Economic analysis of intravenous immunoglobulin and plasma exchange therapies for the treatment of Guillain-Barré syndrome in a university-based hospital in the south of Brazil

Avaliação econômica do uso de imunoglobulina intravenosa e de plasmaferese no tratamento da Síndrome de Guillain-Barré no Hospital de Clínicas de Porto Alegre

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Abstract

Background: direct costs for treating Guillain-Barré Syndrome (GBS) represent a significant financial burden to public hospitals. Few studies compared the cost of plasma exchange (PE) treatment with human intravenous immunoglobulin (IVIg).

Aim: to compare the cost of two therapies for GBS: IVIg and PE. Secondary objective was to evaluate compliance to IVIg prescription guidelines of the Pharmacy and Therapeutics Committee (PTC).

Methods: a cross-sectional study included 25 patients with GBS admitted in a university affiliated hospital from June, 2003 through June, 2008. The costs of IVIg (N=20) and PE (N=5) were evaluated through the cost minimization method, considering direct medical costs yield by the management of the institution. Patients receiving treatments other than PE or IVIg were excluded. Data were collected by medical records review. Clinical endpoint was disability on discharge, established by the 7-point scale of Hughes. Compliance to the PTC guidelines was evaluated considering the dose and prescription regime of IVIg.

Results: twenty-five participants, ranging from 2 to 70 years of age, were included. No difference occurred in any medical variables related to the treatment or in the main clinical outcome measured by the Hughes' scale. The mean direct cost of PE treatment was US$ 6,059± 1,701 per patient, and the same expense for IVIg was US$ 18,344±12,259 (P= 0.035). Total inpatient cost was US$ 25,730± 18,714 in the PE group, and 34,768± 27,766 (P=0.530) in the IVIg group.

Conclusion: in a university-based hospital, PE is less expensive than IVIg to treat GBS.

Keywords: plasmapheresis; plasma exchange; immunoglobulin; Guillain-Barré syndrome; guideline adherence; cost-benefit analysis, economical analysis

Resumo

Introdução: os custos diretos do tratamento de Síndrome de Guillain-Barré (SGB) representam parcela significativa dos gastos dos hospitais públicos. Poucos estudos compararam os custos de imunoglobulina intravenosa(IGI) e plasmaferese (PE).

Objetivos: comparar os custos de duas terapias para SGB: imunoglobulina intravenosa(IGI) e plasmaferese. Objetivo secundário foi avaliar a adesão à recomendação para uso de imunoglobulina intravenosa da Comissão de Medicamentos da instituição.

Métodos: estudo transversal com análise econômica incluindo 25 pacientes com SGB admitidos em um hospital universitário de junho de 2003 a junho de 2008. O custo do uso de IGI (N=20) e plasmaferese (N=5) foi avaliado pelo método de custo-minimização, considerando custos diretos praticados na instituição. Excluíram-se pacientes que receberam outros tratamentos além dos estudados. Os dados foram coletados do prontuário hospitalar. Incapacidade na alta foi avaliada através da escala de sete pontos de Huges. Adesão às recomendações da Comissão de Medicamentos foi avaliada quanto à dose e regime de IGI prescritos.

Resultados: incluíram-se 25 participantes, com idade entre 2 e 70 anos. As características clínicas basais foram semelhantes entre os grupos de tratamento, assim como a pontuação na escala de Huges na alta. O custo direto por paciente foi de US$ 6,059± 1,701 com plasmaferese e de US$ 18,344±12,259 com IGI (P= 0,03). O custo total de internação foi US$ 25,730± 18,714 e US$ 34,768± 27,766 respectivamente (P=0,53).

Conclusão: plasmaferese tem menor custo que IGI no tratamento de pacientes com SGB em um hospital universitário do sul do Brasil.

***Palavras-chave**: plasmaferese; imunoglobulina; síndrome de Guillain-Barré; análise de custo-benefício; protocolos; análise econômica*

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Since the breakthrough of the polio vaccine, Guillain-Barré Syndrome (GBS) has become the main cause of acute flaccid paralysis in the world, with an incidence varying from 0.6 to 4/100,000 people/year in different studies arround the world(1-3). A Brazilian series of GBS patients disclosed a mean annual incidence of 0.4 cases/100,000 (4). Classified as an "immune-mediated" neuropathy, GBS is characterized by weakness or paralysis affecting more than one limb, usually in a symmetrical fashion, in association with loss of tendinous reflexes and an increased cerebrospinal fluid (CSF) protein count without pleocitosis.

Several studies (5-9) have concluded that efficacy of Intravenous Immunoglobulin (IVIg) or Plasma Exchange (PE) treatment is not statistically different. Direct costs for treating patients with GBS, though small when compared with total disease cost, represent a significant financial burden to public hospitals, where more severe cases are frequently treated. In the United States, in a total load of $1.7 billion US Dollars spent in GBS, direct costs accounted for just 14% of that total (10). Few studies compared the cost of plasma exchange treatment with human intravenous immunoglobulin. Their results are controversial (9-11) and applicability is limited, considering populations with distinct characteristics and economies. Provided that health financing resources are limited, and distributed according to established priorities – which also implies opportunity costs – health institutions develop and institute practice parameters suggesting assistance patterns regarding hospitalization period, diagnostic testing, and treatment applied. In this context, the Pharmacy and Therapeutics Committee (PTC) of the Hospital de Clínicas de Porto Alegre (HCPA) prepared a guideline for the use of intravenous human immunoglobulin in this institution, available since June, 2005, intending to rationalize the IVIg utilization and to minimize costs. The main objective of this study was to compare the cost of PE and IVIg in the treatment of GBS, with the perspective of a public health institution, considering direct sanitary cost. Secondary objective was to evaluate the agreement of staff practice to the guideline yield by the PTC on IVIg utilization in HCPA. The study was approved by the Institutional Review Board of the HCPA.

Methods

A cross-sectional, economical analysis was conducted, including a convenience sample of all patients that had been treated with PE or IVIg due to GBS during the period of June, 2003 through June, 2008 in the HCPA, a public, tertiary care teaching hospital in the city of Porto Alegre, southern Brasil. This hospital has 749 beds, with 22 non-critical wards and three ICU (adult, neonatal and pediatric). Patients with a registered ICD-10 (International Code of Diseases – Tenth revision) G61 (inflammatory polyneuropathies) and G62 (other polyneuropathies) on discharge were sought in the Hospital's computerized data system. Among a total of 53 patients identified, 27 with an ICD-10 G61.0 corresponding to Guillain-Barré Syndrome were selected.

Two individuals with GBS diagnosis in whom only support treatment was needed – due to a mild presentation of disease – were excluded. Data were collected through chart review, and included number of PE sessions, amount of human albumin used in each session, IVIg dose administered, gender, age, admission and length of ICU stay, length of hospital stay, number of mechanical ventilation days, time from the beginning of symptoms, severity on admittance, and disability grade on discharge. Severity of disease on admittance was classified as follows: mild disease, when the patient was able to walk; moderate disease, when the patient was unable to walk, and severe disease, when assisted ventilation was required (7,9,12). Disability grade on discharge, measured by Hughes' scale, was the main efficacy parameter for both treatments (table 1) (9,10).

Table 1: Hughes' Scale for disability related to Guillain-Barré syndrome.

Points	Description
0	Healthy
1	Minor symptoms or signs of neuropathy but capable of manual work
2	Able to walk without support of a stick but incapable of manual work
3	Able to walk with a stick, appliance or support
4	Confined to bed or chair bound
5	Requiring assisted ventilation
6	Dead

Compliance to the guidelines of the PTC (13) was evaluated through the dose and prescription scheme of IVIg. The recommendation is 0,4g/Kilograms of weight/day, during 5 days (4,7,9,14). Economical analysis considered, in advance, both treatments as efficient, as previously demonstrated in the literature. Therefore, the cost-minimization method was applied. Only direct sanitary costs of each treatment – determined by the mean hospital daily expense and specific medications (albumin, human immunoglobulin) expenses were included. Values were converted to US Dollars in 2008 currency.

The mean hospital daily cost in HCPA, as obtained from the institution's management and stratified by sector, includes: medication expenses, personnel, maintenance, depreciation of property, and baseline costs. Medication accounts for 19.95% of the total expense. For cost-analysis, this percentage was subtracted from the hospital daily expense (HDE), and actual values directly related with treatment with PE or IVIg were added to the equation. For the treatment with IVIg, the cost of that medication alone was added, since it is a simple procedure, and the expense for the administration is already included in the HDE. For the employment of PE though, the cost of the procedure itself – US$ 436 per session – was added to the value corresponding to the number of albumin flasks used as a substitute for plasma.

Data were analyzed using the SPSS V.14 software. Descriptive statistics, with central tendency measures were applied. Patient characteristics were compared through the Chi-square, Student t and Mann-Whitney tests, with an alpha error of 5%.

Results

Twenty-five participants, ranging from 2 to 70 years of age, were included in the study. Twenty percent (n=5) were submitted to treatment with PE, using human albumin as replacement for plasma, and 80% (n=20) were treated with IVIg. The majority of the patients presented with moderate disease on admittance, and a third of the patients had some additional morbidity. Baseline characteristics of the patients, stratified by treatment received, are presented in Table 2. No statistically significant difference was observed between the groups.

Table 2: Characteristics of Guillain-Barré syndrome patients at hospital admittance by treatment group.

Characteristics	Treatment		P
	Plasma exchange (N=5)	Immunoglobulin (N=20)	
Male - N(%)	4 (80.0)	12 (60.0)	0.62[a]
Age - N(%)			0.59[b]
0 to 12	1 (20.0)	7 (35.0)	
13 to 40	3 (60.0)	7 (35.0)	
> 40	1 (20.0)	6 (70.0)	
Mean Weight ± DP (Kg)	66.4 ± 17.2	54.7 ± 29.6	0.27[c***]
Severety at admission – N(%)			
Mild	0 (0.0)	1 (5.0)	
Moderate	2 2 (40.0)	13 (65.0)	
Severe	3 (60.0)	6 (30.0)	
Days of untreated symptoms – median (P25 – P75)	5 (3.5 – 9.0)	6 (4.3 – 8)	0.82[d]
Additional morbidities at admission – N(%)	2 (40.0)	7 (35.0)	1.0 [a]

[a] Fisher's exact test - [b] Pearson's chi-square - [c] Student's T test - [d] Mann-Whitney test

Medical characteristics are described in Table 3, and did not differ significantly between groups. Length of hospital stay varied from 2 to 154 days, with a mean of 21.3 ±30 days. Patients admitted with severe disease (9) required mechanical ventilation for 5 to 41 days. Thirty-three percent (N=3) of them did not have additional morbidity on admittance, and only one (11.1%) had no medical complication during hospitalization. Mean length of hospital stay for these patients was 41.2 ± 45.8 days, with 21 days ±14.1 in the ICU and 17.4 days ±12.4 requiring assisted ventilation. One death occurred, two patients persisted on mechanical ventilation, and the remaining patients were discharged with some sort of functional impairment. The majority (N=6) were treated with IVIg.

Table 3: Clinical outcomes of Guillain-Barré patients treated with plasma exchange or intravenous immunoglobulin.

Variables	Treatment		P
	Plasma exchange (N=5)	Immunoglobulin (N=20)	
In-hospital days – Median (P25 – P75)	13 (8 – 40)	9,5 (6 – 22,5)	0.49 [a]
ICU days – Median (P25 – P75)	6 (2.5 – 25.5)	4 (0 – 12)	0.30 [b]
Mecanical Ventilation – N (%)	3 (60.0)	6 (30.0)	0.31 [a]
Mecanical Ventilation days – Median (P25 – P75)	13 (5 – 30)	14 (10 – 29)	0.90 [a]
In-hospital complications– N(%)	2 (40.0)	7 (35.0)	1.0 [a]
Hughes' scale – N(%)			
0 to 3	3 (60)	12 (60)	1,0 [b]
4 to 6	2 (40)	8 (40)	

[a] Mann-Whitney test - [b] Fisher's exact test

Of the five patients treated with PE – two with moderate disease, and three in need of mechanical ventilation – one died, and four were discharged with moderate disease (Hughes 3 or 4). Therefore, none maintained the need for mechanical ventilation after the treatment, what evidences an improvement in at least one point in Hughes' disability scale. Of the 20 patients treated with IVIg, five were discharged with mild disease (0 – 2 score in Hughes' scale), 13 with moderate disease (score 3 – 4) and two remained in the need for mechanical ventilation (score 5).

Table 4 presents the comparison between treatments regarding expenses. In the cost minimization analysis, the preference for the use of PE over IVIg was observed (table 4), with statistically significant difference when direct treatment costs were accounted exclusively (PE US$ 6,059± 1,701 and IVIg US$ 18,344±12,259; P=0.035) . The difference persisted, though not statistically significant, when other direct sanitary costs were added (total hospital daily expenses). Since no difference occurred in any medical variables related to the treatments (length of total hospital stay, days in MV, days in ICU), or in the main clinical outcome measured by the Hughes' scale, it may be concluded that, in HCPA, the PE procedure dominate IVIg strategy.

Table 4: Expenses with treatment and hospital diaries in GBS patients treated with IVIg and PE patients (US Dollar 2008 exchange).

	Plasma exchange (N=5)	Intravenous immunoglobulin (N=20)	P*
	Mean ± DP	Mean ± DP	
Procedure (A)	1,920± 390	-	-
Drug (B)	4,139± 1,349	18,344± 12,259	0,004
Total treatment (C=A+B)	6,059± 1701	18,344±12,259	0,035
Total Hospital Expense#	25,730± 18,714	34,768± 27,766	0,530

**Mann-Whitney test - # C + mean daily cost in HCPA*

Evaluation of compliance with PTC guidelines for intravenous immunoglobulin use included patients admitted after June, 2005. Among a total of 13 patients, two had their doses of IVIg prescribed above the recommended, corresponding to an 84.6% adequacy rate. Analyzing the sum of the inadequate doses, 180g were prescribed in

excess, causing an over expense of US$ 29,880, which contributed for the elevated mean cost of treatment with IVIg, besides causing financial loss. The estimate based on the recommendations of the Pharmacy and Therapeutics Committee, considering 100% adhesion, would result in a mean treatment cost (ward expenses excluded) for an 80Kg GBS patient of US$ 26,514 for IVIg and US$ 5,384 for PE.

Discussion

The main objective of this study was to establish the cost relation between two treatments for GBS. With regard to cost minimization analysis, this study appears to be a pioneering experience in Brazil, since there is no reference to such analysis in our country. We showed that in our environment, a tertiary public university affiliated hospital, plasma exchange is less expensive than intravenous immunoglobulin. In a retrospective study performed at Taipei Veterans General Hospital, Tsai CP and col. (15) showed although drug costs were higher with IVIg, total costs were lower in the IVIg group than in the PE group. But the high costs were related to the cost of complications and assisted ventilation. Patients in the IVIg group had fewer complications and fewer IVIg patients used ventilators, hence the lower costs. This is in accordance with the reduction in cost difference observed when we compared total hospital expense.

The use of PE or IVIg as a strategy to treat GBS in the early stages of the disease is justified, and, with the exception of one patient who died and 2 who remained dependent of assisted ventilation, all others (88%) had their severity grading diminished in at least one point. Taking into account the small sample size, the absence of statistically significant difference in clinical outcomes agree with the literature (7, 9,10,12-14,16). Cochrane review (7) concluded that there is moderate quality evidence that, in severe disease, intravenous immunoglobulin started within two weeks from onset hastens recovery as much as plasma exchange. Complications occurring during the inpatient period held direct relation with the preexisting morbidities and with the severity score on admittance. It is also observed that the cost of the treatment of a patient with GBS is elevated and the mean daily expense was comparable to the mean cost of a severely ill patient under intensive care in our institution (data not showed).

Although there is a stimulus for PE use instead of IVIg from the Pharmacy and Therapeutic Committee, there is no current clinical guideline of PE for GBS treatment in the HCPA. The number of sessions indicated based on the disease severity is well established in the literature (7,8,12,17,18). There is consensus that six sessions are not superior to four for severe cases, and therefore any number of sessions exceeding that may be considered an unnecessary expense. In the present study, despite the reduced number of patients treated (n=5), three of them were submitted to 5 sessions of PE, therefore one unnecessary session at a cost of 1,346 USD, totalizing and exceeding expense of 4,038 USD.

Intravenous human immunoglobulin, being an onerous therapeutic option indicated in several clinical conditions, had its use in HCPA regulated by the PTC from June, 2005. The recommendations had been based in literature review, aiming optimizes clinical outcomes and resources use. The guidelines for the treatment of GBS with IVIg coincide with those established later (2007) by the Brazilian National Government Health Department (19). Compliance rates to the former are considered good, and may be attributed to the medications policy of the institution – established by the PTC – which determines criteria for dispensing medication with institutional control concern. This action intends to qualify assistance, instruction, and to optimize expenses with medication.

Limitations of this study should be considered. The reduced sample size may be responsible for the lack of statistical significance (calculated power for the sample of 33%) when total direct hospitalization costs were compared. The adjusted analysis for the difference in severity of cases, suggested in table 2, and by the also cannot be made. Furthermore, it was not possible to distinguish between axonal and demyellinating polyradiculoneuropathy. There is a tendency in literature to prefer PE in situations such as more severe disease and older ages (20), leading to potential indication bias, and, probably, diminishing the difference in total costs. Finally, the absence of statistical significance in the clinical outcomes, besides being in accordance to the literature, may have occurred for lack of sample power. It must be mentioned also, that HCPA is a large school hospital, with adequate structure evaluable to realize PE, limiting the external applicability of our results.

In conclusion, the strategy of treating GBS with PE dominates IVIg, in the context of a public, high complexity treatment hospital in a developing country. In such settings, economic evaluation studies – especially for expensive treatments – and protocols to guide clinical practice become paramount, providing less expenses, safety, and end-results evaluations.

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