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Original study

Intravenous lidocaine reduces cough but not propofol dose during gastroscopy: a prospective, radomised contolled double-blind study

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Abstract

Background: **To improve patient comfort during gastroscopy, sedation is essential. Propofol can cause adverse effects if underdosed or overdosed. Lidocaine has been suggested as an adjuvant to propofol in this context.**
Objectives: **This study aimed to evaluate propofol consumption when adding intravenous lidocaine during gastroscopy. We also assessed whether intravenous lidocaine reduces the adverse effects associated with inappropriate sedation.**
Design: **Prospective, randomised, controlled, double-blind, single-centre trial.**
Setting: **Day hospital of the Erasme University Hospital, from 21 July to 25 August 2023.**
Methods: **American Society of Anaesthesiologists' physical status 1 or 2 patients, aged < 65 years and undergoing gastroscopy procedure were included. Patients were randomly assigned to receive either 1.5 mg/kg Lidocaine (Lidocaine-group) or placebo (Control-group). Sedation was achieved by the administration of propofol using target-concentration infusion titrated according to the bispectral index.**
Main Outcome Measures: **Primary outcome was propofol consumption between groups. Secondary endpoints included the occurrence of cough, involuntary movements, hypoxaemia, hypotension, tinnitus and metallic taste, as well as the satisfaction of the gastroenterologist.**
Results: **Lidocaine did not reduce propofol consumption but did reduce coughing on gastroscope insertion (9%) compared to placebo (52%) (p=0.002). Rates of involuntary movement, hypotension, desaturation as well as gastroenterologist satisfaction were similar. Only patients who received lidocaine experienced tinnitus (52%; p < 0.001) and metallic taste (28%; p = 0.004).**
Conclusion: **The administration of intravenous lidocaine did not reduce the consumption of propofol, but it did significantly reduce coughing during the insertion of a gastroscope, however without having any clinical effect. A high rate of mild local anaesthetic side effects was associated with lidocaine administration.**
Trial Registration: **Clinicaltrials.gov identifier: NCT05944887**

Keywords: **gastroscopy, lidocaine, propofol, deep sedation.**

This study was presented as a poster at the 36th edition of the Belgian Week of Gastroenterology (Antwerp, Belgium; 2024) as master's thesis of Dr Omar Assam.
Consent statement: Written informed consent was obtained from the patient to publish this report in accordance with the journal's patient consent policy.
Ethics: approval from the Ethics Committee Erasme Hospital (808, route de Lennik, 1070 Brussels; Chairman Pr J.-M. Boeynaems) was received on July 06, 2023, with reference P2023/236 / CCB B4062023000130
Clinical Trials Registry of the United States National Library of Medicine: NCT05944887. Patients were included between July 21 and August 25, 2023.

Introduction

Gastroscopy is a crucial diagnostic and treatment procedure for upper gastrointestinal disorders. Although generally safe and fast, it may cause discomforting symptoms such as cough, nausea, sore throat, bloating and abdominal pain, which can affect the examination's quality[1]. Sedation is often proposed to improve patient comfort and reduce anxiety during gastroscopy. This approach not only increases patient satisfaction but also creates conditions that are more conducive to a successful diagnostic and/or therapeutic examination, thereby increasing the endoscopist's satisfaction[2].

Various sedation methods are available for this purpose. Propofol is the preferred hypnotic agent due to its rapid onset and recovery[2-3]. However, achieving an optimal level of sedation can be challenging when used alone. Inadequate administration may result in insufficient sedation, increasing the risk of coughing, gastro-oesophageal reflux, involuntary patient movements and, in severe cases, laryngospasm. Conversely, higher doses can lead to adverse effects such as excessive sedation, hypotension, hypopnoea and even apnoea[3]. Hypoxaemia remains the main complication of propofol sedation, especially in elderly, overweight, or patients with pre-existing cardiopulmonary disease[4-5].

Various adjuvants have been proposed to reduce the need for propofol while improving the quality of sedation and analgesia during gastroscopy, including opiates, midazolam, dexmedetomidine, and ketamine[3]. However, each of these adjuvants has specific advantages and disadvantages that cannot be ignored during outpatient procedures. Opioids and midazolam, for example, can lead to more severe respiratory depression and slower neurocognitive recovery. Ketamine may cause schizophrenia-like symptoms. When combined with dexmedetomidine, it provides better sedative and analgesic effects while reducing respiratory side effects. However, it may cause prolonged hypotension or bradycardia at low doses.

Lidocaine is a local anaesthetic that has potentially beneficial effects in the context of ambulatory gastroscopy. It can prevent bronchoconstriction and coughing during manipulation of the upper respiratory tract. Additionally, it has analgesic, anti-hyperalgesic and anti-inflammatory properties[6]. Previous studies show that intravenous lidocaine may reduce the bolus induction dose of propofol during gastroscopy in adult patients[7-9]. However, it remains to be investigated whether intravenous lidocaine administered affects propofol consumption, when administered using target-concentration infusion (TCI), or prevents adverse events associated with under- or over-sedation. To address this question, we conducted a prospective, single centre, randomised, double-blind study. The primary aim was to evaluate the effect of an intravenous bolus of lidocaine (1.5 mg/kg) on propofol consumption using TCI. The secondary goals of the study were to assess whether intravenous lidocaine reduces the adverse effects associated with inadequate sedation and improves endoscopist satisfaction.

Methods

Ethical information

This prospective, single-centre, randomised, placebo-controlled, double-blind study was conducted at HUB-Erasme Hospital (Brussels, Belgium) from 21 July to 25 August 2023, in accordance with the Declaration of Helsinki and the CONSORT recommendations for randomised controlled trials. This trial was approved on 06 July 2023 by the local ethics committee (Ethics Committee Erasme Hospital, Brussels, Belgium, Chairperson Prof J-M Boeynaems) with reference P2023/236/CCB B4062023000130 and registered with the Clinical Trials Registry of the United States National Library of Medicine (Registration number: NCT05944887). All patients provided written informed consent.

Inclusion and exclusion criteria

This study included patients aged between 18 and 65 years who were scheduled to undergo gastroscopy under sedation and had an American Society of Anaesthesia (ASA) score of I or II and a body mass index (BMI) between 18 and 30 kg/m2. Patients with a history of allergy to lidocaine, suspected (STOP-BANG score > 5) or confirmed sleep apnoea syndrome (Hwang et al, 2022), impaired liver or kidney function, heart rate < 50 beats per minute, current or previous cardiac arrhythmia, with severe central nervous system disease or mental illness, patients who have undergone local anaesthesia in the last 24 hours or general anaesthesia in the last 7 days, or who have participated in another clinical study in the previous month, as well as pregnant or breast-feeding women were not included in the study. Performing a colonoscopy after gastroscopy was not considered as a contraindication.

Randomisation

Eligible patients were randomly assigned to either the Lidocaine-group or the Control-group. The randomisation was conducted using a pre-established list generated by a computer programme (Sealed Envelope© Ltd. 2022) with a ratio of 1:1

and blocks of 4. The allocation was determined based on the order of patient participation and was sealed in envelopes by collaborators who were not involved in this study. On the day of the endoscopic examination, a colleague who was not involved in the study prepared an 'experimental syringe', which contained either 1.5 mg/kg of lidocaine or normal saline in an equivalent volume, according to the group mentioned in the sealed envelope. This ensures that the patient, anaesthetist, gastroenterologist, and investigators were all blinded to the allocated group.

Protocol

The usual preoperative fasting rules were respected, and no anxiolytic premedication was given. Upon arrival in the examination room, patients were monitored using a pulse oximetry, an automatic cuff positioned on the left arm to measure non-invasive blood pressure (NIBP) every 2.5 minutes and a three-lead electrocardiograph to monitor heart rate and rhythm. The bispectral index (BIS) was measured using a forehead electrode connected to the Bispectral IndexTM Brain Monitoring System (Medtronic, Ireland). A peripheral venous line was inserted into the right upper limb, and a nasal tube was used to administer oxygen at a flow rate of 2 L/min.

Patient was positioned in the left lateral decubitus position. The "experimental bolus", comprising either Lidocaine (1.5 mg/kg) or normal saline, was administered one minute before starting sedation. Lidocaine was administered using the ideal body weight, calculated according to Lorentz's formula, as follows:

- For men: Ideal weight (Kg) = Height (cm) - 100 – ((Height (cm) - 150) / 4)
- For women: Ideal weight (Kg) = Height (cm) - 100 – ((Height (cm) - 150) / 2.5)

Sedation was realised using 1% propofol according to the Schneider model described for TCI, with an initial target concentration effect (Ce) of 3 µg/mL. The target range for BIS was set between 40 and 60. If this target was not achieved during propofol equilibration, propofol Ce was increased in steps of 1 µg/mL. When the target BIS values were reached, and the patient presented a Modified Observer's Assessment of Alertness/Sedation Scale (MOOAS) score < 110, the endoscopist was invited to start the gastroscopy. The sedation was maintained and adjusted throughout the procedure to keep the BIS values between 40 and 60. If the patient exhibited a cough reflex or significant involuntary movements, the target Ce of propofol was increased in increments of 1 µg/mL. Conversely, if the BIS values fell below the threshold of 40, the target Ce of propofol was decreased in steps of 1 µg/mL. At the end of the procedure, propofol administration was suspended, and patients were transferred to the post-anaesthesia care unit (PACU) after recovering a MOOAS score of ≥4. Patients were discharged from the PACU when their Aldrete score was >9. During sedation, if the patient experienced hypoxaemia, defined as a pulsed oxygen saturation (SpO2) < 94%, the following measures were taken in successive stages: a gradual increase in nasal oxygen up to 6 L/min, jaw thrust, assisted ventilation using a face mask, and in critical scenarios, orotracheal intubation and mechanical ventilation. Arterial hypotension, defined as a mean arterial pressure (MAP) < 65 mmHg, was treated with either phenylephrine (50 µg) or ephedrine (6 mg), depending on the patient's heart rate.

Measurements

In alignment with the primary objective of evaluating the quantity of propofol necessary for gastroscopy, the subsequent parameters were documented for analysis: the quantity of propofol needed to reach a Bispectral Index (BIS) within the range of 40-60 at the beginning of the examination, the peak target effect-site concentration (Ce) of propofol achieved and the cumulative consumption of propofol at the point of gastroscope withdrawal. The study also investigated the adverse effects of excessive or insufficient sedation during gastroscope insertion, such as coughing or involuntary movements, desaturation (SpO2 < 94%) and arterial hypotension episodes (MAP < 65 mmHg). Additionally, the study assessed the effects of local anaesthetic toxicity: One minute after the lidocaine bolus, just before the administration of propofol, patients were explicitly asked about the presence of a metallic taste or tinnitus. The study also evaluated the time required to achieve a BIS of 40-60, the total duration of gastroscopy, the length of stay in the PACU, the presence of sore throat, and satisfaction with the gastroenterologist using the visual analogue scale (VAS).

Statistical analysis

The study's primary endpoint was the total consumption of propofol required for gastroscopy. The sample size required for the study was 46 patients, based on an alpha error of 5% (i.e. $p<0.05$), power of 80%, and ED50 of propofol of 1.68 mg/kg and 1.88 mg/kg either using lidocaine or normal saline[9]. IBM SPSS Statistics for MacOsX, version 28.0 was used for statistical analysis. Haemodynamic measurements were analysed using analysis of variance for repeated

measures (ANOVA). Normality was verified using a Shapiro-Wilk test, and sphericity was verified using Mauchly's test. If sphericity was not found, the Greenhouse-Geisser correction method was used. A Pearson Chi-square test was used to compare two distributions and a student's t test was used to compare two means. A p-value <0.05 was considered statistically significant.

Results

46 patients were included out of the 98 patients who underwent gastroscopy at the one-day hospital during the study period. The Flow Chart of this study is presented in Fig. 1. Table I describes patient demographics. The times to achieve adequate sedation and to perform gastroscopy as well as propofol consumption, both in terms of maximum target Ce achieved or total propofol consumption, were similar in both groups, as shown in Table II.

Only one control patient experienced hypotension requiring ephedrine administration (p=0.4). Two patients in the control group and one patient receiving lidocaine experienced hypoxaemia. This was treated by increasing the oxygen supply to 3-4 L/min (p=0.4). None of the patients developed laryngospasm.

Patients who received a bolus of lidocaine experienced less cough on insertion of the gastroscope than patients in the control group, suggesting improved abolition of oropharyngeal reflexes. However, the proportion of patients with involuntary movements and the presence of persistent sore throat were identical between the two groups. More than half of the patients receiving lidocaine experienced adverse effects of local anaesthetics: among the six patients who reported tinnitus, five also described a metallic taste. Gastroenterologists' satisfaction with the ease of performing gastroscopy and length of stay in the PACU were also comparable between the two groups (Table III).

Discussion

This study showed that intravenous administration of 1.5 mg/kg lidocaine during gastroscopy

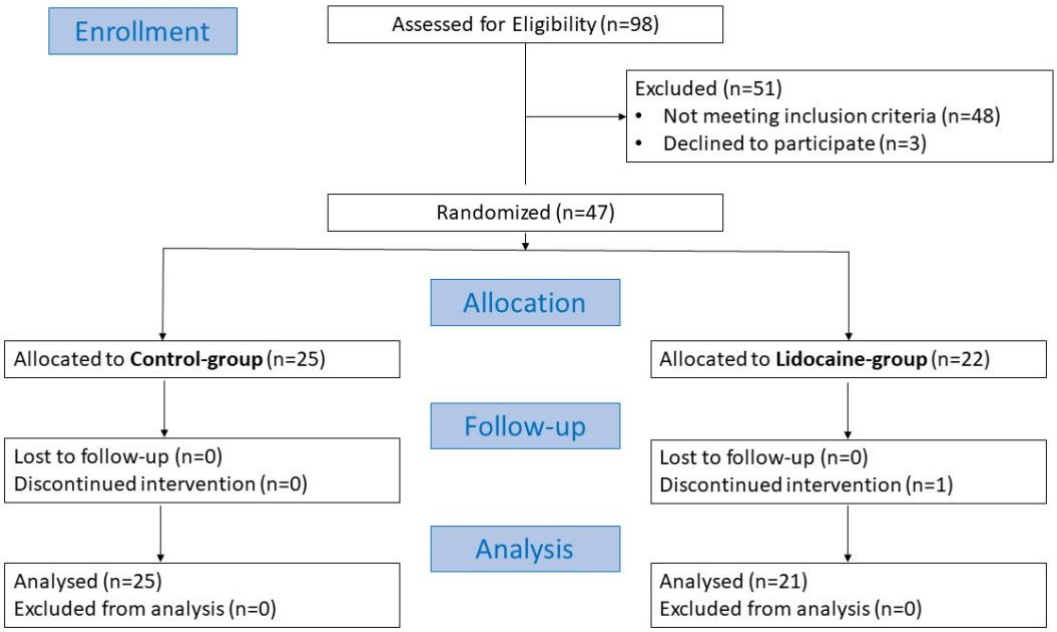

Fig. 1 — Study CONSORT Flow Chart.

Table I. — Patients' demographic and clinical characteristics.

	Control-Group (n=25)	Lidocaine-Group (n=21)	p-Value
Age (years)	44 ± 12	41 ± 13	0.51
Gender (M/F)	9/16	9/12	0.64
BMI (kg/m²)	24 ± 3	24 ± 3	0.88
ASA Score (1/2)	10/15	5/16	0.25

Values are presented as mean ± SD (analysed by student's t test) or number of patients (analysed by a Pearson chi-square test).
Where M, Male; F, Female; BMI, Body Mass Index; ASA, American Society of Anaesthesiologists (ASA) physical status.

Table II. — Time for sedation, gastroscopy duration and propofol consumption.

	Control-Group (n=25)	Lidocaine-Group (n=21)	p-Value
Time for BIS 40-60 (sec)	204 ± 75	233 ± 75	0.34
Duration of gastroscopy (min)	5 ± 2	5 ± 1	0.49
Max target Ce for propofol (µg/mL)	5 ± 2	5 ± 1	0.06
Total propofol consumption (mg)	192 ± 46	199 ± 64	0.69

Values are presented as mean ± SD (analysed by student's t test). BIS, Bispectral Index; Ce, concentration effect.

Table III. — Intraoperative outcome during endoscope insertion, occurrence of adverse effects of lidocaine administration and satisfaction of the endoscopist.

	Control-Group (n=25)	Lidocaine-Group (n=21)	p-Value
Endoscope Insertion Reaction			
Cough	13 (52%)	2 (10%)	0.002*
Involuntary movements	14 (56%)	7 (33%)	0.12
Sore throat	3 (12%)	1 (5%)	0.53
Lidocaine Toxicity Reaction	0	12 (57%)	< 0.001*
Tinnitus	0	11 (52%)	< 0.001*
Metallic Taste	0	6 (29%)	0.004*
Anaphylaxis	0	0	
Time for PACU discharge (min)	44 ± 15	42 ± 15	0.6
Gastroenterologist's satisfaction (VAS)	8 ± 2	8 ± 1	0.22

Data are presented as absolute numbers (%) (analysed by a Pearson chi-square test) or mean ± SD (analysed by student's t test). * Denotes significant change. PACU, post-anaesthesia care unit; VAS, visual analogue scale.

reduced the incidence of cough at the expense of tinnitus and/or metallic taste, side effects of local anaesthetics. Conversely, lidocaine did not affect propofol consumption.

Lidocaine is a local anaesthetic with anti-arrhythmic properties that also presents beneficial effects when administered intravenously in the perioperative period[6], including : 1) anti-inflammatory[11], analgesic[12] and anti-hyperalgesic effects[13], which can reduce the need morphine; 2) reduced postoperative ileus and improved recovery in digestive surgery[14]; 3) attenuation of tracheobronchial reflexes, coughing and respiratory complications during laryngoscopy[15-17], intubation and extubation[18-19]; reduced BIS and hypnotic requirements[20-23]. Based on these last two beneficial effects, it was hypothesised that adding lidocaine during gastroscopy would have a positive effect on sparing propofol and on local reactions to passing the endoscope. In accordance with the safety margins described in the literature and recommendations for these two indications, we chose a single bolus dose of 1.5 mg/kg due to the short duration of the gastroscopy examination[6,8,17,24-25].

The main objective of this study was to evaluate whether the administration of a single intravenous bolus of 1.5 mg/kg lidocaine reduced propofol consumption during a diagnostic gastroscopy procedure, as described in other studies[26-28]. However, the beneficial effect in terms of propofol savings was not observed in this study. One the one hand, this could be explained by the co-administration of sufentanil in the study by Liu et al.[27]; morphine presents indeed a depressant effect on the respiratory and cough centres. On the other hand, the ED50 of propofol, in both the Liu et al. and Qi et al. studies, was determined using the Dixon 'up and down' method by adjusting the bolus of propofol required to insert the gastroscope[27-28]. These studies differ from our own in a number of ways. First, their criterion for sedation was determined by the presence or absence of movement at the start of the study. Then, propofol was administered as a bolus, unlike in our study where propofol was administered using TCI. The dose of propofol they determined was considered effective in half of the patients. To our knowledge, this is the first study in which propofol was administered in the TCI mode and titrated based on the depth of anaesthesia assessed by neuromonitoring rather than solely based on clinical scores. This more gradual sedation, compared with bolus administration, is better

suited to patient needs and may explain the low incidence of hypotension or desaturation observed in both groups.

In these results, the use of lidocaine significantly reduced the incidence of coughing during gastroscope insertion. However, despite this beneficial effect, it did not lead to the expected clinical outcomes. Specifically, there was no improvement in the duration of the examination, gastroenterologist satisfaction or intensity of any sore throat as previously described[17]. Furthermore, when present, coughing did not result in an increased rate of hypoxaemia. Our results differ from those of Hu et al, who reported an overall low incidence of cough, which did not differ whether lidocaine was administered or not[7]. In addition, according to the inclusion criteria, their population was larger, older and predominantly male, whereas ours was predominantly female. In our younger population, some gastroscopy was performed as a preoperative assessment prior to intragastric balloon placement, which is known to be a predominantly female concern[28]. Contrary to Hu et al., we found a significantly higher incidence of cough in patients who did not receive lidocaine (52%). However, the incidence of cough in patients who receives lidocaine was similar, at 11% and 10% respectively, in Hu et al. and in the present study. However, it is unlikely that these differences in sample size, age and sex distribution had any influence on the observed difference in cough. This difference may be explained by the method of propofol administration. Hu et al administered propofol as a bolus, with no standardised or weight-based dose, but titrated to the patient's loss of consciousness. The rate of administration and equilibration time were not reported. This mode of administration probably resulted in a larger and faster bolus of propofol and consequently deeper sedation at the time of gastroscope insertion. This hypothesis is also supported by the higher incidence of hypotension (13% vs. 2%) and hypoxaemia (20% vs. 6%) observed in the Hu et al. study compared to our own study. Our findings also differ from those recently reported by Qi et al., who found that the use of lidocaine decreased the risk of desaturation during endoscopic procedures that combined gastroscopy and colonoscopy[29]. However, it is important to note that the patients in this study were also receiving midazolam and sufentanil, which may have a synergistic effect on the respiratory depression associated with propofol. Moreover, the patients included in this study were young, non-obese and did not have known or suspected sleep apnoea syndrome based on the STOP-BANG questionnaire[30]. Indeed, obese patients[31] and those prone to snoring[32] may be at a higher risk of hypoxemia during endoscopic procedures. This group of patients would therefore be worthy of further investigation. In our study, only one patient experienced an episode of MAP < 65 mm Hg. This could be attributed to the continuous intravenous administration of propofol, which was adjusted according to the patient's level of sedation, objectively assessed by the bispectral index, as mentioned above. Furthermore, it is noteworthy that the selected patients in this study are less likely to experience the cardiovascular depressant effects of propofol compared to older patients (>65 years old) or those who are frailer (ASA ≥ 3). In this context, Hu et al demonstrated that the administration of lidocaine in patients aged over 65 undergoing a gastroscopy resulted in propofol savings, reduction in desaturation, and faster recovery[7].

Although lidocaine has a greater safety margin than other local anaesthetics and the doses used in our study (1.5 mg/kg) were consistent with safe use[6,8,17,24-25], it is still likely to present systemic toxicity. The first symptoms of systemic toxicity are the appearance of a metallic taste, tinnitus, and perioral numbness[12]. In our study, over half of the patients who received lidocaine exhibited symptoms of local anaesthetic toxicity, which in some cases caused anxiety. This rate is much higher than reported in literature[12,33]. To our knowledge, these side effects have not been reported in previous studies of lidocaine administration in endoscopy[9], and may outweigh the risks in young, healthy patients. Patients were also specifically asked to report any metallic taste or tinnitus prior to receiving sedation. The likelihood of reporting adverse effects may have been increased by asking directly about the occurrence of either of these two symptoms. No signs of more serious toxicity affecting the central nervous system (restlessness, convulsions) or cardiovascular system (atrioventricular block, arrhythmias) were observed.

Our study has several limitations. The study is single-centre and has a small sampling size. Firstly, only 51 of the 98 patients scheduled for gastroscopy met the inclusion criteria, of whom 46 were finally analysed. Most gastroscopies were performed prior a screening colonoscopy in patients over 65 years. In addition, due to global trends in obesity rates, many patients had a BMI > 30 kg/m² and underwent gastroscopy as a preoperative assessment for bariatric surgery. Therefore, age >65 years and obesity were the main reasons for non-inclusion. Secondly, it may be questioned whether the sample size of the power test was underestimated when examining the results for Ce max (p=0.058). However, even if we had shown a reduction in Ce max with the

administration of lidocaine, it is unlikely that this would have resulted in any propofol savings in terms of total consumption, given the short duration of the procedure. Furthermore, the potential reduction in Ce max would not have had any clinically relevant impact. In our study, few patients, including those in the placebo group, experienced any haemodynamic or respiratory repercussions due to oversedation. Thirdly, our study focused only on young patients under the age of 65 years who were not obese (BMI < 30 kg/m2), did not have sleep apnoea risk criteria (STOP-BANG score ≤5), and were in good health (ASA I/II), which may explain the low incidence of hypotension and desaturation. Finally, because lidocaine was administered one minute before propofol, patients could report side effects such as metallic taste and tinnitus, making it easy to guess which group they had been assigned to and compromising the 'double-blind' aspect of the trial. This may explain the high incidence of these events, which have not been reported in similar trials.

In conclusion, this study shows that in young and healthy patients, a single intravenous bolus of lidocaine (1.5 mg/kg) combined with propofol sedation administered using TCI and titrated according to BIS analysis has no effect on propofol consumption required for diagnostic gastroscopy. Lidocaine reduced the incidence of coughing during gastroscope insertion without increasing gastroenterologist satisfaction. Although no beneficial effects of intravenous lidocaine on hemodynamic or respiratory complications were observed during endoscopic examination, a non-negligible rate of signs of local anaesthetic toxicity (tinnitus and metallic taste) was observed.

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