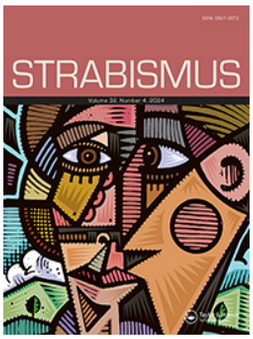

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An evaluation of 30 years' experience in the use of botulinum toxin injections in the management of sixth nerve palsies

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ABSTRACT

Intrroduction: Sixth nerve palsy is the most common type of extraocular muscle palsy. The therapy options in sixth nerve palsies include monitoring with or without conservative treatment, botulinum toxin injections or strabismus surgery. The aim of this retrospective study was to compare botulinum toxin (BT) injections into the medial rectus to conservative treatment in sixth nerve palsies. The rate of patients improved after intervention and treatment outcomes for the two treatment options were be evaluated at a German tertiary referral center.

Methods: A service evaluation was conducted on adult patients with sixth nerve palsy. Patient files were reviewed and data including abduction deficit and size of deviation were collected retrospectively. Patients which presented between January 1987 and April 2022 were considered. Patients were allocated into two treatment groups: BT injected into medial rectus or conservative treatment, which included observation, providing occlusion and Fresnel prisms. Inclusion criteria were attendance of two visits with orthoptic assessment. Exclusion criteria included presence of further oculomotor palsies, strabismus, strabismus surgery and suppression. Non-parametric statistical analysis was conducted using IBM® SPSS Statistics.

Results: A total of 606 adult patients with unilateral or bilateral sixth nerve palsy attended during the named period. A total of 137 adult patients met the inclusion criteria. Of which, 36 had a bilateral palsy, 101 had a unilateral palsy. 45.26% ($n = 62$) were treated with BT injections and 54.75% ($n = 75$) were treated conservatively. The median initial abduction deficit was greater in the BT group, (−4 to −5 after Scott and Kraft) than in the conservative treatment group (−1). The initial angle of deviation at distance was significantly larger in the BT group than in the conservative treatment group ($p = <0.001$). The rate of improvement in the BT group was 24.19% ($n = 15$) and 20% ($n = 15$) in the conservative treatment group. When excluding long-standing palsies rates of improvement in both groups increased to 28.85%. The improvement of the angle of deviation at distance in all patients was greater in the BT group ($p = <.001$). The improvement of abduction in bilateral palsies were greater in the BT group ($p = .016$), but in unilateral palsies, there was no significant difference in abduction improvement in the two treatment groups (OD $p = .3$, OS $p = .406$).

Conclusion: This service evaluation found that BT injection into medial rectus in unilateral and bilateral sixth nerve palsies did not increase the rate of improvement compared to conservative treatment. But BT injections reduced the angle of deviation to a greater extent than conservative treatment. Additionally, BT was able to improve abduction in bilateral palsies to a greater extent than conservative treatment. It is recommended a BT injection is considered in symptomatic bilateral sixth nerve palsies to enable fixation and improved ocular motility. More research is needed to verify reliable clinical guidelines for the use of BT in sixth nerve palsies.

KEYWORDS
Abducens nerve; diplopia; medial rectus muscle; muscle injection; recovery rate

Introduction

Sixth nerve palsies constitute the majority, (30–57%) of all oculomotor palsies.[1,2] All ages can be affected.

The lesion, leading to a sixth nerve palsy, can affect any part of the abducens nerve pathway. The main causes for such lesions are trauma, tumor, microvascular events, aneurysm, inflammatory diseases, viral infections such as Herpes Zoster, or acquired immunodeficiency syndrome. [3–5] 10–34% of causes remain unidentified.[5,6]

Spontaneous recovery commonly occurs in the first six months after onset.[7] In Germany, it is clinical routine to allow a 12 month period for spontaneous recovery before performing surgery.[8] Spontaneous recovery rates vary enormously depending on the etiology, severity, and whether

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the palsy is unilateral or bilateral. Partial recovery occurs in 85.2%.[7] Spontaneous recovery rates vary between 31% and 78.4%.[9,10] In principle, diabetic and traumatic etiologies have a tendency to recover quicker than palsies resulting from a tumor. Even the definition of recovery varies in the literature. In many studies recovery is defined as no diplopia in primary position, angle of deviation at distance ≤10 PD, and improvement of abduction deficit by 10°.[11,12]

Different therapeutic approaches are available such as conservative treatment and an injection with Botulinum Toxin (BT) into the medial rectus (MR) muscle. Conservative treatment is mainly the observation for improvement of the palsy and provision of occlusion and Fresnel prisms. A BT injection into the ipsilateral MR results in a paralyzed muscle. In return the antagonist lateral muscle can act unopposed. This changes the alignment of the eyes and might prevent a potential secondary contracture of the medial rectus.[12,13] In longstanding palsies the contracture of the medial rectus is already present. Yet, an injection is still believed to lead to a sustained effect on improving eye alignment and binocular single vision (BSV).[14] Despite the underlying mechanism is not fully understood. [14–16]

The literature shows conflicting evidence on the effectiveness of BT in sixth nerve palsies. These are shown in Table 1. Some researchers stated an increase in recovery. Others claimed that the proportion of recovered patients does not improve significantly after BT treatment compared to conservative treatment. Recovery rates after BT therapy vary between 64% and 90.3%.[17,18] Comparison of results can be difficult due to varying etiologies, severity and definition of recovery. Therefore, the primary aim of this service evaluation was the comparison of rates of improvement and outcome criteria such as improvement of the abduction deficit and angle of deviation in primary position in a large cohort with two treatment branches. The terminology "improvement after intervention" is used in this article to define a positive change in outcome. This research project used a recovery definition which differentiates from clinical perspective but was used previously in many studies. Recovery is defined as no diplopia in primary position, angle of deviation at distance ≤10 PD, and improvement of abduction deficit by 10°.[11,12] Furthermore, factors leading to treatment decision were identified. Findings aim to aid in a more robust decision-making process.

Methodology

A retrospective service evaluation of treatment outcomes and rates of improvement for sixth nerve palsies were conducted at the University Eye Hospital Bonn, Germany. Adult patients from the age of 18 years with unilateral and bilateral sixth

Table 1. Recovery rates in the literature depending on aetiology presented in chronological order.

	Sample size	Aetiology	Definition of recovery	Treatment	Recovery rate
Rush and Younge (1981)	419	various	not given	conservative	49.6%
Metz and Mazow (1988)	52	various, mainly traumatic	not given	conservative	31%
Murray (1991)	8	traumatic (*n*=7), cerebro-vascular disease (*n*=1)	"full function"	BT	87%
Lee *et al.* (1994)	47	various	complete symptomatic recovery	conservative BT	80% 86%
King *et al.* (1995)	213	various (exclusion of secondary referrals and traumatic palsies)	not given	conservative	78.4%
Mutyala *et al.* (1996)	55	traumatic	absence of restriction of abduction and absence of diplopia	conservative	27%
Holmes and Droste and Beck (1998)	33	traumatic	no diplopia in primary position, distance angle ≤10 PD	conservative	73%
Quah *et al.* (1999)	19	nasopharyngeal meningeoma	esotropia ≤10PD	BT	64%
Holmes *et al.* (2000)	82	traumatic	no diplopia in primary position, esotropia ≤10 PD	conservative BT	71% 73%
Hung and Kao and Sun (2005)	33	traumatic	absence of diplopia in primary position, esotropia <10 PD at 6 months after injury	conservative BT	26.3% .64.3%
Ganesh and Anilkumar and Narendran (2019)	31	diabetic	full resolution 2 months past injection	BT	90.3%
Oh (2022)	156	various	absence of a horizontal deviation or ocular motility restrictions	conservative	82%

nerve palsies of various severity and etiologies who presented between January 1987 and April 2022 were reviewed.

Inclusion criteria comprised of a minimum of two visits. Both visits included a measurement of the angle of deviation at distance and near and measurement of the abduction deficit. Exclusion criteria were additional oculomotor palsies, previous strabismus surgery and previous history of strabismus. The inability to perceive diplopia due to suppression in childhood strabismus, marked amblyopia or reduced visual acuity (VA) was an exclusion criterion.

Participants were divided into two groups based on the therapy they received. Conservative treatment included monitoring of the course of the sixth nerve palsy with or without the use of Fresnel prisms or occlusion. Occlusion and prisms were prescribed in both treatment groups if helpful. BT injections into the MR were performed under EMG-control using onabotulinumtoxinA Botox® or incobotulinumtoxinA Xeomin®. An injection of 0.1 ml equals 2.5 International Units (IU).

Data concerning etiology, the angle of deviation, ocular motility, BSV and VA, were reviewed and data on routine orthoptic examinations were collected from patient files. All available data were transferred into Excel form (Appendix A).

Ethical approval, reference number 049724, was sought and obtained by the Health Sciences School of the University of Sheffield on 10 October 2022. At the study site, the Ethics Committee of the University Eye Hospital Bonn does not require ethical approval for retrospective analysis of anonymized data sets. Participants were not identifiable, therefore no informed consent was required. Exclusively data from routine examinations were used.

Statistical analysis

The Shapiro–Wilk Tests of Normality was conducted to assess for normality. Non-normal distribution was found and therefore non-parametric statistical tests were conducted. The Mann-Whitney U test was calculated. These analyses were performed using IBM® SPSS Statistics.

The restriction of motility had to be converted to enable statistical analysis. A specific motility grading was implemented, Table 2 provides a deeper understanding of this scaling system and a comparison to the Scott and Kraft grading. In free space restrictions are plotted using minus signs at different levels to describe the severity of a motility deficit. Abduction is judged by the assumption of a physiological abduction of 50°. The scale ranges from a negative sign in two brackets to three negative signs.

Results

In total, 606 patient files were reviewed in a retrospective manner. A total of 469 patients were excluded due to various reasons, in 47% due to missing data. A total of 137 patients were included in this service evaluation. Their baseline characteristics in the two treatment groups concerning gender, age, visual acuity and median follow-up period are rather homogenous but heterogenous concerning the affected eye(s). This is displayed in Table 3.

Etiologies were classified into six groups: trauma, microvascular, neoplasm, idiopathic, aneurysm and all other, etiologies were summarized as others. These categories were based on categories used in a review by Azarmina and Azarmina.[19] Idiopathic summarizes all cases in

Table 2. Conversion of motility deficits measured by different methods into motility grading.

Scaling in German motility scheme	Abduction ability	Used grading in this investigation	Uniocular/monocular excursion in mm	Grading described by Scott and Kraft
- - -	No abduction/eye remains in convergent position	7		− 5
- - (-)	Slight movement in adduction possible	6		−5
- -	Movement till midline/not beyond midline, max. 5° past ML	5	0-1.0	−4
- (-)	5-15° abduction	4	1.1-3.5	−3
-	20°-25° abduction	3	3.6-5.3	−2
(-)	30-35° abduction	2	5.4-7.1	−1
((-))	40-45° abduction	1	7.2-8.9	−1
No deficit	50° abduction	0	9-10	0

Table 3. Baseline characteristics.

	BT Group		Conservative treatment group	
patients	*n* = 62		*n* = 75	
gender	45.26% male	54.74% female	52.0% male	48.0% female
age (years)	53.5 (range 20–81)		57.0 years (range 20–85)	
affected eye				
OD	41.94% (*n* = 26)		25.33% (*n* = 19)	
OS	40.32% (*n* = 25)		41.33% (*n* = 31)	
bilateral	17.74% (*n* = 11)		33.33% (*n* = 25)	
visual acuity (decimal)				
OD	0.8 (range 0.1–1.5)		1.0 (range 0.1–1.5)	
OS	0.8 (range 0.1–1.5)		1.0 (range 0.1–1.5)	
follow-up period	5.5 (range 1–108) months		5.5 (range 0.5–59) months	
longstanding palsies	16.12% (*n* = 10)		30.67% (*n* = 23)	

OD: oculus dexter/right eye, OS: oculus sinister/left eye, averages are calculated as median and shown with full range, longstanding defined as a duration >6 months.

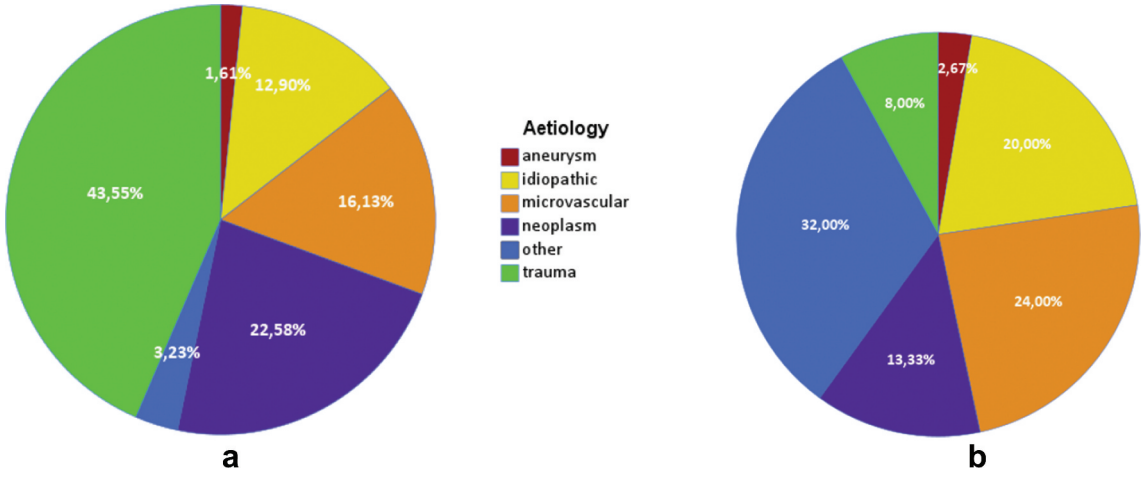

Figure 1. (a). Aetiology of sixth nerve palsy in the botulinum toxin group. (b). Aetiology of sixth nerve palsy in the conservative treatment group.

which no cause could be found despite a detailed investigation. Distribution of etiologies differed distinctively in the two groups and is shown in Figure 1a,b.

A Mann–Whitney U test was conducted to determine whether there was a difference in the angle of deviation at distance between the groups before therapy started. The results indicated a significant difference between groups [U = 3657.00, p = <0.001]. It indicated a larger initial angle of deviation at distance in the BT group. This analysis was repeated for the angle of deviation at near. It also indicated a larger median angle of deviation at near in the BT group [U = 3536.50, p = <0.001]. This data is displayed in Table 4.

Table 4. Initial characteristics concerning angle of deviation, motility restriction.

	BT group	Conservative treatment group
angle of deviation at distance	45.00 PD (±28.51, range 10–200 PD)	25.00 PD (±17.16, range 0–80 PD)
motility restriction*		
OD	6	3
	(± 1.468, range 2–7)	(± 1.485, range 1–6)
OS	5	3
	(± 1.491, range 2–7)	(± 1.755, range 1–7)
visual acuity (decimal)		
OD	0.8 (range 0.1–1.5)	1.0 (range 0.1–1.5)
OS	0.8 (range 0.1–1.5)	1.0 (range 0.1–1.5)
follow-up period	5.5 (range 1–108) months	5.5 (range 0.5–59) months

convergent angle of deviation, *motility restriction uses scaling specifically implemented for this research project, compare Table 2 for deeper understanding.

The initial grading of motility was given in every patient. The grading is scaled as follows: a higher number, maximum seven reflects a marked motility deficit, whereas "zero" reflects a normal ocular motility.

Table 4 also shows a more severe initial median motility deficit of the right eye in the BT group, [U = 435.50, p = <0.001]. Similarly, the initial median motility deficit in the left eye was significantly more severe in the BT group, [U = 612.00 p = <0.001. This also accounts for bilateral palsies, [U = 232.00, p = <0.001] with the more sever abduction deficit in the BT group.

Due to missing data concerning AHP and BSV in most patients and the resulting low statistical significance, no calculation was conducted.

All BT patients received a minimum of one BT injection into the MR of the affected eye(s). Dose ranging from 0.05 to 0.2 ml, where 0.1 ml equals 2.5 International Units (IU). Median dosage was 0.1 ml (±0.44, range 0.05–0.2 ml). Further injections were performed if needed. Surgeon 1 provided care for 48 patients (77%) and used a median dosage of 0.1 ml. Surgeon 2 performed 14 injections and used a median of 0.2 ml.

Thirty-nine patients (62.9%) observed adverse events (AE). AE rates of surgeon 1 and surgeon 2 were comparable, respectively 62.5% and 64.3%. Most common was a depression deficit accompanied by vertical diplopia (46.8%; n = 29). 16.1% (n = 10) of the patients developed an adduction deficit with a divergent deviation in certain positions of gaze. This was portrayed as an inevitable consequence of a BT injection into the MR. Eight patients (= 12.9%) had a divergent angle at distance in primary position viewed as an overcorrection that represents the adduction deficit and is defined as an AE. 8.1% (n = 5) developed a ptosis. Another 6.5% of patients (n = 4) developed other AEs.

Statistically the initial differences were accounted for by calculating change scores. A Mann-Whitney U test was conducted for the change score of the angle of deviation and indicates a significant difference [U = 2965.50, p=<.001] in the treatment groups with a higher deviation change score post therapy in the BT group. This implied a significantly better ocular alignment in the BT group.

Furthermore, change scores were calculated for the grading of the motility to assess the outcome criteria motility. When calculating the change score of motility with a Mann-Whitney U test for the right eye, it indicated that there is no significant difference in the groups, [U = 279.50, p = .3]. Similarly, it also indicated that there is no significant difference between the groups for the left eye, [U = 420.0, p = .406]. On the contrary, the Mann–Whitney U test for bilateral change score of motility indicated a significant difference between the two groups, [U = 183.0, p = .016] with better improvement of ocular motility in the BT group.

The calculation of rates of improvement might add to clarification with these ambiguous findings. Due to the lack of data concerning BSV, the analysis was conducted excluding this criterion. In the BT group, 15 (24.19%) patients achieved the outcome criteria. In the conservative treatment group, 15 (20%) patients, achieved the outcome criteria. When recalculating rates of improvement without longstanding palsies at initial visit, rates changed. Both groups achieved a rate of improvement of 28.85% (n = 15). These findings indicated a bias toward non-improvement in longstanding palsies and overall, the results suggest that BT injections in this service evaluation do not alter rates of improevement in sixth nerve palsies with recent onset. Information about the duration of the palsy is included in Table 3.

An initial objective was to identify factors that influence the decision-making process. In this cohort, patients with microvascular etiology and in the category "others" were less likely to be treated with BT. Furthermore, patients with larger initial deviations and more severe abduction deficit were more likely to be treated with BT. Typically conservative treatment was chosen for cases with low level of symptoms. Strabismus surgery was commonly chosen in longstanding palsies with angles of deviation >40 PD but the duration of a palsy was not given in every patient. Therefore, a statistical evaluation was not feasible.

Discussion

The aim of this service evaluation was to evaluate rates of improvement depending on the chosen therapy approach. It is important to note that the

comparison of groups is compounded by deviating initial characteristics. An unexpected finding in this service evaluation were low rates of improvement in the BT group, as well as in the conservative group, 24.19% and 20%, respectively. Adjusted for chronicity, rates increased to 28.85% in both groups. This confirmed the findings of Lee et al.[20] who also did not find significantly different recovery rates in the two treatment branches. However, they found higher levels of recovery rates, 86% in the BT group and 80% in the conservative treatment group. A possible explanation are smaller median angles of deviation which are believed to lead to a better outcome (17.8 PD in the conservative treatment group and 28.6 PD in the BT group).[7]

Ganesh et al.[18] performed BT injections in diabetic sixth nerve palsies with a median convergent angle of deviation of 30 PD and a median abduction deficit of −3. The initial ocular motility grade in the BT group and initial angle of deviation of this service evaluation were more severe which makes comparability of results difficult and presents an advantage for the recovery rates in the diabetic cohort.

Another study by Holmes et al.[11] compared the two treatment approaches exclusively in traumatic sixth nerve palsies. The initial median motility grade in both groups was 5. This is comparable to this study. They reported a recovery rate of 73% in the BT group and 71% in the conservative treatment group. The focus on traumatic palsies resulting in exclusion of severe pathologies might be an explanation for the variances.

The discrepancy with previous studies concerning rates of improvement in both treatment branches could be attributed to a bias toward non-recovery in tertiary referral centers such as the University Eye Hospital Bonn. Furthermore, due to the interdisciplinary approach combining all state-of-the-art medical specialists at a University Hospital complex patient cases with severe pathologies are more likely. It seems feasible that this results in a bias toward non-recovery. Some researchers excluded certain etiologies and found higher spontaneous recovery rates,[10,21] 78.4% and 73%, respectively.

Another bias toward non-recovery might be a high number of longstanding palsies at initial visit at our clinic. Some studies excluded patients who presented later than 4 or 6 weeks of onset to reduce this bias.[6,7]

Adverse Events after BT muscle injections due to diffusion in neighboring structures in the narrow orbital circumstances are not unlikely. Transient ptosis and vertical deviation are the most likely AEs but the prevalence of complications varies greatly.[22] Transient ptosis was reported to occur in 8% to 62.5%.[20,23] In this cohort, a transient ptosis occurred in 8.1%. The most common AE in this cohort was vertical diplopia or depression deficit (46.8%). Other researchers state that this complication occurred in 7.3–16%.[20,24] An adduction deficit resulting in exotropia in primary position was rarely reported in the literature but occurred in 12.9% of this cohort. Only one other research group, Ganesh et al.[18] reported this AE in 3.2% of their patients. It is important to note that the timing of the follow-up appointment is crucial to detect overcorrections, and might distort recovery rates if residual BT effect is present.

Another crucial functional outcome criterion is BSV. Few studies in the literature provided detailed information on the quality of BSV post-injection. One exception is a study by Repka et al.[14] 32.0% of patients perceived a restored BSV in primary position. Lee et al.[20] reported full recovery of BSV in 80% of controls and 95.5% of BT patients. However, in this retrospective study limited data on BSV at discharge visit were available.

In the literature, no dose response curve is available for extraocular muscle BT injections. A dosage between 2.5 and 5 IU (Botox® or Xeomin®) was mostly used, rarely 10 IU. A higher dosage is supported by some researchers in the literature of 5–10 IU,[11,25] whereas others used a similar dosage as was used in this service evaluation.[17,20]

Research groups that used a similar injection dose as this study showed a tendency for smaller median angles of deviation. This was exemplified in the work of Lee et al.[20] They used 2.5 IU at a mean initial deviation of 28.6 PD. Patients with a larger angle of deviation >40 PD might profit from a higher dose of 5–10 IU.

Limitations of this service evaluation

The generalizability of the results is limited by the population of patients featured in a tertiary referral

center. The reliability of the data is impacted by the retrospective nature of this service evaluation. Furthermore, unstandardized follow-up periods might shift rates of improvement. A major advantage is the large sample size which resulted in a higher statistical power and provides a good indication of likely outcomes.

Further research

More research is needed to provide less descriptive but good quality research. This is required to verify reliable clinical guidelines for the use of BT in unilateral and bilateral sixth nerve palsies.[12] A prospective, controlled, and randomized multicenter study with heterogenous etiologies and standardized follow-up periods is needed.

Conclusion

While the role of strabismus surgery in sixth nerve palsies is established in chronic cases, the role of BT injections into the MR during the acute phase is still discussed due to conflicting evidence.

A comparison between a conservative treatment approach and BT injections into the MR in sixth nerve palsies, focussing on rates of improvement and improvement of motility, as well as angle of deviation was performed.

The initial characteristics in the two treatment branches were significantly different with larger initial deviation angles at distance and more marked motility restrictions in the BT group.

Significantly lower rates of improvement were found in both groups compared to the literature. No significant differences were found between groups. The rate of improvement in the BT group was 24.19% ($n = 15$) and 20% ($n = 15$) in the conservative treatment group. When excluding longstanding palsies rates in both groups increased to 28.85%. But the improvement of the angle of deviation was superior in the BT group. The improvement of motility restrictions in bilateral palsy was favorable in the BT group. In unilateral palsies, no significant differences occurred. Conclusionary, according to the available data a prophylactic effect of BT cannot be demonstrated. Although, the improved reduction of the angle of deviation in the BT group is of clinical importance and appreciated from a patient's perspective.

On the basis of this analysis, no generalized recommendation of BT injections in recent onset sixth nerve palsies is justifiable. Practitioners should consider a BT injection in paralyses, especially bilateral, to ensure easier fixation. Patients with a microvascular or inflammatory etiology, as well as patients with longstanding palsies and low level of symptoms are less eligible for BT injections. Further research is needed to verify reliable clinical guidelines for the use of BT in sixth nerve palsies.[12]

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Data availability statement

Data available on request from the authors.

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Appendix

Appendix A

Data Collection.

Examples of data collection in Excel Spreadsheet.

ID	age	gender	aetiology	eye	BT	B or X	Prism	occlusion	date initial visit	initial abduction deficit (-)
example 1	65	m	trauma	OD	Y	B	Y	N	16.05.1994	- -
example 2	75	f	microvascular	OS	N	-	N	Y	28.01.2002	- - -
example 3	77	f	tumor	OD + OS	N	-	Y	N	24.03.2020	-

initial PCT D	initial PCT N	initial excursion (mm)	initial AHP	VA OD	VA OS	initial BSV field (°)	AE BT	date int visit
ET 30	ET 5	0	right turn 20°	1.0	1.0	diplopia till 20° left gaze	vertical deviation	16.08.1994
ET 80	ET 30	rests in adduction	N	1.0	0.9	NK	N	N
ET 40	ET 10	OD/OS 5	N	0.9	0.7	NK	N	N

int abduction	int PCT D	int PCT N	int excursion (mm)	int AHP	date dis	dis abduction	dis PCT D
- (-)	ET 15 RHT 5	RHT 5	3	right turn 10°, chin depression	20.12.1994	-	ET 10
N	N	N	N	N	20.02.2003	free	0
N	N	N	N	N	25.06.2021	OD/ OS (-)	ET 10

dis PCT N	dis AHP	dis excursion (mm)	dis BSV field (°)	duration initial - dis. (months)
0	right turn 5	5	diplopia till 5° right gaze	7
0	N	9	NK	13
0	N	OD 8 OS 8	NK	14

Note: Separation of the excel file and presentation in landscape due to large file size.

Abbreviations: m: male, f: female, Y: yes, N: no, B: BOTOX®, X: Xeomin®, ET: esotropia, RHT: right hypertropia, PCT: prism cover test, D: distance, N: near, AHP: abnormal head posture, VA: visual acuity, BSV: binocular single vision, NK: not known, AE: adverse event, int: intermittent visit, dis: discharge visit