Botulinum Toxin Treatment Versus Conservative Management in Acute Traumatic Sixth Nerve Palsy or Paresis

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Purpose: Botulinum toxin (BTX), injected into the ipsilateral medial rectus muscle, has been advocated for the management of acute traumatic sixth nerve palsy or paresis. We conducted a multicenter, nonrandomized, data collection study to evaluate recovery rates of patients treated with either conservative measures or BTX. ***Methods:*** All members of the American Association for Pediatric Ophthalmology and Strabismus and the North American Neuro-Ophthalmology Society were invited to enroll patients with acute traumatic sixth nerve palsy or paresis during a 2-year period (between March 1996 and February 1998). The BTX group was defined as patients who received a BTX injection within 3 months of injury. Recovery at 6 months from injury was defined as absence of diplopia in the primary position and a distance esotropia of no more than 10 PD in the primary position. Nonrecovered patients with less than 6 months of follow-up (n = 15) were excluded. ***Results:*** Eighty-four eligible patients were enrolled by 46 investigators. Sixty-two patients (74%) were treated conservatively and 22 (26%) with BTX. Sixty-two patients (74%) had unilateral palsy, and 22 (26%) had bilateral palsy. Recovery rates were similar between BTX and conservatively treated patients (overall: 73% vs 71%, $P = 1.0$; unilateral: 81% vs 83%, $P = 1.0$; bilateral: 50% vs 38%, $P = 0.66$, respectively). ***Conclusions:*** In this prospective multicenter study of acute traumatic sixth nerve palsy or paresis, patients treated with either BTX or conservative measures had similar high recovery rates. (J AAPOS 2000;4:145-9)

Botulinum toxin (BTX), injected into the ipsilateral medial rectus muscle, has been advocated in the management of acute traumatic sixth nerve palsy or paresis.[1-6] Scott and Kraft[2] suggested that in conservatively managed cases, contracture of the medial rectus muscle may prevent complete resolution of diplopia despite complete recovery of lateral rectus muscle function. They postulated that botulinum toxin reduces contracture of the medial rectus muscle and allows for more complete restoration of ductions.[2]

In a previous prospective, multicenter, data collection study,[7] we reported a high spontaneous recovery rate in acute traumatic sixth nerve palsy. We continued our multicenter, nonrandomized, data collection study to evaluate recovery rates in additional cases of acute traumatic sixth nerve palsy or paresis treated either conservatively or with BTX.

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Presented in part at the 25th Annual Meeting of the American Association for Pediatric Ophthalmology and Strabismus, Toronto, Ontario, Canada, April 15-18, 1999.

Supported by the National Institutes of Health grant EY11578 (J.M.H.), Research to Prevent Blindness, Inc, and the Mayo Foundation.

Submitted April 22, 1999.

Revision accepted September 15, 1999.

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1091-8531/2000/$12.00 + 0 ***75/1/103875***

doi:10.1067/mpa.2000.103875

METHODS

All members of the American Association for Pediatric Ophthalmology and Strabismus (AAPOS) and the North American Neuro-Ophthalmology Society (NANOS) were invited to enroll patients with acute traumatic sixth nerve palsy during a 2-year period (between March 1996 and February 1998). The results of the conservatively managed cases have been previously reported.[7,8] Inclusion criteria were chosen to parallel those that might be used for a future randomized treatment trial (Table 1). Although a history of head trauma was a required inclusion criterion, the physical nature of the trauma was not recorded. The enrollment window was within 2 months of injury for the first year of the study[7] and was extended to within 3 months of injury in the second year of the study. Forty-five patients were enrolled in the first year and 54 in the second year. Comparison of the patient demographics (age, race, sex) and palsy characteristics (severity, laterality, time to presentation) revealed no clinically meaningful differences between patients according to enrollment year[8]; therefore, these data were combined for analysis.

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Volume 4 Number 3 June 2000

TABLE 1. Inclusion criteria

Initial exam within 3 months of injury (2 months during first year of enrollment)
Inability to fully abduct one or both eyes
History of head trauma
Diplopia in the primary position
Visual acuity at least 20/200 in each eye
Distance esotropia at least 10 PD
Absence of a third nerve palsy
No previous treatment with botulinum toxin or surgery

The BTX group was defined as patients who received an injection within 3 months of injury. The dose of BTX was 5 IU per injection in all but 4 patients; 3 patients received 2.5 IU and 1 patient 10 IU per injection. Patients who received BTX after 3 months (n = 5) were considered "conservatively managed" and classified as "nonrecovered."

Data collected at enrollment included the date of injury, age, gender, ethnicity, degree of abduction deficit, and angle of deviation (in PD measured by simultaneous prism and cover test in the primary position at a distance of 6 m). Abduction deficit was recorded on the scale described by Scott and Kraft[2]: zero (normal), –1 (to 75% full rotation), –2 (to 50% full rotation), –3 (to 25% full rotation), –4 (to midline), and –5 (inability to abduct to the midline). A "complete" palsy was defined as –4 or –5 abduction deficit and "incomplete" as –1, –2, or –3. For purposes of analysis in bilateral cases, the severity of the palsy was defined as the abduction deficit of the worst eye.

A reminder was sent to each participating investigator at 6 months after injury to obtain follow-up data on diplopia, abduction deficit, and angle of deviation. No defined "window" was specified, except that the examination should be as close to, but not less than, 6 months after the injury. Investigators arranged intervening follow-up visits according to their usual routine. Recovery was defined as the absence of diplopia in the primary position and a distance esotropia of no more than 10 PD in the primary position. The latter criterion was used to prevent patients with residual moderate esotropia but suppression (ie, no diplopia) from being classified as "recovered." If recovery, as defined above, had been documented before 6 months from injury, follow-up was considered "complete," and the patient was classified as "recovered."

Of 99 initially eligible patients, 15 nonresolved patients had less than 6 months of follow-up and were excluded from further analysis. Eight of these excluded patients were seen only at enrollment, 3 had less than 1 week of follow-up, 3 had less than 1 month of follow-up, and 1 had 4 months of follow-up. No patients underwent eye muscle surgery during the 6 months of follow-up.

Proportions were compared by using Fisher exact tests; exact 95% CIs of proportions were calculated by using StatXact software version 4.01 (Cytel Software Corporation, Cambridge, Mass). Unadjusted and adjusted (single covariate) risk ratios of recovery between BTX and conservatively treated patients were estimated by the Mantel-Haenszel method by using SAS software version 6.12 (SAS Institute Inc, Cary, NC). In addition, multivariable (≥2 covariates) adjusted odds ratios and exact 95% CIs were estimated with LogXact software version 2.1 (Cytel Software Corporation). Because the study outcome (recovery) was common, odds ratios were subsequently corrected to more closely approximate risk ratios.[9]

Institutional review board approval was obtained by the principal investigator (J.M.H.) at the data coordinating center (Mayo Clinic, Rochester, Minn). Data that could be used to identify a specific patient were confidential and not transmitted from the study ophthalmologist to the data coordinating center.

RESULTS

Description of the Cohort

Eighty-four eligible patients with complete follow-up (as defined earlier) were enrolled by 46 investigators. Ages ranged from 2 to 79 years (median, 20 years); 37% of patients were female, and 65% were white (Table 2).

There were no clinically meaningful differences in demographic or palsy characteristics when the 84 patients with complete follow-up were compared with the 15 excluded patients. Specifically, 26% of the included patients received BTX compared with 20% of the excluded patients; 60% of the included patients had a complete palsy (–4 or –5) compared with 67% of the excluded patients.

Patients were initially seen by the ophthalmologist investigator between 0 and 85 days from the date of injury (median 26 days, Table 2). The outcome examination for "nonrecovered" patients was performed within 174 days and 261 days from injury. In 49 of 60 patients classified as "recovered," the outcome examination was performed within 6 months from injury (no additional follow-up data were requested on these patients). For the 11 "recovered" patients who were seen after 6 months of injury, the outcome examination was performed between 191 and 336 days.

Treatment Groups

According to our study criteria, 62 of the 84 patients (74%) were classified as having been treated conservatively and 22 (26%) as having been treated with BTX. Patients in the BTX group tended to have more severe abduction deficits and larger angles of esotropia at the time of initial examination, and this was controlled for in the analysis (Table 2).

For the BTX-treated patients, there was a median delay of 22 days between the first visit and the BTX injection (range, 0 to 68 days; quartiles, 0 and 29 days). Nine of the 22 patients were treated within a week of initial presentation, 7 of these on the day of presentation. Twenty of the 22 BTX patients received a single injection; 1 patient received 2 injections, and 1 patient received 3 injections.

The overall patient recovery rate was 71% (95% CI, 61%-81%), occurring in 16 of 22 BTX cases (73% [95%

TABLE 2. Patient characteristics according to treatment group

	Overall (n = 84)	Conservative treatment (n = 62)	Botulinum treatment (n = 22)
Age in years [median (quartiles)]	20 (12.5, 34.5)	18 (13, 36)	24.5 (12, 33)
Female [No. (%)]	31 (37%)	26 (42%)	5 (23%)
Race			
African American	8 (10%)	3 (5%)	5 (23%)
American Indian	1 (1%)	0 (0%)	1 (5%)
Asian	3 (4%)	2 (3%)	1 (5%)
White	55 (65%)	45 (73%)	10 (45%)
Hispanic	5 (6%)	5 (8%)	0 (0%)
Other	4 (5%)	2 (3%)	2 (9%)
Unknown	8 (10%)	5 (8%)	3 (14%)
Time from injury to first exam (%)			
0-7 d	18 (21%)	13 (21%)	5 (23%)
8-14 d	11 (13%)	6 (10%)	5 (23%)
15-31 d	18 (21%)	14 (23%)	4 (18%)
32-61 d	32 (38%)	27 (43%)	5 (23%)
>61 d	5 (6%)	2 (3%)	3 (14%)
Bilateral palsy (%)	22 (26%)	16 (26%)	6 (27%)
Severity of abduction deficit in worst affected eye (%)			
–1	7 (8%)	7 (11%)	0 (0%)
–2	8 (10%)	6 (10%)	2 (9%)
–3	19 (23%)	15 (24%)	4 (18%)
–4	26 (31%)	18 (29%)	8 (36%)
–5	24 (29%)	16 (26%)	8 (36%)
Esotropia* (%)			
10-19 PD	18 (24%)	16 (30%)	2 (10%)
20-29 PD	16 (22%)	13 (24%)	3 (15%)
30-39 PD	19 (26%)	13 (24%)	6 (30%)
40-49 PD	7 (9%)	4 (7%)	3 (15%)
≥50 PD	14 (19%)	8 (15%)	6 (30%)

*Missing cases (conservatively treated group = 8, BTX group = 2).

TABLE 3. Recovery by treatment group

	Conservative treatment		BTX treatment		
	Total No.	No. of recovered patients (%)	Total No.	No. of recovered patients (%)	Risk ratio (95% CI)
Overall	62	44 (71%)	22	16 (73%)	1.03 (0.75, 1.39)
Baseline abduction deficit*					
Incomplete (–1 to –3)	28	26 (93%)	6	6 (100%)	1.08 (0.87, 1.34)
Complete (–4 to –5)	34	18 (53%)	16	10 (63%)	1.18 (0.70, 1.98)
Adjusted	—	—	—	—	1.14 (0.83, 1.55)
Baseline esotropia†					
<50	46	38 (83%)	14	12 (86%)	1.04 (0.79, 1.36)
≥50	8	2 (25%)	6	2 (33%)	1.33 (0.24, 7.40)
Adjusted	—	—	—	—	1.06 (0.79, 1.43)
Time from injury to first exam					
0-7 d	13	11 (85%)	5	4 (80%)	0.95 (0.59, 1.53)
8-30 d	18	14 (78%)	9	7 (78%)	1.00 (0.65, 1.53)
>30 d	31	19 (61%)	8	5 (63%)	1.02 (0.55, 1.89)
Adjusted	—	—	—	—	0.99 (0.74, 1.34)

*Severity for the bilateral cases was defined as the abduction deficit of the worst eye.
†Esotropia data missing for 10 patients (conservatively treated = 8, BTX = 2).

CI, 50%-89%]) and 44 of 62 conservatively managed cases (71% [95% CI, 58%-82%]; $P = 1.0$, Table 3). Compared with the conservatively treated group, the risk ratio for recovery with BTX was 1.03 (95% CI, 0.73-1.39; Table 3) and did not appreciably change after adjustment for severity of abduction deficit on presentation, esotropia on presentation, or time from injury to initial examination (Table 3). When we adjusted simultaneously for severity, laterali-

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ty, and time to presentation, the adjusted risk ratio for recovery with BTX was 1.14 (95% CI, 0.70-1.35).

Separate analysis of patients with unilateral and bilateral palsy revealed similar recovery rates in BTX and conservatively managed cases (unilateral: 81% vs 83%, $P = 1.0$; bilateral: 50% vs 38%, $P = 0.66$, respectively).

DISCUSSION

In this prospective multicenter study of acute traumatic sixth nerve palsy or paresis, the recovery rate was high and similar in patients who received BTX within 3 months of injury (73%) and in those who were treated conservatively (71%).

Potential biases to consider in the interpretation of the results include: (1) selection of patients for BTX treatment based on factors that might be associated with the probability of recovery, (2) lack of masking in assessing recovery, and (3) exclusion of patients with incomplete follow-up. None of these seem to be likely explanations for our failure to detect a benefit for the BTX treatment.

Although patients in the BTX group tended to have more severe nerve palsies, there was no indication of confounding caused by this or any other measured variable when assessed in the analysis. However, deferral of BTX treatment by the investigator to determine whether the patient would show signs of spontaneous recovery could bias against finding a treatment effect, in that such patients may have a lower probability of recovery. Although there was a delay from the time of the first examination until the injection of BTX for most patients in the treatment group, there was no indication that this was a source of appreciable bias. Patients treated within 1 week of the initial examination showed no better recovery than patients treated later (78% [7 of 9] versus 69% [9 of 13], respectively, $P = 1.0$). Nevertheless, such a comparison is limited by low statistical power.

If bias is present from lack of masking of outcome examinations, we speculate that it typically favors the active treatment group. We therefore suggest that lack of masking is an unlikely source of bias in our reporting of comparable recovery rates between groups.

There were 15 patients whom we excluded because of incomplete follow-up. If we assumed that all such patients failed to return for follow-up because of the resolution of their symptoms, then the recovery rate would be 76% (95% CI, 55%-91%) in the BTX group and 76% (95% CI, 64%-85%) in the conservatively treated group ($P = 1.0$).

We previously reported a high spontaneous recovery rate of acute traumatic sixth nerve palsy or paresis in a subset of the current cohort.[7] This high spontaneous recovery rate had not been previously described.[1,10-12] As we have discussed,[7] the discrepancy between our study and other studies is most likely due to incomplete follow-up or inclusion of nontraumatic cases in the previous series.

This high spontaneous recovery rate compromised the ability of our study to evaluate the benefit of treatment. If our finding of a spontaneous recovery rate of 70% is a good estimate of the true rate, then we had 80% power to detect only a true recovery rate with BTX of close to 100%.

Although we have not shown a benefit to BTX treatment for acute sixth nerve palsies, there may be clinical settings in which it might be of value. It is plausible that injection of BTX might be indicated in young children to allow binocularity and prevention of amblyopia. It is possible that earlier binocularity and reduction of diplopia would improve the visual function and quality of life of adult patients. It is also possible that some nonrecovered patients might benefit from BTX treatment because it allows for a simpler surgical procedure to take place, such as a horizontal rectus muscle procedure rather than a transposition procedure, as suggested by others.[2,13]

This study confirms our previous conclusions[7] regarding the lack of feasibility for a randomized treatment trial. Although there is a great deal of interest in the use of botulinum toxin in acute traumatic sixth nerve palsy, a prospective randomized study is not feasible because of the large numbers of patients that would be needed to give the study acceptable statistical power.

We thank the following investigators for their participation in this study: William Astle, MD, Calgary, Alberta, Canada; Steven Awner, MD, Buffalo, NY; Robert Baker, MD, Lexington, Ky; John Bishop, MD, Corpus Christi, Tex; Mark Borchert, MD, Los Angeles, Calif; Donna Brown, MD, Richmond, Va; David Coats, MD, Houston, Tex; Oscar Cruz, MD, St Louis, Mo; Kimberlee Curnyn, MD, Elk Grove, Ill; John DeVaro, MD, Savannah, Ga; Savjeev Dewan, MD, Alliance, Ohio; Gary Diamond, MD, Philadelphia, Pa; Sean Donahue, MD, PhD, Nashville, Tenn; Mitchell Drucker, MD, Tampa, Fla; Eric Eggenberger, MD, East Lansing, Mich; Keith Engel, MD, Minneapolis, Minn; Robert Enzenauer, MD, Englewood, Colo; Sharon Freedman, MD, Durham, NC; Aviva Gal, MD, Milwaukee, Wis; Balaji Gupta, MD, Chicago, Ill; Veronica Hauviller, MD, Buenos Aires, Argentina; Umar Kayabasi, MD, East Lansing, Mich; S. Kelman, MD, Baltimore, Md; Natalie Kerr, MD, Memphis, Tenn; Angela King, MD, San Antonio, Tex; Robert Labutta, MD, Washington, DC; Scott Lambert, MD, Atlanta, Ga; Klara Landau, MD, Zurich, Switzerland; Richard Legge, MD, Omaha, Neb; Andrew Levada, MD, Waterbury, Conn; Robert McFadzean, MD, Glasgow, Scotland; Thomas Mehelas, MD, Toledo, Ohio; Joseph Miller, MD, Tuscon, Ariz; David Mittleman, MD, Park Ridge, Ill; Brian Mohney, MD, Johnson City, Tenn; Anthony Murray, MD, Cape Town, South Africa; Nancy Newman, MD, Atlanta, Ga; Paolo Nucci, MD, Milan, Italy; Harry O'Halloran, MD, Lexington, Ky; John O'Neill, MD, Washington, DC; Miguel Paciuc, MD, Mexico City, Mexico; Evelyn Paysse, MD, Houston, Tex; Maria Pesheva, MD, Dallas, Tex; J. W. R. Pott, MD, Groningen, The Netherlands; Michael Repka, MD, Baltimore, Md; Alan Richards, MD, Shreveport, La; Gary Rogers, MD, Columbus, Ohio; Nicholas Sala, DO, Erie, Pa; Timothy Saunders, MD, Charlotte, NC; Martha Schatz, MD, Lackland AFB, Tex; Stuart Seiff, MD, San Francisco, Calif; Luis Serrano, MD, Ponce, Puerto Rico; Kyle Smith, MD, Temple, Tex; Richard Sogg, MD, Campbell, Calif; Naval Sondhi, MD, Indianapolis, Ind; Abraham Spierer, MD, Tal Hashomer, Israel; James Sprague, MD, McLean, Va; David Stager, MD, Dallas, Tex; Julia Stevens, MD, Lexington, Ky; Visvaraja Subrayan, MD, Petaling Jaya, Malaysia; Thomas Teather, MD, Melbourne, Fla; Benjamin Ticho, MD, Oak Lawn, Ill; Floyd Warren, MD, Newark, NJ; R. Grey Weaver, MD, Winston-Salem, NC; Robert Wiggins, MD, Ashville, NC; Jan Winkleman, MD, Ypsilanti, Mich; and Edwin Wortham V, MD, Richmond, Va.

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