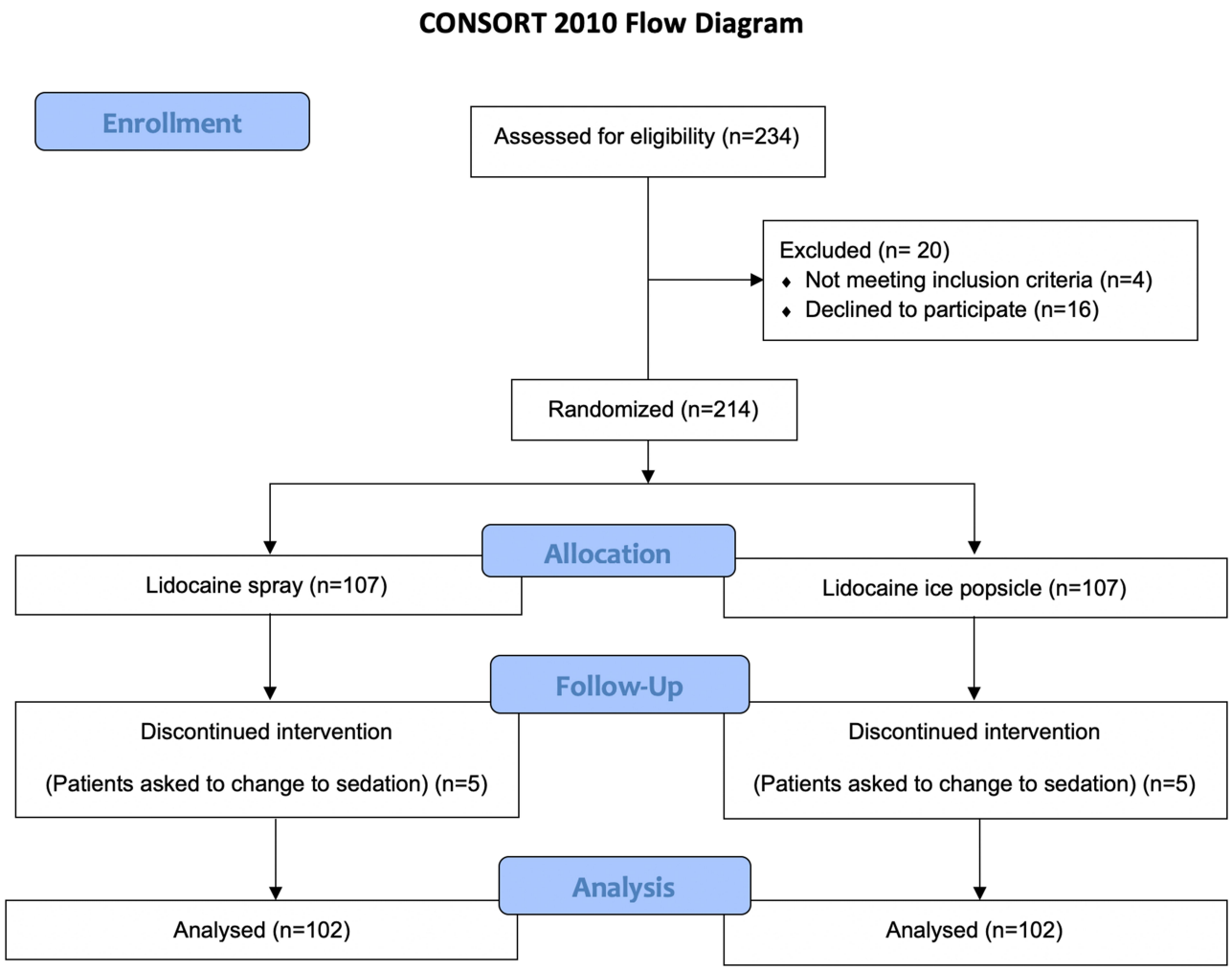

Figure 2 CONSORT flow diagram.

for Social Sciences, SPSS, Inc., Chicago, IL, USA). A p-value <0.05 was considered to be statistically significant.

Results

A total of 234 patients were evaluated for study inclusion. Four were excluded because of one case of previous oropharyngeal surgery, one case of nasopharyngeal cancer with post-radiation treatment, and two cases with a history of corrosive ingestion. Sixteen patients declined to provide informed consent. Next, 214 patients were randomized; 107 in each group. After randomization, 5 patients in each group discontinued the study because they asked to change to the type of sedation. Finally, a total of 204 patients were analyzed (Figure 2).

The two groups were not significantly different (p > 0.05) in terms of age, sex, BMI, smoking, alcohol intake, and prior endoscopy (Table 1). The main clinical for EGD was dyspepsia.

Pre-endoscopic anxiety was not significantly different between the groups. The participants' procedural evaluation results demonstrated lower NRS scores for discomfort and pain with higher patient satisfaction in the lidocaine ice popsicle preparation group (Table 2). There was also a significantly higher NRS score for the lidocaine ice popsicle preparation in terms of endoscopist satisfaction and also a significantly lower gag reflex score. The mean times to perform the EGD and EGD accompanied by biopsy were very similar in both groups. Intra-endoscopic oxygen desaturation was identified in patients in Gp A and in one patient in Gp B, but this difference was not statistically significant. No patient suffered bradycardia or hypotension. Only two participants who had received the lidocaine spray could not tolerate the procedure and proceeded to the intervention with sedation.

Discussion

EGD is an established technique for investigating disorders of the gastrointestinal tract. Endoscopes must be inserted through the mouth and this leads to patient anxiety, discomfort, coughing, and gagging, which may make the experience all together unpleasant.[5,6,11–13,17–25] Intravenous anesthesia is an option for EGD but holds the risk of adverse events such as bradycardia, hypotension, and respiratory depression, particularly when administered by non-anesthetists.[26,27,30–33] The use of topical pharyngeal anesthesia reduced the use and risk of intravenous sedation and directed researcher's attention towards alleviating the gag reflex, pain, discomfort, and improving tolerability of unsedated patients and towards studies to ascertain how to improve tolerability.

Many publications report the use of different local anesthetic preparations such as viscous lidocaine solution,[17,18] lozenges,[19,20] lollipops,[21] and nebulized

Table 1 Patient Characteristics of Each Group

Unsedated EGD Patients	Group A: Lidocaine Spray n=102	Group B: Lidocaine Ice Popsicle n=102	*p*-value
Age, mean ± SD, years	59.86 ± 9.36	57.75 ± 13.43	0.119
Sex Male/Female, n (%)	52 (50.89)/50 (49.11)	54 (52.94)/48 (47.06)	0.781
Body weight (kg)	61.87 ± 2.12	61.27 ± 9.89	0.742
Height (m)	1.64 ± 0.05	1.65 ± 0.07	0.579
BMI† (kg/m^2)	22.72 ± 0.52	22.13 ± 3.43	0.209
Current smoker, n (%)	18 (17.65)	22 (21.57)	0.483
Current alcohol drinker, n (%)	29 (28.43)	34 (33.33)	0.451
Indication for EGD			
Cancer screening, n (%)	16 (15.69)	14 (13.73)	0.694
Reflux, n (%)	12 (11.76)	15 (14.71)	0.538
Dysphagia, n (%)	2 (1.96)	4 (3.92)	0.409
Dyspepsia, n (%)	38 (37.26)	36 (35.29)	0.772
Epigastrium pain, n (%)	12 (11.76)	11 (10.78)	0.826
Anemia, n (%)	9 (8.82)	12 (11.77)	0.492
Other, n (%)	13 (12.75)	10 (9.8)	0.509
Prior experience of EGD, n (%)	17 (16.67)	13 (12.74)	0.432

Abbreviation: †BMI, body mass index.

Table 2 Evaluation of Unsedated Upper Gastrointestinal Endoscopy

	Group A: Lidocaine Spray	Group B: Lidocaine Ice Popsicle	*p*-value
Endoscopist			
Endoscopists' satisfaction, mean ± SD, 0–10 NRS†	7.28 ± 1.44	7.8 ± 0.89	0.0022
Easy esophageal instrumentation, mean ± SD, 0–10 NRS†	7.49± 0.92	7.71 ± 0.89	0.089
Gag reflex, mean ± SD, 0–4 NRS†	1.3 ± 0.66	1.02 ± 0.61	0.0016
Participants			
Anxiety, mean ± SD, 0–10 NRS†	6.34 ± 2	6.29 ± 1.9	0.868
Procedural discomfort, mean ± SD, 0–10 NRS†	6.54 ± 1.34	5.95 ± 1.21	0.0012
Pain score, mean ± SD, 0–10 NRS†	5.38 ± 1.85	4.51 ± 2.01	0.0015
Patients' satisfaction, mean ± SD, 0–10 NRS†	7.74 ± 0.82	8.08 ± 0.82	0.0039
Endoscopic outcome			
Oxygen desaturation, n (%)	3 (2.94)	1 (0.98)	0.315
Bradycardia, n (%)	0 (0)	0 (0)	0
Hypotension, n (%)	0 (0)	0 (0)	0
Procedural duration, mean ± SD, minutes	9.59 ± 1.72	9.44 ± 0.71	0.488
• Only EGD, n (%)	19 (18.6)	18 (17.6)	0.86
• Duration, mean ± SD, minutes	7.58 ± 0.5	7.83 ± 0.51	0.139
• EGD with biopsy, n (%)	83 (81.4)	84 (82.4)	0.86
• Duration, mean ± SD, minutes	10.05 ± 1.56	9.78 ± 0.71	0.212
Complete endoscopy, n (%)	102 (100)	102 (100)	0
Need for sedation, n (%)	2 (1.96)	0 (0)	0.157

Abbreviation: †NRS, numerical rating scale.

lidocaine,[22] but the efficacy and tolerability of these techniques are still under debate. We, therefore, developed the idea of a lidocaine popsicle preparation and reviewed lidocaine stability data under different freezing conditions.[28,29] We proposed that a lidocaine ice popsicle preparation as an unconventional preparation for an anesthetic agent that could reduce the stress of unsedated EGD patients during the ~5 minutes required for melting. Nonetheless, we found that the patients' pre-procedural anxiety scores were similar.

Compared to spray preparations, the lidocaine ice popsicle preparation was superior in terms of reducing the gag reflex, improving patient satisfaction, discomfort, and pain. The ice popsicle melted slowly and may have increased the exposure to lidocaine on the pharyngeal mucosa. To compensate for this potential advantage, we repeated the lidocaine spray after 5 minutes so that the total dose of lidocaine was the same for both groups. Ice popsicles are popular in Thailand because of the yearlong hot climate; thus, Thai people are accustomed to them and this may have had a positive collateral effect of increased relaxation prior to the insertion of the endoscope. Recent studies have demonstrated the efficacy of ice as an alternative to lidocaine 5% gel[23] and as a nonpharmacological intervention for pain management for dental procedures.[34–38] Walco et al reported a 13-year-old leukemia patient who had difficulty swallowing pills was helped by using progressively larger pieces of ice, which helped to keep gagging and choking to a minimum,[39] consistent with the concept of alternative adjunct therapies to improve the patient's comfort.[40] The cold temperature might decrease neural transmission of stimuli in the thin unmyelinated neurons[41,42] and local vasoconstriction may slow down lidocaine metabolism and absorption with a greater local anesthetic effect.[43] The ice contact time of five minutes was safe and did not lead to tissue damage.[43]

The power calculation for study indicated a sample size of 214 patients was needed for this study. After randomized allocation 107 patients to each group, five patients asked the endoscopist to perform sedation before starting the endoscopic intubation in each group, a rate estimated to be 4.67%, which demonstrated differences in the outcome. Further, two participants in the lidocaine spray group could not tolerate the endoscope and needed

sedation, both had high anxiety scores. For a small number, neither procedural time nor satisfaction NRS (1.96% in the lidocaine group) had been affected, with duration being 12 and 13 minutes, endoscopists' satisfaction NRS scored two and two, and patients' satisfaction NRS were five and five, respectively. The endoscopic examination of unsedated diagnostic EGD did not routinely involve oxygen supplementation at our endoscopy center. All patients were continuously and closely monitored for oxygen saturation and vital signs. Oxygen supplementation was given to the underlying disease patient when required. A total of four patients experienced oxygen desaturation during the EGD; two were aged 73 and 76, and two were obese by BMI 34.69 and 37.20, consistent with the published literature[14–16] and our previous experience. Oxygen was administered via nasal cannula and the patients put in the left lateral position with satisfactory resolution.

The study was interrupted from January to May 2020 due to the COVID-19 pandemic in Thailand. The principal mode of transmission of coronavirus is airborne and contact[44–46] and this had implications for performing EGDs. Droplets may be produced after spraying the lidocaine on the pharynx,[47,48] although there is less of a concern with the lidocaine popsicle, which is probably a better option. The lidocaine ice popsicle can melt at room temperature after removal from the refrigerator, which would be fast in summer, especially in Thailand. The lidocaine ice popsicle needs to be stored in the freezer before use, which thus required the availability of a refrigerator as a potential limitation. Another limitation of this study was small number of participant numbers which limited our statistical power, although some findings were still significant. Some findings may have been due to chance, given the multiple comparisons.

Conclusion

We have shown that both lidocaine preparations were safe and effective in producing local anesthesia and were liked by patients, aside from the unpleasant taste. The lidocaine ice popsicle was associated with less discomfort, pain and gagging and was preferred by patients, which supported its higher satisfaction by patients. Additional larger studies are required to reconfirm our results and more work is needed to improve the taste of lidocaine.

Abbreviations

EGD, esophagogastroduodenoscopy; TCTR, Thai Clinical Trials Registry; BMI,body mass index; NRS, numerical rating scale.

Data Sharing Statement

The datasets used and/or analyzed during the present study are available from the corresponding author on reasonable request.

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Author Contributions

All authors contributed to data analysis, drafting, and revising the article, have agreed on the journal to which the article will be submitted, gave final approval of the version to be published, and agree to be accountable for all aspects of the work.

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Disclosure

The authors report no conflicts of interest or financial ties to disclose.

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