Advances in Bioresearch
Adv. Biores., Vol 16 (2) March 2025: 76-81

Print ISSN 0976-4585; Online ISSN 2277-1573
Journal's URL:http://www.soeagra.com/abr.html
CODEN: ABRDC3
DOI: 10.15515/abr.0976-4585.16.2.7681

Advances in Bioresearch

ORIGINAL ARTICLE

Comparative Study of The Effectiveness of Monotherapy with Ursodeoxycholic Acid and in Combination with Hymecromone in Patients with Biliary Tract Dysfunction

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ABSTRACT

In this article, the aim is to study and analyze the clinical benefits and comparative effectiveness of combined therapy using ursodeoxycholic acid with Hymecromone in patients with biliary tract dysfunction. Material methods include a comprehensive review of clinical trials and patient outcomes, focusing on the efficacy of the combined treatment over traditional therapies. Results indicate a significant improvement in symptom relief and liver function markers among patients receiving the combined therapy compared to those undergoing standard treatment protocols. The conclusion highlights the potential of this combined approach as a promising intervention for managing biliary tract dysfunction, advocating for further research and consideration in clinical practice.

Keywords: *treatment, functional dyspepsia, biliary tract dysfunction, ursodeoxycholic acid, hymecromone.*

Received 04.02.2025 Revised 26.02.2025 Accepted 12.03.2025

How to cite this article:
Pulat S. Z, Mirvasit M.K, Nargiza I. P , Shakhnoza A.S, Lola J.M. Comparative Study of The Effectiveness of Monotherapy with Ursodeoxycholic Acid and in Combination with Hymecromone in Patients with Biliary Tract Dysfunction. Adv. Biores. Vol 16 [2] March 2025. 76-81

INTRODUCTION

Biliary tract dysfunction is a common clinical syndrome that significantly impairs the quality of life in patients. It presents with a wide range of symptoms including abdominal pain, jaundice, and liver function test abnormalities, often leading to increased morbidity. The treatment has evolved over the years, with the introduction of pharmacological therapies that attempt to improve bile flow and symptoms. Ursodeoxycholic acid (UDCA) is a bile acid that has been widely used in the management of various biliary disorders. It works by increasing bile flow, reducing cholestasis, and exerting cytoprotective effects on hepatocytes. However, despite its benefits, some patients fail to respond optimally to UDCA monotherapy, prompting the search for combination therapies. Hymecromone, a spasmolytic agent, has been proposed to enhance the effectiveness of UDCA by alleviating biliary colic as well as by enhancing the overall biliary dynamics. The combination of UDCA with Hymecromone can exert a synergistic action, and hence the clinical results can be enhanced. In this paper, we perform

comparative analysis to determine the effectiveness of monotherapy using UDCA versus its combination with Hymecromone in patients suffering from biliary tract dysfunction. Using clinical outcomes, symptom relief, and biochemical indices, we try to determine the most suitable form of treatment for this challenging condition. With this research, we hope to provide valuable information for the clinical management of biliary disease to ultimately benefit patient care.

MATERIAL AND METHODS

In gastroenterological practice today, there is a persistent trend towards an increase in biliary tract diseases. This is the most common reason for patients to seek a gastroenterologist after functional dyspepsia[1]. The reasons for such visits usually include various so-called functional disorders of the Oddi sphincter and/or gallbladder (GB). Motor disorders of the biliary tract and sphincter tone, mainly the Oddi sphincter, play an important role in the pathogenesis of this symptom complex. To date, there are many contradictory points in determining the clinical criteria for biliary dysfunction and, accordingly, the main pharmacological approaches to its correction. Currently, in international practice, the Rome IV criteria are the main document defining the diagnosis and treatment strategy for this category of patients, focusing on problems of visceral hypersensitivity. However, practice shows that it is not always possible to rely on these treatment protocols. The World Congress of Gastroenterologists in Bangkok in 2002 came to the conclusion that evidence, not agreement, is necessary for evidence-based medicine. Additionally, it was mentioned that disorders with a variable link between "dysfunction - symptom" rather than clearly defined illnesses should be used to categorize Oddi sphincter dysfunction [2]. Furthermore, it was underlined that inflammatory injury, mechanical blockage, or autonomous denervation are all known causes of poor GB emptying. It is not totally apparent if delayed GB emptying may be regarded as a distinct clinical issue (nosological type) in the absence of these factors. These are significant considerations that are intended to stimulate more study in order to comprehend the clinical scenario in question [3].

According to Y.S. Zimmerman, prolonged stasis of bile in the biliary tract due to hypomotor dysfunction of the gallbladder and hypertonicity of the Oddi sphincter stimulates the growth of secondary inflammatory and stagnant processes in it and may even serve as a triggering component in the development of cholelithiasis [7]. In the practice of gastroenterologists in Uzbekistan, the diagnosis of biliary dysfunction is extremely rare, and these patients are observed and treated with the diagnosis of chronic acalculous cholecystitis (code K81). Accordingly, the diagnosis of biliary dysfunction and chronic acalculous cholecystitis in the daily practice of a gastroenterologist and therapist can be accompanying diagnoses or synonyms.

There is a considerable number of publications by researchers on the etiology, pathogenesis, classification, differential diagnosis, and clinical manifestations of biliary dysfunction [5]. However, many questions regarding differentiated and effective pharmacotherapy of this pathology remain unresolved. In cases of dysfunction of the gallbladder, caused by a disruption in its tone, and dysfunction of the Oddi sphincter, systemic spasmolytic agents are often used [4]. However, when using these drugs, in addition to their direct effect on the smooth musculature of the biliary tract, systemic effects on the musculature of additional systems and organs are also observed, which in some cases leads to the development of adverse effects and often limits the use of these drugs. Accordingly, one of the significant questions in the therapy of biliary tract disorders is the search for drugs that possess the most physiological mechanism of correcting existing disorders and have minimal side effects. One such drug is undoubtedly hymecromone [6, 8, 9]. In Uzbekistan, it is sold under the trade name "Odeston", and the registration certificate belongs to the company "Adamed Pharma S.A.". The official guidelines on employing the medication hemecromone state, tablets have a dosage of 200 mg. The maximum daily dose is 1200 mg, and the recommended course of treatment is 2-3 weeks. In Europe, the dosage of tablets is 200–400 mg, and the daily dose varies from 600 to 2400 mg. Hymecromone is mainly used because it has choleretic and spasmolytic effects.

Our research aimed to evaluate the clinical benefits of combined therapy of ursodeoxycholic acid (UDCA) at a dose of 12-15 mg/kg/day with Hymecromone (at dosages of 600 and 1200 mg/day) in patients with biliary tract dysfunction.

Patients diagnosed with chronic acalculous cholecystitis were divided into representative groups, comparable in terms of gender, age, medical history, and features of the clinical course of the disease. Following were the research groups into which the patients were split: Group 2 consisted of 107 randomized patients who received combined therapy with UDCA at a dose of 12–15 mg/kg/day along with 200 mg of Hymecromone three times a day (600 mg/day) for three weeks in a row. Group 3 consisted of 156 randomized patients who received combined therapy with UDCA at a dose of 12–15

mg/kg/day along with 400 mg of Hymecromone three times a day (1200 mg/day) for three weeks in a row.The duration of observation for each patient was 21 days.

RESULTS AND DISCUSSION

Clinical effects of the conducted comparative studies comparing the use of UDCA and its combination with Hymecromone at dosages of 600 and 1200 mg in patients with biliary dysfunction were evaluated based on the intensity of abdominal pain and dyspeptic symptoms (Table 1). The severity of clinical symptoms was assessed using a 3-point system, where "0" indicated the absence of symptoms and "3" points indicated severe symptoms of the disease. Abdominal pain syndrome was assessed based on the combination of pain and heaviness in the right hypochondrium, as in most patient surveys, individuals often had difficulty in determining the severity of biliary pain. Analysis of the obtained results showed significant relief of both abdominal pain symptoms and dyspeptic symptoms in the first group of patients receiving UDCA. Following were the research groups into which the patients were split: Group 2 consisted of 107 randomized patients who received combined therapy with UDCA at a dose of 12–15 mg/kg/day along with 200 mg of Hymecromone three times a day (600 mg/day) for three weeks in a row. Group 3 consisted of 156 randomized patients who received combined therapy with UDCA at a dose of 12–15 mg/kg/day along with 400 mg of Hymecromone three times a day (1200 mg/day) for three weeks in a row.

Furthermore, the comparative analysis between the group of patients receiving UDCA and Hymecromone 600 mg, as presented in Table 3, showed more significant relief dynamics in such investigated parameters as pain in the right hypochondrium, constipation, and flatulence.

Greater disparities were observed in the group of patients taking 1200 mg of Hymecromone together with UDCA every day. These differences, particularly the degree of relief of symptoms such as nausea, pain in the right hypochondrium, flatulence, belching, and constipation, were significantly greater compared to the two previous observation groups (Table 1).

Table 1: **The dynamics of clinical symptoms in patients before and after treatment.**

Complains	UDCA, n=105		Hymecromone 600+UDCA, n=107		Hymecromone 1200+UDCA, n=156	
	before	after	before	after	before	after
Bitterness In The Mouth	2.01±0.11	0.16±0.05***	2.21±0.07	0.32±0.04***	1.89±0.09	0.13±0.04***^&&
Nausea	2.09±0.09	0.23±0.05***	1.81±0.07^	0.20±0,03***	1.72±0.09^	0.07±0,02***^&&
Heaviness And Pain In The Right Hypochondrium	2,39±0.08	0.43±0.05***	2.31±0.06	0.34±0.04***^	2.20±0.10	0.21±0.06***^&&
Flatulence	2,26±0.07	0.55±0.05***	1.94±0.08^	0.33±0.05***^^	2.01±0.09^	0.11±0.03***^&&
Belching	2.07±0.09	0.26±0.04***	1.44±0.08^^^	0.26±0.04***	1.47±0.10^^^	0.14±0.03***^
Constipation	1.9±0.12	0.43±0.05***	1.2±0.09^^^	0.17±0.03***^^	1.32±0.11^^	0.12±0.03***^^^
Diarrhea	0.48±0.09	0.08±0.03***	0.44±0.07	0.10±0.03***^^	0.31±0.07	0.12±0.03*

Note: * - significantly compared to UDCA indicators (** - P <0.01)

Note: * - significantly compared to indicators before treatment (* - P <0.05; ** - P <0.01; *** - P <0.001)

^- significantly compared to UDCA indicators (^ - P <0.05; ^^ - P <0.01; ^^^ - P <0.001)

& - significantly compared to Hymecromone 600+UDCA indicators (& - P <0.05; && - P 0.01)

The following findings, which are shown in Table 2, are from a research that looked at how the medicines under investigation affected the gallbladder's motor-evacuation capacities following a choleretic breakfast test in individuals with biliary disease. When the initial gallbladder volumes of the observed patients were compared before and after a 3-week course of treatment, the difference was significant: the patients receiving UDCA showed a 17.2% decrease in gallbladder volume at fasting; the patients receiving UDCA and Hymecromone 600 mg showed a 12.4% decrease; and the patients receiving a combination of UDCA and Hymecromone 1200 mg per day showed a 13.6% decrease.

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Finally, the degree of gallbladder emptying after the choleretic breakfast compared to the beginning of the treatment course in the 1st group of patients was 16.5%, in the 2nd group of patients - 26.9%, and finally in the 3rd group of patients - 20.8%. Following therapy, the degree of gallbladder emptying was 20.0% for the same patients receiving UDCA, 31.3% for the group getting UDCA and Hymecromone 600 mg, and 35.9% for the group receiving UDCA and Hymecromone 1200 mg daily.

The observed patients' motor-evacuation function of the gallbladder improved dynamically as a result of the conducted instrumental studies: this improvement was significant in the UDCA group (20.8%), in patients receiving a combination of UDCA and Hymecromone 600 mg (16.4%), and in the group receiving UDCA and Hymecromone 1200 mg (72.6%).

Table 2: **The dynamics of gallbladder volume in patients before and after treatment.**

Gallbladder Volume (см^2)		UDCA, n=105	Hymecromone 600+ UDCA n=107	Hymecromone 1200+ UDCA, n=156
before treatment	before breakfast	53.4±1.9	37.2±1.3***	36.1±0.92***
	after breakfast	44,6±2,1&&	27.2±0.91***&&&	28.6±0.76***&&
after treatment	before breakfast	44.2±1.3	32.6±0.81***	31.2±0.72***
	after breakfast	35.4±1.6&&&	22.4±0.58***&&&	20.0±0.54***&&&^

Note: * - significant compared to UDCA indicators (* - P<0.05; ** - P<0.01; *** - P<0.001)
^ - significant compared to Hymecromone 600+UDCA indicators (^ - P<0.05)
& - significant compared to before breakfast indicators (& - P<0.05; && - P<0.01; &&& - P<0.001)

Before therapy, no pathological aberrations were found in any of the patients' studied peripheral blood parameters in any of the three groups of patients with chronic cholecystitis that were evaluated. Following the period of therapy, observations revealed that all peripheral blood parameters stayed within normal limits and that the tested drug's use had no adverse effects on hemoglobin, leukocytes, ESR, or any other parameter. We looked at the blood bilirubin and aminotransferase levels in the same patient group to rule out any possible hepatotoxic effects of Hymecromone. According to the research, the majority of patients' average bilirubin and aminotransferase levels matched normal ranges. When the ALT level in the third patient group was first within 1.2 times the normal range, it was suspected that the patients also had concurrent non-alcoholic fatty liver disease, which was in the steatosis stage. All serum aminotransferase and bilirubin levels were within normal limits during the Hymecromone medication cycle.

OUTCOMES

One of the current issues in the treatment of biliary dysfunction is the rational use of medications that possess the most physiological mechanism of correcting disrupted bile formation and secretion processes. Ideally, choleretic therapy involves the use of drugs with choleretic, cholekinetic, and spasmolytic pharmacodynamic effects. According to existing protocols for the treatment of biliary dysfunction, the use of ursodeoxycholic acid (UDCA) is recommended. UDCA intake restores disrupted cholesterol metabolism by reducing low-density lipoprotein (LDL) levels and increasing high-density lipoprotein (HDL) levels, as well as reducing the cholesterol saturation index of bile. The use of UDCA medications leads to improvement in clinical symptoms, regression of pathological changes in the gallbladder wall, and normalization of lipid metabolism. Its pharmacodynamic effect involves saturating the pool of bile acids with tertiary bile acid - UDCA. This normalizes the colloidal-solubilization properties of bile and its rheological parameters. Thus, UDCA possesses the qualities of a "true" cholagogue. Nevertheless, the issues associated with biliary dysfunction are not limited to disruptions in the processes of bile formation; they also involve disruptions in the processes of bile secretion as a result of modifications in the motor-evacuation function of the biliary tract, which occurs at the gallbladder, bile duct, and Oddi sphincter levels. The issue of biliary dysfunction therapy necessitates a multifaceted strategy that includes the use of cholekinetic, spasmolytic, and choleretic medicines. However, the challenge with this therapy lies in the anatomy of the bile ducts, where there are no myocytes, meaning there is no muscular component, and its motility is regulated by the presence of NO-associated endothelial lining. Consequently, the target for spasmolytic drugs is exclusively the gallbladder itself and

the Oddi sphincter. The most optimal solution to this problem is to include the medication hymecromone in the pharmacotherapy regimen for biliary disorders. This medication has pronounced spasmolytic and cholagogic effects. It selectively exerts its pharmacodynamic effect on the bile ducts and the Oddi sphincter, without affecting intestinal peristalsis or reducing arterial pressure. By exerting its cholagogic action, hymecromone not only increases bile volume but also enhances the secretion of its components. It reduces bile stasis and prevents cholesterol crystal deposition. Furthermore, by activating NO synthase, it exerts a primary pharmacodynamic action on the mucosal membrane of the bile ducts. Hymecromone facilitates timely and unhindered bile flow into the duodenum by ensuring the extrahepatic and intrahepatic bile ducts empty harmoniously. Hymecromone doesn't directly cause choleretic action, but it does improve enterohepatic recirculation of bile acids, which are involved in the first stage of bile production, by allowing bile to pass into the digestive system. Hymecromone has an advantage over other spasmolytics since it has less of an impact on other smooth muscles, especially the intestines and cardiovascular system. Hymecromone does not enhance the contractile function of the gallbladder; instead, it simultaneously relaxes the Oddi and Lutkens sphincters. Due to the fact that it does not cause "biliary colic," as many other choleretic ogic drugs do, it is safe for individuals with cholelithiasis and does not raise bile duct pressure. Hymecromone improves digestion (removing mild to severe chronic biliary insufficiency) and positively influences intestinal motility, which results in normalization of stool by boosting bile flow into the intestinal lumen.

As demonstrated by comparative studies evaluating the effectiveness of UDCA alone and in combination with hymecromone in patients with biliary pathology, all treatments exhibited varying degrees of positive effects. In the group receiving UDCA alone, this was primarily manifested by alleviation of dyspeptic symptoms and to a lesser extent by improvement in the motor-evacuation capabilities of the gallbladder. This is understandable because UDCA possesses the properties of a "true" choleretic. The drug enhances bile formation processes and enriches the bile composition with non-toxic tertiary bile acids. This contributes to both increased bile volume and improved rheological properties. However, the drug lacks cholekinetic pharmacodynamic effects, meaning UDCA cannot exert a spasmolytic effect on the tone of either the gallbladder or the bile ducts and Oddi's sphincter.

Abdominal discomfort and dyspeptic symptoms were found to be significantly reduced in the patient group receiving a combination of UDCA and hymecromone at a dosage of 600 mg/day. These benefits were not as noticeable in the UDCA-only group.

The most noticeable improvements were shown in the patients receiving a combination of UDCA and hymecromone at a dose of 1200 mg/day in terms of reducing dyspeptic symptoms and stomach discomfort, as well as improving motor-evacuation performance. These effects were attributed to the spasmolytic influence on the sphincters of the bile ducts and the elimination of "functional obstruction" of bile outflow.

CONCLUSIONS

1. The study revealed a significant improvement in indicators in the majority of patients in the observed groups (84.7% in the UDCA group, 85.9% in the UDCA + Hymecromone 600 mg group, 87.9% in the UDCA + Hymecromone 1200 mg group).
2. Against the background of the conducted therapy in patients with biliary dysfunction and diagnosed with "chronic cholecystitis," a more pronounced reduction in symptoms of biliary dyspepsia and abdominal pain syndrome a reduction in the occurrence of detecting bile/cholangiopancreatography sludge according to ultrasound data, and restoration of motor-evacuation function were noted with the combined use of UDCA and hymecromone, which results from the selective spasmolytic effect of the drug.
3. Comparative evaluation of the effectiveness of hymecromone at doses of 600 mg/day and 1200 mg/day in combination with UDCA showed that symptom relief of biliary dysfunction had a dose-dependent effect, and the use of a dose of 1200 mg/day hymecromone had a more pronounced clinical effect.

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