https://doi.org/10.22416/1382-4376-2021-31-4-37-44

Efficacy of Hymecromone in Post-Cholecystectomy Patients

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Background. The cholecystectomy is the major cause of sphincter of Oddi dysfunction (SOD), that may be classified as post-cholecystectomy syndrome (PCES). Treatment of PCES requires in most of the cases application of selective antispasmodic drugs.
Aim. To evaluate efficacy and safety of hymecromone in patients with post-cholecystectomy SOD, to compare standard and reduced doses of hymecromone.
Methods. Overall, 26 patients were enrolled in non-interventional comparative study: 2 males, 24 females, aged from 25 to 74 years. All patients underwent cholecystectomy for symptomatic gallstone disease within 1 to 10 years prior to beginning of the study. All patients were diagnosed to have SOD according to Rome IV Diagnostic Criteria for functional biliary sphincter of Oddi disorder (E1b). All patients underwent hymecromone monotherapy for 3 weeks. Patients were randomized to group A and B to receive full-dose or half-dose of the drug respectively.
Results. Abdominal pain completely subsided in 85 % of patients, significant improvement was found for bloating and diarrhea. Mild increase in fasting common bile duct (CBD) diameter after treatment (7.23 ± 0.99 vs 6.78 ± 1.01; $p = 0.029$) was attributed to choleretic action of hymecromone. Hymecromone resulted in significant improvement of CBD response to fatty meal stimulation (ΔCBD): –1.08 ± 0.46 mm vs –0.10 ± 0.33 mm pretreatment ($p = 0.016$). Degree of improvement was more pronounced in the group A (full-dose) as compared to group B (half-dose) for abdominal pain ($Z = 2.74$, $p = 0.031$), bloating ($Z = 2.63$, $p = 0.035$) and constipation ($Z = 2.61$, $p = 0.038$)
Conclusion. Hymecromone demonstrated itself to be an effective and safe drug, that may be applied both in standard and half dose. However, the efficacy of full-dose is higher both for the treatment of biliary pain and dyspeptic symptoms. Transabdominal ultrasound may be applied as a reliable test for both prediction of treatment efficacy and to monitor patients state during treatment course.
Keywords: gallstone disease, cholelithiasis, sphincter of Oddi dysfunction, post-cholecystectomy syndrome, fatty meal sonography, pain
Conflict of interests. The current study was supported by “Adamed” Russia pharmaceutical company.

For citation: Okhlobystin A.V., Ufimtseva A.K., Tatarkina M.A., Okhlobystina O.Z., Ivashkin V.I. Efficacy of Hymecromone in Post-Cholecystectomy Patients. Russian Journal of Gastroenterology, Hepatology, Coloproctology. 2021;31(4):37–44. https://doi.org/10.22416/1382-4376-2021-31-4-37-44

Эффективность гимекромона у пациентов с постхолецистэктомическим синдромом

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Введение. Холецистэктомия является основной причиной дисфункции сфинктера Одди (ДСО), которую можно рассматривать как одно из проявлений постхолецистэктомического синдрома (ПХЭС). Основой медикаментозной терапии ПХЭС в большинстве случаев служит применение селективных спазмолитиков.
Цель. Оценить эффективность и безопасность приема гимекромона в стандартной и в уменьшенной дозе (половина стандартной) у пациентов с ДСО после холецистэктомии.
Методы. В неинтервенционное сравнительное исследование были включены 26 пациентов: 2 мужчин, 24 женщины, в возрасте от 25 до 74 лет. Всем пациентам была выполнена холецистэктомия по поводу желчнокаменной болезни с клиническими проявлениями за 1–10 лет до начала исследования. У всех пациентов была диагностирована ДСО в соответствии с Римскими IV диагностическими критериями функционального расстройства сфинктера Одди (E1b). Всем пациентам назначена монотерапия гимекромоном на 3 недели: пациенты были рандомизированы в группы А и В, которые получали полную или половинную дозы препарата соответственно.

Результаты. Боль в животе была полностью купирована у 85 % пациентов, значительное улучшение отмечено в отношении вздутия живота и диареи. Незначительное увеличение диаметра ОЖП натощак после лечения (7,23 ± 0,99 мм по сравнению с исходным 6,78 ± 1,01 мм (p = 0,029)) может быть связано с желчегонным действием гимекромона. Продемонстрировано значительное улучшение ответа ОЖП на стимуляцию желчегонным завтраком (ΔОЖП) –1,08 ± 0,46 мм, тогда как до начала терапии он составлял –0,10 ± 0,33 мм (p = 0,016). Степень улучшения самочувствия пациентов была более выраженной в группе А (полная доза) по сравнению с группой В (половина дозы) в отношении абдоминальной боли (Z = 2,74, p = 0,031), вздутия живота (Z = 2,63, p = 0,035) и запора (Z = 2,61, p = 0,038).
Выводы. Гимекромон показал себя эффективным и безопасным препаратом, который можно применять как в стандартной, так и в половинной дозе. Стандартная доза оказалась более эффективной для купирования билиарной боли и диспепсических симптомов. Трансабдоминальное УЗИ — надежный диагностический тест для прогнозирования эффективности лечения и мониторинга состояния пациентов во время курса лечения.
Ключевые слова: желчнокаменная болезнь, холедохолитиаз, дисфункция сфинктера Одди, постхолецистэктомический синдром, ультразвуковое исследование с пробным завтраком, боль
Конфликт интересов: Исследование выполнено при поддержке фармацевтической компании «Адамед» (Россия).

Для цитирования: Охлобыстин А.В., Уфимцева А.К., Татаркина М.А., Охлобыстина О.З., Ивашкин В.Т. Эффективность гимекромона у пациентов с постхолецистэктомическим синдромом. Российский журнал гастроэнтерологии, гепатологии, колопроктологии. 2021;31(4):37–44. https://doi.org/10.22416/1382-4376-2021-31-4-37-44

Background

Laparoscopic cholecystectomy is considered the treatment of choice for symptomatic gallstone disease (GSD). The first cholecystectomy was performed in Russia by famous surgeon Yu.F. Kosinsky in 1889, first laparoscopic cholecystectomy was done by prof. Yu.I. Gallinger and A.D. Timoshin in 1991 [1]. Over 50,000 these operations were performed annually in the UK and Ireland and more than half a million these were done annually in the USA. Overall, cholecystectomy is an established successful operation which provides total relief of preoperative symptoms in more than 90 % of patients. Post-cholecystectomy syndrome (PCES) is defined as the recurrence of symptoms similar to those experienced before the cholecystectomy [2]. This usually takes the form of upper abdominal pain (mainly right hypochondrial pain) and dyspepsia, with or without jaundice. The incidence of PCES according to the Russian literature has been reported to be as high as 5 to 25 % [3–5]. Gender may affect not only the risk of the GSD development, but the PCES as well: the incidence of recurrent symptoms was 43 % among female patients, while it was only 28 % in males. The causes of PCES include organic disorders (biliary strictures, retained calculi, chronic biloma or abscess, long cystic duct remnant, sphincter of Oddi stenosis) and functional, most common of which is sphincter of Oddi dysfunction (SOD) [6]. This requires application of modern radiological tests computed tomography (CT), magnetic resonance imaging (MRI), endoscopic ultrasound (EUS) to conclusively establish the diagnosis. Currently, the only reliable method is biliary manometry which unfortunately, is both difficult to perform and associated with considerable risk of pancreatitis. In addition to this, even if manometric evidence of SOD is obtained, it does not always prove that it is the cause of the patient's symptoms.

SOD can result from a true stenosis or secondary to spasm of the sphincter. In the majority of cases, the dysfunction continues to present problems both in terms of diagnosis as well as treatment. Although muscle spasm is thought to play a significant role in these cases, the response to non-selective antispasmodics (e.g., nitrates and calcium channel antagonists) has been disappointing [7]. Sphincterotomy is considered to be effective treatment for stenosis of sphincter of Oddi, though associated with significant risk of bleeding, secondary infection of sterile biloma/ascites, pancreatitis [8]. Pharmacological treatment of SOD is based on dietic advice (frequent small meals) and repetitive courses of antispasmodic medications, combined to ursodeoxycholic acid. Unfortunately, the rate of response to antispasmodic medications is low, that requires both choosing the most effective and safe drug and careful selection of patients.

Methods

Overall, 26 patients were enrolled in non-interventional comparative study: 2 males, 24 females, the age of patients ranged from 25 to 74 years (mean age was 57.4 ± 3.2 years). All patients underwent cholecystectomy for symptomatic gallstone disease within 1 to 10 years prior to the study onset and developed new symptoms or symptom aggravation following gallbladder surgery. Patients had no signs, that could meet Cambridge criteria of chronic pancreatitis and no

prior sphincter intervention. All patients were diagnosed to have SOD according to Rome IV Diagnostic Criteria for functional biliary sphincter of Oddi disorder (E1b): presence of biliary pain; common bile duct (CBD) dilation (>6 mm) and/or transient elevation of liver enzymes; absence of bile duct stones or other structural abnormalities [6, 9]. Organic causes of bile duct obstruction were excluded using imaging modalities: computed tomography (CT), magnetic resonance imaging (MRI), endoscopic ultrasound (EUS), and/or transabdominal ultrasound (US).

Mean BMI was 26.20 ± 1.28 kg/m^2. Normal weight was seen in 35.7 % of patients, 42.9 % of patients were overweight and obesity was present in the remaining 21.4 %. All patients underwent routine physical examination, complete blood count, serum biochemistry (alanine and asparagine transaminases, gamma-glutamyl transpeptidase, alkaline phosphatase, bilirubin, amylase, creatinine, glycose, triglycerides).

Symptom severity was assessed using the 4-point scale (from absent to severe), the change of symptoms was evaluated as Δ score: post-treatment score — initial score.

Disability of patients due to abdominal pain was assessed using the Recurrent Abdominal Pain Intensity and Disability (RAPID) questionnaire [10, 11]. The RAPID score is the patient's recall of how much productivity in 3 domains (paid work or school, household activities, and non-work activities) was lost in the prior 90 days due to abdominal pain episodes ranging from 0 to 270. The RAPID score has 4 grades: grade 1 indicates 6 days or less; grade 2, 7 to 10 days; grade 3, 11 to 20 days; and grade 4, 20 days or more. RAPID score was 8.07 ± 1.51. Fifty percent of patients had RAPID grade 1, 28.6 % — grade 2, 21.4 % — grade 3.

Abdominal ultrasound was performed for all patients in our study in the transverse, sagittal, and oblique planes that best demonstrated the entire biliary tree in fasting state, recording the largest of diameter of the CBD. Then a standard fatty meal (chocolate bar with 200 mg of normal yogurt) was used for stimulation and the reexamination was done in forty-five minutes to one hour after fat ingestion again recording the largest size of the CBD [12]. Increase in diameter of greater than 2 mm (at 45 min) compared with baseline was used as a marker of SOD [13].

All patients were randomized to 2 groups, 13 patients each who subsequently received full daily dose of hymecromone (400 mg tid, group A) or half-dose of hymecromone (200 tid, group B) for 3 weeks. Hymecromone (Odeston, Adamed, Russia) was prescribed as monotherapy, patients allowed no other drugs with antispasmodic or choleretic mechanism of action.

The statistical analyses were performed in SPSS statistics package version 26.0 (IBM, Armonk, NY). Normality was assessed using Q-Q plots and Shapiro Wilk test. Continuous variables are presented as mean values with standard deviations (SD) or median values with interquartile range (IQR), as appropriate.

For categorical variables Wilcoxon signed rank test was applied with calculation of standardized test statistic and p value for asymptotic significance (2-sided test). Missing data were handled using listwise deletion. Statistical significance was defined as $p < 0.05$.

Results

Patients characteristic

Background clinical symptoms in the studied patient are represented in the Table 1.

All complete blood count and blood biochemistry parameters were within the normal range.

According to abdominal US data the mean fasting CBD diameter was 7.07 ± 0.63 mm, after fatty meal stimulation — 6.73 ± 0.66 mm (Fig. 1). Fatty meal test prior to hymecromone treatment resulted in no significant change of CBD size: –0.10 ± 0.33 mm.

Table 1. Initial clinical symptom score distribution in studied patients

	Abd. pain	Nausea	Bloating	Constipation	Diarrhea
None	14.3	69.2	15.4	69.2	53.8
Mild	14.3	15.4	23.1	0	23.1
Moderate	42.9	0	46.2	7.7	7.7
Severe	28.6	15.4	15.4	23.1	15.4
Total	100.0	100.0	100.0	100.0	100.0

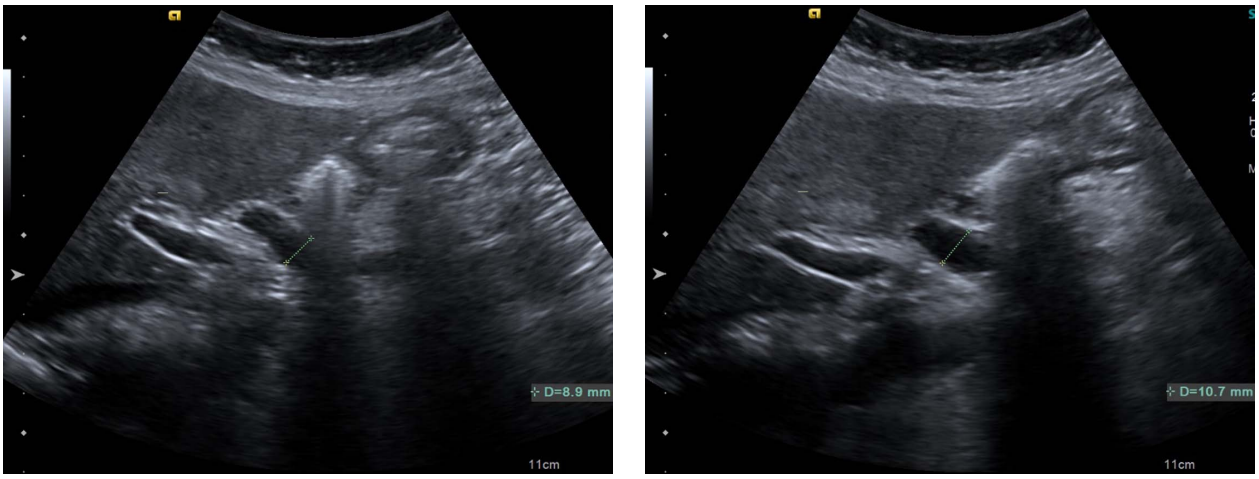

Fig. 1. Measurement of common hepatic/bile duct diameter in a patient with SOD before (8.9 mm) and after the test meal stimulation (10.7 mm)
Рис. 1. Измерение диаметра общего желчного (печеночного) протока у пациента со спазмом сфинктера Одди натощак (8,9 мм) и после стимуляции (10,7 мм, т.е. наблюдается расширение протока, что свидетельствует о спазме сфинктера)

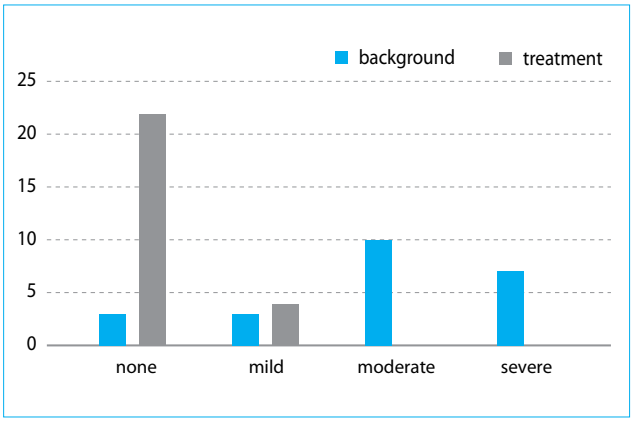

Fig. 2. Scores of abdominal pain before and at the end of treatment course
Рис. 2. Интенсивность боли в животе до начала и к концу курса терапии (баллы)

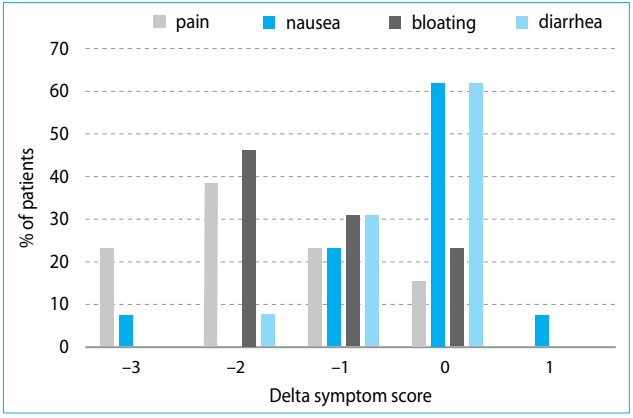

Fig. 3. Changes in the symptom scores at the final day of hymecromone intake as compared to the day 0 (Δ scores = post-treatment score-pre-treatment score)
Рис. 3. Разность выраженности симптомов у пациентов к концу курса терапии гимекромоном и таковой до начала лечения (Δ симптома)

Overall treatment efficacy evaluation

Abdominal pain intensity significantly decreased in all patients (Z = 2.976, p = 0.003), it completely subsided in most of the cases (22 patients, 85 %, Fig. 2). Nausea dynamics was somewhat less pronounced: the symptom disappeared in 3 patients (p = NS), 2 patients noted mild increase in nausea intensity (Figure 3). Bloating severity significantly decreased in all of 31 % study patients (Z = 2.889, p = 0.004), and it completely subsided in 15 % of the cases. No significant changes in constipation were detected (Z = 1.857, p = 0.063), however patients noted significant improvement in diarrhea severity (Z = 2.121, p = 0.034).

There was a mild increase in fasting CBD diameter after treatment: initial CBD size was 6.78 ± 1.01, posttreatment 7.23 ± 0.99; the difference was significant in paired differences test (mean difference 0.46 ± 0.17, 95 % CI:-0.85 to –0.06, t = –2.67, p = 0.029). At the end of hymecromone treatment CDB diameter after test meal slightly increased in comparison to pretreatment size, but the difference was not statistically significant: posttreatment CBD was 6.68 ± 0.88 mm, while pretreatment CBD was 6.16 ± 0.77 (mean

difference 0.52 ± 0.30, 95 % CI –0.17 to 1.2, t = 1.74, p = 0.120).

It was found, that hymecromone resulted in significant improvement of CBD response to fatty meal stimulation (ΔCBD): if pretreatment ΔCBD was –0.10 ± 0.33 mm, post-treatment ΔCBD was –1.08 ± 0.46 mm. According to paired differences test the dynamics was statistically significant: 0.98 ± 0.32 mm (95 % CI: 0.23–1.72, t = 3.05, p = 0.016).

Overall, 4 patients at the day of treatment termination were completely satisfied by its efficacy, 10 — rather satisfied, 10 — evaluated the effect as neutral and 2 were rather unsatisfied.

Comparison of hymecromone 600 mg/day to 1200 mg/day

No statistically significant differences between group A (full daily dose dose) and B (half daily dose) before study onset in age, gender, body weight, body mass index (BMI), symptom severity, blood biochemistry and treatment satisfaction were found.

No difference between groups A and B in terms of symptom improvement were noted, however the degree of improvement was more pronounced in the group A as compared to group B for abdominal pain (Z = 2.74, p = 0.031, Fig. 5), bloating (Z = 2.63, p = 0.035) and constipation (Z = 2.61, p = 0.038).

According to Wilcoxon signed ranks test the difference between post-treatment and initial pain scores was significant in the group A (median = –2.50, Z = –2.56, p = 0.011), while it did not reach the level of significance in the group B (median = –1.60, Z = –1.84, p = 0.066).

Fatty meal sonography results were more pronounced in group A: ΔCBD dynamics was –1.70 ± 0.28 mm, (95 % CI –0.84 to 4.24), as compared to group B: ΔCBD dynamics was –0.77 ± 1.00 mm, 95 % CI –0.15 to 1.69), however in both cases the difference was not statistically significant in subgroups (Fig. 6).

Discussion

According to the review of 17 studies the prevalence of SOD after laparoscopic cholecystectomy ranged from 3 % to 40 % [14]. Accurate diagnosis of SOD remains a challenge and reliable predictors of a favorable response to treatment are lacking [15]. Manometry of sphincter of Oddi is still regarded to be a gold standard for this diagnosis

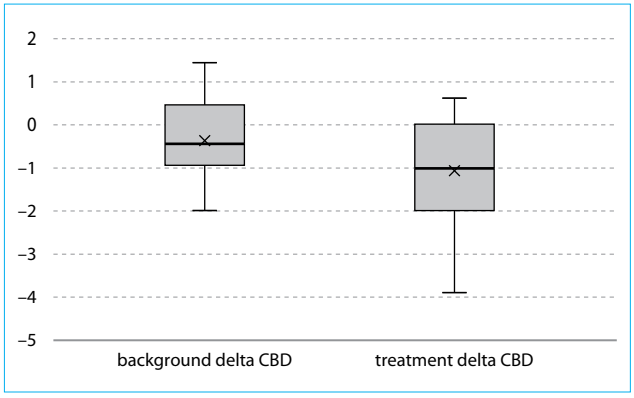

Fig. 4. Treatment effect according to ultrasound fatty meal test: response to stimulation before and at the end of treatment course
Рис. 4. Изменение диаметра ОЖП после стимуляции пробным завтраком (мм) в результате терапии гимекромоном

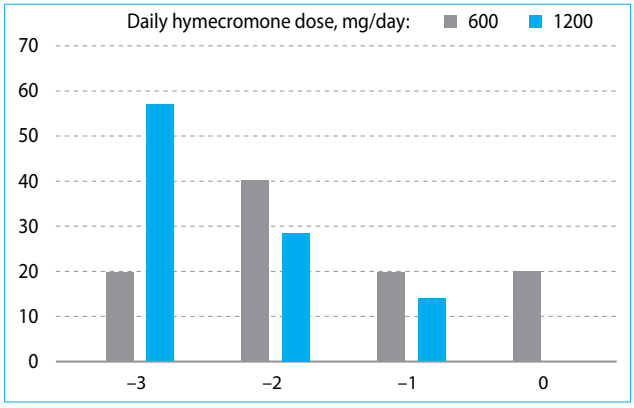

Fig. 5. The difference between post- and pre-treatment pain (Δ) for group A (hymecromone 1200 mg/day) and group B (600 mg/day)
Рис. 5. Динамика интенсивности боли в животе в конце курса лечения по сравнению с исходным уровнем (Δ) в группе А (гимекромон 1200 мг/сут) и группе В (600 мг/сут)

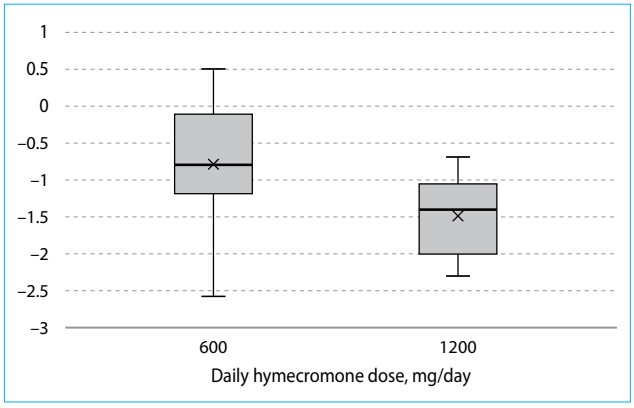

Fig. 6. Comparison of CBD response dynamics in groups A (1200 mg/day) and B (600 mg/day)
Рис. 6. Сравнение результатов УЗ-пробы (изменение диаметра ОЖП после стимуляции) к окончанию курса терапии гимекромоном в группе А (1200 мг/сут) и В (600 мг/сут)

according to the latest Rome IV diagnostic criteria but is invasive and carries significant risk of post-procedure pancreatitis [6]. Hepatobiliary scintigraphy has been used in the evaluation of SOD but it exposes the patient to ionizing radiation, lacks anatomic information regarding biliary tree, reports regarding accuracy are inconsistent and correlation with manometry results has been poor [16]. Secretin-stimulated MRCP has the potential to be the ideal imaging modality in evaluating SOD, as it can provide both functional and anatomic information, however the procedure is expensive, not covered by insurance and requires secretin injection, that is currently not registered for medical application by the Ministry of Health of Russian Federation [17]. In our study we chose fatty meal sonography as affordable quite reliable method for assessment of biliary tree emptying, that is an important criterion for diagnosing SOD [9]. Unfortunately, the test meal is not standardized and different types of stimulators are applied by now: 40 g of corn oil [18], 20 g coconut oil [12], chocolate and yoghurt combination, chocolate yoghurt combination and the 15 g coconut oil [12] or fatty emulsion for parenteral nutrition (Lipomul) [13].

Absence of significant change of CBD size after fatty meal intake before hymecromone treatment onset indicates presence of SOD in studied patients with PCES.

Mild increase in fasting CBD diameter after treatment (0.46 ± 0.17 mm) may reflect mild increase in bile secretion of the background of hymecromone treatment, as it was shown, that hymecromone increased biliary excretion of sodium and enhanced formation of the bile acid- independent fraction of canalicular origin, mediated by the active transfer of sodium into the canaliculi [19]. Hymecromone is capable of modifying the composition of the bile by decreasing concentration of cholesterol [20].

Hymecromone demonstrated good safety and tolerability both improving patients symptoms and normalizing sphincter of Oddi response to stimulation. No major adverse effects were noted, most of patients were completely satisfied by the treatment efficacy.

Using the full vs half hymecromone dose resulted in more than double effect on CBD size according to abdominal ultrasound data, though, due to high variance of the results the difference was not significant. This requires more thorough selection of patients to further studies — not only of the basis of clinical symptoms and absence of sphincter of Oddi stenosis, but also according to stimulation test results.

Hymecromone has also been reported to have antioxidant properties, antitumor, antifibrotic [21], radical scavenging activity [22] that may require long-term courses of the drug to decrease the progression of sphincter of Oddi fibrosis.

Conclusion

Hymecromone demonstrated itself to be an effective and safe drug, that may be applied both in standard and half dose. However, the efficacy of full-dose is higher both for biliary pain and dyspeptic symptoms. Patients with SOD after cholecystectomy should be prescribed hymecromone at a dose of 1200 mg per day. Transabdominal ultrasound may be applied as a reliable test for both prediction of treatment efficacy and to monitor patients state during treatment course.

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Submitted: 28.07.2021 Accepted: 19.08.2021 Published: 30.09.2021
Поступила: 28.07.2021 Принята: 19.08.2021 Опубликована: 30.09.2021

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