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The Use of L-Menthol in Endoscopic Transpapillary Interventions. Prospective Randomized Dual-Center Study

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Aim: to study the effect of L-menthol on duodenal peristalsis, the results of cannulation of the papilla, the effectiveness and safety of endoscopic retrograde transpapillary interventions (ERTI).
Material and methods. A prospective two-center randomized placebo-controlled trial was carried out from January to November 2022 in two centers. The study included 126 patients, 69 (54.8 %) men and 57 (45.2 %) women, mean age — 62.1 ± 1.8 years. The inclusion criteria were age 18–75 years, indications for ERTI, absence of previous endoscopic papillotomy, absence of allergy to menthol, consent to participate in the study. After randomization, the main group ("L") included 70 patients, the control group — 56. Patients in group "L" were irrigated with 25 mL (160 mg) of L-menthol (Spectavium), patients in the control group — with 25 mL of saline solution. Peristaltic activity was studied before and three minutes after administration of the drug. The intensity of peristalsis was assessed according to a modified Hiki scale: 0 points — complete absence of peristalsis; 1 point — single peristaltic waves; 2 points — intense peristalsis, little amenable to straightening at maximum insufflation; 3 points — pronounced peristalsis.
Results. Three minutes post-irrigation, the suppression of peristaltic waves was noted in the experimental group "L": 0 points — 63 (90 %) patients, 1 point — 6 (8.6 %) patients, compared to the control, with no change in peristalsis ($p < 0.05$). Successful selective cannulation was achieved in 64 (91.4 %) patients of group "L" and in 41 (73.2 %) — of the control group ($p < 0.05$). Non-cannulation endoscopic papillotomy had to be used in 6 (8.5 %) cases in group "L" and in 14 (25 %) cases in the control group. In general, successful cannulation was achieved in 100 % of patients in group "L", and in 94.5 % — in the control group ($p < 0.05$). The duration of the intervention was significantly reduced in group "L" — 40 ± 2.5 vs. 50.3 ± 3.6 min. Among the complications, only intraoperative bleeding was registered (2 (2.9 %) — group "L", 5 (8.9 %) — the control group), which was eliminated endoscopically in all cases.
Conclusion. The use of L-menthol during ERTI helps to achieve noticeable inhibition of peristalsis, promotes successful cannulation, reduces the intervention time, minimizes the risk of intraoperative complications. Thus, L-menthol has demonstrated its effectiveness and safety, which makes it possible to use it in the arsenal of combating enhanced peristalsis during ERTI.
Keywords: endoscopic retrograde cholangiopancreatography, peristalsis, L-menthol
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Применение L-ментола при эндоскопических транспапиллярных вмешательствах. Проспективное рандомизированное двуцентровое исследование

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Цель исследования: изучение влияния препарата L-ментола на перистальтику двенадцатиперстной кишки (ДПК), результаты канюляции устья большого сосочка ДПК, эффективность и безопасность эндоскопических ретроградных транспапиллярных вмешательств (ЭРТВ).

Материалы и методы. Представлены результаты проспективного двуцентрового рандомизированного плацебо-контролируемого исследования. С января по ноябрь 2022 г. в двух клиниках в научную работу были включены 126 пациентов: 69 (54,8 %) мужчин и 57 (45,2 %) женщин, средний возраст — 62,1 ± 1,8 года. Критериями включения были возраст 18–75 лет, наличие показаний к ЭРТВ, отсутствие предшествующей эндоскопической папиллотомии, отсутствие аллергии на ментол, согласие на участие в исследовании. После рандомизации в основную группу «L» вошли 70 пациентов, в контрольную — 56. Пациентам из группы «L» проводилось орошение просвета ДПК 25 мл (160 мг) L-ментола (Спектавиум), пациентам в контрольной группе — 25 мл физиологического раствора. Перистальтическую активность изучали до и через 3 минуты после введения препарата. Интенсивность перистальтики оценивали по модифицированной шкале Hiki: 0 баллов — полное отсутствие перистальтики, 1 балл — единичные перистальтические волны, 2 балла — интенсивная перистальтика, мало поддающаяся расправлению при максимальной инсуффляции, 3 балла — выраженная перистальтика.

Результаты. Через три минуты в группе «L» отмечено угнетение перистальтических волн: 0 баллов — 63 (90 %) пациента, 1 балл — 6 (8,6 %) больных; в контрольной группе перистальтика ожидаемо сохраняла свою интенсивность ($p < 0,05$). Успешная селективная канюляция достигнута у 64 (91,4 %) пациентов группы «L» и у 41 (73,2 %) пациента контрольной группы ($p < 0,05$). К неканюляционной эндоскопической папиллотомии прибегли в 6 (8,5 %) случаях в группе «L» и в 14 (25 %) — в контрольной группе. В целом успешная канюляция была достигнута у 100 % пациентов группы «L» и у 94,5 % — в контрольной группе ($p < 0,05$). Продолжительность вмешательства значимо сократилась в группе «L»: 40 ± 2,5 vs. 50,3 ± 3,6 минуты. Среди осложнений было зарегистрировано только интраоперационное кровотечение (2 (2,9 %) — группа «L», 5 (8,9 %) — контрольная группа), которое во всех случаях было устранено эндоскопически.

Заключение. Применение L-ментола во время ЭРТВ помогает добиться заметного угнетения перистальтики, способствует успешной канюляции, сокращает время вмешательства, минимизирует риск интраоперационных осложнений. Таким образом, L-ментол продемонстрировал свою эффективность и безопасность, что позволяет использовать его в арсенале борьбы с усиленной перистальтикой при проведении ЭРТВ.

Ключевые слова: эндоскопическая ретроградная холангиопанкреатография, перистальтика, L-ментол

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Introduction

Endoscopic retrograde transpapillary interventions (ERTI) are the gold standard for minimally invasive treatment of several pancreato-biliary diseases [1–3]. A key stage of any retrograde intervention is the successful cannulation of the duodenal papilla to access the gallbladder and pancreatic ductal systems. Catheterization longer than 5 minutes or with over 5 attempts increases the risk of complications, mainly acute post-manipulative pancreatitis [2–6]. Several factors prevent the selective cannulation of duodenal papilla. The active duodenal peristalsis complicates the instrument position in relation to the papilla. This inevitably increases the number of cannulation attempts and the papillary area swelling, reducing the successful intervention rate and provoking acute post-manipulative pancreatitis.

Drugs suppressing the gastrointestinal peristalsis and quickening the catheterization of the duodenal papilla in the minimum number of attempts have several usage restrictions and contraindications. One of the drugs reducing the peristaltic activity during ERTI is hyoscine butyl bromide in ampules (Buscopan), which is not registered in the Russian Federation. No domestic analogue of this drug is available. Besides, this drug has several side effects [7–9]. Another drug to reduce the motility of the duodenum is glucagon, but its major indications are different, and therefore several adverse events are observed, such as tachycardia, increased blood pressure, skin rash, and itching [10–12]. The high cost also limits the use of glucagon.

The search for another peristalsis-decreasing drug that combines efficacy, safety, ease of use, and accessibility is needed. An example of this kind of new drugs could be L-menthol, a biologically safe component of cosmetics, food, and household chemicals. It is also used in the treatment of irritable bowel syndrome and functional dyspepsia [13–16]. Several studies showed the effect of L-menthol in gastrointestinal peristalsis suppressing [17–20], but none evaluated its use in ERTI of the pancreatobiliary region.

The aim of our research was to study the effect of L-menthol on duodenal peristalsis, the results of the cannulation of the mouth of the duodenal papilla, and the effect and safety of endoscopic retrograde interventions.

Material and methods

We have developed a protocol for a prospective randomized double-blind study on the use of L-menthol in ERTI. The inclusion criteria for the study were: age from 18 to 75 years; indications for retrograde interventions; intact duodenal papilla (with no previous surgery); intensive duodenal peristalsis precluding the papillary cannulation and subsequent ERTI; absence of allergy to L-menthol; and consent to take part in the study. The non-inclusion criteria were: age less than 18 and over 75 years; absence of indications for ERTI, history of papillosphincterotomy; absence of intensive peristalsis, allergy to L-menthol; refusal to take part in the study. Directly in duodenoscopy, the patients were stratified randomly by the closed-envelope method into two groups with irrigation of the bulb and the vertical section of duodenum before the start of duodenal papillary cannulation with 25 mL of solution containing 160 mg of L-menthol (Spectavium; group "L") or with a similar volume of saline (control, group "C").

The study included patients treated in the State Regional Clinical Hospital of Kazan and the State Clinical Hospital No. 31 of Moscow Health Department from 01.01.2022 to 01.12.2022. During this period, 126 patients were included in the study in the two clinics: 69 (54.8 %) men and 57 (45.2 %) women aged 33 to 75 years (mean age — 62.1 ± 1.8 years). After randomization, group "L" included 70 patients: 42 (60 %) men and 28 (40 %) women (mean age — 61.9 ± 1.9 years); group "C" included 56 patients: 27 (48 %) men and 29 (52 %) women (mean age — 61.8 ± 2 years). The groups were comparable in gender and age ($p > 0.05$). Table 1 shows indications for ERTI and features of the pancreatobiliary anatomy.

In both centers, similar endoscopic equipment was used for ERTI: therapeutic duodenoscopes TJF-150 and TJF-180 with at least 3.8-mm instrumental channel (Olympus, Japan); endoscopic blocks EVIS Exera III (Olympus, Japan), and a standard set of instruments for duodenal papilla cannulation and endoscopic papillosphincterotomy (bulbous and needle papillotomes, catheters, and conductor strings from various manufacturers). In each clinic, interventions were performed by two leading specialists with maximum experience in endoscopic retrograde interventions.

As a solution of L-menthol, the biologically active additive Spectavium (Pharma-Sever CJSC, Russia) was used. To increase precision and minimize the penetration of the solution onto the camera lens, it was irrigated through a catheter; that could somewhat complicate intraoperative visualization because of the oily structure of the menthol solution.

Peristalsis was assessed in duodenoscopy before and three minutes after the drug administration. Modified Hiki scale [19] was adapted for the duodenum to estimate the peristaltic wave intensity, with Grade 0 meaning the absence of peristalsis; Grade 1 — a few contraction waves that overlap the duodenal lumen by no more than half the lumen; Grade 2 — the isolated peristaltic waves that overlap the duodenal lumen by over the half the lumen, not fully straightened with the maximum insufflation of carbon dioxide through a duodenoscope; and Grade 3 — the active peristalsis, with maximum gas insufflation not allowing the complete straightening of the intestinal lumen. Grade 2 and 3 peristalsis hampered the intervention on the duodenal papilla, and Grade 0 and 1 peristalsis was mostly considered comfortable for ERTI.

When evaluating the effectiveness of the drug, we evaluated the intensity of peristalsis three minutes after administration of the drug, the success of cannulation of duodenal papilla, the need for non-cannulation endoscopic papillosphincterotomy, the total duration of the intervention, and the specific complications (bleeding, retroduodenal perforation, and acute post-manipulative pancreatitis). Statistical analysis and evaluation of differences were performed with the Statistica software.

Results

Figure 1 shows the intensity of primary peristalsis. Before the administration of the drug,

Table 1. Indications for retrograde intervention and features of the anatomy of the pancreaticobiliary zone
Таблица 1. Показания к ретроградному вмешательству и особенности анатомии панкреато-билиарной зоны

Parameter *Параметр*	Group "L", *n* (% *Группа «L», n (%))*	Group "C", *n* (%) *Группа «К», n (%)*	Total, *n* (%) *Всего, n (%)*
Bile duct stones *Холедохолитиаз*	42 (60 %)	25 (44.6 %)	67 (53.2 %)
Pancreatic tumor *Опухоль головки поджелудочной железы*	2 (2.9 %)	0	2 (1.6 %)
Klatskin's tumor *Опухоль Клацкина*	2 (2.9 %)	2 (3.6 %)	4 (3.2 %)
Acute pancreatitis *Острый панкреатит*	3 (4.3 %)	2 (3.6 %)	5 (4.0 %)
Chronic pancreatitis *Хронический панкреатит*	3 (4.3 %)	1 (1.8 %)	4 (3.2 %)
Bile duct stones + papillostenosis *Холедохолитиаз + папиллостеноз*	3 (4.3 %)	2 (3.6 %)	5 (4.0 %)
Papillostenosis/stricture of the terminal part of the common bile duct *Папиллостеноз/стриктура терминального отдела холедоха*	1 (1.4 %)	15 (26.8 %)	16 (12.7 %)
Papillostenosis + parapapillary diverticulum *Папиллостеноз + парапапиллярный дивертикул*	1 (1.4 %)	0	1 (0.8 %)
Bile duct stones + parapapillary diverticulum *Холедохолитиаз + парапапиллярный дивертикул*	13 (18.6 %)	9 (16.1 %)	22 (23.8 %)
Total *Итого*	70	56	126 (100 %)

the activity of peristaltic waves in both groups was equal: in group "L", Grade 3 and 2 peristalsis was recorded in 38 (54.3 %) and 30 (42.9 %) patients, in group "C", an intense peristalsis was recorded in 24 (42.9 %) and 32 (57.1 %) cases ($p > 0.05$). Three minutes after irrigation of the duodenal lumen with Spectavium in the experimental group, peristaltic waves were suppressed noticeably to Grade 0 in 63 (90 %) patients and Grade 1 in 6 (8.6 %) patients; in the control group, the peristalsis maintained the original intensity ($p < 0.05$) (Fig. 1).

The main results of ERTI depending on the use of L-menthol, including success and complication rates, are presented in the Table 2.

The average duration of intervention in the experimental group was significantly lower than that of the control (40.0 ± 2.5 vs. 50.3 ± 3.6 minutes, respectively; $p < 0.05$). Successful selective catheterization of the duodenal papilla was achieved in 64 (91.4 %) patients of group "L" and only in 41 (73.2 %) patients in group "C" ($p < 0.05$). Non-cannulation endoscopic papillotomy was needed much less frequently — in 6 (8.5 %) vs. 14 (25 %) cases ($p < 0.05$). Successful catheterization was achieved in all patients in the main group and in 53 (94.5 %) patients in the control group. This enabled the planned interventions presented in Table 3. Figure 2 shows the radiographs of the most common interventions.

Out of three patients of group "C" with unsuccessful attempts to catheterize the duodenal papilla, one patient with a proximal block on the background of a Klatskin tumor was treated with an external-internal drainage, and two other with a stricture of the terminal choledochus reached endoscopic decompression during the second stage of ERTI a few days after the primary intervention.

The effect of the drug enabled all necessary interventions. In one patient (1.4 %) with signs of "complex" choledocholithiasis (multiple concretions of the common bile duct, intradiverticular arrangement of duodenal papilla), a resumption of

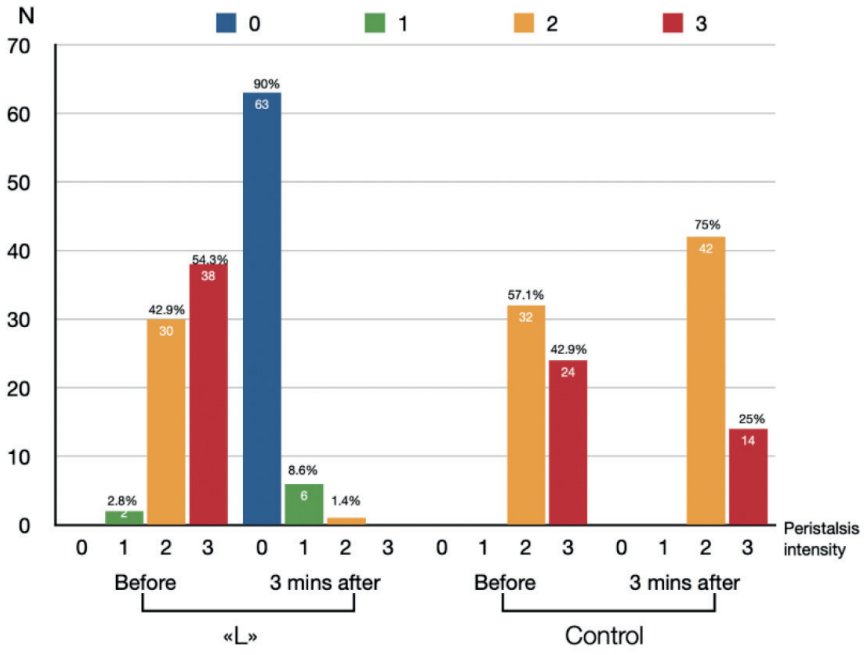

Figure 1. Histogram of peristalsis intensity before drug administration and three minutes after administration in the main and control groups

Рисунок 1. Гистограмма интенсивности перистальтики до введения препарата и через три минуты после введения в основной и контрольной группах

Table 2. Main indicators of the effectiveness of L-menthol use compared to the control group

Таблица 2. Основные показатели эффективности применения L-ментола по сравнению с контрольной группой

Parameter ***Параметр***	**Group "L", *n* (%)** ***Группа «L», n (%)***	**Группа «К», *n* (%)** ***Group "C", n (%)***	***p***
Time of intervention, min *Продолжительность вмешательства, мин*	40.0 ± 2.5	50.3 ± 3.6	< 0.01
Need for non-cannulation endoscopic papillotomy, *n* (%) *Необходимость неканюляционной эндоскопической папиллотомии, n (%)*	6 (8.5 %)	14 (25 %)	< 0.01
Selective cannulation of the major duodenal papilla, *n* (%) *Селективная канюляция большого сосочка двенадцатиперстной кишки, n (%)*	64 (91.4 %)	41 (73.2 %)	< 0.01
Overall success of major duodenal papilla cannulation, *n* (%) *Общий успех канюляциыи большого сосочка двенадцатиперстной кишки, n (%)*	70 (100 %)	53 (94.5 %)	< 0.05
Complications (intraoperative bleeding), *n* (%) *Осложнения (интраоперационное кровотечение), n (%)*	2 (2.9 %)	5 (8.9 %)	< 0.01
Complete absence of peristalsis after administration of the drug (0 points) *Полное отсутствие перистальтики после введения препарата (0 баллов)*	63 (90 %)	0	< 0.01

Table 3. Performed endoscopic interventions
Таблица 3. Проведенные эндоскопические вмешательства

Intervention ***Название вмешательства***	**Group "L", *n* (%)** ***Группа «L», n (%)***	**Group "C", *n* (%)** ***Группа «К», n (%)***	**Total, *n* (%)** ***Всего, n (%)***
Bile duct stone extraction *Литоэкстракция из холедоха*	45 (62.3 %)	29 (51.8 %)	74 (58.7 %)
Lithotripsy + Stone extraction *Литотрипсия + литоэкстракция*	11 (15.7 %)	4 (7.1 %)	15 (11.9 %)
Билиодуоденальное стентирование *Biliary stenting*	7 (10 %)	9 (16.1 %)	16 (12.7 %)
Nasobiliary drainage *Назобилиарное дренирование*	3 (4.3 %)	7 (12.5 %)	10 (7.9 %)
Bile duct stone + pancreatic stone extraction + major pancratic duct stenting *Холедохолитоэкстракция + вирсунголитоэкстракция + стентирование главного панкреатического протока*	1 (1.4 %)	0	1 (0.8 %)
Pancreatic stenting *Панкреатическое стентирование*	3 (4.3 %)	2 (3.6 %)	5 (4.0 %)
Biliary stenting+ major pancratic duct stenting *Билиарное стентирование + стентирование главного панкреатического протока*	0	2 (3.6 %)	2 (1.6 %)
Atypical endoscopic papillosphincterotomy (stage 1) *Атипичная эндоскопическая папиллосфинктеротомия (1-й этап)*	0	3 (5.4 %)	3 (2.4 %)
Total *Всего*	70 (100 %)	56 (100 %)	126

peristalsis to Grade 0 to 3 was noted by the end of the intervention (45 min). However, the effect of the drug enabled all the stages of the operation (endoscopic retrograde cholangiopancreatography, endoscopic papillosphincterotomy, mechanical lithotripsy, and lithoextraction) and complete sanitation of the bile ducts. Of note, no cardiorespiratory disorders were registered in any patient during the intervention.

In both groups, ERTI was complicated by intraoperative bleeding, 2 (2.9 %) patients of group "L" and 5 (8.9 %) patients of group "C". In all situations, the bleeding was stopped endoscopically. No other complications were noted, including acute post-manipulative pancreatitis or deaths.

Discussion

The suppression of the peristalsis by L-menthol is considered to be caused by inhibition of the Na-Ca transporting ATPase in smooth muscle cell membranes [17]. Several high-quality studies have confirmed the effectiveness of menthol in inhibiting gastric and colon peristalsis [18–20]. In example, N. Hiki et al. found a significant inhibition of gastric peristalsis by the mucosa irrigation with menthol solution in a randomized study. The study involved 167 patients (85 — in the main group, 82 — in control group). In the main group, the antral gastric mucosa was irrigated with 160 mg of L-menthol through a spray catheter. In the control group, a saline solution was used as a placebo. Peristalsis was assessed before and 135 seconds after the irrigation. Complete suppression of peristalsis was observed in 35.6 % of patients in the main group vs. 7.1 % in control group, with the end-endoscopy peristalsis not exceeding Grade 1 in the absolute majority of cases (77.8 %) in the main group [19]. The study enabled the introduction of the technique into routine practice of diagnostic upper gastrointestinal endoscopic examinations in Japan. Importantly, the study was aimed solely at assessing gastric peristalsis and did not include an examination of the duodenum. In a recent meta-analysis, Q. You

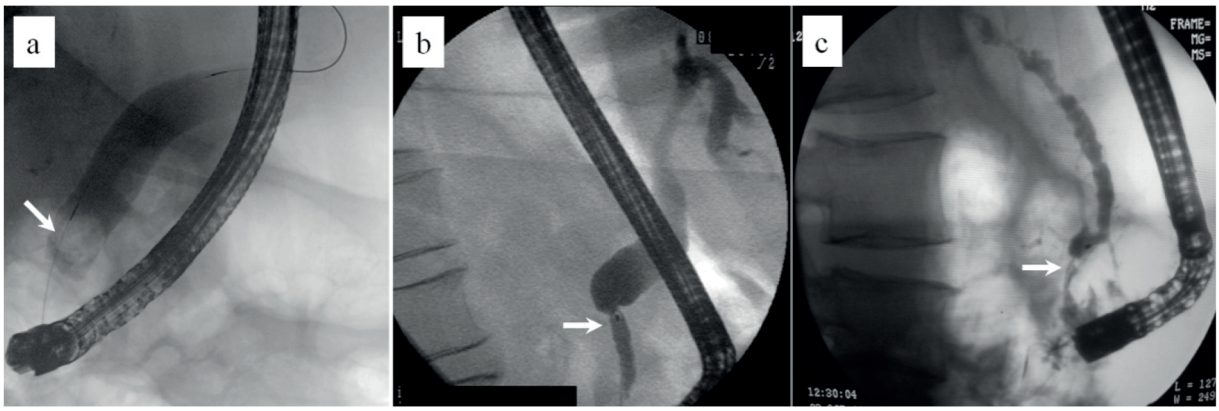

Figure 2. Endoscopic retrograde cholangiopancreaticography: *a* — common bile duct stone (stone is indicated by an arrow); *b* — stricture of the distal parts of common bile duct (indicated by an arrow); *c* — stricture of the distal parts of the main pancreatic duct in chronic pancreatitis (indicated by an arrow)

Рисунок 2. Эндоскопическая ретроградная холангиопанкреатография: *a* — холедохолитиаз (конкремент в просвете холедоха указан стрелкой); *b* — стриктура дистальных отделов холедоха (указана стрелкой); *c* — стриктура дистальных отделов панкреатического протока при хроническом панкреатите (указана стрелкой)

et al. confirmed the significant suppression of colon peristalsis during colonoscopy, both diagnostic and operative. Suppression of peristalsis in these cases decreased the pain during the device insertion, reduced the complications and the total duration of interventions [20]. When analyzing the world literature, we have not found a single study of the effect of menthol on the duodenal peristalsis in ERTI. Of note, P. Katsinelos et al. compared other drugs inhibiting the duodenal motility in similar cases [21]. The authors conducted a randomized double-blind study to assess the effect of a combination of nitroglycerin and glucagon on the success of selective cannulation of duodenal papilla and prevention of acute post-manipulative pancreatitis. Patients from the main group ("A") received siz spray doses of nitroglycerin sublingually (2.4 mg) and 1 mg of glucagon intravenously before the intervention. In the control group ("B"), patients received six doses of sterile water sublingually and 20 mg of hyoscine butyl bromide intravenously. Table 4 compares the results of this study with our data.

Despite the numerical superiority in the sample of the compared study, the advantage of L-menthol over hyoscine butyl bromide can be noted both in terms of the frequency of selective cannulation and

Table 4. Comparison of the results of using L-menthol with the data of P. Katsinelos et al. [21]
Таблица 4. Сравнение результатов применения L-ментола с данными P. Katsinelos et al. [21]

Parameter *Параметр*	**Group A** *Группа А*	**Group B** *Группа В*	**Group "L"** *Группа «L»*
Number of patients *Количество пациентов*	227	228	70
Selective cannulation of the major duodenal papilla, % *Селективная канюляция большого сосочка двенадцатиперстной кишки, %*	95.2 %	82.2	91.4 %
The need for non-cannulation endoscopic papillotomy, *n* (%) *Необходимость неканюляционной эндоскопической папиллотомии, n (%)*	11 (4.9 %)	39 (17.1 %)	6 (8.5 %)
Frequency of acute post-manipulation pancreatitis, % *Частота острого постманипуляционного панкреатита, %*	3.1 %	7.46 %	0

the need for non-cannulation endoscopic papillotomy. Also, we noted no acute post-manipulative pancreatitis cases in our patients, which shows a high precision of work on the area of duodenal papilla. The combination of nitroglycerin with glucagon is highly efficient. However, these drugs have limitations to use and cannot be recommended to every patient. Given the low risk of adverse reactions and adverse events, L-menthol has an undeniable advantage. Our preliminary results show the effectiveness and safety of the drug in patients requiring endoscopic papillosphincterotomy in the presence of intensive peristalsis of the duodenum. However, some unresolved issues remain. We have not estimated the exact duration of action and the minimum duodenal peristalsis-suppressing concentration of the drug. The further study and data obtaining will allow an in-depth analysis of the results.

Conclusion

The first experience of using irrigation of the duodenal mucosa with L-menthol solution at the initial stage of endoscopic transpapillary interventions showed an noticeable inhibition of peristalsis, more successful selective catheterization of the duodenal papilla, and reduced duration of intervention. L-menthol weakens the duodenum motility during manipulations on the duodenal papillary area effectively and safely. The results make it possible to use the drug in difficult situations with intensive peristalsis of the duodenum.

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