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Л.Ю. Ильченко [1], С.А. Парфенов*[2], И.Е. Тумаев [3]

[1]— ФГАОУ ВО РНИМУ им. Н.И. Пирогова Минздрава России, Москва, Россия
[2] — ООО «Межрегиональное бюро судебных экспертиз», Санкт-Петербург, Россия
[3]— Клиническая больница имени С.Р. Миротворцева Государственного бюджетного образовательного учреждения высшего образования «Саратовский Государственный Медицинский Университет имени В.И. Разумовского» Министерства Здравоохранения Российской Федерации, Саратов, Россия

КЛИНИКО-ЭКОНОМИЧЕСКАЯ ЭФФЕКТИВНОСТЬ ПРЕПАРАТА РЕМАКСОЛ В ЛЕЧЕНИИ АЛКОГОЛЬНОГО ГЕПАТИТА В РЕАЛЬНОЙ ПРАКТИКЕ

L.Yu. Il'chenko[1], S.A. Parfenov*[2], I.Ye. Tumayev[3]

[1]— Pirogov Russian National Research Medical University, Moscow, Russia
[2] — OOO «Interregional Bureau of Forensic Examinations», Saint Petersburg, Russian Federation
[3]— Saratov State Medical University named after V.I. Razumovsky, Saratov, Russia

Real-World Clinical and Economic Efficacy of Succinate-Based Therapy with Remaxol of Alcohol Hepatitis

Резюме

Проведено проспективное исследование в условиях реальной клинической практики с целью клинико-экономической оценки применения сукцинатсодержащих препаратов у пациентов с алкогольной болезнью печени. Основной анализируемый фактор — длительность госпитализации в днях. Были включены 60 пациентов с алкогольной болезнью печени и превышением трансаминаз более двух норм и аммиака в крови более полутора норм, из которых у 36 в составе комплексной терапии использовались сукцинат-содержащие препараты (основная группа), а 24 — не получали их (группа контроля) на базе двух медицинских центров «Городская клиническая больница им. В.М. Буянова», г. Москва» и «Клиническая больница им. С.Р. Миротворцева СГМУ» Саратов в период с 2019 по 2022 гг.

Динамика показателей клинико-инструментального статуса в группах не отличалась (V=0,35; F=0,87; p=0,614). По результатам клинико-экономической оценки, применение препаратов, содержащих сукцинаты в комплексной терапии алкогольной болезнью печени, позволяет медицинскому учреждению экономить до 8,3 % затрат за счет сокращения в среднем на 2,42 койко-дня сроков госпитализации пациентов.

Ключевые слова: *Алкогольная болезнь печени, алкогольный гепатит, ремаксол*

Конфликт интересов

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*Контакты: Парфенов Сергей Александрович, e-mail: sa.parfenov1988@yandex.ru
*Contacts: Parfenov Sergey Alexandrovich, e-mail: sa.parfenov1988@yandex.ru
ORCID ID: https://orcid.org/0000-0002-1649-9796

Abstract

A real-world study with clinical and economic assessment of the use of succinate-containing drugs in patients with alcoholic liver disease was conducted. The study was based on data from Buyanov City Clinical Hospital in Moscow and Mirotvortsev Clinical Hospital in Saratov. The period of the study was from 2019 to 2022. The main analyzed factor was the duration of hospitalization and 60 patients with alcoholic liver disease and blood transaminases exceeding two norms and blood ammonia more than one and a half norms were included in the study. Of 60 patients 36 used succinate-containing drugs as part of complex therapy (main group) and 24 did not receive them (control group).

The dynamics of indicators of clinical and instrumental status of patients did not differ in both groups (V=0.35; F=0.87; p=0.614). The modelling by Markov chains was performed. The use of succinate-containing drugs demonstrated 8.3 % reducing of costs per case of alcoholic liver disease cure due to the average reduction of hospitalization by 2.42 days.

Key words: *Alcoholic liver disease, alcoholic hepatitis, remaxol*

Conflict of interests

The study was conducted with the support of NTFF POLYSAN LLC.

Sources of funding

The study was conducted with the support of NTFF POLYSAN LLC. The study was conducted with the support of NTFF POLYSAN LLC. NTFF POLYSAN LLC had no influence on determining the structure of the study, analyzing the obtained material, interpreting the materials and writing the article.

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ALD — alcoholic liver disease, ALT — alanine aminotransferase, AST — aspartate aminotransferase, GGTP — gamma glutamine transpeptidase, DF — Maddrey's discriminant function, EE — economic evaluation, RCP — real-life clinical practice, SCPs — succinate-containing products, NCT — Number Connecting Test, AP — alkaline phosphatase

Relevance

The problem of chronic alcoholism is still relevant, despite the fact the population is highly socialized and intellectually developed. According to a systematic review by G. Max et al. [1], deaths from alcohol consumption account for approximately 10 % of the employable world population. According to an analysis by the Federal State Statistics Service (Rosstat), in 2017 the incidence of alcoholism in Russia was 1,304,600 people [2]. Chronic alcohol consumption is one of the most common external causes of hepatic disorders. Ethanol intoxication over a number of years can result in one of the three key forms of alcoholic liver disease (ALD): alcoholic steatosis (60–90 % of all cases), alcoholic hepatitis (10–30 % of all cases) and alcoholic cirrhosis (8–20 % of all cases) [3].

Modern medical care for patients with ALD includes a wide range of measures to reduce the intoxication load for the body, prevention of further damage to hepatic tissue and progression to a life-threatening disease — cirrhosis. The professional medical community constantly improves the quality of care and timely updates clinical guidelines, taking into account both Russian and foreign experience [2].

Active introduction of new treatment methods and regimens, as well as new medicinal products to the comprehensive management of ALD requires evaluation not only of clinical efficacy of medication, but also economic feasibility, which ensures quality care to many patients. Usually, economic evaluation (EE) starts from the commencement of commercial distribution of the product and/or its inclusion in a certain system of reimbursement and ends with product withdrawal from the pharmaceutical market.

One of the tools used to gather information for EE is the data from the real-life clinical practice (RCP) [4, 5]. A distinctive feature of EE is its non-interventional nature, associated with some limitations, e.g. no placebo groups or passive control. Specifically, with personified therapy, the use of high-potency products and development of patient discharge criteria, as in ALD patients [2], by the end of in-patient care, patients do not demonstrate any differences in clinical parameters; and even statistically confirmed differences cannot be treated as markers of high efficacy (higher efficiency) of a certain product. At the same time, the rate of action onset also differs and impacts the overall performance — duration of hospitalisation. In-patient bed-days is a key criterion to evaluate not only the clinical, but also economic efficiency of a medicinal product, since reduction in the duration of therapy allows increasing the bed turnover, and the number of paid cases of treatment increases, while costs reduce, thus ensuring significant savings for the medical institution.

Succinate-containing products (SCPs) are among reputable products for the therapy of adult patients with ALD and are included in the current clinical guidelines [2]. By boosting cell resistance to hypoxia, which is a common sign of any chronic inflammation, SCPs improve membrane resistance to peroxidation and activate reparative processes [6]. Overall, products from similar groups are actively used not only in ALD, but also in other chronic [7, 8] and acute conditions [9-11].

At the same time, economic evaluation of SCPs in the real-life practice has not been performed yet, defining the relevance and the objective of this study.

Materials and Methods

Given the objective of an economic evaluation of the use of SCPs in patients with ALD, we have conducted a prospective real-life clinical study at two study sites: V. M. Buyanov City Clinical Hospital (Moscow) and S. R. Mirotvortsev Clinical Hospital of the Samara State Medical University (Saratov) in 2019–2022.

Patients were diagnosed with ALD if they had a history of alcoholism, relevant CAGE and AUDIT scores, identified markers of hepatic pathology (steatosis or steatohepatitis, enhanced echogenicity, increased transaminases or GGTP, etc.).

ALD therapy included fluid maintenance, hepatoprotectors, glucocorticoids where necessary, and ursodeoxycholic acid. Some patients received infusions Remaxol 400 ml per day.

Inclusion criteria:

1. Patients with ALD (ICD code: K70)
2. Age: 25–70 years old, both males and females
3. 1.5-fold increase in reference values of blood ammonia (PoketChem) (80–300 μmol/L), at least 2-fold increase in ALT or AST vs. ULN (NLT 80 U/L)
4. Signed informed consent from.

Not included were the patients with the following clinical conditions: HIV infection, syphilis, TB, acute infectious disease, Child-Pugh class C hepatic cirrhosis, viral cirrhosis, obstructive jaundice, autoimmune hemolytic anaemia (positive Coombs' test), insulin-dependent diabetes mellitus, malignancy, acute cerebrovascular accident or acute coronary syndrome, hemodialysis-dependent patients, any decompressed condition, mental disorders, pregnancy, breastfeeding, surgical pathologies.

Key analysed factor: duration of hospitalisation (days). Numerous exclusion criteria were due to the need to eliminate the impact of other medical conditions on this clinical and economic efficacy endpoint.

Recorded clinical parameters, used by the medical professional to decide whether the patient was fit for discharge from the in-patient clinic, included: transaminase activity (AST and ALT), gamma glutamine transpeptidase (GGTP), alkaline phosphatase (AP), conjugated and free bilirubin, Maddrey's discriminant function (DF) results, and Number Connecting Test (NCT) results. These parameters were recorded on day 1, day 5 and day 9 and were entered to the database.

During the study, data from 60 ALD patients were collected, of which 36 patients were treated with SCPs as part of their combined therapy (main group) and 24 patients did not receive SCPs — Remaxol (controls).

A distinguishing feature of RCP data is non-randomisation, which can be a reason for the absence of the balance in interfering variables between treatment groups. The non-handling of such variables inevitably leads to bias of an estimate and incorrect conclusions, while the non-interventional nature of an RCP study can cause missing data, since referral to an assessment depends not on the protocol, but on the doctor's opinion.

Statistical data processing was performed using Python 3.9 and IBM SPSS v 23. Given the features of RCP data, it was supplemented by multiple imputation and propensity score matching 1 : 1 on a smaller sample size. Patients were selected using the method to calculate the odds of randomisation to any of the groups using logistic regression with the inclusion of recorded values of transaminases, GGTP, AP, bilirubin, Maddrey's DF, and NCT. Changes in the clinical and instrumental status were evaluated using MANOVA (Pillai's V-trace) with the inclusion of the change factor (visit: days 1, 5 and 10) and its correlation with the grouping factor (group * visit). Duration of hospitalisation was compared using Student–Welch t-test. Since the time to discharge is time-to-event data, survival rates were compared using Gehan generalised Wilcoxon Z-test.

In order to evaluate the economic feasibility, a Markovian chain was used to model the transition between "in-patient patient" and "discharged", with the generation size of 10,000 patients. For each group, the odds of discharge on each day were calculated using Kaplan–Mayer survival analysis. During modelling, the cost of therapy of the "in-patient patients" was calculated. After modelling, costs per group were compared, and savings (overpaid amount) were evaluated in the main group vs. controls.

The significance threshold to discard zero hypotheses of the lack of difference was $p = 0.05$.

The study was approved by the Ethics Committee of the Autonomous Non-Profit Organisation Central Bureau of Forensic Examination No. 1, Order No. 65 dated 10 December 2018.

Results

Following the interim analysis, missing data were found to be accidental (Little criterion: $\chi^2 = 1565.9$, $p \approx 1.0$), making it possible to perform MICE (Multiple Imputation by Chained Equations) imputation. Then, propensity score matching 1 : 1 was performed. The smaller group (controls) included 24 subjects; 24 subjects were selected from the main group as well. Baseline characteristics of subjects in the study groups are presented in Table 1.

Changes in clinical and instrumental status in the groups did not differ ($V = 0.35$; $F = 0.87$; $p = 0.614$), while overall it was statistically significant ($V = 0.80$; $F = 6.40$; $p < 0.001$). MANOVA results demonstrate that the change factor accounted for approx. 80 % of the dispersion (partial $\eta^2 = 0.799$), while its interference with the grouping factor did not have any statistically significant impact.

Analysis of duration of hospitalisation is presented in Table 2.

Table 1. Population baseline characteristics

Parameter	Succinate-based therapy (n=24)	Control (n=24)
Age	50,71 (11,92)	51,67 (11,12)
Male	9 (37,50 %)	6 (25,00 %)
Capillary blood Ammonia	99,23 (34,84)	90,95 (30,38)
Maddrey's index	23,35 (14,2)	30,96 (27,44)
Number connection test	79,63 (25,5)	86,46 (27,06)
Alanine aminotransferase	138,42 (152,09)	130,44 (169,25)
Aspartate aminotransferase	168,27 (99,98)	151,02 (119,74)
Alkaline phosphatase	398,54 (367,73)	402,08 (281,99)
Gamma-glutamyl transpeptidase	562,8 (599,91)	421,63 (416,55)
Direct bilirubin	36,55 (36,14)	47,99 (70,5)
Indirect bilirubin	39,48 (31,05)	81,25 (133,9)

Note: data presented as mean (standard deviation) or count (%), there is no statistically significant difference between groups on baseline

Table 2. Mean hospital time comparison results comparison

Parameter	Overall (n=48)	Succinate-based therapy (n=24)	Control (n=24)
Days in Hospital	14,00 (3,60)	12,79 (3,06)†	15,21 (3,74)†
Survival median	–	12,75	16,00

Note: data presented as mean (standard deviation); † — differences between groups are statistically significant (t=-2,45; df=46; p=0,018).

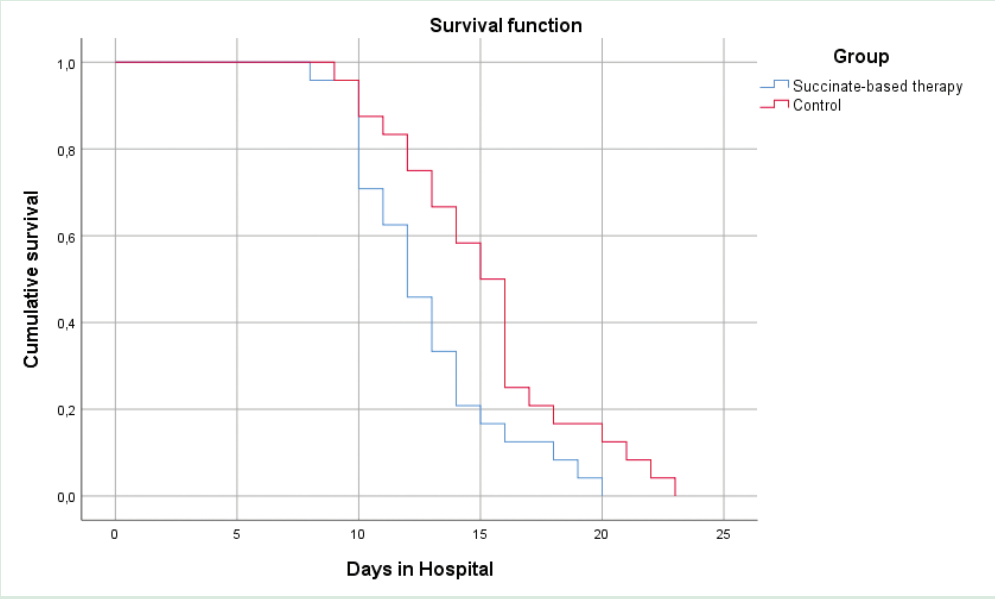

Figure 1. *Survival comparison of group of therapies of Alcohol Hepatitis*

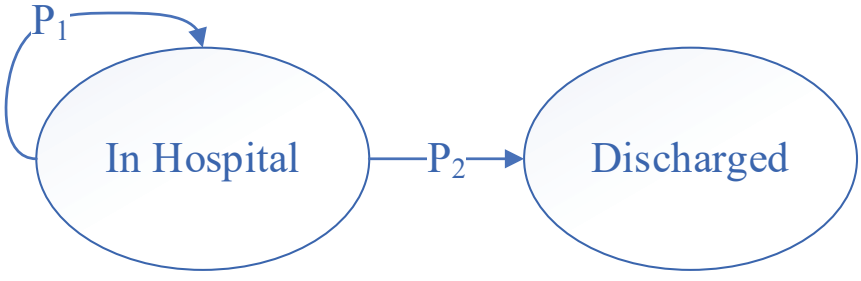

Figure 2. *Marcov's chain scheme*

Таблица 3. *Расчетные вероятности выписки пациентов с АБП в анализируемых группах*
Table 3. *Discharge probabilities in experimental and control group*

Day	Succinate-based therapy	Control
0	0,000	0,000
1	0,000	0,000
2	0,000	0,000
3	0,000	0,000
4	0,000	0,000
5	0,000	0,000
6	0,000	0,000
7	0,000	0,000
8	0,042	0,000
9	0,000	0,042
10	0,250	0,083
11	0,083	0,042
12	0,167	0,083
13	0,125	0,083
14	0,125	0,083
15	0,042	0,083
16	0,042	0,250
17	0,000	0,042
18	0,042	0,042
19	0,042	0,000
20	0,042	0,042
21	-	0,042
22	-	0,042
23	-	0,042

The next step was to analyse survival (Fig. 1). The survival functions demonstrated statistically significant difference ($Z = 5.69$; $df = 1$; $p = 0.017$), making it possible to use the calculated probability (Table 3) in modelling.

The Markovian chain, used to describe the transition between "in-patient patient" and "discharged", is given in Figure 2. For it to be functional, it was assumed that at a given time unit (day) a patient has "P_1" probability to stay in the in-patient clinic or "P_2" probability to be discharged; no provisions were made for other outcomes (death, complication, adverse events, etc.). No reverse transition is possible. Taking into account the two mutually exclusive conditions ($P_1+P_2= 1.0$), Table 3 contains only the odds of discharging the patient from the in-patient clinic (P_2).

Given that the average duration of hospitalisation in the total population was 14 days, modelling covered this period. Costs were calculated on the basis of the clinically statistical group. st04.003 "Non-viral hepatic diseases (level 1)"; rate of RUB 35,997.97 (taking into account the coefficient and relative cost intensity, excluding the rest coefficients), according to the State Program guarantees of free provision of medical services to citizens Qing aid for 2023 and for the planning period 2024 and 2025. Therefore, the cost of a bed-day during a 14-day in-patient hospitalisation is RUB 2,571.28 net of input intensity coefficient, etc.

The modelling result is presented in Figure 3.

The modelling demonstrates that the cost savings of a medical institution resulting from a shorter period of hospitalisation when using SCPs (Remaxol 400 ml per day for 10 days) in the combined therapy of ALD was 8.3 %.

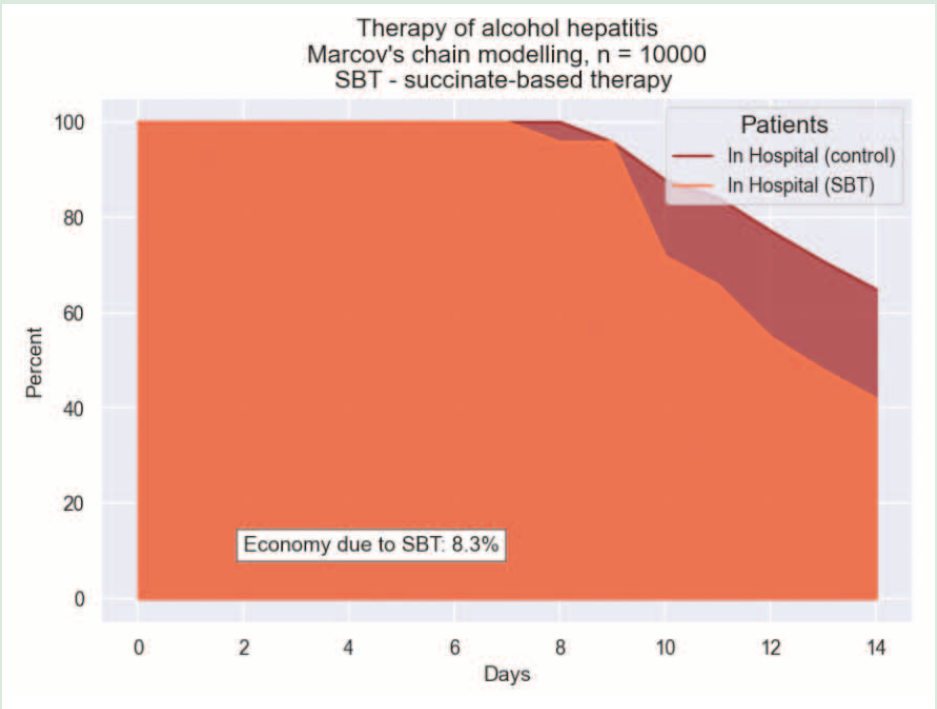

Figure 3. *Marcov's chain modelling of alcohol hepatitis treatment with and without succinate-based therapy*

Discussion

Succinate-containing products offer metabolic support in a chronic inflammation or in an acute condition. Their clinical efficacy has been demonstrated in a number of medical conditions, where these products are used in a combined therapy.

The key point of SCPs application is the oxidative process, inevitably associated with ALD [12, 13]. Less active free-radical oxidation, tissue hypoxia compensation and antioxidant defence reconstruction facilitate faster recovery and reduce duration of hospitalisation. A similar study [14] demonstrated that the use of antihypoxic and antioxidative products helped to mitigate consequences of liver impairment.

Of note, no adverse drug reactions were recorded in this study.

This study provided an economic evaluation of SCPs in the management of patients with alcohol liver damage. Earlier discharge (2.42 days earlier on the average) reduces costs of a medical institution by 8.3 %. Similar studies demonstrate their economic efficiency as a result of complication prevention by using SCPs in the primary treatment regimens [15], or by reducing duration of hospitalisation [16]. At the same time, no economic evaluations of SCPs have ever been performed in Russia on the basis of the real-life practice.

This study has some limitations.

First, it took into account only the clinical statistical costs. However, this indicator is integral and allows evaluating a wide range of costs incurred by a medical institution, from procurement of medications to salaries to healthcare professionals.

Second, the modelling did not take into account possible deaths, complications and adverse events from SCP therapy. This is due to the small size of the study groups and the absence of such outcomes in the groups. No doubt, PCP studies can assess rare outcomes as well, and as soon as SCP therapy is more common, the process modelling can be updated for in-patient therapy of patients with ALD.

Conclusions

The economic evaluation demonstrated that when a medical institution uses succinate-containing products in the combined therapy of ALD, its savings are up to 8.3 % as a result of the reduction of hospitalisation duration on the average by 2.42 bed-days.

This study can be used in the real-life clinical practice as a starting point for the selection of optimal treatment regimens for patients with alcohol liver damage. As long as there are enough data on the real-life clinical practice, modelling can be repeated in order to obtain a more accurate result.

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Ильченко Л.Ю. (ORCID ID: https://orcid.org/0000-0001-6029-1864): концепция и дизайн исследования, написание текста

Парфенов С.А. (ORCID ID: https://orcid.org/0000-0002-1649-9796): концепция и дизайн исследования, сбор и обработка материала, написание текста, редактирование

Тумаев И.Е. (ORCID ID: https://orcid.org/0000-0002-1542-8291): сбор и обработка материала, написание текста

Author Contribution:

All the authors contributed significantly to the study and the article, read and approved the final version of the article before publication

Il'chenko L.Yu. (ORCID ID: https://orcid.org/0000-0001-6029-1864): the concept and design of the study, writing the text

Parfenov S.A. (ORCID ID: https://orcid.org/0000-0002-1649-9796): the concept and design of the study, collection and processing of material, writing the text editing

Tumayev I.Ye. (ORCID ID: https://orcid.org/0000-0002-1542-8291): collection and processing of material, writing the text

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