

Cost effectiveness of using terlipressin to treat hepatorenal syndrome

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ABSTRACT – Background – Hepatorenal syndrome (HRS) is the most severe form of acute kidney injury in patients with advanced cirrhosis, and it is associated with high mortality. It is usually diagnosed according to criteria defined by the International Ascites Club. Currently, the most frequently indicated pharmacological therapy for the treatment of HRS is a combination of splanchnic vasoconstrictors (terlipressin or norepinephrine) in combination with albumin. With the progressive increase in healthcare spending, it is important to conduct a cost-effectiveness analysis of pharmacological treatment in patients who are diagnosed with HRS. **Objective** – To perform a cost-effectiveness assessment for the use of terlipressin in combination with albumin to treat HRS in patients with cirrhosis. **Methods** – Economic evaluation of cost-effectiveness based on secondary data from studies showed the efficacy of terlipressin therapy compared with norepinephrine combined with albumin or albumin alone. The cost-effectiveness analysis was calculated using an incremental cost-effectiveness ratio (ICER), and a sensitivity analysis was developed by varying the values of therapies and probabilities. The Brazilian real was the currency used in the analysis, and the results were converted to US dollars. **Results** – After selection, eligibility, and evaluation of the quality of publications, the results demonstrated that administration of terlipressin or norepinephrine in combination with albumin in patients diagnosed with HRS type 1 was efficacious. The cost of treatment with terlipressin in combination with albumin was USD \$1,644.06, administration of albumin alone was USD \$912.02, and norepinephrine plus albumin was USD \$2,310.78. Considering that the combination therapies demonstrated effectiveness, the incremental cost of terlipressin and norepinephrine in combination with albumin was USD \$666.73, and an effectiveness of 0.570 was found for terlipressin in combination with albumin and 0.200 for norepinephrine in combination with albumin. The incremental effectiveness was 0.370, and the ICER was USD \$1,801.97. Thus, the parameters of increasing cost per therapy and ICER indicated that the combined therapy of terlipressin plus albumin was cost effective compared to albumin alone or norepinephrine plus albumin in a public single-payer healthcare system. **Conclusion** – A cost-effectiveness analysis showed that terlipressin in combination with albumin when administered concomitantly to patients who were diagnosed with type 1 HRS is cost-effective compared to norepinephrine in combination with albumin administered in a controlled environment.

Keywords – Hepatorenal syndrome; cost-effectiveness evaluation; terlipressin; health care costs; norepinephrine; gastroenterology.

INTRODUCTION

Acute kidney injury (AKI) is a common complication of cirrhosis, with a prevalence of 27–53% of hospitalized cirrhotic patients who are admitted after an episode of acute decompensation, and it is associated with high morbidity and mortality⁽¹⁻⁴⁾. Hepatorenal syndrome (HRS) is a specific type of AKI that usually occurs in patients with advanced cirrhosis with ascites and portal hypertension, and it is characterized by reduced glomerular filtration rate (GFR) and renal plasma flow (RPF)^(5,6).

The pathophysiology of AKI is related to renal vasoconstriction that causes hypoperfusion of the organ in response to the decrease in the volume of effective blood and renal inflammation, which induce microvascular changes. In decompensated cirrhosis, both vasodilation secondary to portal hypertension and systemic inflammation that are induced by intestinal bacterial translocation tend to cause this renal vasoconstriction and subsequent development of HRS⁽⁷⁾.

Despite advances in understanding of the HRS pathophysiology, treatment has evolved minimally in recent years even with

splanchnic vasoconstrictors used in combination with albumin⁽⁸⁾. The development of new drugs is necessary for patients to achieve liver transplantation with a good outcome, which is the definitive goal for treating patients with this condition.

The use of albumin in combination with vasoconstrictors, such as terlipressin and norepinephrine⁽⁹⁾, leads to a significant reduction in mortality compared to albumin use alone or no treatment⁽¹⁰⁻¹²⁾. HRS resolves in approximately half of the patients who are treated with combination therapy using terlipressin or norepinephrine plus albumin⁽¹³⁾. The recommended doses in this combination therapy are as follows: 20 to 40 g/day of albumin and 0.5 to 2 mg of terlipressin every 4 or 6 h intravenously (IV) as a bolus or 0.5 to 3 mg/h of norepinephrine administered as a continuous IV infusion to achieve a mean arterial blood pressure increase of 10 mmHg for up to 14 days of treatment⁽¹⁴⁾.

Both vasoconstrictors used in combination with albumin represent a significant cost with respect to the management of HRS patients. In addition, the use of norepinephrine requires a continuous infusion pump, which is usually found in an intensive care environment, and this also impacts treatment costs.

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In healthcare systems where public resources are limited because of increasing healthcare demands, cost-effectiveness assessments for incorporating and evaluating available treatments has become essential to implement and maintain public health policies within the country. The progressive increase in costs and the increasing need for public health systems to conduct health technology assessments (HTAs) to assist in decision-making allow the development of models that consider the available technologies along with their safety and effectiveness.

Therefore, the objective of this study was to determine the cost-effectiveness of combination therapies including albumin and terlipressin (first group) and norepinephrine and albumin (second group) to treat patients with HRS, using as a reference the *Hospital das Clínicas da Faculdade de Medicina da Universidade de São Paulo, Brazil*.

METHODS

This study cost-effectiveness assessment study comprised a systematic review of articles that were published in the PubMed, LILACS, and Scopus databases until April 2020, and these articles described combination therapy with either albumin and terlipressin or albumin and norepinephrine that was administered to cirrhotic patients who were diagnosed with HRS type 1. The search terms used were Hepatorenal syndrome, evaluation of cost-effectiveness, terlipressin and clinical trial. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) method was used for most items in this systematic review which was performed by two independent reviewers. Duplicate articles were removed and some were excluded with justification. In the end, eligible articles were selected. Albumin alone and midodrine were not considered because they have no relevant efficacy compared to combination

therapies. A duration of 365 days was used because the outcome, which is based on the time to mortality from the disease, and the costs related to the study do not exceed one year.

One of the criteria used to diagnose HRS is the serum creatinine level, and a serum creatinine value of ≥ 1.5 mg/dL was used until 2015 after which the European Association for Liver Studies guidelines were updated and the criterion the creatinine level was changed to ≥ 0.3 mg/dL within 48 hours^(1,6). The criteria used to define partial and/or complete response to treatment was based in the protocol of Clinical Practice Guidelines – Renal Impairment of 2018⁽¹⁵⁾. In this analysis, adverse reactions were not considered because they can resolve after stopping administration of the causative agent⁽¹⁶⁾.

The data obtained using the Management System of the Table of Procedures, Drugs, Orthoses, Prostheses, and Materials of the Brazilian (SIGTAP) of SUS (Brazilian Unified Health System) were divided into the following two groups: (1) values related to hospitalization and administration of terlipressin in combination with albumin; or (2) values related to hospitalization and administration of norepinephrine in combination with albumin. In both groups, values with complications that were related to the disease and patient follow-up were included.

The total cost of patient hospitalization, including the values for the hospital service and those related to professional tasks, was related to the average time of treatment. The perspective of this study is from the direct payer, the SUS. Direct medical costs are the reimbursement that is made to the Hospital das Clínicas da Faculdade de Medicina da Universidade de São Paulo, which are paid by the Unified Health System in Brazil.

Statistical analysis

An economic cost-effectiveness analysis was performed using a decision tree mathematical model (FIGURE 1). The tree was

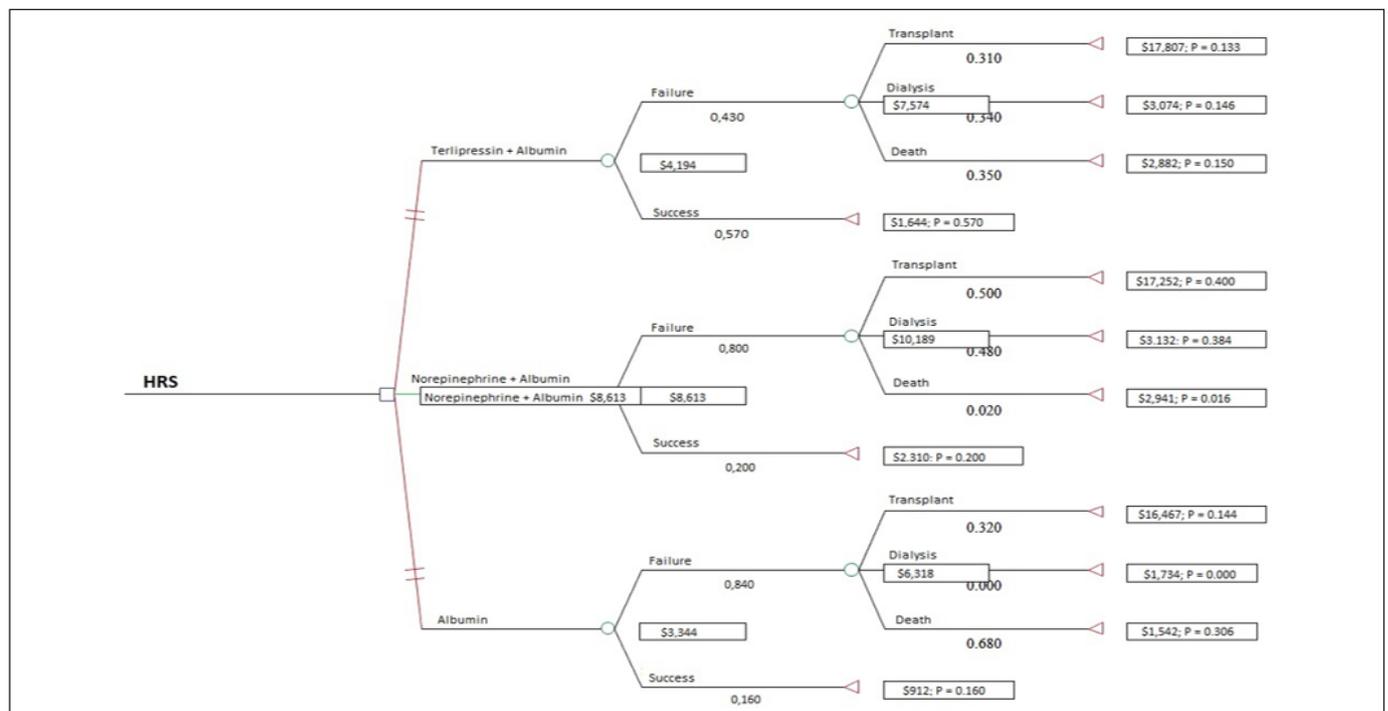


FIGURE 1. Decision tree and its cost-effectiveness results. The square in the figure indicates a decision point, the circles indicate the points of chance and the triangles indicate the outcomes (measured in effectiveness).

designed including the cost of selected drugs and hospitalization as variables (considering the values of inputs and related hospital activities). TreeAge® software (TreeAge Software, Williamstown, MA, USA) was used to build the model. A sensitivity analysis was performed for the probability variables (effectiveness) and values. The probability values that were used in the decision tree were based on the studies that are called the “gold standard”, which are studies that obtained the maximum score on the Jadad scale⁽¹⁷⁾.

The probabilistic sensitivity analysis was performed based on multivariate simulations that included the cost and probability values. This type of analysis was chosen because the costs related to the treatment and the probability values could have interfered with the results.

RESULTS

Selected studies and quality assessment

A search of the PubMed, LILACS, and Scopus database yielded 92 studies. After removing duplicates articles, 51 went to the next phase. 43 articles were removed with justification, most were studies that evaluated patients diagnosed with type 2 HRS and/or were not randomized. Eight studies were selected (FIGURE 2) using the Jadad scale, which evaluates the quality of the study (where a score of three points or greater is considered to be of high quality). Five studies had a score of three points on the scale and three studies had the maximum score of five points⁽¹⁸⁻²⁵⁾.

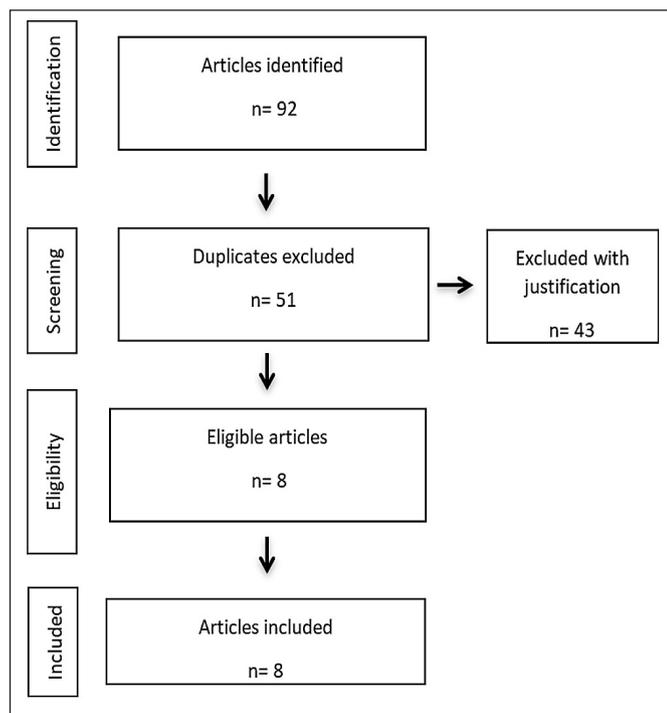


FIGURE 2. Flowchart of the article selection process.

Cost data

The cost data for treating patients with type 1 HRS were obtained from the Management System of the Table of Procedures, Drugs, Orthoses, Prostheses, and Materials of the Brazilian SUS. The maximum treatment time that was included was 14 days, and the maximum time frame for the data was 365 days (time horizon).

The total cost of treatment for a patient after a diagnosis of type 1 HRS, including the cost of medications at the recommended doses and examinations for 14 days, was USD \$1,644.06 in the terlipressin and albumin combination therapy group. In this group, the medications were administered without the need to be in a controlled environment, and thus, the costs were lower than in the other group. In the group of patients who received norepinephrine and albumin combination therapy, the total cost of treatment was USD \$2,310.78, and patients in this group were admitted to the intensive care unit. The higher costs in this group are due to the need to pay for SUS per day.

The cost for hospitalized patients who underwent liver transplantation and 14 days of treatment was USD \$15,509.14 including administering the combination of terlipressin and albumin therapy and USD \$14,895.67 for the group of patients who received the combination of norepinephrine and albumin (TABLE 1). The norepinephrine group had a lower cost compared to the terlipressin group because the cost of norepinephrine is lower than that of terlipressin.

TABLE 1. Cost of combination therapies compared with albumin alone.

Terlipressin + Albumin	14 days	12 months
Medicine	\$1,644.06	\$1,644.06
HRS transplant	\$15,509.14	\$46.18
HRS dialysis	\$822.00	\$5,112.39
HRS attendance	–	\$184.73
Death	\$630.48	–
Albumin	14 days	12 months
Medicine	\$912.02	\$912.02
HRS transplant	\$15,509.14	\$46.18
HRS dialysis	\$822.00	\$5,112.39
HRS attendance	–	\$184.73
Death	\$630.48	–
Norepinephrine + albumin	14 days	12 months
Medicine	\$2,310.78	\$2,310.78
HRS transplant	\$14,895.67	\$46.18
HRS dialysis	\$822,00	\$5,112.39
HRS attendance	–	\$184,73
Death	\$630,48	–

HRS: Hepatorenal Syndrome. The currency: Brazilian real was used, and the results were converted to US dollars.

A small number of patients could undergo outpatient and hemodialysis treatment, and the cost of this treatment in 1 year was USD \$882.00 for 14 days and USD \$5,112.39 for 14 days in the norepinephrine and terlipressin groups, respectively. For patients who were treated in an outpatient manner, the total amount in 1 year was USD \$184.73 regardless of the group, and this included the amount that was spent on examinations every 3 months.

For patients who died, the mean time of 14 days was considered, whose cost was \$630.48, associated with the cost of different therapies for HRS.

The amounts were converted from Brazilian reais to US dollars using the exchange rate from September 22, 2020 (1US\$ = 5.47 reais).

Probability

The transition probabilities related to the outcomes (transition between health conditions) in the transplant patients, follow-up (success), or if they were on dialysis or died were obtained through the selected articles. The probabilities among the possible states of the patients are represented as percentages (%), and the time described in the studies is presented in days (TABLE 2).

Decision tree

The decision tree was built taking into account the cost of each strategy that was used and the possibilities in each group (FIGURE 1). For the decision tree design, the probabilities from the articles that were considered to be the “gold standard”, which was defined as articles that obtained the highest score in the Jadad qualification, were included.

In the terlipressin and albumin combination group, three possible events could have occurred: (1) 31% probability of having a liver transplant; (2) 34% probability of the patient being on hemodialysis; and (3) 35% probability of death. The cost of treatment for these patients was USD \$1,644.06, and there was an effectiveness of 0.570 for success.

In the norepinephrine and albumin combination group, there was a 50% probability of having a liver transplant, a 48% probability of hemodialysis, and a 20% probability of death. The cost of treatment for these patients was USD \$2,310.87 with an effectiveness of 0.200 for success.

Albumin is present in the decision tree for comparative purposes only.

Incremental cost-effectiveness ratio

Because Brazil is not willing to pay a threshold as recommended by the World Health Organization (WHO), we performed the calculation using a threshold that was three-times the Gross National Product (GNP) per capita, which was USD \$ 18,939.48 in 2019.

The incremental cost-effectiveness ratio (ICER) calculation was performed for the two associated comparators that have therapeutic effectiveness, and the results were as follows: (1) for terlipressin plus albumin, the cost was USD \$1,644.06 and the effectiveness was 0.570; and (2) for norepinephrine plus albumin, the cost was USD \$2,310.87 and the effectiveness was 0.200. The incremental cost and effectiveness were USD \$666.73 and 0.370, respectively. The ICER was USD \$1,801.97 for the clinical outcome, as shown in TABLE 3. The incremental value is below the threshold that was suggested by the WHO, indicating that the strategy of using combination therapy with terlipressin and albumin is cost effective.

TABLE 3. Incremental cost-effectiveness ratio.

	Terlipressin + albumin	Norepinephrine + albumin
Cost	\$1,644.06	\$2,310.78
Incremental Cost	\$666.73	–
Effectiveness	0.570	0.200
Incremental effectiveness	0.370	–
ICER	\$1,801.97	–

ICER: incremental cost-effectiveness ratio. The currency: Brazilian real was used, and the results were converted to US dollars.

TABLE 2. Evolution probabilities of patients with hepatorenal syndrome.

	Terlipressin + albumin		Albumin		Norepinephrine + albumin		Reference
	Probability (%)	Time (days)	Probability (%)	Time (days)	Probability (%)	Time (days)	
Transplant	31	90	32	90			(23)
	30	180	30	180			(22)
	67	30			50	30	(25)
Dialysis	42	15	0	15			(21)
	34	4			48	4	(20)
Attendance	27	90	19	90			(18)
	42	15	0	15			(21)
	43	180	37	180			(22)
	57	90	55	90			(23)
	42	180	16	180			(19)
	48	14			20	14	(20)
Death	83	30			25	30	(25)
	45	14			48	14	(24)
	43	90	45	90			(23)
	57	180	63	180			(22)
	51	14			80	14	(20)
	34	48			25	40	(25)
	55	14			52	14	(24)

Sensitivity analysis

The lowest cost for acquiring terlipressin varied as did the probabilities of success and failure for each comparator. Overall, seven cost and probability variables were tested concurrently by calculating the incremental costs and incremental effectiveness (TABLE 4). The ICER result for each variation did not exceed the defined value of USD \$18,939.48 for the Brazilian GNP and did not change the results of the study.

TABLE 4. Sensitivity analysis.

Terlipressin + albumin		Norepinephrine + albumin		ICER
Probability	Cost	Probability	Cost	
0.570	\$1,644.06	0.200	\$2,310.78	\$1,801.96
0.570	\$1,644.06	0.250	\$2,310.78	\$2,083.52
0.430	\$1,539.68	0.480	\$2,310.78	\$15,422.30
0.480	\$1,539.68	0.430	\$2,310.78	\$15,422.30
0.570	\$1,539.68	0.250	\$2,310.78	\$2,409.73
0.830	\$1,644.06	0.480	\$2,310.78	\$1,904.93
0.430	\$1,644.06	0.480	\$2,310.78	\$13,334.55
0.450	\$1,644.06	0.200	\$2,310.78	\$2,666.91

ICER: incremental cost-effectiveness ratio. The currency: Brazilian real was used, and the results were converted to US dollars.

DISCUSSION

HRS is a serious complication that results from the progression of liver disease. Thus, in periods during which costs are a fundamental part of good quality-oriented management, it is necessary for healthcare institutions to start using low-cost but effective technologies. With the creation of the National Commission for the Incorporation of Technologies (CONITEC) in SUS in 2011 and through economic health assessments, the Ministry of Health now has relevant information that is used in the decision to incorporate, change, or not change a technology for SUS.

In the present study, the most frequently used therapies to treat patients who were diagnosed with HRS were compared by evaluating the quality of the research via the Jadad method. We found several published studies describing therapeutic strategies to treat the disease, and several treatment options for HRS have been described^(18,19). The best treatment was vasoconstrictors and albumin used in combination. There are several available vasoconstrictors, and the most frequently studied vasoconstrictors are terlipressin and norepinephrine. Both of these medications have similar effectiveness in reversing kidney injury and improving survival, as described in several previous studies, but terlipressin was shown to be superior to the other vasoconstrictors in a recently published study⁽²⁰⁾.

Thus, we focused on and systematically analyzed publications that showed the efficacy of the selected medications, and we found comparisons between the administration of albumin alone and the administration of albumin in combination with terlipressin. In all

studies, albumin alone did not produce an improvement in health status, and thus, the survival rate was lower or zero^(21,22). Short-term administration of terlipressin in combination with albumin has been well studied^(23,26), and this regimen may lead to a reduction in mortality compared to placebo in patients with HRS⁽²⁷⁾.

Initial studies have shown that norepinephrine produced a response that was similar to terlipressin for the reversal of kidney injury and safety. Recent studies have shown that terlipressin produces a better effect, but norepinephrine is associated with a lower cost, and there is a lack of studies that evaluated the costs in our country^(24,25).

Similar to terlipressin, norepinephrine is administered to patients who have been diagnosed with HRS. However, terlipressin can be used in a nursing environment, while norepinephrine must be administered exclusively in an intensive care environment⁽²⁸⁾, so we examined the costs of the active medications and of the patients' treatment location. However, for patients where the indication may be intensive care due to the severity of the condition, a bias may be found.

The materials and medicines that are used in Brazilian public hospitals are purchased through a bidding process, which means that under equal conditions, the lowest cost/ and the best quality are chosen. Thus, when a technology is incorporated into SUS, costs tend to decrease because the supplier company will have a constant demand to manufacture the product. The amount of the resources that were measured in this study was obtained using the macro costing technique, which presents the values that were obtained using the system records in an objective manner. However, although the method of micro costing allows a high degree of detail, it is indicated when the need for valuation is related to a greater weight of human resources, but this was not the main focus of this research.

Some countries use a limit of willingness to pay, which means that they establish a maximum value to acquire a certain technology. However, due to the lack of standardization, the WHO defines the calculation of the incremental value of a treatment as three-times the annual income per capita because it considers the increase in health expenditures over time^(29,30). Because Brazil does not determine the cap on the amount payable for a technology, the WHO guidance is followed; therefore, in this analysis, the amount of USD \$18,939.489 was the spending cap that was used to define whether the strategy was economically viable.

Considering the data presented in the decision tree, the efficacy of terlipressin compared to norepinephrine seems to be greater. However, other values, such as specialized professionals, dedicated environment, examinations, and support materials, must also be considered because it is not sufficient to only consider if the cost of a therapy is lower.

A Brazilian study also evaluated the economic impact of treating HRS with terlipressin or norepinephrine both in combination with albumin and both in the public and private healthcare sectors. The terlipressin treatment strategy was shown to be the most economical in both scenarios. In the SUS evaluation, the results were also similar⁽³¹⁾ as were those found in the present study.

Treatment with norepinephrine in combination with albumin was less cost-effective because it exceeded the value of the defined spending ceiling due to the high costs that are associated with hospitalization. Finally, we can conclude that administering terlipressin in combination with albumin in the ward environment to treat patients with type 1 HRS and cirrhosis using SUS is cost-effective.

Recently, a randomized clinical trial compared the safety and efficacy of terlipressin that was administered by continuous IV infusion to an IV bolus application, and the results showed similar response rates for treating patients with HRS⁽¹⁴⁾. In addition, the mean daily effective dose of terlipressin was significantly lower in the group that was treated using a continuous infusion compared to the group that was treated with an IV bolus, and the rate of adverse events was also significantly lower in the group that was treated with a continuous IV infusion⁽¹⁴⁾. These results suggest that this HRS treatment modality may be even more cost-effective if lower doses of the drug can be used without loss of efficacy and with a lower risk of side effects, a lower rate of treatment suspension, and greater benefit with its use. In a cost analysis from the hospital perspective, the need for an infusion pump and nursing should be considered, however, the study was carried out from the perspective of the SUS where these costs are introduced. Thus, this form of application has been used recently to manage patients with decompensated cirrhosis and HRS in our hospital⁽³²⁾. Finally, our study has few limitations. First, adverse reactions and their costs were not considered, and secondly, patients who were admitted to the ICU were not considered.

CONCLUSION

The present study used a cost-effectiveness analysis to show that treating patients who were diagnosed with type 1 HRS with albumin and terlipressin in combination is cost-effective compared to albumin and norepinephrine in combination that are administered in an ICU setting.

Authors' contribution

LM Ferreira collected the data, statistical analysis and wrote the manuscript. Terrabuio DR, Ferreira CM, Mazo DFC contributed to the critical review of the manuscript and LBP Haddad contributed to the study design, discussion of results, final approval of the manuscript and guided the research.

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RESUMO – Contexto – A Síndrome Hepatorrenal (SHR) é a forma mais grave de lesão renal aguda em pacientes com cirrose avançada, estando diretamente associada a alta taxa de mortalidade. Normalmente é diagnosticada seguindo critérios definidos pela International Ascites Club (IAC). Atualmente, as terapias farmacológicas mais indicadas no tratamento da SHR são a combinação de vasoconstritores esplâncnicos (terlipressina ou norepinefrina) associados à albumina. Com o aumento progressivo dos gastos em saúde, torna-se relevante realizar uma análise de custo-efetividade do tratamento farmacológico em pacientes com diagnóstico de SHR. **Objetivo** – Realizar avaliação de custo-efetividade do uso da terlipressina associada à albumina no tratamento da SHR em pacientes com cirrose. **Métodos** – Avaliação econômica de custo-efetividade, com base em dados secundários de estudos publicados com resultado da eficácia da terapia com terlipressina, em comparação com norepinefrina combinada com albumina ou apenas albumina. A análise de custo-efetividade foi calculada usando a razão de custo-efetividade incremental (RCEI) e uma análise de sensibilidade foi desenvolvida variando os valores das terapias e probabilidades. O real foi a moeda utilizada na análise. **Resultados** – Após a seleção, elegibilidade e avaliação da qualidade das publicações, os resultados demonstraram que a administração da associação de terlipressina ou norepinefrina com albumina em pacientes diagnosticados com SHR tipo 1 possui eficácia comprovada. Os custos do tratamento com a terapia combinada de terlipressina com albumina foram de USD \$1,644.06, administração de somente albumina USD \$912.02 e norepinefrina mais albumina USD \$2,310.78. Considerando as terapias combinadas com efetividade terapêutica comprovada, isto é, terlipressina e norepinefrina associada a albumina, o custo incremental foi de USD \$666.73 e efetividade de 0,570 para o grupo da terlipressina associada a albumina e de 0,200 para o grupo da norepinefrina associada a albumina. A efetividade incremental foi de 0,370 e o valor da RCEI foi de USD \$1,801.97. Assim, os fatores de incremento do custo por terapia e razão de custo-efetividade incremental definem que a terapia combinada de terlipressina mais albumina é custo efetiva quando comparada a administração de somente albumina ou norepinefrina no cenário do sistema único de saúde. **Conclusão** – O estudo demonstrou por meio de uma análise de custo-efetividade que a terlipressina associada à albumina quando administrada concomitantemente a pacientes com diagnóstico de SHR tipo 1 é custo-efetiva quando comparada à albumina sozinha e com norepinefrina associada à albumina administrada em um ambiente controlado.

Palavras-chave – Síndrome hepatorenal; avaliação de custo-efetividade; terlipressina; custos de cuidados em saúde; norepinefrina; gastroenterologia.

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