

# TERLIPRESSIN VERSUS NORADRENALINE FOR HEPATORENAL SYNDROME. Economic evaluation under the perspective of the Brazilian Public Health System

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**ABSTRACT - Background** - Terlipressin and noradrenaline are the best studied treatments for hepatorenal syndrome, and there is no evidence of superiority of one over the other regarding to efficacy. While the former drug is more costly, the latter requires admission into an intensive care unit. **Objective** - The aim of this study was to perform an economic evaluation, comparing treatments for hepatorenal syndrome with terlipressin and noradrenaline. **Methods** - For the economic evaluation, a cost-minimization analysis was performed. Direct medical costs of the two treatment strategies were compared under the perspective of the Brazilian Public Health System as the third-party payer. A probabilistic sensitivity analysis was performed. **Results** - The costs of treatments with terlipressin or noradrenaline were 287.77 and 2,960.45 International Dollars (Int\$) respectively. Treatment using terlipressin would save Int\$2,672.68 for the Public Health System for each hospital admission related to hepatorenal syndrome. In the probabilistic sensitivity analysis, it was verified that the cost of the treatment with noradrenaline could vary between Int\$2,326.53 and Int\$3,644.16, while costs related to the treatment using terlipressin are not variable. **Conclusion** - The treatment strategy using terlipressin was more economical than that using noradrenaline under the perspective of the Brazilian Public Health System as the third-party payer.

**HEADINGS** - Hepatorenal syndrome. Vasoconstrictor agents. Health evaluation.

## INTRODUCTION

Renal failure, especially hepatorenal syndrome (HRS), has a deep impact on the survival of cirrhotics<sup>(2,7)</sup>. Medical treatment for HRS consists of using albumin and a vasoconstrictor<sup>(9)</sup>. Terlipressin and noradrenaline probably are the most studied vasoconstrictors for HRS, and randomized controlled trials<sup>(1,3,10,11)</sup> and systematic reviews<sup>(4,6,8)</sup> have failed to show superiority of one over the other.

Regarding economic aspects, terlipressin is a much more expensive drug than noradrenaline<sup>(1,3,10,11)</sup>. On the other hand, noradrenaline requires administration in an intensive care setting, while terlipressin can be used in regular wards, a fact that also must be considered when evaluating the costs associated to each treatment strategy<sup>(5)</sup>.

This study aims at performing an economic evaluation, comparing the treatment of HRS in cirrhotic patients using terlipressin or noradrenaline,

under the perspective of Sistema Único de Saúde (SUS), the Brazilian Public Health System, as the third-party payer.

## METHODS

Considering the absence of evidence of difference in efficacy between terlipressin and noradrenaline for the treatment of HRS, a cost-minimization strategy was chosen for the economic analysis. The analysis was conducted under the perspective of SUS. Direct medical costs were considered for the analysis. Gross costing methodology was used to identify costs, since most reimbursements paid by SUS are predefined according to codifications of kinds of procedures performed and diseases treated and, therefore, a fixed amount is paid in most situations, not taking into consideration specific items used by the patients. Costs were presented as International Dollars (Int\$). Conversion from Brazilian Reais to International

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Dollars was done using purchasing power parity conversion factor, as provided by the World Bank for the year of 2013 (<http://data.worldbank.org/indicator/PA.NUS.PPP>).

Data collection on costs was based on a hypothetical hospitalization of an average patient with HRS. Hypothetical prescriptions developed considering that HRS was the patient's only decompensation were previously published<sup>(6)</sup>. Albumin doses were the same for both treatment strategies. Under the studied perspective, official reimbursement costs for SUS were used, as presented in the national public health database for hospitalizations (Sistema de Informações Hospitalares do Sistema Único de Saúde SIH/SUS - DATASUS) for June 2014.

Considering the uncertainty regarding the values of doses of drugs and lengths of treatments, probabilistic sensitivity analyses were planned. Since, under the perspective of SUS, a fixed amount is paid as reimbursement for patients treated in regular wards, the amount paid for the treatment of a patient with terlipressin in a regular ward would not vary according to the dose of the drug nor to the duration of its use. On the other hand, for patients admitted to an intensive care unit (ICU), a daily fee is paid in addition to that predefined amount. Therefore, the reimbursement paid by SUS for the treatment with noradrenaline would vary according to the length of stay in the ICU. Nevertheless, the dose of noradrenaline used would still not interfere with the reimbursement paid. Consequently, only the probabilistic sensitivity analysis considering the length of treatment with noradrenaline was performed. Data on treatment durations were derived from a previously published single-arm meta-analysis<sup>(6)</sup>. TreeAge Pro 2011 software was used in order to conduct the probabilistic sensitivity analysis. A normal distribution was assumed. One hundred thousand simulations were run in the model and generated a 95% credible interval (95% CrI). Negative values were truncated.

## RESULTS

Under the studied perspective, the cost of the treatment with terlipressin for the base-case scenario was Int\$287.77, while the cost of the treatment with noradrenaline was Int\$2,960.45. Treatment using terlipressin would save Int\$2,672.68 for SUS for each hospital admission related to HRS. The composition of the costs involved in both treatment strategies which are actually reimbursed by SUS is shown in Table 1. The costs of other used items are included in the reimbursement value of the hospitalization in a regular ward or in an ICU, and they are not reimbursed separately.

In the probabilistic sensitivity analysis considering the duration of treatment with noradrenaline, it was verified that the cost of the treatment with noradrenaline could vary between Int\$2,326.53 and Int\$3,644.16 (mean of Int\$2,960.29, standard deviation - SD=142.02, 95% CrI=2,680.54-3,238.66). As previously stated, costs related to the treatment strategy using terlipressin are not variable under the evaluated perspective and, therefore, would remain at Int\$287.77.

TABLE 1. Composition of costs of treatment for hepatorenal syndrome under the perspective of Sistema Único de Saúde (the Brazilian public health system)

Resource	Costs in International Dollars (Int\$)
Hospitalization for treatment of liver diseases in a regular ward*	Int\$221.55
Gastroenterologist assistance during hospitalization	Int\$37.08
Diagnostic paracentesis	Int\$7.62
Ascites cytology	Int\$6.61
Abdominal ultrasonography	Int\$14.91
Intensive care unit rate (per day)*	Int\$315.92

\*Values include costs with personnel, equipments, materials, tests and medication.

## DISCUSSION

HRS is a dramatic complication of cirrhosis, and its treatment is based on the use of vasoconstrictors and albumin. This study, evaluating the economic aspects of the treatment strategies involving terlipressin or noradrenaline under the perspective of SUS, demonstrated that the treatment strategy using terlipressin is more economical than that using noradrenaline.

The results presented here are in agreement with those recently published for the perspectives of a general hospital providing health care for SUS and of a major Brazilian private health insurance<sup>(6)</sup>. On the other hand, they oppose the previous suggestions that treating patients with noradrenaline would be more economical<sup>(1,3,10,11)</sup>. This can be explained by the fact that, until recently<sup>(6)</sup>, authors had evaluated only the costs of the vasoconstrictor drugs themselves, and not other costs involved in the treatments.

The present study brings an original contribution because it is the first ever published evaluating the economic aspects of the treatment of HRS under the perspective of SUS as the third-party payer, the governmental perspective. Even when patients treated under SUS coverage were previously evaluated, the analysis was performed from the perspective of the hospital providing such care<sup>(6)</sup>, which involves costs that are different from those reimbursed by the government. In the Brazilian Public Health System, health care provider institutions usually pay for the actual costs of treatments, while reimbursements paid by the government are generally predefined according to codifications of kinds of procedures performed and diseases treated and, therefore, they may be superior or inferior to actual costs. Moreover, the present results are robust, since the probabilistic sensitivity analysis demonstrated that the treatment strategy using terlipressin would be more economical than that using noradrenaline through all the range of the 95% credible interval.

Despite not being the objective of this study, a reflection on a societal perspective seems interesting. Under the perspective of society, there would not be many other differences between treatments to consider, except for the fact that the terlipressin strategy could spare an intensive care bed. It is difficult to put a value on having an available ICU bed for a critical patient that might arrive at the hospital, but it is of common sense that ICU beds must be used rationally. Since high occupancy in ICUs is a major problem, the possibility of sparing an ICU bed by treating HRS with terlipressin should be considered. Governments could study the possibility of stimulating the choice for the terlipressin strategy in order to save costs and to spare ICU beds. With this purpose, considering the dose and length of treatment with terlipressin for the base-case scenario as previously published<sup>(6)</sup>, they could consider offering a financial incentive of up to 65% of the cost of terlipressin itself to hospitals and it would still save costs and ICU beds (data not shown).

A limitation of this study could be the fact that the costs of the vasoconstrictors themselves were not accounted for. Nevertheless, under the studied perspective, this is exactly what happens. Besides, when this evaluation was performed under the perspective of a general hospital providing health care for SUS and these costs were taken into consideration, the terlipressin strategy also was more economical<sup>(6)</sup>.

Brazilian guidelines on health technology assessment do not advise on how costs of drugs used during hospitalizations should be evaluated, since they are not reimbursed separately. This should be a matter of discussion in order to standardize methodology.

## CONCLUSION

In conclusion, the present study shows that treating HRS with terlipressin is more economical than treating it with noradrenaline under the perspective of SUS. Decision makers could consider stimulating the choice for the terlipressin strategy in the treatment of HRS in order to save costs and ICU beds.

## Authors' contributions

**Mattos AZ:** study concept and design; acquisition of data; analysis and interpretation of data; drafting of the manuscript; statistical analysis; approval of the final version of the manuscript. **Mattos AA:** study design; acquisition of data; analysis and interpretation of data; critical revision of the manuscript for important intellectual content; approval of the final version of the manuscript. **Ribeiro RA:** study design; analysis and interpretation of data; critical revision of the manuscript for important intellectual content; statistical analysis; approval of the final version of the manuscript.

Mattos AZ, Mattos AA, Ribeiro RA. Terlipressina versus noradrenalina para síndrome hepatorenal. Avaliação econômica sob a perspectiva do Sistema Público de Saúde Brasileiro. *Arq Gastroenterol.* 2016,53(2): 123-6.

**RESUMO - Contexto** - Terlipressina e noradrenalina são os tratamentos mais estudados para a síndrome hepatorenal, e não há evidência de superioridade de uma em relação à outra quanto à eficácia. Enquanto aquela droga tem maior custo, esta requer que o paciente esteja internado em uma unidade de terapia intensiva. **Objetivo** - O objetivo deste estudo foi realizar uma avaliação econômica, comparando os tratamentos da síndrome hepatorenal com terlipressina e com noradrenalina. **Métodos** - Para a avaliação econômica, uma análise de custo-minimização foi realizada. Os custos médicos diretos das duas estratégias terapêuticas foram comparados sob a perspectiva do Sistema Público de Saúde Brasileiro como terceiro-pagador. Uma análise de sensibilidade probabilística foi realizada. **Resultados** - Os custos dos tratamentos com terlipressina ou noradrenalina foram de 287,77 e 2960,45 Dólares Internacionais (Int\$) respectivamente. O tratamento utilizando terlipressina economizaria Int\$2672,68 para o Sistema Público de Saúde a cada internação hospitalar por síndrome hepatorenal. Na análise de sensibilidade probabilística, verificou-se que o custo do tratamento com noradrenalina poderia variar entre Int\$2326,53 e Int\$3644,16, enquanto os custos relacionados ao tratamento utilizando terlipressina não são variáveis. **Conclusão** - A estratégia terapêutica utilizando terlipressina foi mais econômica que aquela utilizando noradrenalina sob a perspectiva do Sistema Público de Saúde Brasileiro como terceiro pagador.

**DESCRITORES** - Síndrome hepatorenal. Vasoconstritores. Avaliação em saúde.

## REFERENCES

1. Alessandria C, Ottobrelli A, Debernardi-Venon W, Todros L, Cerenzia MT, Martini S, et al. Noradrenalin vs terlipressin in patients with hepatorenal syndrome: a prospective, randomized, unblinded, pilot study. *J Hepatol.* 2007;47:499-505.
2. Fagundes C, Barreto R, Guevara M, Garcia E, Solà E, Rodríguez E, et al. A modified acute kidney injury classification for diagnosis and risk stratification of impairment of kidney function in cirrhosis. *J Hepatol.* 2013;59:474-81.
3. Ghosh S, Choudhary NS, Sharma AK, Singh B, Kumar P, Agarwal R, et al. Noradrenaline vs terlipressin in the treatment of type 2 hepatorenal syndrome: a randomized pilot study. *Liver Int.* 2013;33:1187-93.
4. Gluud LL, Christensen K, Christensen E, Krag A. Systematic review of randomized trials on vasoconstrictor drugs for hepatorenal syndrome. *Hepatology.* 2010;51:576-84.
5. Martín-Llahí M, Pépin MN, Guevara M, Díaz F, Torre A, Monescillo A, et al. Terlipressin and albumin vs albumin in patients with cirrhosis and hepatorenal syndrome: a randomized study. *Gastroenterology.* 2008;134:1352-9.
6. Mattos AZ, Mattos AA, Ribeiro RA. Terlipressin versus noradrenaline in the treatment of hepatorenal syndrome: systematic review with meta-analysis and full economic evaluation. *Eur J Gastroenterol Hepatol.* 2015;28:345-51.
7. Moreau R, Jalan R, Gines P, Pavesi M, Angeli P, Cordoba J, et al. Acute-on-chronic liver failure is a distinct syndrome that develops in patients with acute decompensation of cirrhosis. *Gastroenterology.* 2013;144:1426-37.
8. Nassar Junior AP, Farias AQ, D' Albuquerque LA, Carrilho FJ, Malbouisson LM. Terlipressin versus norepinephrine in the treatment of hepatorenal syndrome: a systematic review and meta-analysis. *PLoS One.* 2014;9:e107466.
9. Salerno F, Gerbes A, Ginès P, Wong F, Arroyo V. Diagnosis, prevention and treatment of hepatorenal syndrome in cirrhosis. *Gut.* 2007;56:1310-8.
10. Sharma P, Kumar A, Shrama BC, Sarin SK. An open label, pilot, randomized controlled trial of noradrenaline versus terlipressin in the treatment of type 1 hepatorenal syndrome and predictors of response. *Am J Gastroenterol.* 2008;103:1689-97.
11. Singh V, Ghosh S, Singh B, Kumar P, Sharma N, Bhalla A, et al. Noradrenaline vs. terlipressin in the treatment of hepatorenal syndrome: a randomized study. *J Hepatol.* 2012;56:1293-8.