Incremental cost-effectiveness analysis of using antitetanus immunoglobulin via intrathecal route to the treatment of tetanus

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Introduction

- Tetanus is caused by an exotoxin produced by the *Clostridium tetani*

- Tetanospasmin is transported intra-axonally to the CNS, inhibits the inhibitory neurons leading to the clinical syndrome of tetanus (rigidity, muscle spasms and, if severe, autonomic dysfunction)

- Frequent complications: respiratory infection and respiratory failure

- Lethality: 6 to 60%

- Treatment requires intensive supportive care preferably in intensive care units

Gouveia *et al.* Mortality trend due to accidental tetanus from 1981 to 2004 in Pernambuco and analysis of the impact on intensive care unit attendance. Rev Soc Bras Med Trop, 2009.
Poudel *et al.* Tetanus. Kathmandu University Medical Journal, 2009.
Nolla-Sallas *et al.* Severity of tetanus in patients older than 80 years: comparative study with younger patients. Clin Infec Dis, 1993

1. To estimate the incremental cost of treatment of tetanus using the intrathecal route and the average cost of treatment of tetanus using the intramuscular route by:

- Level of tetanus severity

- Hospitalization stay

- Respiratory assistance

- Respiratory infection

2. To estimate the incremental cost of using antitetanus immunoglobulin by the intrathecal route compared to the intramuscular route for the treatment of tetanus.

Methods

- Randomised controlled trial: patients were randomised to receive antitetanus immunoglobulin by either the intrathecal and intramuscular routes (treatment group, 58 patients) or intramuscular route (control group, 62 patients)

- Patients admitted to a referral hospital in Recife from July 1997 to July 2001

- Patient clinical progression was assessed by severity level for different intervals of time (from Day 0 to Day 10): Day 2, Day 4, Day 6, Day 8, and Day 10

Miranda-Filho *et al*. Randomised controlled trial of tetanus treatment with antitetanus immunoglobulin by the intrathecal or intramuscular route. BMJ, march, 2004.

Clinical classification of tetanus patients

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Grade I

Trismus + dysphagia + generalized rigidity (present in more than one segment - head, trunk, arms and legs – of the body), with no spasms

Grade II

Mild and occasional spasms (generally after a stimulus)

Grade III

Severe and recurrent spasms, usually triggered by minor stimuli (light, sound, measurement of vital signs, light touch, opening the eyes) or imperceptible stimuli

Grade IV

Same features as grade III + syndrome of sympathetic nervous system hyperactivity

Methods

Assessed outcomes for the cost analysis:

- clinical progression by level of severity,

- hospital stay,

- respiratory assistance,

- respiratory infection

Methods

- Perspective of analysis: public health system (Unified Health System – SUS)

- All costs were estimated using standard methodology, where the mean use of resource was multiplied by the unit cost of the referred resource to produce the estimated direct mean cost incurred by the public health system

- To test the robustness of estimates, we use sensitivity analysis, which indicates how the estimates would react to percentages changes in the value of the parameters of the model. The analysis was applied to the cost categories. We assumed that the vectors were increased or decreased by 10, 20 and 50%.

Results

Table 1. Effectiveness measure

Effectiveness measure	Control Group	Study Group	p-value
Clinical progression	N = 60	N = 58	
Improvement	23 (38%)	36 (62%)	
Deterioration	37 (62%)	22 (38%)	0,005
Hospital stay in days (average)	N=52	N=54	
≤15 (8.5)	14 (27%)	23 (43%)	
16-30 (23)	17 (33%)	19 (35%)	
>30 (55.5)	21 (40%)	12 (22%)	0,03
Respiratory assistance in days (average)	N= 30	N =20	
≤10 (5.5)	4 (13%)	9 (45%)	
11-20 (15.5)	12 (40%)	7 (35%)	
>20 (41)	14 (47%)	4 (20%)	0,01
Respiratory Infection	N = 62	N = 58	
Yes	42 (68%)	29 (50%)	
No	20 (32%)	29 (50%)	0,07

Results

Table 2. Average number of days of hospitalization by severity level of tetanus

Severity Level	Average number of days of hospitalization
Grade I	14
Grade II	24
Grade III	30
Grade IV	38

Results

Table 3. Unit costs

Cost item (per day, otherwise stated)	Grade I	Grade II	Grade III	Grade IV	Average for All Grades
Overheads	0.0035	0.0035	0.0035	0.0035	0.0035
Personnel	1.09	1.09	1.09	1.09	1.09
Antibiotics to treat respiratory infection	0.00	10.94	17.31	19.44	11.92
Antibiotics to treat urinary infection	0.00	0.00	0.00	27.22	6.81
Other drugs	4.61	1.91	3.79	3.43	3.44
Consumables	13.24	3.98	5.94	6.39	7.39
Tests	5.20	3.17	10.12	3.43	5.48
Gases (respiratory assistance)	158.74	183.54	229.06	255.24	391.56
Gases: depreciation of equipment per patient	64.65	64.65	64.65	64.65	64.65
3000 UI Immunoglobulin for intramuscular use per patient	188.42	188.42	188.42	188.42	188.42
1000 UI Immunoglobulin for intrathecal use per patient	576.21	576.21	576.21	576.21	576.21
Training for intrathecal application per patient (Study Group only)	13.67	13.67	13.67	13.67	13.67

Results

Table 4. Cost per severity of tetanus without immunoglobulins

Grade	Cost per day
Grade I	247.54
Grade II	272.35
Grade III	317.87
Grade IV	344.04
Average all Grades	295.45

3000 UI Immunoglobulin costs for intramuscular use per patient: U$ 188.42

Results

Table 5. Incremental cost per Severity of Tetanus by Different Study Groups

Days of Admission	Grade I	Grade II	Grade III	Grade IV	Total	Incremental cost
Day 2						
Control	7,615	7,269	12,267	5,693	32,844	
Study	10,492	12,573	8,854	1,278	33,197	353
Day 4						
Control	4,951	7,081	12,715	6,881	31,627	
Study	9,407	12,528	5,722	1,376	29,032	-2,595
Day 6						
Control	5,446	6,536	10,807	8,257	31,047	
Study	8,912	11,439	4,450	0	24,800	-6,246
Day 8						
Control	4,456	8,715	10,807	6,193	30,171	
Study	11,387	8,715	3,179	0	23,281	-6,890
Day 10						
Control	4,456	5,992	10,807	4,129	25,383	
Study	10,892	5,447	3,179	1,376	20,894	-4,490

Results

Table 6. Incremental Cost per Hospital Stay, Respiratory Assistance and Respiratory Infection

Outcomes	Average time in days (range)	Control Group US$ (n)	Study Group US$ (n)	Increment US$
Hospital Stay	8.5 (2-15)	35,158.41 (14)	57,760.25 (23)	
	23 (16-30)	115,520.50 (17)	129,111.15 (19)	
	55.5 (31-80)	344,345.63 (21)	196,768.93 (12)	
	-	**495,024.54**	**383,640.33**	**-111,384.22**
Respiratory Assistance	5 (1-10)	4,132.96 (4)	9,299.15 (9)	
	15.5 (11-30)	38,436.49 (12)	22,421.29 (7)	
	41 (21-61)	118,615.84 (14)	33,890.24 (4)	
	-	**161,185.29**	**65,610.68**	**-95,574.61**
Respiratory Infection	Yes	**11,024.16 (42)**	**7,611.92 (29)**	**-3,412.24**

Table 7. Incremental Cost-Effectiveness Analysis of Two Strategies for the Treatment of Tetanus

Therapy	Total costs after 10 Days	Number of patients	Incremental cost	Remark
Intramuscular route (Control Group)	151,073	62		
Inthratecal route (Study Group)	131,204	58	-19,869	Dominated

Results

Table 8. Sensitivity Analysis: Respiratory Assistance Cost Vector Was Increased or Decreased by 10, 20 and 50% to Indicate the Likely Boundaries of Costs

Average time in days (range)	Control Group						
	-10%	-20%	-50%	best estimates	10%	20%	50%
5 (1-10)	4,546.25	4,959.55	6,199.43	4,132.96	3,719.66	3,306.36	2,066.48
15.5 (11-30)	42,280.14	46,123.79	57,654.74	38,436.49	34,592.84	30,749.19	19,218.25
41 (21-61)	130,477.42	142,339.01	177,923.76	118,615.84	106,754.26	94,892.67	59,307.92
	Study Group						
	-10%	-20%	-50%	best estimates	10%	20%	50%
5 (1-10)	10,229.07	11,158.98	13,948.73	9,299.15	8,369.24	7,439.32	4,649.58
15.5 (11-30)	24,663.42	26,905.54	33,631.93	22,421.29	20,179.16	17,937.03	11,210.64
41 (21-61)	37,279.26	40,668.29	50,835.36	33,890.24	30,501.22	27,112.19	16,945.12
	Comparing Both Groups						
Incremental cost	-10%	-20%	-50%	best estimates	10%	20%	50%
5 (1-10)	5,682.81	6,199.43	7,749.29	5,166.20	4,649.58	4,132.96	2,583.10
15.5 (11-30)	-17,616.73	-19,218.25	-24,022.81	-16,015.20	-14,413.68	-12,812.16	-8,007.60
41 (21-61)	-93,198.16	-101,670.72	-127,088.40	-84,725.60	-76,253.04	-67,780.48	-42,362.80

Conclusion

- Treatment of tetanus via the intrathecal route is highly cost effective

- The intrathecal intervention is dominant over the intramuscular route (incremental cost is negative) and should be implemented

- On average, over US$ 111 thousands would be saved in hospitalization stay if the intrathecal route is implemented

- Sensitivity analysis showed costs savings are robust by 10, 20 and 50% costs variation (more critical parameter: respiratory assistance)

Thank you

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