BOTULINUM NEUROTOXIN IN THE MANAGEMENT OF ESSENTIAL INFANTILE ESOTROPIA

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A thesis submitted to the Faculty of Health Sciences, University of the Witwatersrand, in fulfillment of the requirements for the degree of Doctor of Philosophy.

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Declaration

I, Ismail Mayet, declare that this thesis is my own work. It is being submitted for the degree of Doctor of Philosophy at the University of the Witwatersrand, Johannesburg It has not been submitted before for any degree or examination at any other University.

Signed on the 20th day of January 2022 in Johannesburg

Dedication

To my parents who afforded me an education against many odds

Goolam Husain 1923-2011

&

Amina Mayet 1928-2020

Publications arising from the Research

1. Mayet I, Ally N, Alli H, Tikly M, Williams S. Botulinum Neurotoxin injections in Essential Infantile Esotropia – a comparative study with surgery in large angle deviations. 2021 Jan. 35:3071-3076

2. Mayet I, McGee S, Ally N, Alli H, Tikly M, Williams S. Cost Comparison between Botulinum neurotoxin and surgery in the treatment of infantile esotropia in a tertiary public hospital. BMJ(Open) Ophthalmology 2021July

3. Mayet I, Ally N, Alli H, Tikly M, Williams S. Response to botulinum neurotoxin injections in large angle infantile esotropia – a post hoc analysis. JAAPOS 2022 April e 1-5.

Presentations arising from the research

1. Use of Botulinum neurotoxin in the management of infantile esotropia. Presented at the Wits ophthalmology Research Day Symposium, November 2019

2. Can Botulinum Neurotoxin be considered as first line therapy in Infantile esotropia in resource constrained regions? Presented at the first African Ophthalmic conference, October 2021

3. Botulinum Neurotoxin in Infantile Esotropia.
   Presented at Ophthalmic Society of South Africa Annual Congress – Sun City March 2022

Abstract

Introduction: To address the unmet need of delay in surgical correction of infantile esotropia (IE), a randomized clinical trial was undertaken to assess the efficacy and cost benefit of botulinum neurotoxin injection therapy (BNT) compared to surgery, which is the standard of care in IE, in children attending a large tertiary ophthalmology service in South Africa.

Methods: In the first part, children <6years diagnosed with IE were randomized to receive either BNT injections (maximum of 3) or surgery with medial rectus muscle recessions. Clinical success was defined as alignment within 10 prism dioptres (PD) of orthotropia. A bottom-up cost comparison for the two procedures was done. In the second part, an open label study, the efficacy, and predictors of response to BNT injections in children with large and very large angle IE were investigated. The outcome of subsequent surgery in failed cases was analyzed.

Results: Of the101 children with a mean (SD) age of 26.9 (14.5) months and a baseline angle of esotropia (AoE) of 62 (12.8) PD, 54 and 47 were randomized to BNT and surgery arms respectively. At 6 months of follow up, a successful outcome was seen in 20 (37%) and 33 (70.25%) respectively. Surgery was significantly more successful than BNT (OR=4.01,95%CI 1.74-9.22). Receiver operator characteristic analysis showed children under 21 months and AoE of <50PD at baseline were most likely to benefit from BNT therapy. Cost analysis of children achieving a successful outcome was significantly lower with BNT. Mean cost for eventual success was comparable for the 2 arms (ZAR9158.08 and ZAR9124.27 for the BNT and Surgery arms respectively (p=0.26)).

The open labelled study of 117 children showed a mean (SD) reduction of 34.5PD (18) or 55.2% from baseline AoE after a mean of 2.2 injections. Age at intervention and size of esotropia were significant predictors. In those children who did not achieve a successful outcome with BNT, subsequent surgery may require less muscle recessions than what would have otherwise been necessary to correct the original AoE. Ninety percent had a favourable outcome with one surgical procedure in the study.

Conclusion: Children <21 months old with a baseline AoE <50PD are most likely to benefit from BNT. Benefits of treating this subgroup of children with IE are that it is less costly compared to surgery and has the potential to reduce the waiting list for surgery in a resource constrained setting. Long term studies are needed to assess the impact of BNT on higher functions like stereopsis.

Preface

What started as a conscious attempt at reducing the long waiting lists for strabismus surgery and the quest for alternative less time-consuming procedures became the motivation to introduce botulinum neurotoxin therapy (BNT) in the management of infantile esotropia. Historically, corrective procedures have often been viewed as cosmetic interventions and thus relegated down the priority surgical lists. At St John Eye Hospital, the busiest eye hospital in the country, the waiting period for surgery in children with strabismus is greater than a year. Despite the ever-increasing number of new cases year on year, the number of cases (approximately 8 cases per month) undergoing surgery remained the same in 2003 and 2004 compared to 2009 and 2010.

Given that delay in surgery related to the age of the child impacts negatively on outcome, a pilot study with BNT was undertaken in 2013 as an alternative method of correcting IE. Some children did benefit from BNT but there was no formal comparison of BNT to surgery. Hence a prospective study, which forms the basis of this thesis, was undertaken to understand better the role and benefits of BNT in a resource constrained environment serving mainly indigent children. The study, over a 5-year period, was made possible with the support of a generous donor. Given the results of the study, I believe BNT provides a viable option to surgery in a subgroup of children living in developing countries. The work also provides new insights on relative costs of BNT and surgery which is important to governments or funding agencies. The thesis is in a submissive format, with chapter 1, a background and literature review with objectives of the thesis, chapter 2, 3, and 4 are based on the articles published and finally chapter 5, the conclusion.

In conducting this study, I wish to extend my gratitude to:

1. The Anglo-American Fund for the grant which allowed us to perform surgery on weekends to catch up with the backlog of cases.

2. The Department of Anaesthetics for making their medical staff available on weekends.

3. The management of St John – Chris Hani Baragwanath Academic Hospital for allowing me to use the theatre facilities.

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5. Mrs. Adelaide Molopane who volunteered as a study coordinator.

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Abbreviations

AoE	angle of esotropia
ABC	activity-based costing
Ach	acetyl choline
BNT	botulinum neurotoxin
BMR	bilateral medial rectus muscles
CEA	cost effective analysis
CUA	cost utility analysis
CR	complete response
DTN	dorsal terminal nucleus
EE	economic evaluation
ET	esotropia
ETROP	early treatment of retinopathy of prematurity
IE	essential infantile esotropia/congenital esotropia
GDP	gross domestic product
NR	no response
OKN	optokinetic nystagmus
NOT	nucleus of the optic tract
PD	prism diopter
PR	partial response
Rec	recession
Res	resection

UMR	unilateral medial rectus muscle
XT	exotropia
ZAR	South African Rands

CHAPTER 1

BACKGROUND AND LITERATURE REVIEW OF INFANTILE ESOTROPIA

1.1. Introduction

"A wise man is one that does not say everything he thinks but rather thinks about everything he says" Rumi

Strabismus management accounts for a sizeable load of the paediatric ophthalmology clinic at our institution. Majority of these are essential infantile esotropia (IE) requiring surgery. Surgery is relatively time consuming and, in a region where theatre time is limited, the number of children awaiting surgery is ever increasing. The delay in surgery is unacceptable and the need to explore chemo-denervation using botulinum neurotoxin (BNT) injections, to allow more children earlier intervention, formed the basis of this research thesis. Studies using BNT in African children, with predominantly large angle deviations have not been undertaken. Several aspects of BNT use needed investigation before adopting BNT as a first line therapy over of surgery. These include the age of intervention, the severity of the esotropia, the expected change in the angle, the response surgery after BNT injection and finally the economic cost in managing these children.

1.2. Problem Statement.

There is an unacceptable waiting lists for strabismus surgery at the St John Eye Hospital. Hence the need for alternative non-surgical shorter procedures such as BNT injection.

1.3. Hypothesis

Botulinum neurotoxin is an acceptable alternative to surgery in resource limited settings.

1.4. Study Objectives

a. To compare outcomes in patients with IE receiving BNT injections to those undergoing standard surgical care.

b. To establish if age of intervention or angle of deviation impacts on outcome and to identify children most likely to benefit from BNT injections

c. To establish the degree of change in the angle of deviation from baseline to post injection and in failed cases, whether subsequent surgery performed for the new angle was stable.

d. To compare the economic costs between surgery and BNT in a government-based or public hospital.

The study was registered with the Pan African Clinical Trial Registry (PACTR201508001241218).

1.5. Literature review

1.5.1 Preamble

For normal vision, the image of an object of interest comes to a focus on the same foveal point of the retina in each eye, referred to as corresponding points. This is a state of orthophoria or alignment (von Noorden, 1988a). In animals with the two eyes placed more centrally such as animals of prey and primates this feature allows simultaneous perception of images (binocularity), fusion of images and depth perception. In strabismus the visual axes of the two eyes are different and images fall on non-corresponding points. This state of misalignment impacts on the normal development in children and has a functional impact in children and adults with strabismus (von Noorden 1988a). Strabismus, squint and misalignment are used synonymously.

1.5.2. Prevalence of Strabismus and Esotropia

Global prevalence of strabismus has been reported to be 1.93%, 1.23% for exodeviations and 0.77% for esodeviations. (Hashemi et al., 2019). In Asia exotropia was seen in 61-72% of strabismus patients (Chia et al., 2007)(Yu et al., 2002).

In industrialized countries accommodative esotropia, requiring spectacle correction, is the most common type of esotropia in children while IE accounts for 8.4 % of cases (Mohney, 2007). In contrast, IE is reported to be the most common type of strabismus in Africa, accounting for 74% of esotropia of children in a South African population (Tinley and Grötte, 2012) and over 80% in a study from the Cameroon (Dohvoma et al., 2020).

1.5.3. Classification

Strabismus can be horizontal, vertical, or torsional. Horizontal deviations are further either convergent strabismus (esodeviation) or divergent strabismus (exodeviation). If there is a constant or manifest squint then the suffix “tropia” is used and if evident only after breaking down fusion, the suffix “phoria “is used. Generic classification is shown in figure 1.1.

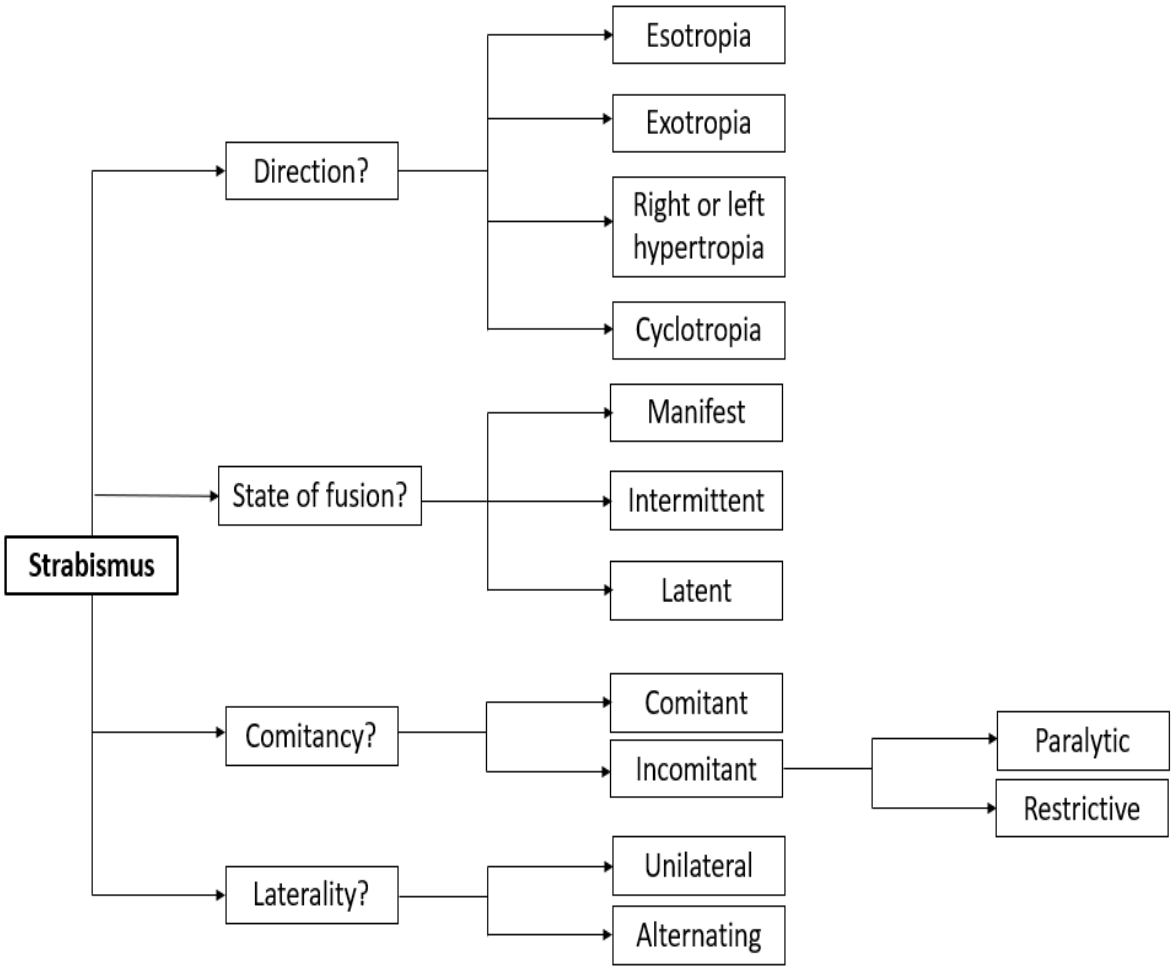

Fig. 1.1: Generic Classification of Strabismus adapted from von Noorden (von Noorden 1988b)

1.6. Comitant esotropia

Comitant deviation is when the angle of the deviation is the same regardless of which eye is fixating or in the direction of gaze tested. Incomitancy is due either to paralytic or restrictive causes. Comitant esotropia further are sub-divided into:

Refractive /accommodative esotropia – requiring hyperopic glasses or just for near vision (the high accommodative convergence/accommodative ratio).

Infantile esotropia – which has an early age of onset (before 6months of age). Children cross fixate, using the convergent eye to look at objects in the opposite field of gaze.

Late onset esotropia – which has an onset after 3 years of age and not due to refractive cause and thought to be decompensated infantile esotropia.

Esotropia associated with neuro-behavioral disorders – e.g., Downs syndrome.

Sensory esotropia – esotropia resulting from poor vision, usually in one eye.

Nystagmus blockage syndrome – in children with infantile nystagmus would favour convergence to minimize the nystagmus

Example of comitant esotropia are shown in figure 1.2.

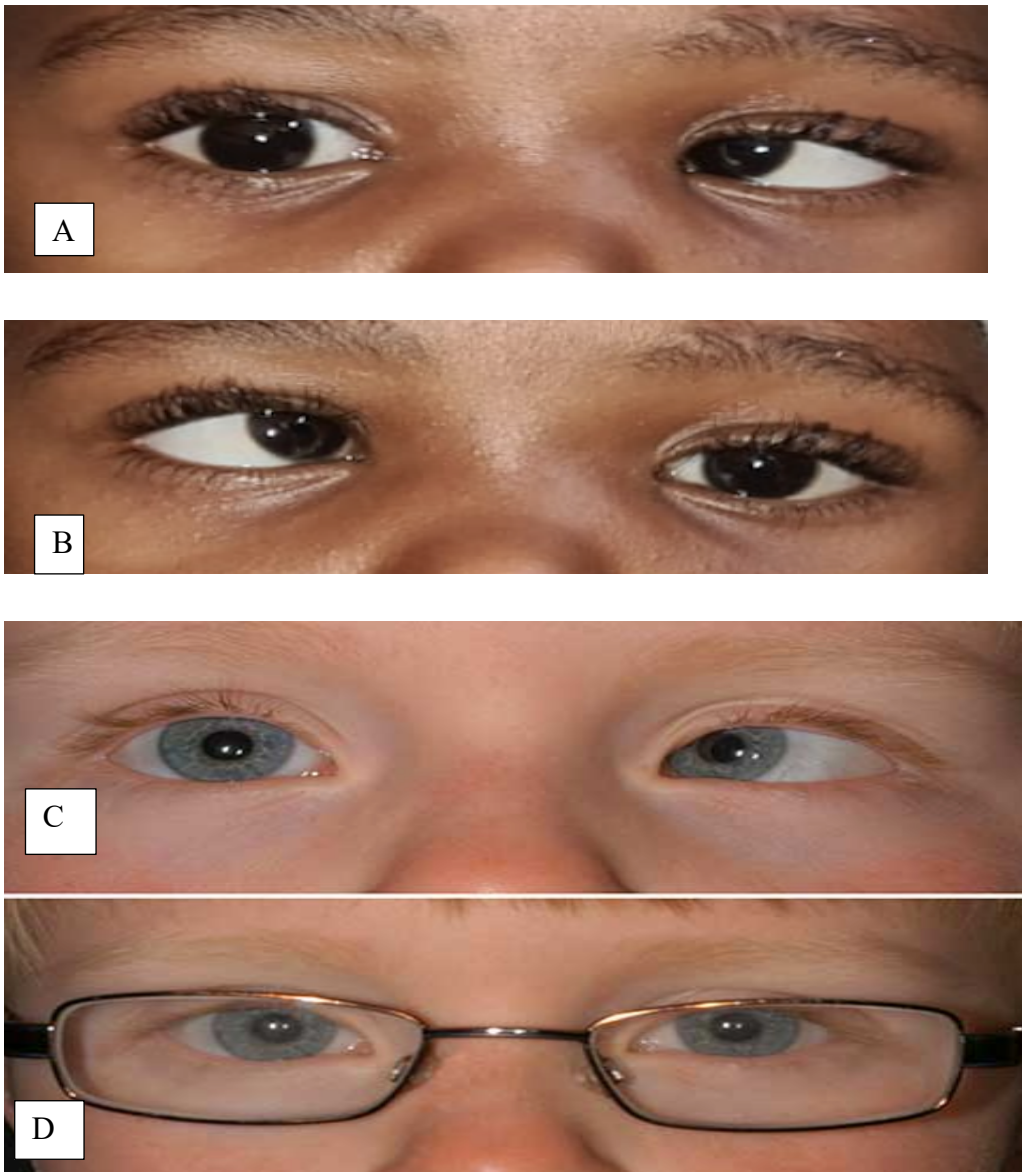

Figure 1.2: infantile esotropia with the light reflex displaced towards temporal iris in eye that is esotropic. A. with left eye fixating. B with left eye fixating, with associated hypertropia secondary to right inferior oblique overaction. *(see text below)*

C shows accommodative esotropia and D complete alignment with hyperopic spectacle correction.

(C &D with permission IOWA Ophthalmology tutorials)

1.6.1 Infantile esotropia

Infantile esotropia, also referred to as congenital esotropia, has an early onset, usually by three months of age and is characterized by alternating large angle of deviation of one eye with cross fixation and may have associated features unique to IE such as:

Fusional maldevelopment nystagmus (FMN) also called latent or latent manifest nystagmus is seen in children with IE due the interruption of binocularity. It is the only type of nystagmus that alternates the fast phase towards the fixating eye(von Noorden, 1988b).

Asymmetrical optokinetic (OKN) response which is a sensitive way of differentiating infantile esotropia from other types of comitant esotropia. Testing one eye's response to an OKN drum, movement from temporal to nasal visual field elicits a smooth pattern while movements from nasal to temporal elicits a sluggish response (Wright, 1996).

Dissociative vertical deviation (DVD) which is an upward drift of the non-fixating eye thought to overcome FMN (Guyton et al., 1998) or may be part of subcortical primitive reflex (Ten Tusscher, 2017).

Pattern deviations, either A or V patterns (less commonly lambda, X or Y) which causes the degree of esotropia to differ in up gaze and downgaze and thought to be either due to superior or inferior oblique muscle over or under action or differing vectors of pull of the horizontal muscles in up and down gaze (Helveston, 1993).

Complications of Infantile esotropia

Amblyopia. During misalignment one eye is always straight while the other deviates. In a developed brain this would result in diplopia. However, in a pliable brain of a child the image of the deviated eye is suppressed. Continuous suppression leads to involutional changes in the primary visual cortex resulting in poor vision called amblyopia which is reversible if treated early (von Noorden, 1988b)(Parks, 1969). Amblyopia is however uncommon in IE patients as these children generally alternate fixation between the two eyes and cross fixate. (von Noorden,1988).

Failure to develop binocular fusion and stereopsis. The visual system is underdeveloped in neonates and is monocular. Binocular cortical neurons in the striate or visual cortex develop abruptly at around 3-5months of age in normal and infants with strabismus. These binocular neurons reach maturation by 6months of age. Prolonged misalignment beyond a critical period would result in involution of these binocular neurons and loss of fusion and stereopsis (Birch et al., 1998).

Assessment of esotropia

In the assessment of children with suspected misalignment it is firstly important to confirm the presence of a squint and then to quantify the angle of esotropia (AoE). Confirming the presence of a squint is achieved by the light reflex test, cover/uncover test in which the eye under cover would deviate, and the alternate cover test. (von Noorden, 1988b)

Esotropia is measured by estimating the relative position of a light reflex from the center of the pupil (Hirschberg test)– a 1mm decentration of the light reflex corresponds to a 15PD deviation, or by using prisms to either align the light reflex (Krimsky test) or measure the misalignment in prism diopters (PD) with cover tests, observing refixation shift on removing the cover over the deviated eye and neutralizing the shift with prisms.

Esotropia can be seen in infants during binocular development which may be intermittent and resolves by 3 months of age. If the esotropia persists beyond 4 months spontaneous resolution is unlikely (Horwood, 2003).

1.6.2. Aetiology of Infantile Esotropia

Why IE develops in otherwise normal infants remains unclear. Two terms need to be defined which are central to the discussion and the development of visual maturation in infants:

Sensory fusion occurs when a visual object falls on corresponding retinal points, either foveal or peripheral in each eye, allowing the appreciation of binocular single vision, fusion and stereopsis. Final processing occurs in the striate or visual cortex.

Motor fusion arises from retinal disparity (images falling on non-corresponding points) that are integrated by vergence movements (movement of the two eyes) to fuse the images. The mechanisms are initiated in the motor centre in the parieto-occipital and temporal cortex and relayed to the brain stem (von Noorden, 1988a). This ocular motor system includes optokinetic nystagmus (OKN) that tracks motion across the visual field, smooth pursuit that maintains a moving target on the fovea and vergence mechanism that are disjunctive, i.e., moving the eyes in opposite directions (convergence or divergence) to maintain bifoveation.

In neonates the neuronal structures are immature. Primitive subcortical reflexes are primarily operating. These reflexes are initiated in the pretectal midbrain by the nucleus of the optic tract (NOT) and the dorsal terminal nucleus (DTN) of the accessary optic system. In animals, these subcortical nuclei assist the vestibular system to maintain steady fixation. In neonates these systems lead to a preference to track stimuli moving temporal to nasal (ear to nose) and are responsible for features associated with IE, as discussed above (Wong et al., 2003).

Fig 1.3 illustrates the visual pathway showing decussated nasal retinal fibers and non-decussated temporal retinal fibers (optic tract), relaying to the lateral geniculate body (LGB) and via optic radiation to the striate cortex, layer 4C. Additional relay from the LGB occurs to the pretectal nuclei directly.

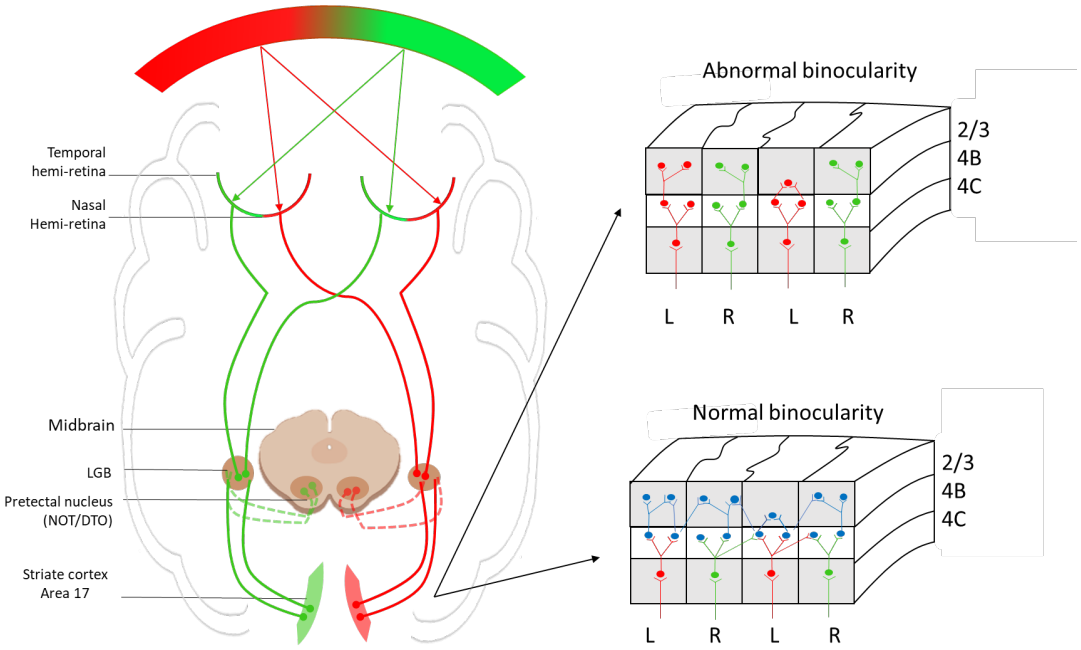

Fig 1.3: Schematic illustration of the visual pathway and connections in visual cortex in normal and abnormal binocularity (*courtesy of Dr Lieschen Branders)*

Animal studies pioneered by Nobel prize winners, Hubel and Wiesel have demonstrated that the primary visual cortex in each hemisphere has a retinotopic representation from both eyes arranged in vertical alternating columns (ocular dominance columns). The foveal columns in each hemisphere are adjacent to each other (Wurtz, 2009). Fusion results from horizontal axonal connections between adjacent columns in layer 4B and layers 2-3. The length of two horizontal axonal connections spans 4.4^0 or 8.8PD, allowing the potential for fusion and gross stereopsis in the presence of very small AoE referred to as microtropia or monofixation syndrome (Parks, 1969)

Cells in the LGB and layer 4C of the striate cortex are monocular columns, receiving input from the hemiretina of one eye and binocularity is established in layer 4B and layers 2-3. These binocular cell axons then relay to the associate visual cortex in the temporal lobe then to the motor nuclei responsible for smooth pursuit. In strabismus, binocularity in layer 4B does not occur and fibers remain monocular and relay as such to the smooth

pursuit centre. Binocular neurons from this motor centre relay to the brain stem and suppress the pretectal NOT and DTN nuclei. In conditions where binocularity does not develop, pretectal reflexes persists resulting in asymmetric OKN, fusional maldevelopment nystagmus (FMN) and dissociated vergence movements (DVD) (Ten Tusscher, 2017)(Wong, 2008)

In the last century two opposing theories have been proposed regarding the aetiology of IE: Worth's sensory theory suggests an inherent defect in the central sensory fusion mechanisms and that this was uncorrectable, and surgery was largely a cosmetic procedure. Chavasse's motor theory postulates a problem in the motor supply to the extra ocular muscles (von Noorden, 1988a). More recent research would seem to disprove the former theory. Experimental studies (Fawcett et al., 2005) in the 1990s demonstrated the development of binocular cells in the visual cortex of monkeys, both in orthotropic and strabismic eyes, at about 3-5 months of age. These cells are responsible for sensory fusion indicating no inherent defect in the sensory system. They further demonstrated that these binocular cells began to involute within six weeks of inducing esotropia.

Why then do some infants develop esotropia? It has been postulated that some cerebral insult, hypoxic, toxic or ischaemic, affecting the parieto-occipital cortex or geniculate-cortical pathways leads to projection problems to the visual cortex. (Tychsen, 2007).

Others have suggested that there is a problem with baseline or resting tone in extra ocular muscles (esotonus) due to vergence maldevelopment that favours convergence. The neural mechanism for this increased tone is probably at the subcortical level. Early in development, only neurons driven by nasally directed motion are present and temporally directed motion cells develop later. An arrest of development would therefore favour a convergence or esotropic shift (Brodsky, 2012).

1.6.3. Risk factors for infantile esotropia

Although no clear causal relationship exists for IE, several risk factors have been reported to be associated with esotropia:

Hereditary: Strabismus has been shown to have a hereditary pattern in 30% of cases (Maconachie et al., 2013) especially in syndromic conditions. Population studies have identified gene loci for further investigation in comitant esotropia, such as *STBMS1* on chromosome 7p, inherited as either autosomal recessive or dominant (Parikh et al., 2003) (Rice et al., 2009) and the gene cluster *NPLOC4-TSPAN10-PGE6G* on chromosome 17 present in 8.4% of one study population (Plotnikov et al., 2019).

However most genetic studies do not differentiate between the various sub-types of esotropia (Shaaban et al., 2009). Accommodative esotropia appears to have a stronger hereditary pattern than IE (Ziakas et al., 2002)(Çorak Eroğlu et al., 2020). At best the inheritance has a multifactorial or complex pattern in IE, abnormalities in pregnancy and birth appear to be more relevant than hereditary factors (Matsuo et al., 2001).

Premature and small for gestational age: VanderVeen reported the prevalence of strabismus of 42.2% in infants from the ETROP study and 14% prevalence in extreme preterm babies, the majority having esotropia (VanderVeen et al., 2016). In another study the prevalence of strabismus was 2% in term babies, 12% in preterm babies >28weeks and 22% in those <28weeks (Fieß et al., 2017). Possible reasons may be the increased risk of intracerebral haemorrhage or hypoxia involving the optic radiation/visual cortex area.

Maternal smoking: Several studies have shown the increase prevalence of strabismus associated with both quantity of cigarettes smoked and continuation late into pregnancy as a risk factor (Yang et al., 2019)(Pathai et al., 2010).

Maternal opiate use: In a single study opiate use was reported to be associated with a 10 fold increase risk of developing strabismus (Gill et al., 2003).

Neonatal misalignments: Infant studies report misalignment to be common at 1-3 months of age, tending to be intermittent, varying in frequency and usually convergent in direction. These tend to lessen over time as visual maturation progresses and, in most infants, resolved by 4 months of age. Previous studies have shown that infants who exhibit long periods of esotropic misalignment in this early period, have large angles (>40PD) or persisted beyond 4 months of age have a greater risk of developing IE (Horwood, 2003) (Pediatric Eye Disease Investigator Group, 2002).

1.7. Management of Infantile Esotropia

1.7.1. Benefits of intervention:

Establishment of binocular vision. Based on observations it became clear that early intervention in correcting the esotropia may prevent the involution of cells in the visual cortex and thus potentially improve binocular vision and stereopsis (depth perception). Moreover, a landmark study by Ing showed that in children with esotropia, development of stereopsis depends on the age at which alignment is corrected. In this study of 162 patients, 73% of children that were aligned by 12 months of age, developed stereopsis while 58% developed stereopsis if aligned by 12 - 24 months of age, albeit subnormal (Ing, 1983). These findings have been confirmed by other later studies (Wright et al., 1994)(Helveston et al., 1999) (Muz and Sanac, 2020). Of particular importance is that children who had corrective surgery after 24 months of age failed to develop stereopsis (von Noorden, 1988b)(D. M. Taylor, 1972). Wong has elegantly graphically summarized studies reporting potential for stereopsis based on age of surgery (fig.1.4).

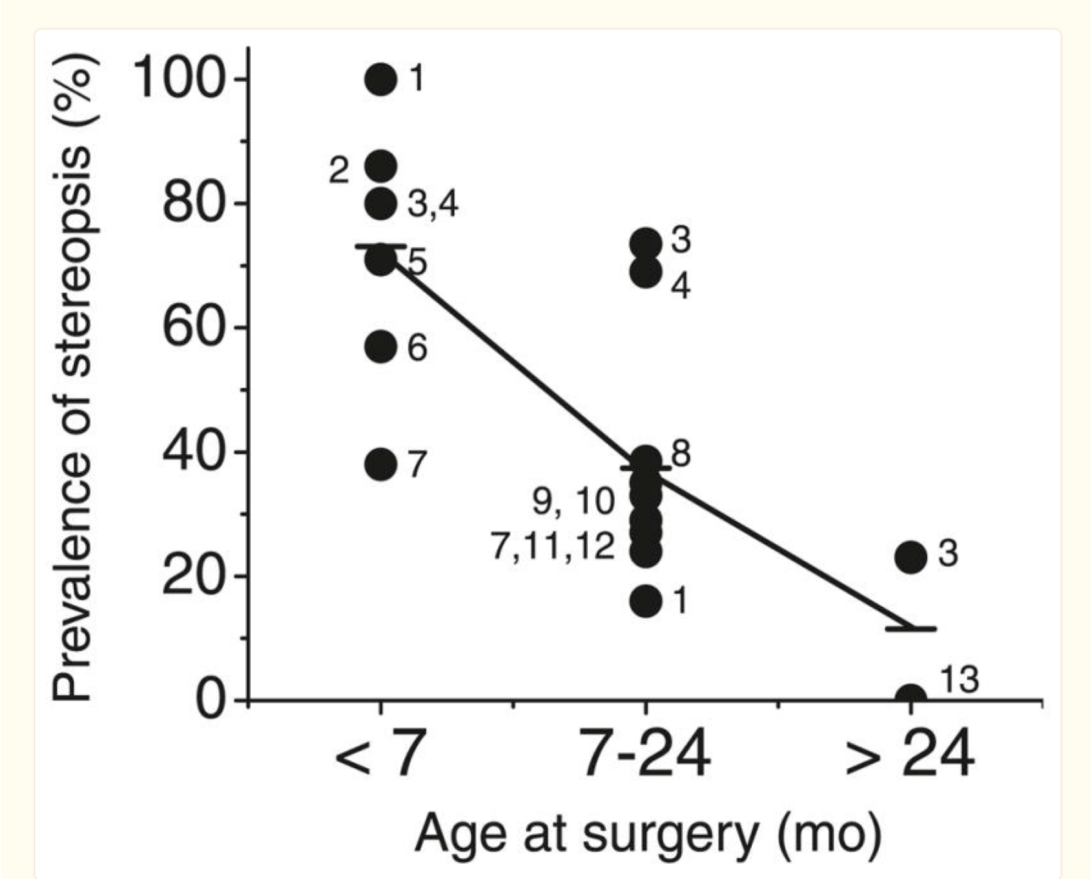

Fig 1.4: Graph matching age at surgery to stereopsis in multiple studies. (Wong, 2008)

1 (Birch et al., 2000) 2 (Ing, 1995) 3 (Ing, 1983) 4 (Ing and Okino, 2002) 5 (Wright et al., 1994b) 6 (Birch et al., 1998)

7 (Birch and Stager, 2006) 8 (Birch et al., 1995) 9 (Birch et al., 1990) 10 (Kushner and Fisher, 1996)

11 (Hiles et al., 1980) 12 (Zak and Morin, 1982) 13 (D M Taylor, 1972)

1.7.2. Additional benefits of alignment

Psychosocial development. In children that may not attain binocular vision, it is still beneficial to align children**.** Several studies (Durnian et al., 2010) (Xu et al., 2016) have highlighted the psycho-social effects of strabismus and the benefit of alignment in children and adults. In a quality-of-life questionnaire, squint patients scored on average 60(%). Those aligned with surgery scored 79(%), which was comparable to normal controls who scored 80(%), demonstrating the positive psychological effect of alignment at any age (Durnian et al., 2010).

*Improvement in binocular visual f*ield. An improvement in the binocular visual field has been reported in one study of children with IE, comparing pre and post-operative fields (Quah and Kaye, 2004)

Corrective surgery has been the treatment of choice in IE (Ing, 1983)(Helveston et al., 1999)(Helveston et al., 1983)**.** Chemo-denervation using botulinum neurotoxin (BNT) has been tried as an alternative to surgery (Rosenbaum, 1996)**.**

1.8. Surgery

1.8.1. Principals of Surgery

The aim of surgery is to align the eyes and establish binocularity, fusion and ultimately stereopsis. As discussed above, binocularity is more likely to occur if alignment is attained early in life.

Von Noorden (von Noorden, 1988b) summarized four possible outcomes of IE surgery:

I. Orthotropia with fusion
II. Microtropia with possible fusion
III. Small angle (<20PD) residual esotropia/consecutive exotropia
IV. Large angle residual esotropia/consecutive exotropia.

The first two outcome of surgery, either orthotropia or the microtropia, are obviously desirable. High grade (central) fusion is almost never achieved and hence, peripheral fusion is the best achievable outcome (von Noorden, 1988a). Small residual misalignment (<20PD) is an acceptable outcome in children where fusion is not possible (Simonsz and Kolling, 2011). For large misalignments re-operations are necessary. Generally, the six week post operative assessment of alignment is a reliable predictor of long term outcome in IE (Pediatric Eye Disease Investigator Group et al., 2009) (Weakley and Parks, 1990).

The principle of surgery is to weaken overactive muscles, by recessions and to strengthen underactive muscles by resections. Practically, recession involves disinserting a muscle from its initial insertion and refixing it more posteriorly on the globe while resection involves shortening a muscle by resecting a piece of that muscle. The amount of recession or resection is determined by published nomograms (Table 1.1) based on the angle of squint. Surgery of the medial rectus muscle results in a 4PD change with every millimeter of muscle recession or resection, while surgery of the lateral rectus muscle results in a 2PD change with each millimeter.(Kushner and Morton, 1984) The success rate of surgery especially for IE ranges from 64% to 84% (von Noorden, 1988a)(Helveston et al., 1999)(Kushner and Morton, 1984)(Scott et al., 1986).

1.8.2 Uncertainties in IE surgery and need for additional surgery

As stated above, early surgery renders the best opportunity for binocular vision. However the need for additional surgery appears greater in infants than older children (Altinsoy et al., 2016) (Simonsz and Eijkemans, 2010) (Louwagie et al., 2009). Reasons include overcorrection, undercorrection, development of inferior oblique overaction (IOOA), (DVD). The latter two were observed in 41% of cases at mean of 3years of age, and 44.3% at a mean age of 5years, respectively, in one study (Lee and Dyer, 1983) and 68% and 51% in another study (von Noorden, 1988a).

Larger baseline AoE >60PD have been shown to require more extensive or multiple surgeries (Bachar Zipori et al., 2020). Optimal surgery in this group is controversial. Several published reports on 3-4 muscle surgery showed a success rate varying from 61-77% (Lee and Dyer, 1983) (Camuglia et al., 2011), and on 2 muscle large recessions, a success rate of 67-88% (Tolun et al., 1999a) (Nelson et al., 1987). In contrast, a randomised comparative study by Wan et al reported a success rate of only 23% overall, when comparing 3 muscle (recession/resection) surgery, maximal 2 muscle recessions only and 2 muscle recession augmented with BNT, as primary procedures with the latter associated with better success rate (Wan et al., 2018).

Consecutive exotropia can occur early post-surgery period (6weeks to 3years). Known risk factors are amblyopia, hyperopia, adduction deficit, inferior oblique overaction (Bryselbout et al., 2019) (Gong et al., 2016) and prematurity (Park and Oh, 2015). Late exotropia can develop 5 to 20 years later. This has been attributed to stretching of the scar of the recessed muscle over time, shown to be as much as 3-4mm (Ludwig and Chow, 2000).

Table 1.1. Suggested nomogram for recti muscle surgery in infantile esotropia (Rosenbaum and Santiago, 1999)

Angle of esotropia (PD)	**Bimedial rectus muscle recession (mm)**	**Unilateral medial rectus recession/lateral rectus resection (mm)**
15	3.0	3.0/4.0
20	4.0	4.0/4.5
25	4.5	4.5/5.0
30	5.0	5.0/5.5
35	5.5	5.5/6.5
40	6.0	6.0/7.5
45	6.5	6.5/8.0
50	7.0	7.0/8.5
60	7.5	7.5/9.0

1.9. Botulinum neurotoxin therapy

1.9.1. Physiology and mechanism of action of BNT

Botulinum neurotoxin (BNT) produced by *Clostridium botulinum* causes flaccid paralysis of skeletal muscles by preventing the release of acetylcholine at the neuromuscular junction. Acetylcholine is the neurotransmitter that is stored in vesicles of the nerve endings. On electrical stimulation vesicles are incorporated into the plasma membrane, exocytosis, and release of acetylcholine (Ach) then occur. Fusion proteins, called SNARE proteins, facilitate this process. There are two such proteins, viz SNAP25 and Syntaxin 1a, found on the plasma membrane and one, VAMP2, found on vesicles. The interaction of these SNARE proteins causes adherence of the vesicles to the plasma membrane which causes the release of Ach. There are seven isoforms of the BNT (A-G). BNT-A is a covalent protein, consisting of a heavy chain that binds to the plasma membrane and releases the active light chain (150kDA) which play a key role in cleavage of the SNARE proteins preventing adherence to the Ach vesicles (Chen, 2012). Figure 1.5 shows illustration of mechanism of action.

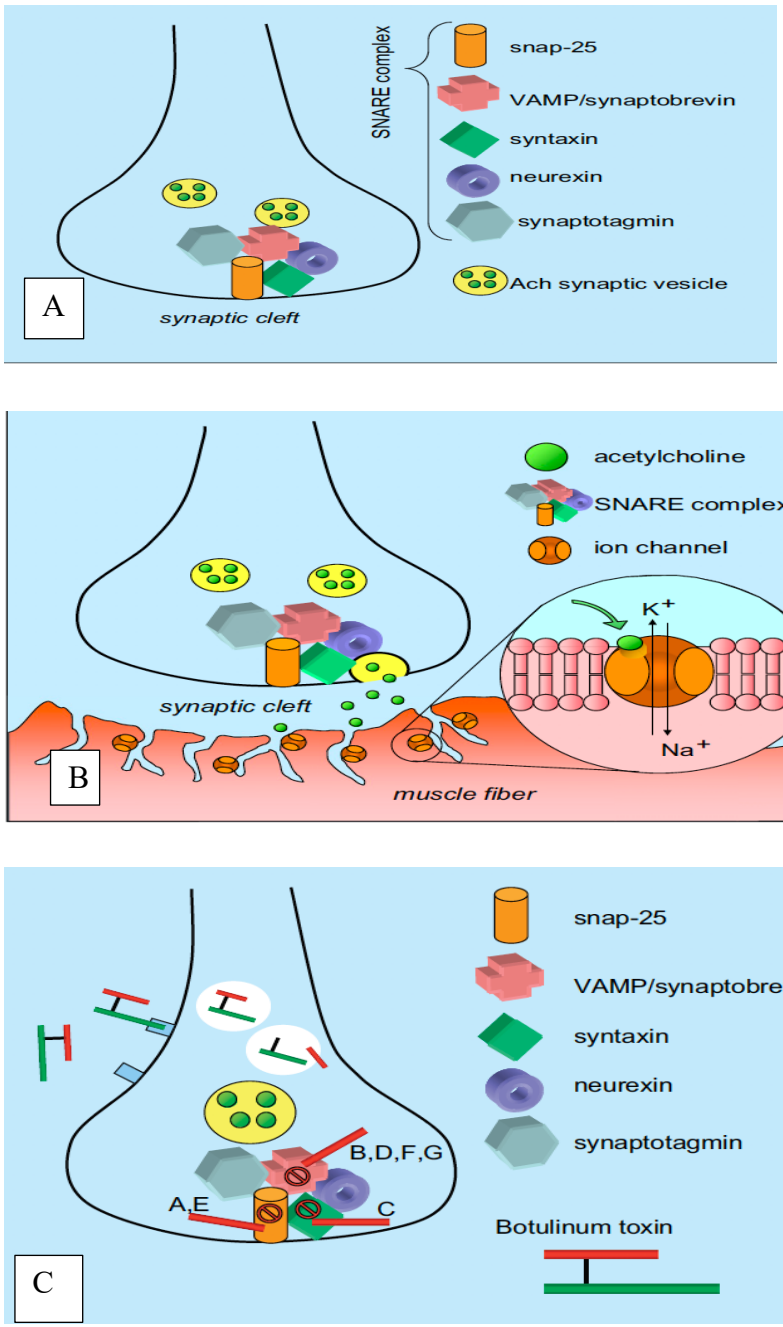

Fig. 1.5 Diagrammatical illustration of mechanism of action of BNT

A. Terminal nerve endings at the neuromuscular junctions showing close contact between acetyl choline (Ach) vesicles and SNARE proteins

B. on depolarization SNARE protein aggregate and fuse with Ach vesicle and facilitate Ach release which binds to Ach receptor and cause opening of ion channels

C. Light chain of BNT binds to SNARE proteins and prevent release of Ach (Dutton and Fowler, 2007).

There has been only one published paper on the histopathological changes in extraocular muscle following BNT injections. The authors report extensive fibrosis and atrophy of the muscle fibers which appeared dose related (Li et al., 2016).

1.9.2. History

Historically, BNT was first recognized causing fatal food poisoning in 1822 by German physician Justine Kerner in people eating contaminated sausages.

Clostridium botulinum was isolated 1895 by Ermergen and in 1928, Sommer isolated the neurotoxin and it's first clinical use was by Scott in 1980 in the management of strabismus (Dutton and Fowler, 2007).

1.9.3. Clinical Uses of Botulinum neurotoxin injections

Botulinum neurotoxin injection pioneered by Alan Scott in the treatment of strabismus has subsequently been widely used for a variety of clinical conditions including neurological, dermatological, urological, oromandibular, orthopaedic and ophthalmic conditions and aesthetics (Guida et al., 2018)(Kaynak-Hekimhan, 2010) (Argyriou et al., 2021).

Its use in the treatment of strabismus was first reported in 1980 first in animal models (Scott, 1980) and then in humans (Scott, 1980). He used Onabotulinum A under the trade name of Oculinum which later was bought by Allergan and re-marketed as Botox^{R} which is presently widely used. Another type, Abobotulinum A known as Dysport^{R} is used in some countries but generally requires double the Botox units to be comparable in efficacy (Karsai and Raulin, 2009). Later, Incobotulinum A trading as Xeomin^{R} which has only the purified active neurotoxin, has longer shelf life, does not need refrigeration and is two times more potent than Botox has been used in various conditions but no reported use in strabismus (Field et al., 2018).

In a study of 413 patients with all types of strabismus Scott *et a*l reported that 61% of patients maintained their alignment after a follow- up of at least 6 months. In this study, BNT was sequentially injected in one muscle at a time with a mean of 1.7 injections per patient. Two other studies reported similar outcomes. In a case series, of 30 patients with IE, Campos *et al*. reported an

85% success in alignment by injecting both medial recti(Campos et al., 2000). McNeer *et al*. similarly reported an 89% success rate after injecting 76 patients (McNeer et al., 1998). In contrast, an earlier study by Biglan *et al*. reported a poor outcome in IE (Biglan et al., 1989). In one of a few prospective studies, Campomanes *et al* (de Alba Campomanes et al., 2010) showed an overall 66% alignment success rate with surgery compared to 45% with BNT. When stratifying outcomes based on the degree of angle of strabismus, alignment using BNT was achieved in 36% of patients with angles >30PD and 60% of patients with angles that where <30PD, indicating that BNT may be more effective in smaller angles of squints. BNT was also shown to be more effective in infants than older children presumably due to the increase tightness of muscles with age (de Alba Campomanes et al., 2010)(McNeer and Tucker, 2010).

Magoon et al showed that alignment at six months following BNT injection, was maintained after two years of follow up (Magoon, 1989). This stability has been confirmed by others (McNeer et al 1998) (Campos et al 2000).

Botulinum neurotoxin has been used alone or in combination with sodium hyaluronate (SH) injected into the medial rectus muscle with similar outcome on alignment but with less complications associated with SH use (Pandey et al., 2020). The use of BNT with SH needs further research.

Botulinum neurotoxin has also been used to augment or potentiate surgery in large angle squints. In a prospective study, Lueder *et al* reported little difference between augmented surgery with BNT and conventional surgery requiring three-muscle surgery (Lueder et al., 2012). A similar outcome was reported earlier (Khan, 2005) indicating that augmented surgery is as effective as conventional surgery for large angle esotropia. Wan et al in a prospective study established that BNT use intraoperatively, yielded 1.7PD more effect per millimeter of muscle recessed than without BNT use (Wan et al., 2018). In a UK study, Rowe *et al.* (Rowe and Noonan, 2012) showed that the percentage of change in the angle of deviation was 52-60% for esotropia following BNT injection compared to baseline angle measurement.

The injection is well tolerated, safe and repeated doses do not appear to diminish the effects of the toxin. Gardner *et al.* injected on average 34 times in adult patients with various forms of chronic strabismus. They demonstrated not only the safety of BNT but also the cost of BNT of £711/injection compared to £952 for conventional surgery (Gardner et al., 2008).

All the above studies reported few complications, such as ptosis and vertical squints but all were self- limiting. In one study ptosis occurred in 8.4%, vertical deviation in 2% and haemorrhage in 1%. All of these resolved over a few weeks (Rowe et al., 2010).

In a meta-analysis of BNT in IE, identifying 11 published articles. Issaho et al reported a mean baseline AoE of 25-40PD, with a reduction of 17-35PD from baseline with mean number of injections of 1 to 2.2. Table 1.2 summarizes the different studies (Issaho et al., 2017)

Table 1.2: summary of studies using Botulinum Neurotoxin for Infantile Esotropia (Issaho et al 2017)

Study	**No. of patients**	**Success rate (%)**	**Mean follow up (months)**	**Mean age (months)**	**Preop Deviation (PD)**	**Variation on Deviation (PD)**	**Dose (IU)**	**Mean no. of injection**
Scott et al	61	66.0	29.0	25.0	43.00	-33.0	_	2.2
De Alba Campomannes et al	322	45.0	22.6	16.7	38.8	_	_	1.60
McNeer et al	41	93.0	36.5	7.80	36.3	-34.6	2.5	2.0
McNeer et al	35	86.0	36.5	25.6	30.0	-27.7	2.5	1.5
Benabent et al	40	53.0	6.0	21.6	25.8	-17.3	7.0	1.0
Campos et al	60	88.0	62.4	6.5	35.5	_	3.0	1.0
McNeer et al	27	100	12.0	7.0	43.0	-42.0	2.5	2.0
McNeer et al	30	100	12.0	25.0	31.0	-29.0	2.5	1.6
Scott et al	58	66.0	30.0	23.0	43.0	-31.0	_	2.1
Cheng et al	24	37.5	6.0	35.8	39.3	-18.0	_	1.0
Gur soy et al	25	68.0	84.0	10.0	40.6	_	4.0	1.4

1.9.4. Outstanding Issues with Botulinum Toxin Use in IE.

A Cochrane review of BNT in strabismus revealed that there have been no RCT studies in IE (Rowe and Noonan, 2017).

The cost effectiveness of using BNT versus surgery has not been investigated from an economic health perspective.

From the analysis above

The exact dosage required for the degree of esotropia remains unclear. More specifically, what is the response to an incremental increase in dosage. There are a wide range of dosages used, ranging from 2.5IU to 10IU/muscle. There is some evidence that indicates that larger doses do not necessarily result in a better response. In fact, analysis seem to show that for every increase of 1IU injected, there is a 0.1% reduction in success, however larger doses tend to be used for large baseline AoE (Issaho et al., 2017). In a more recent prospective study of 56 patients, dose incrementation of 2.5IU for <20PD through to 10IU for >40PD was reported to be safe and more efficient, however the study reports success of 75% with 2.5IU, 37.5% for 5IU, 42.8% for 7.5IU and 28% for 10IU suggesting more the effect of the degree of esotropia than the dosage (Alshamlan et al., 2021).

The method of administration of BNT injections into extraocular muscles varies. Initial studies used electromyogram (EMG) to ensure muscle penetration of the needle (Scott, 1980)(McNeer et al., 2000). The use of EMG has been identified as a problem in children under general anaesthesia and, together with its limited availability, has necessitated toxin delivery via a transconjunctival injection into the muscle. This approach has been reported to be safe, efficacious and time saving (Benabent et al., 2002)(de Alba Campomanes et al., 2010). Campos et al injected BNT under direct visualization, isolating the medial rectus muscle via conjunctival incision with good outcomes (Campos et al., 2000). However, this approach is more time consuming and requires conjunctival suturing. The transconjunctival approach is the one adopted in our hospital and shown in fig.1.6 and fig.1.7 showing preoperative and post operative outcome.

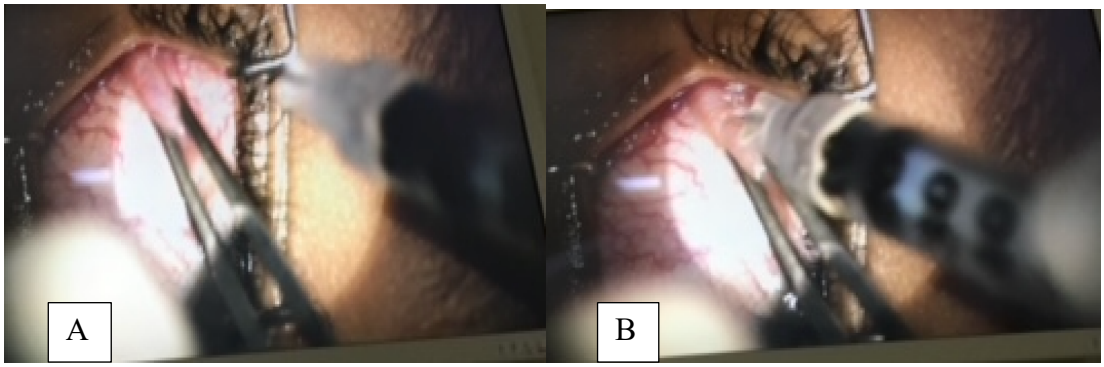

Fig 1.6: Trans-conjunctival injection method employed to inject BNT at St John Eye Hospital – A: medial rectus grasped with a muscle forceps. B: BNT in insulin syringe injected into the belly of the grasp muscle.

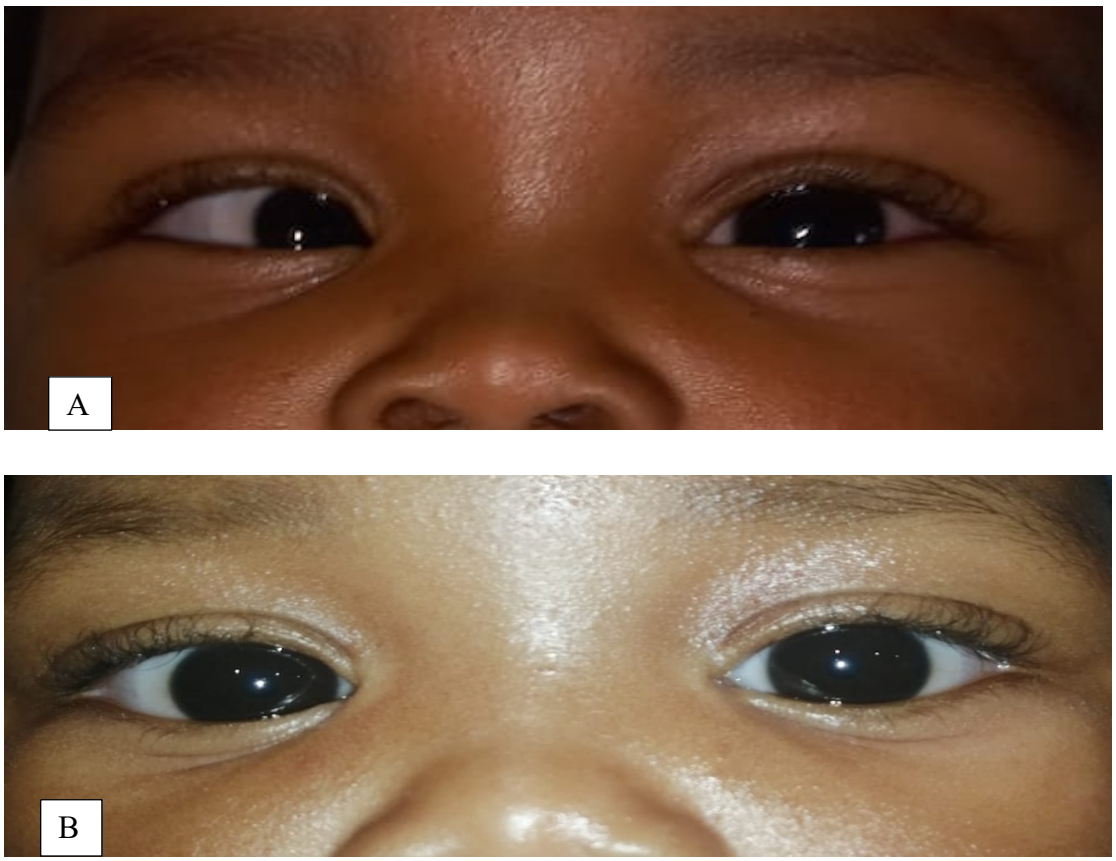

Fig1.7 infant with IE from St John Eye Hospital, at 10months (A) and 13months (B) of age.

A. pre-injection showing a 40PD esotropia
B. post-injection showing corneal reflex centered and symmetrical (orthotropic)

Many of the studies include children with small to moderate baseline AoE. Our patient profile is characterised by large and very large baseline AoE and late presentation. Reports on the response to BNT injections in large AoE are limited as well as response in older children. While several studies reported on the need for surgery in 22-25% of children (Scott et al 1980) (de Alba Campomanes et al 2010) following BNT injections, none report on the stability of subsequent surgery.

1.10. Economic considerations

Health economics can be assessed in various ways.

1.10.1 Value based medicine considers value of an intervention from either a societal or patient perspective and these include:

1. Cost minimization analysis – where 2 types of interventions with similar outcomes are compared with respect to monetary costs.

2. Cost benefit analysis – compares moneys spent for the intervention to the moneys saved because of the intervention. A typical example is the cost of laser treatment for retinopathy of prematurity compared to the cost of blindness because of untreated retinopathy.

3.Cost effectiveness analysis (CEA)– compares moneys spent to the gain in years in the quality of health or vision and is related to;

4.Cost utility analysis (CUA)– is the favoured method of assessing cost effectiveness, gives a monetary value on quality adjusted life years (QALYs) gained. Quality can be measured by means of a utility score and be quantified. By convention, utility score has a value from 0 (death) to 1 (perfect health). The value is calculated by asking patients what proportion of their remaining life are they willing to give up in exchange for a better utility score

(time trade off method), e.g., willingness to give up ¼, would then be subtracted from 1.0, to give a score of 0.75. Strabismus in adults confers a utility score of 0.85 and subsequent alignment confers a score of 0.93, a gain of 0.08. If the benefit is expected to last 20years then the QALY gained would be 20 x 0.08 = 1.6 QALY. For vision, an additional score of 0.93 x 20 = 18 QALY is added to reflect the quality of vision gained.

The amount calculated per QALY deemed cost effective varies from country to country, based on the gross domestic product (GDP) per capita. In the USA $50 000/QALY, In the United Kingdom, £20 000/QALY (Brown and Brown, 2004). These methods have not been validated in children and hence CUA are difficult to apply in children.

Beauchamp et al reported on the CUA of $1632/QALY in adults strabismus and by extrapolation $1155/QALY in children (Beauchamp et al., 2005) making strabismus surgery very cost effective. In a United Kingdom studies on the screening and treatment of amblyopia have reported both to be cost effective (Carlton et al., 2008).

1.10.2. Hospital costing of procedures to either the state or funders is another way of addressing health economics. These are important in budget allocations.
Costing can be done “Top to Bottom” where an average unit cost per patient or procedure is calculated (so called global fee), or a patient specific costing referred to as “Bottom Up” where itemized costing is done per individual patient or procedure. In a hospital setting bottom-up method is more accurate. (Mercier et al 2014)

Other than Gardner et al (Gardner et al. 2008) mentioned above, no published data have reported on the cost of surgery and BNT use in strabismus.

CHAPTER 2

BOTULINUM NEUROTOXIN INJECTIONS IN ESSENTIAL INFANTILE ESOTROPIA – A COMPARATIVE STUDY WITH SURGERY IN LARGE ANGLE DEVIATIONS

Abstract

Purpose: To compare botulinum neurotoxin (BNT) injections to surgery as first line therapy in large angle essential infantile esotropia (IE).

Patients and methods: Children between the ages 6 months and 6 years with IE of ≥40 prism diopters (PD) were randomised to either a maximum of 3 BNT injections or surgical intervention of bimedial rectus muscle recession for angles ≤60PD and augmented with BNT injection in angles >60PD. Time taken for each procedure was documented. Orthophoria or misalignment of ≤10PD was regarded as a complete response (CR). Follow-up visits were done at 3, 6, 12 and 24 weeks.

Results: Mean (SD) age and baseline angle of esotropia were 26.9 (14.5) months and 61.9PD (12.8), respectively for the overall cohort. The proportion of children who achieved CR was significantly higher in the surgery arm compared to the BNT injection arm (OR= 4.01, 95% CI 1.74-9.22) but the time taken was 6 times longer ($p<0.0001$). In the BNT arm, 55.2% of children aged ≤24 months and 16% of children > 24 months achieved CR. In children with esotropia ≤60PD, CR was achieved in 50% while those with esotropia > 60PD CR was achieved in 25%.

Conclusion: Surgery remains the gold standard for the treatment of esotropia, but BNT injection is a safe and effective alternative in children ≤24m and with smaller angles of esotropia ≤60PD in resource limited centers.

Introduction

Essential infantile esotropia (IE), also referred to as congenital esotropia, has an early onset of approximately six months of age. It is characterised by a large angle of deviation and accounts for 8.4% of esotropia cases (Mohney, 2007). Surgical correction is the preferred standard management and is associated with reported success rates of between 64% to 80% (Kushner and Morton, 1984b)(Tolun et al., 1999b)(Wan et al., 2018). Ing has shown that early surgical intervention and correction of the misalignment may result in the development of stereopsis (Ing, 1983a). In his study, children surgically aligned before 12months of age developed some degree of stereopsis in 73% and those aligned after 18months developed stereopsis in 58%. Others have shown that children aligned after 24months of age did not develop stereopsis (D M Taylor, 1972)(von Noorden, 1988b).

In developing countries like South Africa, IE is reported to be the most common type of strabismus, accounting for 74% of esotropia in childhood (Tinley and Grötte, 2012). Timeous intervention presents a major challenge in resource-constrained settings such as the public health sector in our country.

Following the introduction by Scott (Scott, 1980) of botulinum neurotoxin injection therapy (BNT) in the treatment of various strabismic conditions, BNT has gained popularity as an alternative treatment option for IE. Results, however, have been mixed. Success rates have varied from 36% to 78% and are related to the degree of strabismus and the age of intervention (McNeer and Tucker, 2010)(de Alba Campomanes et al., 2010).

The current waiting time for strabismus surgery at our tertiary centre is more than a year from the time of initial presentation and a delay in surgery is known to compromise various aspects of a child's visual development with regard to fusion and stereopsis (Ing, 1983)(D M Taylor, 1972)(von Noorden, 1988b) as well as to cause long-term psychosocial issues (Pathai et al., 2010). A randomised controlled study was undertaken to compare BNT injection to surgical correction as a first-line treatment for large angle IE. In a Cochrane review, Rowe and Noonan identified 6 RCT associated with BNT use in

strabismus, 2 in infantile esotropia and no RCT comparing BNT to surgery in large angle esotropia (Rowe and Noonan, 2017).

Study Methods

A prospective, randomised unblinded study comparing BNT to surgery in IE was conducted from January 2015 to January 2018, in a large tertiary hospital. The study was approved by the Human Research Ethics Committee of the University of the Witwatersrand (Approval no. M140225) and conducted in accordance with the tenets of the Declaration of Helsinki.

Inclusion criteria: Children with onset of esotropia before 6months of age; with large angle IE, defined as esotropia of ≥ 40 prism diopters (PD), between the ages of 6 months and 6 years at baseline; informed written parental consent.

Exclusion criteria: Children with significant pattern deviation, neurological impairment, and hyperopia of > +5.00 diopters.

Children underwent a full examination including a cycloplegic refraction, fundus examination and orthoptic assessment. Those with a refractive error ≥ +2.50DS were initially given their prescription and if there was no change or minimal change in their esotropic angle, patients were classified as IE and enrolled in the study.

Children were stratified according to 2 age categories: those ≤ 24 months and those >24 months. Stratification based on 24 months rather than 12 months was necessary in view of the low enrollment number in the very young age group and based on previous findings of the potential of developing fusion before and after 24 months (von Noorden, 1988). Within each age category, participants were randomised by an independent study assistant and assigned to either the BNT (odd numbers) or surgery (even numbers) arms. *Figure 2.1* shows the schematic randomisation and follow up.

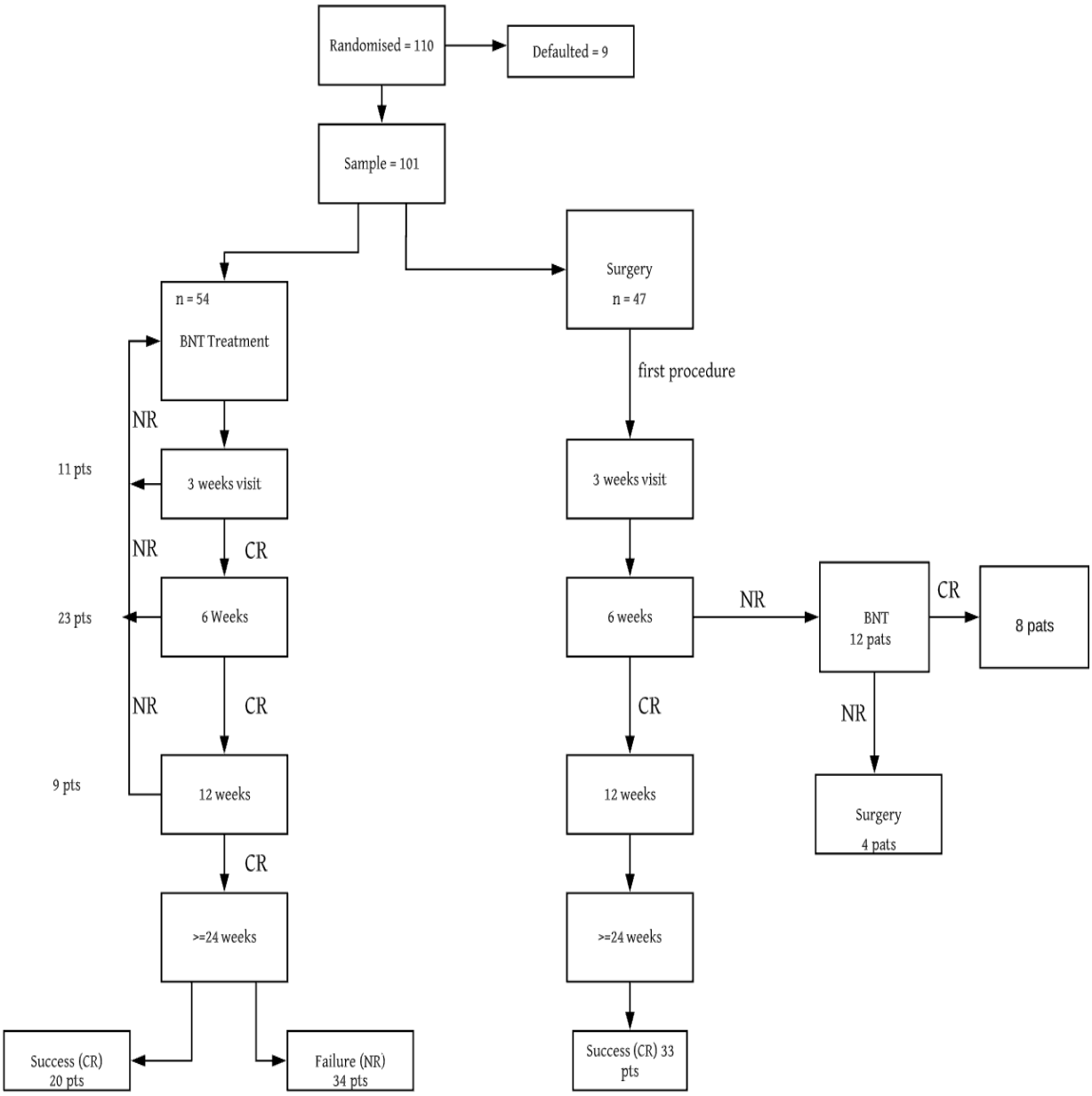

Figure 2.1 Schematic flow diagram of study patients. BNT: Botulinum Neurotoxin; CR: Complete response; NR: No Response

In the BNT arm (of Figure 1), botulinum neurotoxin (Botox ™ Allergan) was injected in each medial rectus muscle, administered sub-conjunctively after the muscle was grasped using forceps as described by Benabent et al (Benabent et al., 2002). All children received an initial dose of 5 units (U) that was repeated, for a maximum of 3 injections if the esotropia was > 10PD at visits at 3, 6, 12 or 24 weeks following the last injection. The dosage at subsequent visits depended on the degree of esotropia, 5U for deviations ≥40PD and 3U for deviations < 40PD.

In the surgical arm, children underwent standard bilateral medial rectus muscle recession surgery for esotropia ≤ 60PD. The medial recti were recessed to a maximum of 7mm. with 3U of BNT given intraoperatively to each recessed muscle in cases >60 PD to augment the recessions. No child had 3 muscle surgery for the larger angles as an initial procedure.

Participants in both arms were assessed at 3-, 6-, 12- and 24-weeks post-procedure (patients in the surgery arm were also seen day 1 post-surgery) for possible complications. Children in the BNT arm who had an unacceptable outcome after 3 injections were offered surgery after a stable angle measurement on 2 successive visits, one month apart. In the surgical arm, all unacceptable outcomes with residual esotropia, received BNT into the recessed muscles at the six weeks post-operative visit and surgery as the third procedure, if required once a stable angle was attained on 2 consecutive visits.

Outcome measure: Complete response (CR) was defined as orthotropia or residual esotropia of ≤10PD (Von Noorden et al., 1972), partial response (PR) as residual esotropia of >10PD and ≤20PD and deemed acceptable by the parents, and failures or non-response (NR) as >20PD.

The total theatre time taken for each arm of the study was also recorded.

Sample size

A sample size of 98 (49 per arm) was calculated using a Pearson Chi-squared test with the proportion of success set at 0.65 for the surgery arm and 0.37 for the BNT arm at a power of 80% and an alpha level of 0.05.

Statistical Analysis

Data analysis was restricted to children followed up for at least 24 weeks after the last procedure. The Chi-squared test or two-tailed Fisher's exact test were used to compare binary variables between groups. Continuous variables were analyzed using the Wilcoxon rank sum test. Univariate and multivariate logistic regression models were used to assess the effect of intervention adjusting for age and angle of deviation at baseline on the outcome. A p-value <0.05 was considered significant. Statistical analysis was performed using Stata 15.1 (STATA Corp, Texas) and MedCalc (MedCalc Software, Belgium).

Results

Of the 55 children randomised to each arm initially, 101 children, 54 in the BNT arm and 47 in the surgery arm had adequate follow up of at least 24 weeks after the last procedure. Of the defaulting children, 1 was in the BNT arm and 8 in surgery arm. The mean (SD) age was 26.9 (14.5) months and median (IQR) baseline angle of esotropia was 60 (55-70) PD for the entire cohort with no significant difference between the two arms (Table 2.1). Total theatre time was significantly shorter for the BNT arm compared to the surgical arm, mean (SD) 11 (1.5) and 72 (5) minutes, respectively, 95% CI 10.46 -11.31 and 69.93-74.32 respectively.

Table 2.1: Baseline characteristics of study population

Variable	**All subjects N=101**	**Surgery arm N=47**	**BNT arm N=54**	**p value**
Female (%)	61 (60.3)	27 (57.4)	34 (63)	0.57
Age in months				
Mean (SD)	26.9 (14.5)	29.4 (15.2)	24.7 (13.6)	0.15
Baseline AoE (PD)				
Median (IQR)	60 (55-70)	60 (55-70)	65 (50-70)	0.7
Degree of Esotropia no. (%)				
40-60PD	50	24 (51.1)	26 (44.4)	
>60PD	51	23 (48.9)	28 (51.9)	

PD = prism diopters; SD = standard deviation; IQR = interquartile range:

AoE = angle of esotropia

As shown in Table 2.2, CR was achieved in a significantly higher proportion of children in the surgery arm (70.2%) after single procedure compared to the BNT arm (37%). Of 20 children who achieved CR in the BNT arm, 11 (55%) achieved it with one injection, 5 (25%) after the second injection and 4 (20%) after the third injection.

Table 2.2: Outcome after 24 weeks of last intervention in infantile esotropia comparing surgery and botulinum neurotoxin

	Surgery arm CR (%)*	**BNT arm CR (%)**	**OR (95% CI)**	**P value**
Total	33 (70.2)	20 (37)	4.01 (1.74-9,22)	0.001
by age group (months)				
≤24m	15/21(71.4)	13/26 (50)	2.03 (0.61-6.72)	0.24
>24m	18/26 (69.2)	4/25 (16)	11.81(3.05-45.81)	0.0002
by AoE				
≤60PD	17/24 (70.8)	13/26 (50)	2 (0.64-6.29)	0.37
>60PD	16/23 (69.6)	7/28 (25)	8.5(2.4-20.09)	0.0005

*Outcome after one surgical procedure

CR = Complete response AoE = Angle of esotropia

Univariate analysis of subgroups stratified by age showed that the proportion of patients that achieved CR was not significantly different between the 2 arms for children ≤24 months, whereas it was significantly better in the surgery arm in children >24 months (OR 11.81,95%CI:3.05-45.81, p=0.002). When comparing subgroups stratified by degree of baseline esotropia, there was no significant difference between the two arms for children with esotropia ≤60PD, but significantly better in the surgery arm in children with esotropia >60PD (OR=8.5, 95%CI:2.4-30.09, p=0.0005). (Table 2)

Multivariate logistic regression analysis for the BNT arm showed age and degree of baseline esotropia were significant independent predictors. Receiver Operating Characteristic (ROC) curve analysis using univariate predictors, degree of baseline esotropia and age, yielded an area under the curve (AUC) of 70% and 66% respectively. The optimal threshold sensitivity/specificity modelled by our data was 50PD for degree of esotropia (fig 2.3) and 21 months for age (fig 2.4).

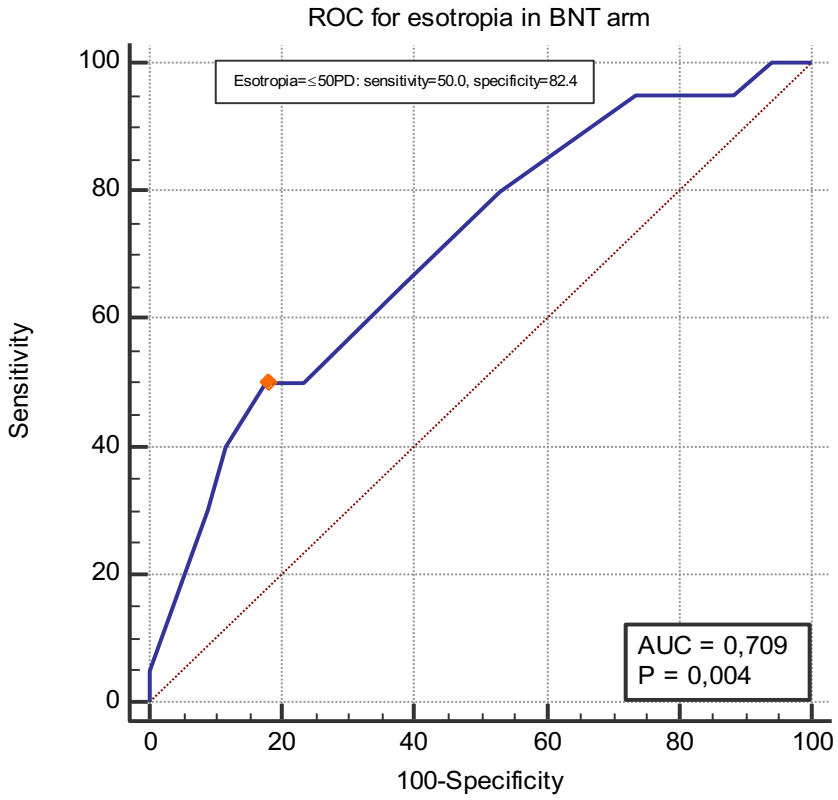

Figure 2.2: ROC curves in BNT for angle (PD): orange dot=Youden Index (values in text box above)

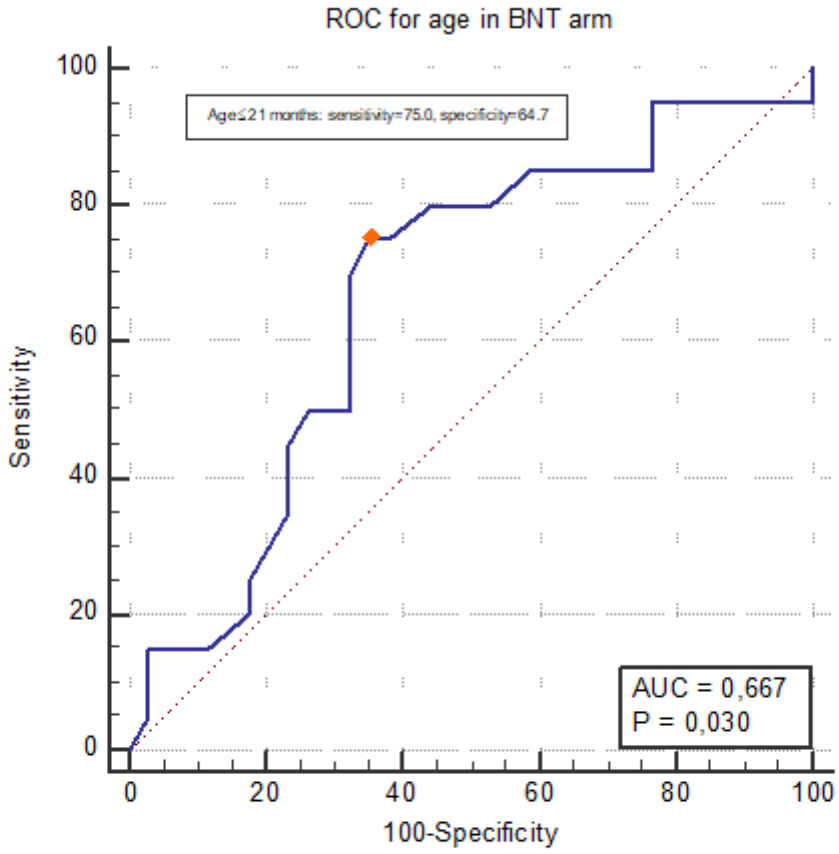

Figure 2.3: ROC curves in BNT for age: orange dot=Youden Index (values in text box above)

In the BNT arm, 7 children (13%) had PR and 27 children (50%) had NR. Of the 27 NR children, 21 had subsequent surgery - 11 of these achieved CR and 2 PR at 24weeks post-surgery follow-up. Eight children failed to return for their follow up visits. Ultimately, CR and PR were achieved in at least 40 (74.1%) of children in the BNT arm within a year of the initial procedure.

Complications in the BNT arm were partial transient ptosis in 9 children (16.7%), which resolved within 6-8 weeks, transient vertical deviation in 3 children (5.6%) and consecutive exotropia in 13 children (24.1%). Seven of the children with exotropia were associated with CR. There were no cases of globe perforation, infections or chemosis following BNT injections.

In the surgical arm, of the 47 children, 24 had large angle esotropia and the 23 children had very large angle esotropia requiring surgery with BNT

augmentation. CR was achieved in 17 (70.8%) and 16 (69.6%) respectively, with one procedure. Of the 14 children who failed to achieve CR, 12 had residual esotropia and 2 exotropia. All the 12 children with esotropia received 3U of BNT as a second procedure and CR was achieved in 8 children while 4 children needed additional surgery.

The 2 children with exotropia, received BNT to the lateral rectus muscles as initial therapy followed bimedial rectus muscle advancement and had final NR. In total, 45 children (95.7%) had a CR or PR in the surgery arm. There were no major complications of surgery such as slipped or lost muscles, globe perforation or anaesthetic related issues.

Discussion

In this prospective randomised control study, surgery was superior to BNT in our cohort of children with large angle esotropia, however BNT has a definite role as primary treatment option in selected children. Surgery was associated with equally good outcomes irrespective of the age of the child or the degree of esotropia. While previous studies using BNT showed the best outcome in infants (Campos et al., 2000), our study did not have sufficient numbers to consider the very young separately. Crude analysis of the BNT arm versus the surgery arm, however, did show comparable outcomes to surgery in children $\leq$ 24 months of age and with a baseline esotropia $\leq$ 60PD. This association remained valid in the multivariate analysis with non-significant odds ratios between the BNT and surgery arms in patients $\leq$ 24 months and $\leq$ 60PD. This is further supported by ROC curve analysis which indicated that children below 21 months of age and those with esotropia < 50PD are more likely to have complete resolution.

In a systematic review 9 papers were reviewed describing the use of BNT in the management of IE. Most of the studies were non-comparative and success rate varied from 37.5% to 100% (Issaho et al., 2017). The high-success-rate studies were associated with small to moderate angles of esotropia while studies of large angles reported lower success rates.

The results of this study show a similar trend to that of de Alba Campomannes et al (de Alba Campomanes et al., 2010) for large angle esotropia. In their study large angle esotropias of >30PD treated with BNT were associated with a success rate of 36%. All our study children had angles ≥ 40PD with a success rate of 37% but angles ≤ 60PD were associated with 50% success. BNT in younger children had a significantly higher success rate (55.2%) than older children (16%). The explanation is probably based on increasing contracture of the medial rectus muscles over time (McNeer et al., 2000). In our cohort, a better response was seen with one injection, and we found lower success rates for second and third injections.

The present study reaffirms the safety of BNT (Issaho et al., 2017) as there were no adverse events associated with BNT injections.

Exotropia after the first injection was a good predictor of success as shown by Campos et al (Campos et al., 2000). In our study 7 of 13 patients with exotropia after the first injection were associated with CR. This represented over a third of all successful cases. In cases where BNT failed to correct the esotropia, alignment with surgery was achieved within a reasonable time interval. On average, it was found that surgery took six to seven times longer than BNT. In resource-constrained settings the short procedure-time for BNT allows many more patients to gain access to treatment at a potentially earlier age.

Our need to recognize cosmetically acceptable small angles (PR) highlights the real problems encountered in developing countries, where functional outcome and potential for fusion may not be a priority. With BNT use at least 50% of our patients overall achieved CR and PR. Another compelling reason for BNT use is the absence of serious complications and that an exact angle measurement may not be essential. This obviates the need for specialist orthoptist. Orthoptists are few and seldom service public sector hospitals in South Africa.

The number of participants achieving a cosmetically acceptable result in the surgical arm was more impressive as only two patients were deemed failures. However, the number of patients that dropped out pre-operatively in this arm may highlight parental reservations concerned with surgery.

The results of this study support the use of BNT in large angle deviations as augmentation to surgery. Leuder reported a favourable outcome with augmented surgery in 17 out of 23 patients (73%) (Lueder et al., 2012). Our study showed a similar outcome in patients with augmented surgery. This would eliminate the need for three-muscle surgery and thus allow for shorter theatre-time.

Limitations: The study only followed children for 6 months following the last procedure and late esodrift may still be an issue. The scope of the study addressed only motor response and did not test for fusion in children that were aligned. No attempt was made to establish parental satisfaction or dissatisfaction. We were unable to recruit children younger than 10 months to confirm the reported higher rate of success in this very young age category(de Alba Campomanes et al., 2010b)(Campos et al., 2000). The study also did not compare 3 muscle surgery to surgery with augmented BTX which could have added another comparative arm.

Conclusion

Surgery is still the gold standard of managing large angle infantile esotropia. However, BNT is a viable primary treatment option for infantile esotropia. BNT is safe and a short procedure and could be considered as a first line intervention in developing countries where resources are limited with respect to waiting time for surgery. Further, BNT was found to be more effective in children $\leq$24 months of age and with baseline angles of $\leq$60PD of esotropia.

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CHAPTER 3

TEMPORAL RESPONSE TO BOTULINUM NEUROTOXIN INJECTIONS IN LARGE ANGLE INFANTILE ESOTROPIA: A POST HOC ANALYSIS.

Abstract

Purpose: to determine the anticipated reduction of baseline angle of esotropia (AoE) and identify predictors of change following botulinum neurotoxin (BNT) injections in large angle infantile esotropia (IE).

Methods: this was a prospective longitudinal study of children <10 years of age diagnosed with IE >30PD, given either1,2 or 3 BNT injections. Success was recorded, a change from baseline AoE was observed and predictors of reduction were analyzed. For this study children were further sub-divided into group 1 (≤60PD) and group 2 (>60PD). Outcome of subsequent surgery in failed cases were analyzed.

Results: There were 117 children, 55 in group 1 and 62 in group 2. Mean age (SD) was 30.3(18.8) months. Mean baseline AoE was 62.5(13.1) PD, 51.4(8.4) and 73(7.5) in groups 1 and 2 respectively. Mean number of injections were 2.2(0.7). Success was achieved in 25.6% (33.4 and 16.2% in group 1 and group 2 respectively) The percentage mean reduction of AoE post BNT injection was 55.2% (26), (p=0.001) Five reverted to baseline AoE. Age and baseline AoE were significant predictors of reduction (p=0.04 and 0.004). There were 32 children that had subsequent surgery, 22 were followed up for minimum of 6months and 20 were aligned within 10PD of orthotropia.

Conclusion: In large angle esotropia there was an anticipated reduction of approximately 50% of baseline AoE which was greater in younger children, smaller baseline AoE. Number of injections was a marginal predictor. Subsequent surgery appeared to be stable and required less recessions than would normally have been needed for the original angle of esotropia.

Introduction

Infantile esotropia (IE) is the one of the most common types of strabismus in childhood and in sub-Saharan Africa accounts for up to three quarters of childhood strabismus (Tinley and Grötte, 2012). Timely intervention presents a major challenge in resource-constrained settings. In the public health sector in South Africa children with strabismus often have to wait 18 months or longer for surgical correction, the treatment of choice for IE (von Noorden, 1988).

Botulinum neurotoxin injection therapy (BNT) has gained popularity as an alternative to surgery in the management of IE. BNT is a protein produced by clostridium botulinum that reversibly blocks the neuromuscular junction by preventing the release of acetyl choline causing a paralysis of striated muscle and fibrosis (Li et al., 2016). This reversibility is due to sprouting of new nerve terminals (Holds et al., 1990). Success rates with BNT as primary therapy have been reported to vary between 33-89% (de Alba Campomanes et al., 2010)(Campos et al., 2000). Moreover, BNT is used intraoperatively as an adjunct to surgery for large angle esotropia with reported satisfactory outcomes of 60-80% (Lueder et al., 2012) (Ozkan et al., 2006) (Wan et al., 2018).

In order to address unmet needs of early intervention for IE in our institution and to establish the role of BNT as primary intervention for IE, in a recently randomized clinical trial (RCT) comparing BNT to surgery as a primary treatment, we reported a satisfactory outcome of 37% with BNT, better in subgroups of children with angle of esotropia of <50PD and under the age of 21months (52%) (Mayet et al., 2021). BNT for large angle IE (>30PD) has been less well studied. A study by de Alba Campomanes et al showed children with esotropia >30PD a satisfactory outcome with BNT was achieved in 36% of cases (de Alba Campomanes et al., 2010). Relevant to our situation, BNT procedures took mean theatre time of 11minutes compared to 72 minutes for standard surgery, potentially allowing 20 more children per

theatre list, the opportunity for earlier intervention which is crucial for the development of fusion and stereopsis (Ing, 1999).

Furthermore, published data on the effect of BNT injections on change of angle relative to baseline esotropia are sparse. In small angle IE, Campos et al reported a change of 30PD with 1 injection in 60 children with a mean baseline angle of 35PD after 5 years of follow up (Campos et al., 2000), similarly McNeer et al showed a mean change of 40PD after 3 years of follow up (McNeer et al., 2000). Issaho et al in subsequent meta-analysis of 11 studies of IE treated with BNT showed an average change in angle of 37PD from a mean baseline of 38PD (Issaho et al., 2017). However, it remains unclear whether the change in the degree of esotropia is a function of the size of the baseline deviation. Moreover, there are few reported data on the effect of the number of BNT injections on the change in angle of esotropia (AoE) (Issaho et al., 2017) and the outcome with subsequent surgery in children with an unsatisfactory response to BNT.

Given the paucity of data on the effectiveness of BNT in large angle IE, we explored the outcome of one or more BNT injections in children with large angle IE, not only for success in alignment but also the effect of variable number of injections on the baseline AoE at a tertiary center in South Africa. A secondary aim of the study was to investigate outcome of surgery in children with residual IE following BNT. The study was approved by the Human Research Ethics Committee of the University of the Witwatersrand.

Patients and Methods

A longitudinal prospective study of children <10 years with large angle IE of >30PD, treated with BNT. The study was conducted from 2015-2019. Diagnosis of IE was based on a history of onset of esotropia before 6 months of age. Children underwent full orthoptic examination and cycloplegic refraction prior to BNT injections. All children with hyperopic correction >

+2.00DS were prescribed appropriate spectacle correction and if after 2months no change in AoE was measured with glasses, the diagnosis of IE was accepted. Study children were examined by an experienced orthoptist and AoE was measured for distance and near, using prism alternate cover test in most cases and Krimsky test for a few children on occasions. For this study, near deviation angles were used for analysis and standardization and on all subsequent visits. Exclusion criteria were 1) significant pattern deviation, 2) hyperopic correction >plus 5.00DS and > 10PD between near and distance measurements. 3) and neurological disorders. Study population included children from the RCT study comparing BNT to surgery in IE (Mayet et al., 2021), and children treated in an open-labelled study of BNT for IE. Included in the RCT where children ≤6years of age, randomized to either the BNT or surgery arms with AoE of >30PD. In the BNT arm, a maximum of 3 injections of BNT were administered. Repeat injections were given if residual esotropia >10PD was measured at follow-up visits. In the case of the open-label cohort of <10years of age, a variable number of 1-3 injections were administered with an option of either repeat injections or surgery, based on parental preference. In all cases, 5 I.U. (0.1ml) of BNT (Botox®-Allergan USA) was injected in both medial rectus muscles as initial therapy. Subsequent injections were given/offered at any of the follow up visits at 6, 12 and 24 weeks. At these visits, 5 I.U. for AoE >30PD and 3 I.U. for AoE ≤ 30PD were given bilaterally. The total cohort was further divided into 2 subgroups, those with esotropia, ≤60PD (group 1) and those with esotropia >60PD (group 2) respectively. Success was defined as alignment within 10PD of orthotropia. BNT injections were started within 1 month of enrollment (6 weeks after initial presentation, except for children given a trial of hyperopic glasses in which case injections were given 2 months after a trial with glasses with no significant change of baseline AoE. Final AoE was assessed after 6months of the last injection. Mean change from baseline angle expressed as a percentage was calculated using $\frac{Baseline\ AoE - Final\ AoE}{Baseline\ AoE} \times 100.$ for each child and a mean calculated for each group.

Adverse events were recorded in the RCT cohort.

Surgical intervention included unilateral or bilateral medial rectus muscle recession, dependent on the residual angle. In children requiring surgery after BNT, surgery was performed after a stable AoE was documented on 2 subsequent visits, first one at 6weeks visit after the last injection, the second, one month later and following a repeat cycloplegic refraction. Post-surgery these children were followed up for a minimum of 6months.

Statistical methods

Chi-square test, or where applicable the two-tailed Fisher's exact test, was applied to compare categorical variables between groups; Student's T test for paired samples was used to compare continuous variables between groups. Univariate and multivariate linear regression analyses were performed to identify predictors of outcome, specifically age of onset, baseline esotropia and number of injections. Data were analysed using STATA 16.1 (Statacorp, College station Texas USA). A *P* value <0.05 was considered significant.

Results

The clinical characteristics, BNT details and changes in AoE are summarized in Table 3.1. The 117 children included in the study, 54 and 63 from the RCT and open-label cohorts had a mean (SD, range) age of 30.3 (18.8,7-100) months and baseline AoE of 62.5 (13.1,35-90) PD. Mean baseline AoE was 51.4(8.4) and 73(7.5) PD for Group 1 and 2 respectively.

Mean reduction in AoE from baseline was 34.5PD (55.2%) for the overall cohort, and 31.5PD (61.3%) and 37.3PD (51.1%) for groups 1 and 2, respectively (p<0.001). Successful outcome was achieved in 30 (25.6%) of the overall cohort, 20 (36.4%) and 10 (16.2%) in groups 1 and 2, respectively [OR (95%CI) = 2.65 (1.13-6.21), p=0.02]. Only 5 children (2 and 3 in each group, respectively) reverted to baseline AoE, i.e., no improvement in AoE

(p=0.0001). Mean (SD) of BNT injections was 2.2 (0.7) for the overall cohort, not significantly different between the 2 groups. Eleven children had dissociative vertical deviation (DVD) and six with latent nystagmus.

Table 3.1 Demographic and clinical characteristics of children with infantile esotropia treated with botulinum neurotoxin therapy

	Overall n=117	**Group 1** 54	**Group 2** 63	***P* value**[§]
Age in months* -	30.3 (18.8)	27.9 (15.5)	32.1 (21.1)	NS
Baseline AoE in PD*	62.5(13.1)	51.4(8.4)	73(7.5)	
Final AoE in PD*	28.0(18)	19.9(14.1)	35.7(17.8)	
% AoE change from from baseline	55.2 (26)	61.3(27.3)	51.1(24.8)	<0.001
Successful outcome -n (%)	30 (25.6)	20 (37)	10 (15.9)	0.02
No. of BNT injections*	2.2	2.1	2.3	NS

*mean (SD), [§]group 1 vs group 2, BNT - botulinum neurotoxin therapy, NS – not significant, PD – prism dioptres, AoE – angle of esotropia

Table 3.2 Linear regression analysis of predictors of change in AoE from baseline to last visit

Variable	Univariate linear regression		Multivariate linear regression	
	β coefficient (95%CI)	*P* value	β coefficient (95%CI)	*P* value
Age	-0.18 (-0.35-0.)01)	0.04	-0.21 (-0.37-0.04)	0.02
Baseline AoE	0.33 (0.15-0.89)	0.004	0.39 (0.15-0.64)	0.002
BNT injections	-2.14 (-10.4-1.4)	NS	-4.53 (-8.78 - -0.28)	0.04

Linear regression analysis for predictors of change in AoE from baseline to last visit are shown in Table 3.2. Age, baseline AoE and number of BNT injections were independent predictors of change of AoE. An increase with each month in age was associated with 0.21PD less reduction from baseline AoE; an increase in baseline AoE of 1PD was associated with 0.39PD less reduction. Comparative scatter plots for the two groups are shown in Figure 3.1. With every additional injection there was a mean reduction of 4.5PD which was marginally significant (p=0.04). Adverse events seen were ptosis in 16.7%, vertical deviation in 5.6% and consecutive exotropia in 24.1%. All of these resolved by 12 weeks.

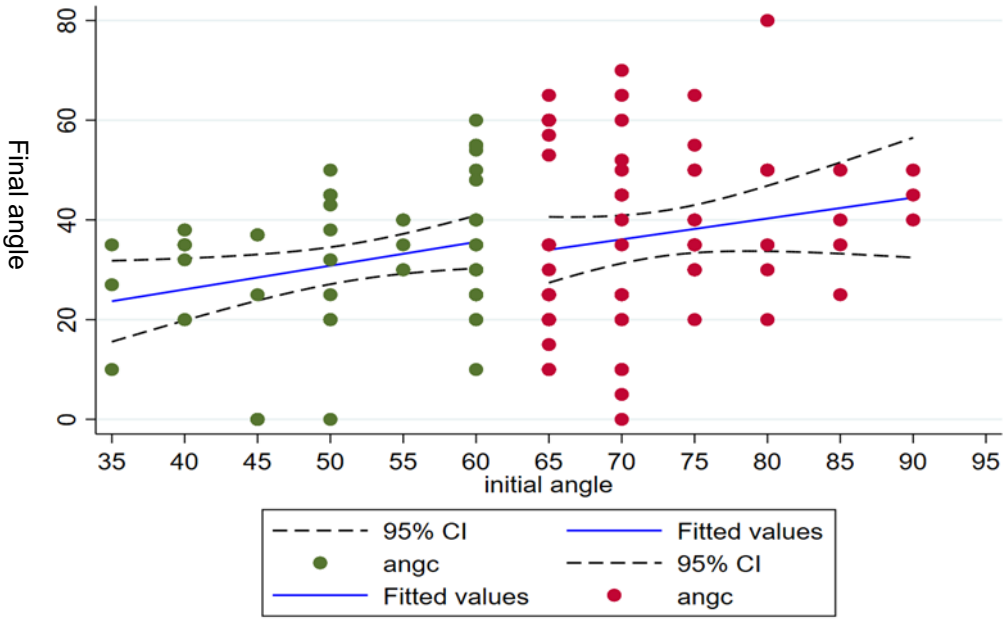

Figure 3.1: Scatter plot showing linear correlation between baseline esotropia and change of angle for large (green) and very large angle esotropia (red)

Of the 87 children who did not meet the criteria for success, 32 underwent surgery, five undergoing only one medial rectus muscle recession and 27 requiring two muscle recession surgery. All required less muscle recessions than that required for their baseline AoE. The remaining 55 patients either were awaiting surgery or refused further intervention. Of the 22 children who were follow-up for a minimum of 6months (mean of 9.6 and range 6-28), 20 were aligned within 10PD of orthotropia after one operation and were stable. (Table 3.3) Consecutive exotropia was seen in one child and another child required resection of lateral rectus as an additional surgical procedure to correct the residual esotropia. Surgery for DVD was not required in any of the cases.

Table 3.3: Outcome of surgery post Botulinum neurotoxin with minimum follow-up of 6 months:

Patients	Baseline angle	Post BNT angle	Surgery-recession	outcome
1	35	25	*UMR 6mm*	ortho
2	40	20	*UMR 5mm*	ortho
3	50	30	*BMR 4mm*	ortho
4	60	35	*BMR 4.5mm*	6PD ET
5	60	30	*BMR 4mm*	5PD ET
6	60	20	*UMR 5mm*	ortho
7	60	30	*BMR 4mm.*	5PD ET
8	65	40	*BMR 5mm*	ortho
9	65	30	*BMR 4mm*	10PD ET
10	65	30	*BMR 4mm*	10PD ET
11	70	28	*BMR 3.5mm*	8PD ET
12	75	45	*BMR 5.5mm*	6PD ET
13	75	40	*BMR 5mm*	5PD ET
14	75	40	*BMR 5mm*	ortho
15	75	20	*UMR 5mm*	10PD ET
16	80	60	*BMR 7mm*	ortho
17	80	50	*BMR 6mm*	10PD XT
18	85	50	*BMR 6mm*	ortho
19	85	45	*BMR 5.5mm*	ortho
20	85	45	*BMR 5.5mm*	15PD ET
21	90	45	*BMR 5.5mm*	ortho
22	90	40	*BMR 5.0mm*	ortho

UMR = unilateral medial rectus recession; BMR = bilateral medial rectus recession; ET = Esotropia; XT = Exotropia; Ortho = orthotropia

Discussion

In this prospective study of large angle IE, mean reduction of AoE from baseline was 55.2% for the overall cohort following a mean of 2.2 BNT injections. All except 5 (4.3%) of the children had a reduction in AoE following BNT. Not surprisingly, relative reduction from baseline in AoE was significantly less in very large angle esotropia. Previous studies of BNT for IE with mean baseline AoE of 33 and 43PD with similar samples sizes and mean number of injections, have shown reductions in AoE of 45.8 and 40.0% (Scott et al., 1990) (McNeer and Tucker, 2010).

Both age and baseline AoE are known to impact on response to BNT in IE generally, as was the case in the present study for both large and very large angle IE. Irrespective of AoE, children ≤24 months responded better than children >24 months. Several previous reports have shown that infants ≤12 months do even better with an average 30PD reduction of AoE from baseline (Campos et al., 2000) (McNeer and Tucker, 2010). By contrast, in children of mean age 33 months, have been found to have a AoE reduction of 17PD (Chen et al., 2013).

Mean number of BNT injections (2.2) were similar for large and very large angle IE groups. There was a marginally significant relationship of percentage change in AoE from baseline and number of BNT injections. Other studies have shown a relationship between the number of BNT injection and extent of reduction in AoE. Issaho et al reported a mean change in AoE of 17.3-18PD with a single BNT injection in 2 studies and 31-42PD with 2 injections in 4 studies (Issaho et al., 2017).

Although not the major objective of the study, a quarter of children achieved successful outcome, 33% of the children with large IE and 15.9% in those with very large IE. Compared to surgery this is a poor response, however in the context of long waiting lists for surgery there is a role for BNT in children treated by ≤24months of age and with baseline AoE ≤60PD. A third would

potentially develop binocular vision who otherwise would not, waiting for surgery.

Given that BNT reduced AoE by more than 50% in very large angle IE, our findings indicate that less muscle recession may be needed in children who require augmented surgery to achieve alignment. This is at odds with some current recommendation of maximal recessions of muscles in combination with BNT (Lueder et al., 2012) (Tuğcu et al., 2017). Our findings may support Wan et al who have suggested a revised surgery nomogram of 1.7PD greater effect per millimeter of recession with BNT in combination with surgery than surgery alone (Wan et al., 2018).

The response to surgery in failed BNT cases has not been reported in the literature.

In the present study successful motor outcomes in these children were achieved in 20/22 children after a single procedure and alignment was stable after 6months follow up. This is comparable to surgery as a primary treatment as evidenced by the results of the RCT (in the surgery arm) where 33/47 were aligned with one procedure (Mayet et al., 2021). A notable benefit was the less extensive recessions required and avoiding 3 muscle surgery altogether. The fact that some children required only 1 muscle recession again implies less theatre time and less discomfort.

The limitation of the study are several, the variable age of presentation inherent in the demographics, our inability to assess higher functions of binocular fusion and stereopsis in children that achieved alignment, the relative short follow up of 6month after final intervention and dose incrementation of BNT on outcome as has been suggested by others (Alshamlan et al., 2021). A relative limitation would be the protracted period to alignment with BNT compared to surgery, however the long surgery waiting period justifies BNT use in our setting.

To summarize BNT was associated with a successful outcome in a quarter of children with large IE. These results suggest that BNT is a viable alternative intervention for large angle IE in surgery resource constraint setting. Young children and smaller baseline AoE were more likely to have a successful outcome with BNT important predictors of reduction of AoE following BNT while the number of injections did not. Moreover, in those children who did not achieve a successful outcome with BNT, subsequently surgery may require less muscle recessions than what would have otherwise been necessary to correct the original AoE.

CHAPTER 4

COST COMPARISON BETWEEN BOTULINUM NEUROTOXIN AND SURGERY IN THE TREATMENT OF INFANTILE ESOTROPIA IN A TERTIARY PUBLIC HOSPITAL

Abstract

Purpose: to compare the cost implications of Botulinum neurotoxin injection (BNT) to surgery in infantile esotropia (IE) in a public/government funded hospital.

Method: A simple costing comparison was undertaken for a randomised clinical trial in IE. Patients were randomized to receive either BNT or standard surgery. The participants in the BNT arm were further subdivided into subgroups based on their age in months (m) and degree of esotropia in prism dioptres (PD) at presentation: G1 ≤ 60PD/24months(m), G2 ≤ 24m/>60PD, G3 >24m/≤60PD, G4 >24m/>60PD. The costs were calculated for each arm from primary treatment to eventual satisfactory outcome defined as orthophoria or microtropia (≤ 10PD). A bottom-up costing analysis was done for single and multiple procedures for each arm. Comprehensive variable costs as well as fixed costs were calculated at each point of intervention and expressed in local currency ZAR (US$1=ZAR15.00). Costing was analysed for surgery and BNT sub-groups (based on clinical success)

Results: There were 101 patients enrolled in the trial. 54 in the BNT arm and 47 in the surgery arm. Cost for single surgery and single BNT was ZAR 7743.04 and 1713.14 respectively. A favourable clinical outcome was achieved in 72% of surgery arm and 37% of BNT arm. The mean cost for eventual favourable outcome in BNT arm was ZAR9158.08 and in surgery arm ZAR9124.27 (p=0.26). Mean cost in G1 was ZAR6328.45,

in G2 ZAR7197.45, in G3 ZAR11891.93 and G4 ZAR12882.44 (p=0.018).

Conclusion: BNT has a cost benefit in IE and is a viable option in the primary treatment of IE in resource constrained regions. Clinical outcomes and economic benefit in smaller angle of esotropia and younger patients are comparable to surgery.

Background

Strabismus or misalignment of the eyes in children is frequently seen in paediatric ophthalmology units. Uncorrected strabismus results in functional impairment with regard to development of binocular vision and possible amblyopia, as well as psychosocial problems (Pathai et al., 2010b). Infantile esotropia (IE) is a common type of concomitant convergent strabismus and in our region accounts for the majority of cases (Tinley and Grötte, 2012). Surgery is the standard of care in IE with a success rate of about 75-80% (Kushner and Morton, 1984). Surgical correction of strabismus in adults has been shown to be highly cost effective in developed countries (Beauchamp et al., 2005).

The duration of surgery is approximately one hour, and this is a significant consideration in resource constrained areas where theatre availability is at a premium. In South Africa and other developing countries, the quest for alternative and less resource intensive procedures are challenging and the need to minimize cost while maintaining quality of service is an ongoing balancing act. Waiting lists for surgical corrections are more than one year due to the large number of children, compounded by the misconception that strabismus repair is largely “cosmetic” and relegated as a low priority procedure in multi-disciplinary hospitals.

Botulinum neurotoxin injections (BNT) have been used as an alternative treatment option (Scott, 1980) (McNeer et al., 1998) (de Alba Campomanes et al., 2010), BNT injections take about twenty percent of the total time in theatre when compared to surgery and are associated with less discomfort and pain. In a meta-analysis Issaho reported on nine studies using BNT for IE with success rates ranging from 37% to 100% (Issaho et al., 2017). It has been reported that BNT is less effective than surgery in large angle esotropia (de Alba Campomanes et al., 2010). In a randomised clinical trial (RCT) conducted

at our institution, we showed that BNT was successful in 37% overall for the cohort but in selected patients, specifically those younger than 24 months and those with an esotropia <50PD, alignment was achieved in over 50% of the study cohort (Mayet et al., 2021).

Economic evaluation (EE) is defined as a "comparative analysis of alternate courses of action in terms of both their cost and consequence" (Drummond and Mooney, 1982). Cost utility analysis (CUA) is a commonly acceptable method of reporting EE and considers cost benefit ratio using quality adjusted life years (QALYs) gained. Benefit or utility gain can be calculated using several methods; Time Trade Off, Standard Gamble or Vision Analogue Scale but none has been validated in children and simple cost comparison may be more appropriate (Thorrington and Eames, 2015). There is a paucity of published articles on the cost of BNT injections in treating strabismus patients and one study showed comparable cost with long term BNT use and surgery in adults (Gardner et al., 2008).

This paper aims to compare the cost implications of BNT and surgery, and to determine a model to predict which group of children with IE may benefit from BNT injections as first line treatment, while keeping overall costs to a minimum.

Methodology

A simple costing analysis was undertaken using the results of a prospective randomised study over a period of 3 years from 2015 to 2018 comparing efficacy of BNT injections to surgery. One aspect of the study was to compare the cost implications between the two procedures to the hospital, both in terms of direct variable and fixed costs. The hospital is a government run hospital in South Africa Gauteng Province and all surgery is funded fully by the government with no reimbursement from health insurance and no co-payment collected from patients.

The detailed protocol for the study is described elsewhere (Mayet et al., 2021) but briefly children between the age of 6months to 6 years, diagnosed with large angle IE, defined as esotropia of ≥40 PD were included.

Children with other forms of esotropia, those with significant patterns and children with neuro-behavioral disorders were excluded.

Children were grouped into 2 age categories, those ≤ 24 months, and those > 24 months of age. Within each age category, participants were randomised by an independent study assistant and assigned to either the BNT (odd numbers) or surgery (even numbers) arms. In the surgery arm children received standard bilateral medial rectus muscle recessions for esotropia of ≤ 60PD and maximum recessions of 7.0mm augmented with 3units of Botox^{R} (Allergan US) in esotropia >60PD. Unsuccessful outcomes defined as misalignment of >10PD were subjected to BNT injections as a second procedure at the 3month visit and a second surgical procedure thereafter in failed cases. In the BNT arm, patients initially received 5unit, repeated at any of the follow up visits at 3, 6, 12 and 24week visits, if alignment was > 10PD. A maximum of 3 injections were given before surgery was offered to correct the residual esotropia. For this study 1 vial of Botox^{R} 100units was used for 8 patients. Injections were given sub-conjunctively as described by Benabent (Benabent et al., 2002) not requiring electromyography needles. The decision of administering a maximum of 3 injections was arbitrary, based on other studies that reported a mean number of 1 to 2.2 injections given in IE (Scott et al., 1990) (McNeer et al., 1998) (de Alba Campomanes et al., 2010).

The time taken in theatre, from anaesthetic induction to transfer out of operating theatre for each procedure was recorded. The procedures were standardised for each arm with one surgeon (IM) performing all procedures. A bottom up, micro-costing (Potter et al., 2020) was done for each of the 2 procedures for a public/government hospital.

Clinical outcome was based on achievement of orthophoria (or within 10PD of orthophoria).

Cost calculations

Variable costs were calculated from the information received from hospital authorities. Salaries of staff were calculated based on annual salary, hourly rate earned for each category of staff (at Department of Public Service and

Administration rates) and the pro rata amount based on time taken for each procedure. Staff salaries calculated were for 1 specialist surgeon, 1 specialist anaesthetist, 1 professional nurse, 2 assistant nurses and recovery professional nurses. Other staff including the pharmacist, orthoptist, porter, hospital clerks, ward nurse and cleaners who were not directly involved with operative procedure were included in fixed costs. Fixed costs also included ward admission (bedding, preparation, food) water and electricity. Fixed costs were calculated based on the daily cost per patient of a hospital admission in a tertiary hospital supplied by the finance division of the hospital. Fixed costs for this study were calculated based on total hospital time of 6hours in the surgery arm and 2hours in the BNT arm. Unit prices of medication and disposable used, were obtained from the hospital pharmacy and procurement office. Although it is difficult to calculate cost of theatre per minute in the hospital, this was estimated using rates used by the private sector and based on a study conducted in the South African comparing costs in the private and public sector (Ramjee, 2013). A portion of the private sector cost was assumed to be basic costs of theatre applicable in the public sector (we assumed a third of the cost calculated in the private sector, based on discounted rates on medicines and disposable in the government/public sector on the one hand and the need for profit and taxes paid in the private sector on the other hand). All calculations were expressed in South African Rands (ZAR) and at the time of the study $1.00 US was equivalent to ZAR15.00 (or ZAR20.00/£1.00 UK).

Various clinical subgroups and their costs were analysed, comparing surgery to single and multiple BNT injection procedures based on our RCT findings. Further analysis was done to assess viability for subsequent surgery in failed cases. Using a simple economic model, costs were calculated for different subgroups and predictions of the cost benefit were then made.

For this analysis the BNT group were divided into 4 sub-groups based on literature reports identifying age of presentation and degree of esotropia to be significant variables (de Alba Campomanes et al., 2010).The subgroups in months(m) and prism dioptres (PD) were as follows: G1 children ≤24m of age and ≤ 60PD; G2 children ≤ 24m and >60PD; G3 children >24m and ≤60PD; G4 children >24m and >60PD.

Statistical Analysis

The total cost in each arm was expressed as means (standard deviation). The difference in cost between the 2 arms was tested using the Wilcoxon rank sum test. The cost difference between the number of procedures in the 2 arms was tested using the Kruskal-Wallis test

Parents of participants did not participate in the design, or conduct, or reporting, or dissemination plans of our research.

Results

Of the 101 patients analysed in this study. 54 patients were enrolled in the BNT arm and 47 in the Surgery arm.

Overall success rate for alignment was 37% in the BNT arm (20.3%, 9.3% and 7.4% with 1,2 and 3 injections respectively) and 70.2% after 1 procedure in the surgery arm. Success in the surgery arm was independent of age and degree of esotropia while in the BNT arm, success was associated with age of intervention and degree of misalignment, with age <21months and degree <50PD being comparable statistically, to surgery alone. Sub-group analysis of the different groups in the BNT arm showed that, G1 had an overall success of 11/16(68.8%), G2 5/15(33.3%), G3 2/10(20 %) and G4 2/13(15.4%). The mean time taken was 11min for BNT injection and 72min for surgery.

Economic Findings

Detailed costing breakdown are shown in table 4.1. Time in theatre cost (ZAR3600 for surgery and ZAR550 for BNT), staff cost (ZAR1649 for surgery and ZAR278.04 for BNT) and consumables (ZAR1001.76 for surgery and ZAR243.80 BNT) were the main cost determinates.

Table 4.1 Itemized costing per procedure for BNT and Surgery expressed in South African Rands (ZAR). $1.00 = ZAR15.00

	Botulinum			**Surgery**		
Item	Unit/pt	Unit cost/pt	Total pt cost	Unit/pt	Unit cost/pt	Total pt cost
Anaesthetic						
Short line	1.0	15.00	15.00			
IV line				1.0	35.00	35.00
Ringers' sol				1.0	8.68	8.68
Propofol(R38/50ml)	5.0	0.76	3.80	5.0	0.76	3.80
Sevoflurane (R792.48/250ml)	10.0	3.68	36.80	20.0	3.17	63.40
Laryngeal tube				1.0	70.00	70.00
Oral mask	1.0	4.00	4.00			
miscellaneous			15.00			15.00
surgical						
gloves	1.0	12.00	12.00	2.0	12.00	24.00
4/0 silk				2.0	81.46	162.92
5/0 vicryl				2.0	119.79	239.58
8/0 vicryl				1.0	138.96	138.96
cautery				1.0	75.00	75.00
Sponges/packet				1.0	48.00	48.00
Botulinum R1552.00/100u*	10.0	15.52	155.20			
Insulin syringes	2.0	1.00	2.00			
Balance salt solution(10ml)				1.0	12.00	12.00
TTO ointment				1.0	48.00	48.00
Time in theatre (min) **	11.0	50.00	550.00	72.0	50.00	3600.00
Staff required						
Surgeon (R462.92/hour)	11.0	7.68	84.52	72.0	7.68	553.10
Anaesthetist (R462.92/hour)	11.0	7.68	84.52	72.0	7.68	553.10
Professional nurse (R150/hour)	11.0	2.50	27.50	72.0	2.50	180.00
Assistant nurse x2 (R120/hour)	11.0 x2	2.00	44.00	72.0x2	2.00	288.00
Recovery nurse (R150/hour)	15.0	2.50	37.50		2.50	75.00
Time in recovery	10.0	25.00	250.00	20.0	25.00	500.00
Fixed costs ***	2 hours	176.25	352.50	6 hours	176.25	1057.50
Total			1713.14			7743.04 #

*Cost of Botulinum 100units/8patients
**Cost of theatre based on gases used, microscope use, bedding @ZAR50/min (assumed 1/3 of private rates)
***fixed cost – include water, electricity, ward stay @ ZAR4600/day, allowing for total hospital time of 2h for BNT and 6h for surgery
cost for surgery if BNT given would be ZAR7900.24

The cumulative costs for multiple procedures for both arms are shown in Table 4.2.

Table 4.2: Summary of cumulative cost in 2 arms (in ZAR)

	Surgery arm n=47		BNT arm n=54		
No. of procedures	Type of procedure	Cumulative cost	Type of procedure	Cumulative cost	P value
1	BMR if ≤ 60PD (19pts) BMR + BNT if >60PD (16pts)	7743.04† 7900.24‡	BNT 5u (11pts)	1713.14	0.0001*
2	BNT 5u (8pts)	9456.18† 9613.38‡	BNT 5u (5pts)	3426.28	
3	LR resection (4pts)	17200.22† 17356.42‡	BNT 5u (4pts)	5139.42	
4	----------	----------	BMR (34pts)	12882.46	
Mean cost		9124.27		9158.08	P=0.26

*Kruskal-Wallis: † surgery only: ‡ surgery augmented with BNT

BMR – bimedial rectus muscle recession, LR -lateral rectus

The cost of a single BNT procedure was found to be ZAR1713.14 (in 11 children), the cumulative cost of BNT injection was ZAR3426.28 for 2 injections (in 5 children) and ZAR5139.42 for 3 injections (in 4 children). The cumulative cost in failed cases requiring surgery was ZAR12882.46 (in 34 children). The cost of single surgical procedure was ZAR7743.04 for esotropia ≤ 60PD and ZAR7900.24 in esotropia >60PD due to the augmented BNT injection. Using Wilcoxon rank sum test there was no statistical difference in the mean cost between the surgical arm and the BNT arm (p=0.26). The mean cost was ZAR9158.08 and ZAR9124.27 in BNT arm and in the surgery arm respectively.

Mean cost (SD) for the subgroups in the BNT arm were 6328.45 (2655) in G1, 7197.45 (3103.73) in G2, 11891.93 (6406.28) in G3 and 12882.44 in G4. In comparing the cost between the different BNT groups there was a clear difference between groups (p =0.018) although the numbers were small in each group.

Scenario model

To better illustrate the cost between the 2 procedures we extrapolated success rates for the surgery and BNT subgroups from the RCT reflecting the efficacy of the 2 procedures for 100 patients in each group. In the surgery arm, 70 would require 1 procedure, 17 would require 2 procedures and 13 would require 3 procedures at total cost of ZAR924466.47 in successfully treating 100 patients. Comparatively, the total cost for BNT would be ZAR567472.25 in arm G1 and ZAR1155711.90 for the G4 subgroup for the similar 100 patient model. (Table 4.3).

Table 4.3: Model predicting total cost for eventual successful outcome for 100 cases in each group based on expected response.

	1st	2nd	3rd	4th	total projected/100
Surgery	7743.04x70	9456.18x17	17199.22x13	0	924466.47
BNT G1	1713.14x38	3426.28x12	5139.42x19	12882.46x31	567472.25
BNT G2	1713.14x13	3426.28x20	0	12882.46x67	949282.19
BNT G3	1713.14x20	0	0	12882.46x80	1064859.60
BNT G4	0	3426.28x8	5139.42x8	12882.46x84	1155711.90

Cost comparison of 100 patients in each group based on actual clinical outcome of original cohort.
Surgery arm: 1st procedure, surgery, 2nd procedure BNT, 3rd procedure surgery in 70, 17 and 13 cases respectively.
BNT arm numbers reflect expected successful outcome with each procedure in the different groups.
G1 children ≤24 months of age and ≤60PD, G2 children ≤24m and >60PD, G3 children >24m and ≤60PD, G4 children >24m and >60PD (cost in ZAR)

Discussion

Surgical correction of strabismus has been demonstrated to be cost effective in studies conducted in adults in the USA, and by extension in children (Beauchamp et al., 2005). Other related strabismus studies have reported probable cost effectiveness in the screening for amblyopia (König and Barry, 2004) (Rein et al., 2012) while cost implications with the use of prescription glasses for various ophthalmic conditions including esotropia have also been reported (Malvankar-Mehta et al., 2018). Such studies have been undertaken in developed countries and in general, economic evaluation analyses are sparse for developing countries (Griffiths et al., 2016). Our study was designed to establish the economic cost in the treatment of infantile esotropia to contain costs.

The study was a simple cost comparison between botulinum neurotoxin injection and surgery which is the standard of care in infantile esotropia in a government run public hospital where most of the population is treated. The study was necessitated by the heavy burden on theatre resources in our region with the consequence that strabismus cases especially in children are often delayed. In performing cost analyses we used activity based costing (ABC) bottom up method as this is deemed appropriate (Mercier and Naro, 2014). The success rate of BNT has been shown to vary and in our study, surgery was twice as successful however, in our setting at least a third of children were aligned at an earlier age using BNT than if they had waited for standard surgery. Moreover, in children (G1) with angles of deviation <60PD and injected at a younger age (<24m) the clinical success was found to be 68% and comparable to surgery but with a clear economic benefit in considering BNT as a first line intervention. Even in G2 and G3 BNT was economically viable and should still be considered as first line option. Surgery should be considered in older children with very large angles (G4).

From our findings the main cost drivers were associated with time spent in theatre, which was 6 x more with surgery, resulting in greater the staff costs followed by consumables needed and anaesthesia.

Limitations: Several difficulties were associated with costing in large government hospitals such as evaluating fixed costs like electricity, water and sanitation that would apply even at times when theatres are not functional. These estimations or assumptions may skew the costs.

The multi dosing of BNT is probably only applicable in public hospitals seeing a lot of strabismus patients and scheduling regular BNT theatre lists.

With the use of BNT, repeat injections require multiple anaesthesia which theoretically increases the risk to the child although the BNT children had shorter anaesthetic time and no intubation. Longer follow up time may be required for stable alignment and reduce the potential for fusion and depth perception. This may be undesirable in developed countries where waiting times for surgery are short. In developing countries these waiting times may be

much longer making BNT a more viable option. The study did not address the indirect cost to the patient and society.

Conclusion

The knock-on effect of time saved with BNT, allowing more children to be treated earlier as well as the cumulative cost involved is a mitigating factor in considering BNT as a viable first line option. This consideration is even more compelling in the subgroup of patients ≤24m of age and ≤ 60PD where the clinical outcome is comparable to surgery and the economic advantage more pronounced. In children ≤ 24m and >60PD and >24m and ≤60PD BNT may economically still be an option. In children >24m and >60PD surgery should be considered as treatment.

CHAPTER 5

CONCLUSION

Strabismus forms a large part of referrals to most paediatric ophthalmology clinics and impacts on the theatre workload in resource constrained settings in the developing world. While surgery remains the gold standard of treatment for IE with a high surgical success rate, it is both time and resource consuming. Botulinum neurotoxin therapy has been used in the treatment of strabismus for at least 40 years and its role as an alternative therapeutic intervention in IE continues to evolve. Uncertainty in its use revolves around the lack of prospective research in the field. Many studies are case series, very few prospective, and in general lack standardization. The situation in low to middle income countries is even more evident with a general lack of research focusing on clinical efficacy and economic viability in many aspects of health care. This research work addressed some of these issues, focusing on the clinical efficacy and cost effectiveness of BNT in comparison to surgery in the management of IE in a tertiary hospital.

Objective 1: *The comparison between BNT and surgical procedures in the treatment of IE in a randomised control trial*.

In this randomized controlled clinical trial of 101 children comparing BNT to surgery for IE, a complete response in the BNT arm was achieved in 37% of children and in children with AoE of <50PD and children <24m of age favourable response was observed in 50%. In comparison, as expected surgery complete response was achieved in 70.2% which would favour surgery as the preferred procedure, however in resource constraint regions at least a third of children benefited from BNT, affording some, the potential to gain binocular vision. Known complications of ptosis, exotropia and vertical deviation were seen in 20% but all were transient and resolved within one month. Early exotropia was associated with higher overall success. Although not a primary objective, the RCT also showed that in very large AoE,

augmenting surgery with BNT is associated with a high success rate and should be preferred over 3-4 muscle surgery.

The study is the first truly randomised trial comparing surgery to BNT injections with a large study cohort. It corroborated the high success rate associated with surgery reported in the literature. Surgery is still the gold standard of managing large angle infantile esotropia. However, BNT is a viable primary treatment option for infantile esotropia. BNT is safe and a short procedure and could be considered as a first line intervention in developing countries where resources are limited with respect to waiting time for surgery. Further, BNT was found to be more effective in children ≤24 months of age and with baseline angles of ≤60PD of esotropia.

Objective 2: To establish if age of intervention or angle of deviation impacts on outcome and to identify children most likely to benefit from BNT injections. Although the initial intention was to stratify children into infants, less than 3 years and older than 3 years, insufficient recruitment of infants into the study resulted in categorizing children into 2 age groups of ≤ 24months and > 24 months. Novel to the study on IE, ROC analysis demonstrated that threshold for optimal response using BNT was 50PD for baseline AoE at 21months of age. Young children and smaller baseline AoE were more likely to have a successful outcome with BNT important predictors of reduction of AoE following BNT while the number of injections did not. Moreover, in those children who did not achieve a successful outcome with BNT, subsequently surgery may require less muscle recessions than what would have otherwise been necessary to correct the original AoE.

Objective 3: To establish the degree of change in the angle of deviation from baseline to post injection and in failed cases, whether subsequent surgery performed for the new angle was stable.

In the open labelled study of 117 children given 1, 2 or 3 injections, a change of the baseline AoE was evaluated in this larger cohort. Mean baseline AoE was 62PD and the mean reduction in baseline AoE was 28PD (55.2%). Age at intervention and size of baseline AoE were significant predictors of degree of change. Number of injections was a marginal predictor. From this finding, a recommendation that response to BNT should be limited to two injections after which surgery should be offered. Previous studies have not reported the response to serial injections.

From previous published studies of large angle esotropia it was anticipated that a lot of our children would require surgery. In those children who did not achieve a successful outcome with BNT, subsequent surgery required lesser muscle recessions than would have otherwise been necessary to correct the original AoE. Alignment was stable after 6months of follow-up. In very large angle esotropia requiring 3 muscle surgery, supplementary BNT use could potentially halve the amount of recession surgery that would be required

Objective 4: To compare the economic costs between surgery and BNT in a government-based or public hospital.

In the final analysis, a cost evaluation comparing surgery and BNT was done. This costing analysis has not been undertaken previously and its importance in low- to middle-income countries is particularly relevant. A detailed breakdown in a bottom-up costing was done. Cost per surgery session was ZAR7743.04 and cost of BNT injection in theatre was ZAR1713.47. Time taken in theatre was the most important cost driver. Statistically the two groups were comparable with the mean cost to eventual success being similar (ZAR9124.27 and ZAR9158.08 for surgery and BNT, respectively). Using a cost-benefit model, younger children with AoE of ≤60PD had a 68.8% clinical success rate with BNT, and it was in this group that BNT was highly cost effective.

The knock-on effect of time saved with BNT, allowing more children to be treated earlier as well as the cumulative cost involved is a mitigating factor in considering BNT as a viable first line option. This consideration is even more

compelling in the subgroup of patients ≤24m of age and ≤ 60PD where the clinical outcome is comparable to surgery and the economic advantage more pronounced. In children ≤ 24m and >60PD and >24m and ≤60PD BNT may economically still be an option. In children >24m and >60PD surgery should be considered as treatment.

Way forward: The studies undertaken lack robustness due to limited number of cohorts. Randomised trials are time consuming and multicentered randomised trials are needed to verify our findings and fill in gaps that remain unanswered such as incremental dosage of BNT based on the size of the angle, methods of administering BNT injection (under direct vision, with electromyography assistance or transconjunctival approach) and the use of alternative synthetic agents such as purified oncobotulinum in strabismus.

On reflection, recruitment of children and the follow up to outcome in the RCT proved to be time challenging and multi-centered trials are more prudent. Our cohort children tended to present at a later age, eliminating the chance of developing binocularity, and the aim of correction should be based on psycho-social grounds in these patients. Priority should be given to children younger than 24m.

In summary, from the study it is recommended that BNT be used as primary management in IE for children less than 24months of age, with a baseline AoE 55PD, that a maximum of 2 injections be tried before offering surgery. Augmenting surgery with BNT in large angle IE should be preferred over 3 muscle surgery as a primary.

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Appendices

Appendix A

Ethics approval

R14/49 Prof Ismail Mayet and Dr Susan Williams

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)

CLEARANCE CERTIFICATE NO. M140225

NAME: (Principal Investigator)	Prof Ismail Mayet and Dr Susan Williams
DEPARTMENT:	Ophthalmology St Johns Eye Hospital Chris Hani Baragwanath Academic Hospital
PROJECT TITLE:	Botulinum Toxin in the Management of Childhood Esotropia
DATE CONSIDERED:	28/02/2014
DECISION:	Approved unconditionally
CONDITIONS:	
SUPERVISOR:	Prof M Tikly
APPROVED BY:	Professor PE Gleaton-Jones , Chairperson , HREC (Medical)
DATE OF APPROVAL:	04/04/2014

This clearance certificate is valid for 5 years from date of approval. Extension may be applied for.

DECLARATION OF INVESTIGATORS

To be completed in duplicate and **ONE COPY** returned to the Secretary in Room 10004, 10th floor, Senate House, University.

I/we fully understand the conditions under which I am/we are authorized to carry out the above-mentioned research and I/we undertake to ensure compliance with these conditions. Should any departure be contemplated, from the research protocol as approved, I/we undertake to resubmit the application to the Committee. I **agree to submit a yearly progress repo rt**.

04/04/2014

Principal Investigator Signature Date

PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES

Appendix B Paper 1

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The ROYAL COLLEGE of OPHTHALMOLOGISTS

ARTICLE

Botulinum neurotoxin injections in essential infantile esotropia—a comparative study with surgery in large-angle deviations

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Abstract

Purpose To compare botulinum neurotoxin (BNT) injections to surgery as first-line therapy in large-angle essential infantile esotropia (IE).

Patients and methods Children between the ages 6 months and 6 years with IE of ≥40 prism dioptres (PD) were randomised to either a maximum of three BNT injections or surgical intervention of bimedial rectus muscle recession for angles ≤60 PD and augmented with BNT injection in angles >60 PD. Time taken for each procedure was documented. Orthophoria or misalignment of ≤10 PD was regarded as a complete response (CR). Follow-up visits were done at 3, 6, 12 and 24 weeks.

Results Mean (SD) age and baseline angle of esotropia were 26.9 (14.5) months and 61.9 PD (12.8), respectively, for the overall cohort. The proportion of children who achieved CR was significantly higher in the surgery arm compared to the BNT injection arm (OR = 4.01, 95% CI 1.74–9.22) but the time taken was six times longer ($p < 0.0001$). In the BNT arm, 55.2% of children aged ≤24 months and 16% of children >24 months achieved CR. In children with esotropia ≤60 PD, CR was achieved in 50% while those with esotropia >60 PD CR was achieved in 25%.

Conclusion Surgery remains the gold standard for treatment of esotropia but BNT injection is a safe and effective alternative in children ≤24 m and with smaller angles of esotropia ≤60 PD in resource-limited centres.

Introduction

Essential infantile esotropia (IE), also referred to as congenital esotropia, has an early onset of approximately 6 months of age. It is characterised by a large angle of deviation and accounts for 8.4% of esotropia cases [1]. Surgical correction is the preferred standard management and is associated with reported success rates between 64 and 80% [2–4]. Ing has shown that early surgical intervention and correction of the misalignment may result in the development of stereopsis [5]. In his study, children surgically aligned before 12 months of age developed some degree of stereopsis in 73% and those aligned after 18 months developed stereopsis in 58%. Others have shown that children aligned after 24 months of age did not develop stereopsis [6, 7].

In developing countries like South Africa, IE is reported to be the most common type of strabismus, accounting for 74% of esotropia in childhood [8]. Timeous intervention presents a major challenge in resource-constrained settings such as the public health sector in our country.

Following the introduction by Scott [9] of botulinum neurotoxin injection therapy (BNT) in the treatment of various strabismic conditions, BNT has gained popularity as an alternative treatment option for IE. Results, however, have been mixed. Success rates have varied from 36 to 78% and are related to the degree of strabismus and the age of intervention [10, 11].

The current waiting time for strabismus surgery at our tertiary centre is more than a year from the time of initial presentation and a delay in surgery is known to compromise various aspects of a child's visual development with regard to fusion and stereopsis [5–7] as well as to cause long-term psychosocial issues [12]. A randomised controlled study was undertaken to compare BNT injection to surgical correction as a first-line treatment for large-angle IE. In a Cochrane review, Rowe and Noonan identified six RCT associated

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with BNT use in strabismus, two in IE and no RCT comparing BNT to surgery in large-angle esotropia [13].

Study methods

A prospective, randomised unblinded study comparing BNT to surgery in IE was conducted from January 2015 to January 2018, in a large tertiary hospital. The study was approved by the Human Research Ethics Committee of the University of the Witwatersrand (Approval no. M140225) and conducted in accordance with the tenets of the Declaration of Helsinki.

Inclusion criteria

Children with onset of esotropia before 6 months of age; with large-angle IE, defined as esotropia of ≥40 prism dioptres (PD), between the ages of 6 months and 6 years at baseline; informed written parental consent.

Exclusion criteria

Children with significant pattern deviation, neurological impairment and hyperopia of >+5.00 dioptres.

Children underwent a full examination including a cycloplegic refraction, fundus examination and orthoptic assessment. Those with a refractive error ≥+2.50 DS were initially given their prescription and if there was no change or minimal change in their esotropic angle, patients were classified as IE and enrolled in the study.

Children were stratified according to two age categories; those ≤24 months and those >24 months. Stratification based on 24 months rather than 12 months was necessary in view of the low enrolment number in the very-young age group and based on previous findings of the potential of developing fusion before and after 24 months [7]. Within each age category, participants were randomised by an independent study assistant and assigned to either the BNT (odd numbers) or surgery (even numbers) arms. Figure 1 shows the schematic randomisation and follow-up.

In the BNT arm, BNT (Botox^{TM} Allergan) was injected in each medial rectus muscle, administered subconjunctively after the muscle was grasped using forceps as described by Benabent et al. [14]. All children received an initial dose of 5 units (U) that was repeated, for a maximum of three injections if the esotropia was >10 PD at visits at 3, 6, 12 or 24 weeks following the last injection. The dosage at subsequent visits depended on the degree of esotropia, 5U for deviations ≥40 PD and 3U for deviations <40 PD.

In the surgical arm, children underwent standard bilateral medial rectus muscle recession surgery for esotropia ≤60 PD. The medial recti were recessed to a maximum of 7 mm with 3U of BNT given intraoperatively to each recessed muscle in cases >60 PD to augment the recessions. No child had three-muscle surgery for the larger angles as an initial procedure.

Participants in both arms were assessed at 3-, 6-, 12- and 24-week post-procedure (patients in the surgery arm were also seen day 1 post-surgery) for possible complications. Children in the BNT arm who had an unacceptable outcome after three injections were offered surgery after a stable angle measurement on two successive visits, 1 month apart. In the surgical arm, all unacceptable outcomes with residual esotropia, received BNT into the recessed muscles at the 6 weeks post-operative visit and surgery as the third procedure if required, once a stable angle was attained on two consecutive visits.

Outcome measure

Complete response (CR) was defined as orthophoria or residual esotropia of ≤10 PD [15], partial response (PR) as residual esotropia of >10 PD and ≤20 PD and deemed acceptable by the parents, and failures or non-response (NR) as >20 PD.

The total theatre time taken for each arm of the study was also recorded.

Sample size

A sample size of 98 (49 per arm) was calculated using a Pearson Chi-squared test with the proportion of success set at 0.65 for the surgery arm and 0.37 for the BNT arm at a power of 80% and an alpha level of 0.05.

Statistical analysis

Data analysis was restricted to children followed up for at least 24 weeks after the last procedure. The Chi-squared test or two-tailed Fisher's exact test was used to compare binary variables between groups. Continuous variables were analysed using the Wilcoxon rank sum test. Univariate and multivariate logistic regression models were used to assess the effect of intervention adjusting for age and angle of deviation at baseline on the outcome. A p value < 0.05 was considered significant. Statistical analysis was performed using Stata 15.1 (STATA Corp, Texas) and MedCalc (MedCalc Software, Belgium).

Results

Of the 55 children randomised to each arm initially, 101 children, 54 in the BNT arm and 47 in the surgery arm had

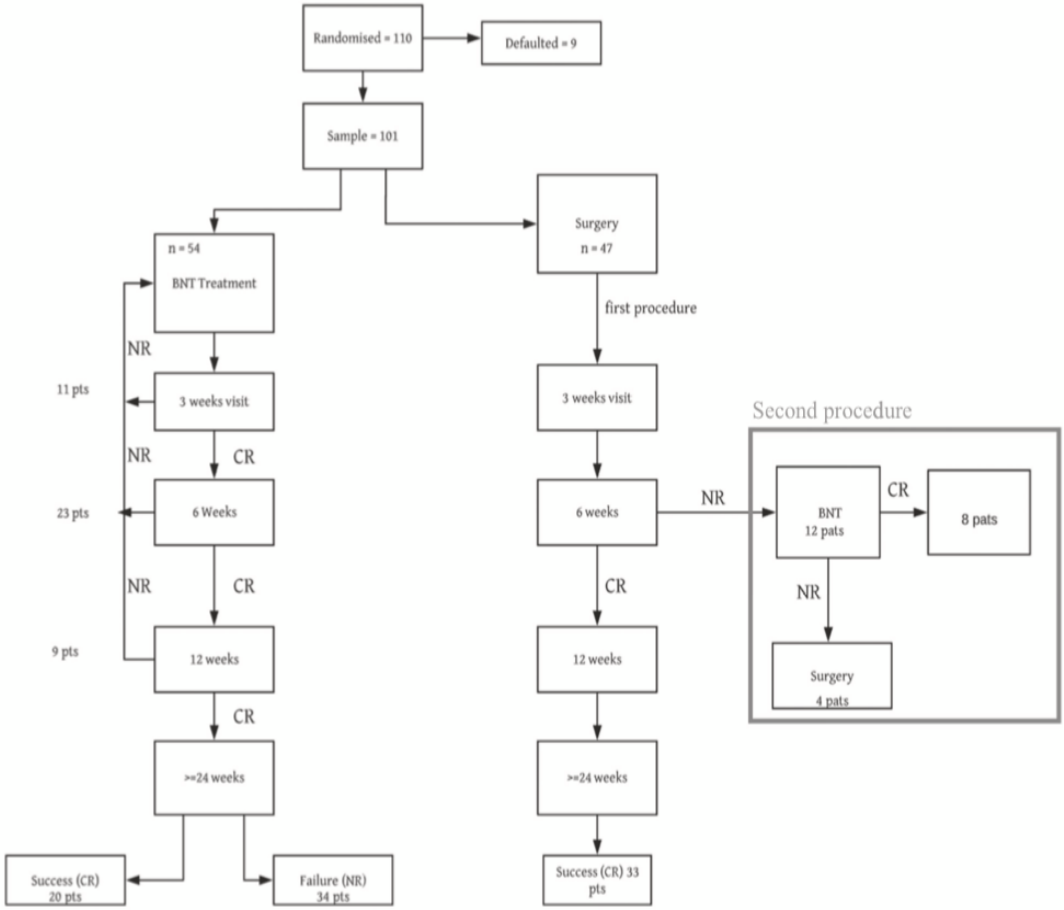

Fig. 1 Schematic flow diagram of study patients. BNT botulinum neurotoxin, CR complete response, NR no response.

Table 1 Baseline characteristics.

Variable	All subjects $N = 101$	Surgery arm $N = 47$	BNT arm $N = 54$	P value
Female gender (%)	61 (60.3)	27 (57.4%)	34 (63.0%)	0.57
Age in months –				0.15
Median (IQR)	24 (14–34)	29 (15–46)	21.5 (14–32)	
Mean (SD)	26.9 (14.5)	29.4 (15.2)	24.7 (13.6)	
Esotropia angle in PD				0.721
Median (IQR)	60 (55–70)	60 (55–70)	65 (50–70)	
Mean (SD)	61.68 (12.81)	62.55 (11.79)	60.93 (13.7)	
Esotropia	$N = 101$			
40–60 PD		24 (51.1%)	26 (44.4%)	
>60 PD		23 (48.9%)	28 (51.9%)	

PD prism dioptres, *SD* standard deviation, *IQR* interquartile range.

adequate follow-up of at least 24 weeks after the last procedure. Of the defaulting children, one was in the BNT arm and eight in surgery arm. The mean (SD) age was 26.9 (14.5) months and median (IQR) baseline angle of esotropia was 60 (55–70) PD for the entire cohort with no significant difference between the two arms (Table 1). Total theatre time was significantly shorter for the BNT arm compared to the surgical arm, mean (SD) 11 (1.5) and 72 (5) minutes, respectively, 95% CI 10.46–11.31 and 69.93–74.32, respectively.

Table 2 Outcome after 24 weeks of last intervention.

	Surgical arm $n = 47$ (%)[a] CR	BNT arm $n = 54$ (%) CR	OR (95% CI)	P value
Total cohort	33 (70.2%)	20 (37%)	4.01 (1.74–9.22)	0.001
By age group				
≤24 months	15/21 (71.4%)	16/29 (55.2%)	2.03 (0.61–6.72)	0.24
>24 months	18/26 (69.2%)	4/25 (16%)	11.81 (3.05–45.81)	0.0002
By degree of esotropia				
≤60 PD	17/24 (70.8%)	13/26 (50%)	2 (0.64–6.29)	0.37
>60 PD	16/23 (69.6%)	7/28 (25%)	8.5 (2.4–20.09)	0.0005

CR complete response.

[a]Outcome after one surgical procedure.

As shown in Table 2, CR was achieved in a significantly higher proportion of children in the surgery arm (70.2%) after single procedure compared to the BNT arm (37%). Of 20 children who achieved CR in the BNT arm, 11 (55%) achieved it with one injection, 5 (25%) after the second injection and 4 (20%) after the third injection.

Univariate analysis of subgroups stratified by age showed that the proportion of patients that achieved CR was not significantly different between the two arms for children ≤24 months, whereas it was significantly better in the surgery arm in children >24 months (OR 11.81, 95% CI: 3.05–45.81, $p = 0.002$). When comparing subgroups stratified by degree of baseline esotropia, there was no significant difference between the two arms for children with esotropia ≤60 PD, but significantly better in the surgery arm in children with esotropia >60 PD (OR = 8.5, 95% CI: 2.4–30.09, $p = 0.0005$) (Table 2).

Multivariate logistic regression analysis for the BNT arm showed that age and degree of baseline esotropia were significant independent predictors. Receiver operating characteristic (ROC) curve analysis using univariate predictors, degree of baseline esotropia and age, yielded an area under the curve of 70% and 66%, respectively. The optimal threshold sensitivity/specificity modelled by our data was 50 PD for degree of esotropia (Fig. 2a) and 21 months for age (Fig. 2b).

In the BNT arm, 7 children (13%) had PR and 27 children (50%) had NR. Of the 27 NR children, 21 had subsequent surgery—11 of these achieved CR and 2 PR at 24 weeks post-surgery follow-up. Eight children failed to return for their follow-up visits. Ultimately, CR and PR were achieved in at least 40 (74.1%) of children in the BNT arm within a year of the initial procedure.

Complications in the BNT arm were; partial transient ptosis in 9 children (16.7%), which resolved within 6–8 weeks, transient vertical deviation in 3 children (5.6%) and consecutive exotropia in 13 children (24.1%). Seven of the children with exotropia were associated with CR. There were no cases of globe perforation, infections or chemosis following BNT injections.

In the surgical arm, of the 47 children, 24 had large-angle esotropia and 23 children had very-large-angle esotropia requiring surgery with BNT augmentation. CR was achieved in 17 (70.8%) and 16 (69.6%), respectively, with one procedure. Of the 14 children who failed to achieve CR, 12 had residual esotropia and 2 exotropia. All of the 12 children with esotropia received 3U of BNT as a second procedure and CR was achieved in 8 children while 4 children needed additional surgery.

The two children with exotropia, received BNT to the lateral rectus muscles as initial therapy followed bimedial rectus muscle advancement and had final NR. In total, 45 children (95.7%) had a CR or PR in the surgery arm. There were no major complications of surgery such as slipped or lost muscles, globe perforation or anaesthetic-related issues.

Discussion

In this prospective randomised control study, surgery was superior to BNT in our cohort of children with large-angle esotropia; however, BNT has a definite role as primary treatment option in selected children. Surgery was associated with equally good outcomes irrespective of the age of the child or the degree of esotropia. While previous studies using BNT showed the best outcome in infants [16], our study did not have sufficient numbers to consider the very young separately. Crude analysis of the BNT arm versus the surgery arm, however, did show comparable outcomes to surgery in children ≤24 months of age and with a baseline esotropia ≤60 PD. This association remained valid in the multivariate analysis with non-significant odds ratios between the BNT and surgery arms in patients ≤24 months and ≤60 PD. This is further supported by ROC curve analysis which indicated that children below 21 months of age and those with esotropia below 50 PD are more likely to have complete resolution.

In a systematic review Issaho et al. identified nine papers describing the use of BNT in the management of IE. Most of the studies were non-comparative and success rate varied

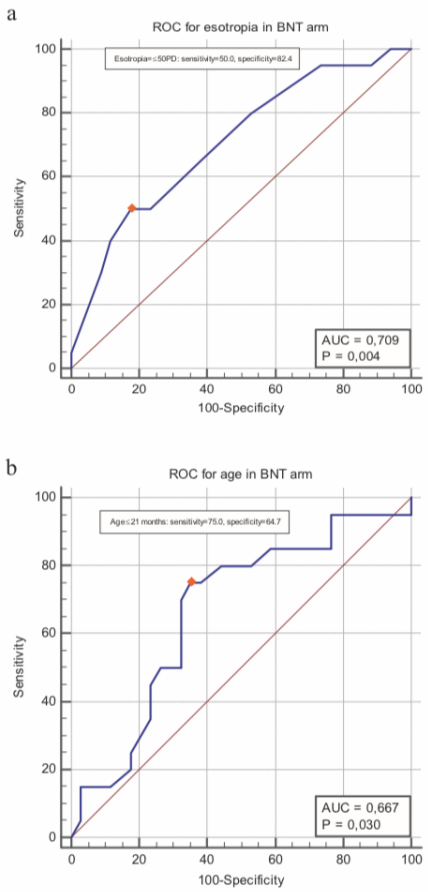

Fig. 2 **a** Receiver Operating characteristic curves (ROC) for initial angle as a predictor for success. **b** ROC curve for age as a predictor for success. Orange dot= Youden index.

from 37.5 to 100% [17]. The high-success-rate studies were associated with small to moderate angles of esotropia while studies of large angles reported lower success rates.

The results of this study show a similar trend to that of de Alba Campomannes et al. [11] for large-angle esotropia. In their study, large-angle esotropias of >30 PD treated with BNT were associated with a success rate of 36%. All our study children had angles ≥40 PD with a success rate of 37% but angles ≤60 PD were associated with 50% success. BNT in younger children had a significantly higher success rate (55.2%) than older children (16%). The explanation is probably based on increasing contracture of the medial rectus muscles over time [18]. In our cohort, a better response was seen with one injection and we found lower success rates for second and third injections.

The present study reaffirms the safety of BNT [17] as there were no adverse events associated with BNT injections.

Exotropia after the first injection was a good predictor of success as shown by Campos et al. [16]. In our study 7 of 13 patients with exotropia after the first injection were associated with CR. This represented over a third of all successful cases. In cases where BNT failed to correct the esotropia, alignment with surgery was achieved within a reasonable time interval. On average, it was found that surgery took six to seven times longer than BNT. In resource-constrained settings the short procedure-time for BNT allows many more patients to gain access to treatment at a potentially earlier age.

Our need to recognize cosmetically acceptable small angles (PR) highlights the real problems encountered in developing countries, where functional outcome and potential for fusion may not be a priority. With BNT use, at least 50% of our patients overall achieved CR and PR. Another compelling reason for BNT use is the absence of serious complications and that an exact angle measurement may not be essential. This obviates the need for specialist orthoptic personnel. Orthoptists are few in number and seldom service public sector hospitals in South Africa.

The number of participants achieving a cosmetically acceptable result in the surgical arm was more impressive as only two patients were deemed failures. However, the number of patients that dropped out pre-operatively in this arm may highlight parental reservations concerned with surgery.

The results of this study support the use of BNT in large-angle deviations as augmentation to surgery. Leuder reported a favourable outcome with augmented surgery in 17 out of 23 patients (73%) [19]. Our study showed a similar outcome in patients with augmented surgery. This would eliminate the need for three-muscle surgery and thus allow for shorter theatre-time.

Limitations

The study only followed children for 6 months following the last procedure and late esodrift may still be an issue. The scope of the study addressed only motor response and did not test for fusion in children that were aligned. No attempt was made to establish parental satisfaction or dissatisfaction. We were unable to recruit children younger than 10 months to confirm the reported higher rate of success in this very-young age category [11, 16]. The study also did not compare three-muscle surgery to surgery with

augmented BTX which could have added another comparative arm.

Conclusion

Surgery is still the gold standard of managing large-angle IE. However, BNT is a viable primary treatment option for IE. BNT is safe and a short procedure and could be considered as a first-line intervention in developing countries where resources are limited with respect to waiting time for surgery. Further, BNT was found to be more effective in children ≤24 months of age and with baseline angles of ≤60 PD of esotropia.

Summary

What was known before

- BNT can be used in various types of strabismus.
- Surgery is the gold standard.
- In IE, BNT is successful in the management of small angles and very-young patients.

What this study adds

- BNT can be used in larger angles of deviation <50 PD.
- Viable option as it takes 5× less time than surgery useful in developing countries with limited resources.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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Appendix C Paper 2

BMJ Open Ophthalmology

Cost comparison between botulinum neurotoxin and surgery in the treatment of infantile esotropia in a tertiary public hospital

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ABSTRACT

Objective To compare the cost implications of botulinum neurotoxin (BNT) injection to surgery in infantile esotropia (IE) in a public/government funded hospital.

Methods and analysis A simple costing comparison was undertaken for a randomised clinical trial in IE. Patients were randomised to receive either BNT or standard surgery. The participants in the BNT arm were further subdivided into subgroups based on their age in months and degree of esotropia in prism dioptres (PD) at presentation: G1 ≤60 PD/24 months, G2 ≤24 months/>60 PD, G3 >24 months/≤60 PD, G4 >24 months/>60 PD. The costs were calculated for each arm from primary treatment to eventual satisfactory outcome defined as orthophoria or microtropia (≤10 PD). A bottom-up costing analysis was done for single and multiple procedures for each arm. Comprehensive variable costs as well as fixed costs were calculated at each point of intervention and expressed in local currency ZAR (US$1=ZAR15.00). Costing was analysed for surgery and BNT subgroups (based on clinical success)

Results There were 101 patients enrolled in the trial. 54 in the BNT arm and 47 in the surgery arm. Cost for single surgery and single BNT was ZAR 7743.04 and 1713.14, respectively. A favourable clinical outcome was achieved in 72% of surgery arm and 37% of BNT arm. The mean cost for eventual favourable outcome in BNT arm was ZAR9158.08 and in surgery arm ZAR9124.27 (p=0.26). Mean cost in G1 was ZAR6328.45, in G2 ZAR7197.45, in G3 ZAR11891.93 and G4 ZAR12882.44 (p=0.018).

Conclusion BNT has a cost–benefit in IE and is a viable option in the primary treatment of IE in resource constrained regions. Clinical outcomes and economic benefit in smaller angle of esotropia and younger patients are comparable to surgery.

Key messages

What is already known about this subject?
- Clinically botulinum neurotoxin (BNT) is a viable option in treating selective group of infantile esotropia, younger children with esotropia of <50 prism dioptres (PD).

What are the new findings?
- The cost–benefit of BNT is comparable to surgery even in larger angles (≤60 PD) due mainly to the shorter time taken in theatre.

How might these results change the focus of research or clinical practice?
- In resource limiting centres, where waiting lists are long, BNT will afford many more children access to timeous correction of their esotropia and reduce the financial cost incurred by funders.

BACKGROUND

Strabismus or misalignment of the eyes in children is frequently seen in paediatric ophthalmology units. Uncorrected strabismus results in functional impairment with regard to development of binocular vision and possible amblyopia, as well as psychosocial problems.[1] Infantile esotropia (IE) is a common type of concomitant convergent strabismus and in our region accounts for the majority of cases.[2] Surgery is the standard of care in IE with a success rate of about 75%–80%.[3] Surgical correction of strabismus in adults has been shown to be highly cost effective in developed countries.[4]

The duration of surgery is approximately 1 hour and this is a significant consideration in resource constrained areas where theatre availability is at a premium. In South Africa and other low-income and middle-income countries, the quest for alternative and less resource intensive procedures is challenging and the need to minimise cost while maintaining quality of service is an ongoing balancing act. Waiting lists for surgical corrections are in excess of 1 year due to the large number of children, compounded by the misconception that strabismus repair is largely 'cosmetic' and relegated as a low priority procedure in multi-disciplinary hospitals.

Botulinum neurotoxin (BNT) injections have been used as an alternative treatment option,[5–7] BNT injections take about 20% of

the total time in theatre when compared with surgery and are associated with less discomfort and pain. In a meta-analysis Issaho *et al* reported on nine studies using BNT for IE with success rates ranging from 37% to 100%.[8] It has been reported that BNT is less effective than surgery in large angle esotropia.[7] In a randomised clinical trial (RCT) conducted at our institution, we showed that BNT was successful in 37% overall for the cohort but in selected patients, specifically those younger than 24 months and those with an esotropia <50 prism dioptres (PD), alignment was achieved in over 50% of the study cohort.[9]

Economic evaluation (EE) is defined as a 'comparative analysis of alternate courses of action in terms of both their cost and consequence'.[10] Cost–utility analysis is a commonly acceptable method of reporting EE and considers cost–benefit ratio using quality adjusted life years gained. Benefit or utility gain can be calculated using several methods; Time Trade Off, Standard Gamble or Vision Analogue Scale but none has been validated in children and simple cost comparison may be more appropriate.[11] There is a paucity of published articles on the cost of BNT injections in treating strabismus patients and one study showed comparable cost with long term BNT use and surgery in adults.[12]

This paper aims to compare the cost implications of BNT and surgery, and to determine a model to predict which group of children with IE may benefit from BNT injections as first line treatment, while keeping overall costs to a minimum.

METHODOLOGY

A simple costing analysis was undertaken using the results of a prospective randomised study over a period of 3 years from 2015 to 2018 comparing efficacy of BNT injections to surgery. One aspect of the study was to compare the cost implications between the two procedures to the hospital, both in terms of direct variable and fixed costs. The hospital is a government run hospital in South Africa Gauteng Province and all surgery is funded fully by the government with no reimbursement from health insurance and no copayment collected from patients.

The detailed protocol for the study is described elsewhere[9] but briefly children between the age of 6 months and 6 years, diagnosed with large angle IE, defined as esotropia of ≥40 PD were included.

Children with other forms of esotropia, those with significant patterns and children with neuro-behavioural disorders were excluded.

Children were grouped into two age categories, those ≤24 months and those >24 months of age. Within each age category, participants were randomised by an independent study assistant and assigned to either the BNT (odd numbers) or surgery (even numbers) arms. In the surgery arm children received standard bilateral medial rectus muscle recessions for esotropia of ≤60 PD and maximum recessions of 7.0 mm augmented with 3 units of Botox (Allergan US) in esotropia >60 PD. Unsuccessful outcomes defined as misalignment of >10 PD were subjected to BNT injections as a second procedure at the 3-month visit and a second surgical procedure thereafter in failed cases. In the BNT arm, patients initially received 5 units, repeated at any of the follow-up visits at 3, 6, 12 and 24-week visits, if alignment was >10 PD. A maximum of three injections were given before surgery was offered to correct the residual esotropia. For this study 1 vial of Botox 100 units was used for eight patients. Injections were given subconjunctivally as described by Benabent *et al*[13] not requiring electromyography needles. The decision of administering a maximum of three injections was arbitrary, based on other studies that reported a mean number of 1–2.2 injections given in IE.[6 7 14]

The time taken in theatre, from anaesthetic induction to transfer out of operating theatre for each procedure was recorded. The procedures were standardised for each arm with one surgeon (IM) performing all procedures. A bottom up, micro-costing[15] was done for each of the two procedures for a public/government hospital.

Clinical outcome was based on achievement of orthophoria (or within 10PD of orthophoria).

Cost calculations

Variable costs were calculated from the information received from hospital authorities. Salaries of staff were calculated based on annual salary, hourly rate earned for each category of staff (at Department of Public Service and Administration rates) and the pro rata amount based on time taken for each procedure. Staff salaries calculated were for one specialist surgeon, one specialist anaesthetist, one professional nurse, two assistant nurses and recovery professional nurse. Other staff including the pharmacist, orthoptist, porter, hospital clerks, ward nurse and cleaners who were not directly involved with operative procedure were included in fixed costs. Fixed costs also included ward admission (bedding, preparation, food) water and electricity. Fixed costs were calculated based on the daily cost per patient of a hospital admission in a tertiary hospital supplied by the finance division of the hospital. Fixed costs for this study were calculated based on total hospital time of 6 hours in the surgery arm and 2 hours in the BNT arm. Unit prices of medication and disposable used, were obtained from the hospital pharmacy and procurement office. Although it is difficult to calculate cost of theatre per minute in the hospital, this was estimated using rates used by the private sector and based on a study conducted in the South African comparing costs in the private and public sector.[16] A portion of the private sector cost was assumed to be basic costs of theatre applicable in the public sector (we assumed a third of the cost calculated in the private sector, based on discounted rates on medicines and disposable in the government/public sector on the one hand and the need for profit and taxes paid in the private sector on the other hand). All calculations were

Table 1 Financial cost per procedure to hospital in Rands (US$1=ZAR15)

	Botulinum			Surgery		
Item	Unit/pt	Unit cost/pt	Total pt cost	Unit/pt	Unit cost/pt	Total pt cost
Anaesthetic						
Short line	1.0	15.00	15.00			
Intravenous line				1.0	35.00	35.00
Ringers sol				1.0	8.68	8.68
Propofol (R38/50 mL)	5.0	0.76	3.80	5.0	0.76	3.80
Sevoflurane (R792.48/250 mL)	10.0	3.68	36.80	20.0	3.17	63.40
Laryngeal tube				1.0	70.00	70.00
Oral mask	1.0	4.00	4.00			
miscellaneous			15.00			15.00
Surgical						
Gloves	1.0	12.00	12.00	2.0	12.00	24.00
4/0 silk				2.0	81.46	162.92
5/0 vicryl				2.0	119.79	239.58
8/0 vicryl				1.0	138.96	138.96
cautery				1.0	75.00	75.00
Sponges/packet				1.0	48.00	48.00
Botulinum R1552.00/100 units*	10.0	15.52	155.20			
Insulin syringes	2.0	1.00	2.00			
Balance salt solution (10 mL)				1.0	12.00	12.00
TTO ointment				1.0	48.00	48.00
Time in theatre (min)†	11.0	50.00	550.00	72.0	50.00	3600.00
Staff required						
Surgeon (R462.92/hour)	11.0	7.68	84.52	72.0	7.68	553.10
Anaesthetist (R462.92/hour)	11.0	7.68	84.52	72.0	7.68	553.10
Professional nurse (R150/hour)	11.0	2.50	27.50	72.0	2.50	180.00
Assistant nurse ×2 (R120/hour)	11.0×2	2.00	44.00	72.0×2	2.00	288.00
Recovery nurse (R150/hour)	15.0	2.50	37.50		2.50	75.00
Time in recovery	10.0	25.00	250.00	20.0	25.00	500.00
*Fixed costs†**	2 hours	176.25	352.50	6 hours	176.25	1057.50
Total			1713.14			7743.04‡

*Cost of botulinum 100 units/8 patients.
†Cost of theatre based on gases used, microscope use, bedding @ZAR50/min (assumed 1/3 of private rates).
‡Cost for surgery if botulinum neurotoxin (BNT) given would be ZAR7900.24.
§Fixed cost—include water, electricity, ward stay @ ZAR4600/day, allowing for total hospital time of 2 hours for BNT and 6 hours for surgery.

expressed in South African Rands (ZAR) and at the time of the study US$1.00 was equivalent to ZAR15.00 (or ZAR20.00/£1.00 UK).

Various clinical subgroups and their costs were analysed, comparing surgery to single and multiple BNT injection procedures based on our RCT findings. Further analysis was done to assess viability for subsequent surgery in failed cases. Using a simple economic model, costs were calculated for different subgroups and predictions of the cost–benefit were then made.

For this analysis the BNT group were divided into four subgroups based on literature reports identifying age of presentation and degree of esotropia to be significant variables.[7 16] The subgroups in months and PD were as follows: G1 children ≤24 months of age and ≤60 PD; G2 children ≤24 months and >60 PD; G3 children >24 months and ≤60 PD; G4 children >24 months and >60 PD.

Statistical analysis

The total cost in each arm was expressed as means (SD). The difference in cost between the two arms was tested using the Wilcoxon rank-sum test. The cost difference between the number of procedures in the two arms was tested using the Kruskal-Wallis test

Table 2 Summary of cumulative cost in two arms (amount in ZAR)

	Surgery arm n=47		BNT arm n=54		P value
Procedures (n)	Type of procedure	Cumulative cost	Type of procedure	Cumulative cost	
1	BMR if ≤60 PD (19 pts) BMR+BNT if >60 PD (16 pts)	7743.04† 7900.24‡	BNT 5 units (11 pts)	1713.14	0.0001*
2	BNT 5 units (8 pts)	9456.18† 9613.38‡	BNT 5 units (5 pts)	3426.28	
3	LR resection (4 pts)	17200.22† 17356.42‡	BNT 5 units (4 pts)	5139.42	
4	–	–	BMR (34 pts)	12 882.46	
Mean cost		9124.27		9158.08	p=0.26

*Kruskal-Wallis: †surgery only: ‡surgery augmented with BNT.
BMR, bimedial rectus muscle recession; BNT, botulinum neurotoxin; LR, lateral rectus.

Parents of participants or the public did not participate in the design, or conduct, or reporting, or dissemination plans of our research.

RESULTS

Of the 101 patients analysed in this study. Fifty-four patients were enrolled in the BNT arm and 47 in the surgery arm.

Overall success rate for alignment was 37% in the BNT arm (20.3%, 9.3% and 7.4% with 1, 2 and 3 injections, respectively) and 70.2% after one procedure in the surgery arm. Success in the surgery arm was independent of age and degree of esotropia while in the BNT arm, success was associated with age of intervention and degree of misalignment, with age <21 months and degree <50 PD being comparable statistically, to surgery alone. Subgroup analysis of the different groups in the BNT arm showed that, G1 had an overall success of 11/16 (68.8%), G2 5/15 (33.3%), G3 2/10 (20 %) and G4 2/13 (15.4%). The mean time taken was 11 min for BNT injection and 72 min for surgery.

Economic findings

Detailed costing breakdown are shown in table 1. Time in theatre cost (ZAR3600 for surgery and ZAR550 for BNT), staff cost (ZAR1649 for surgery and ZAR278.04 for BNT) and consumables (ZAR1001.76 for surgery and ZAR243.80 BNT) were the main cost determinates.

The cumulative costs for multiple procedures for both arms are shown in table 2.

The cost of a single BNT procedure was found to be ZAR1713.14 (in 11 children), the cumulative cost of BNT injection was ZAR3426.28 for two injections (in 5 children) and ZAR5139.42 for three injections (in 4 children). The cumulative cost in failed cases requiring surgery was ZAR12882.46 (in 34 children). The cost of single surgical procedure was ZAR7743.04 for esotropia ≤60 PD and ZAR7900.24 in esotropia >60 PD due to the augmented BNT injection. Using Wilcoxon rank-sum test there was no statistical difference in the mean cost between the surgical arm and the BNT arm (p=0.26). The mean cost was ZAR9158.08 and ZAR9124.27 in BNT arm and in the surgery arm, respectively.

Mean cost (SD) for the subgroups in the BNT arm were 6328.45 (2655) in G1, 7197.45 (3103.73) in G2, 11 891.93 (6406.28) in G3 and 12 882.44 in G4. In comparing the cost between the different BNT groups there was a clear difference between groups (p=0.018) although the numbers were small in each group.

Table 3 Model predicting total cost for eventual successful outcome for 100 cases in each group

	1st	2nd	3rd	4th	Total projected/100
Surgery	7743.04×70	9456.18×17	17 199.22×13	0	924 466.47
BNT G1	1713.14×38	3426.28×12	5139.42×19	12 882.46×31	567 472.25
BNT G2	1713.14×13	3426.28×20	0	12 882.46×67	949 282.19
BNT G3	1713.14×20	0	0	12 882.46×80	1 064 859.6
BNT G4	0	3426.28×8	5139.42×8	12 882.46×84	1 155 711.9

Cost comparison of 100 patients in each group based on actual clinical outcome of original cohort: *surgery arm: 1st procedure, surgery, 2nd procedure BNT, 3rd procedure surgery in 70, 17 and 13 cases, respectively.
G1 children ≤24 months of age and ≤ 60PD; G2 children ≤ 24 months and >60 PD; G3 children >24 months and ≤60 PD; G4 children >24 months and >60 PD (cost in ZAR).
*BNT arm numbers reflect expected successful outcome with each procedure in the different groups.
BNT, botulinum neurotoxin.

Scenario model

To better illustrate the cost between the two procedures we extrapolated success rates for the surgery and BNT subgroups from the RCT reflecting the efficacy of the two procedures for 100 patients in each group. In the surgery arm, 70 would require one procedure, 17 would require two procedures and 13 would require three procedures at total cost of ZAR924466.47 in successfully treating 100 patients. Comparatively, the total cost for BNT would be ZAR567472.25 in arm G1 and ZAR1155711.90 for the G4 subgroup for the similar 100 patient model (table 3).

DISCUSSION

Surgical correction of strabismus has been demonstrated to be cost effective in studies conducted in adults in the USA, and by extension in children.[4] Other related strabismus studies have reported probable cost effectiveness in the screening for amblyopia.[18 19] While cost implications with the use of prescription glasses for various ophthalmic conditions including esotropia have also been reported.[20] Such studies have been undertaken in developed countries and in general, EE analyses are sparse for low-income and middle-income countries.[21] Our study was designed to establish the economic cost in the treatment of IE in an attempt to contain costs.

The study was a simple cost comparison between BNT injection and surgery which is the standard of care in IE in a government run public hospital where the majority of the population is treated. The study was necessitated by the heavy burden on theatre resources in our region with the consequence that strabismus cases especially in children are often delayed. In performing cost analyses we used activity-based costing bottom up method as this is deemed appropriate.[22] The success rate of BNT has been shown to vary and in our study, surgery was two times as successful however, in our setting at least a third of children were aligned at an earlier age using BNT than if they had waited for standard surgery. Moreover, in children (G1) with angles of deviation <60 PD and injected at a younger age (<24 months) the clinical success was found to be 68% and comparable to surgery but with a clear economic benefit in considering BNT as a first line intervention. Even in G2 and G3 BNT was economically viable and should still be considered as first line option. Surgery should be considered in older children with very large angles (G4).

From our findings the main cost drivers were associated with time spent in theatre, which was 6× more with surgery, resulting in greater the staff costs followed by consumables needed and anaesthesia.

LIMITATIONS

Several difficulties were associated with costing in large government hospitals such as evaluating fixed costs like electricity, water and sanitation that would apply even at times when theatres are not functional. These estimations or assumptions may skew the costs.

The multi dosing of BNT is probably only applicable in public hospitals seeing a lot of strabismus patients and scheduling regular BNT theatre lists.

With the use of BNT, repeat injections require multiple anaesthesia which theoretically increases the risk to the child although the BNT children had shorter anaesthetic time and no intubation. Longer follow-up time may be required for stable alignment and reduce the potential for fusion and depth perception. This may be undesirable in developed countries where waiting times for surgery are short. In low-income and middle-income countries these waiting times may be much longer making BNT a more viable option. The study did not address the indirect cost to the patient and society as a whole.

CONCLUSION

The knock-on effect of availing timeous intervention to many more children as well as the cumulative cost involved is a mitigating factor in considering BNT as a viable first line option. This consideration is even more compelling in the subgroup of patients ≤24 months of age and ≤60 PD where the clinical outcome is comparable to surgery and the economic advantage more pronounced. In children ≤24 months and >60 PD and >24 months and ≤60 PD BNT may economically still be an option. In children >24 months and >60 PD surgery should be considered as treatment.

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Appendix D – Paper 3

ARTICLE IN PRESS

Major Article

Response to botulinum neurotoxin injections in large-angle infantile esotropia: a post hoc analysis

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PURPOSE To determine the anticipated reduction of baseline angle of esotropia and identify predictors of change following botulinum neurotoxin (BNT) injections in large-angle infantile esotropia.

METHODS This was a prospective, longitudinal study of children <10 years of age diagnosed with infantile esotropia of >30$^{\Delta}$ and given either 1, 2, or 3 BNT injections. Post-injection change from baseline deviation was recorded, and predictors of reduction were analyzed. For this study, children were further divided into subgroups based on initial deviation of ≤60$^{\Delta}$ (group 1) and >60$^{\Delta}$ (group 2). The outcomes of subsequent surgeries in failed cases were analyzed.

RESULTS A total of 117 children were included, 55 in group 1 and 62 in group 2. Mean age was 30.3 ± 18.8 months. Mean baseline deviation was 62.5$^{\Delta}$ ± 13.1$^{\Delta}$: 51.4$^{\Delta}$ ± 8.4$^{\Delta}$ in group 1 and 73$^{\Delta}$ ± 7.5$^{\Delta}$ in group 2. The mean number of injections was 2.2 ± 0.7. Success was achieved in 25.6% of patients (33.4% in group 1; 16.2% in group 2). The mean percentage reduction of deviation after BNT injection was 55.2% ± 26%, larger in group 1 than in group 2 (61.3% vs 51.1% [P = 0.001]). Five children reverted to baseline deviation. In multivariate analysis, adjusting for number of injections, younger age and larger baseline deviation were significant independent predictors of a larger absolute amount of reduction (P = 0.02, and 0.002, resp.). Thirty-two children had subsequent surgery; 22 were followed for a minimum of 6 months, and 20 were aligned within 10$^{\Delta}$ of orthotropia.

CONCLUSIONS In large-angle esotropia there was a reduction of approximately 50% of baseline deviation, with greater relative reduction for smaller baseline deviations; the absolute change in angle was greater in younger children. Alignment after subsequent surgery appeared to remain stable and surgery required less recession than would have been needed for the original angle of esotropia. (J AAPOS 2022;■:1.e1-5)

Infantile esotropia is one of the most common types of strabismus in childhood and in sub-Saharan Africa accounts for up to three-quarters of childhood strabismus.[1] Timely intervention presents a major challenge in resource-constrained settings. In the public health sector in South Africa, children with strabismus must often wait 18 months or longer for surgical correction, the treatment of choice.[2]

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Botulinum neurotoxin injection therapy (BNT) has gained popularity as an alternative to surgery in the management of infantile esotropia. BNT reversibly blocks the neuromuscular junction by preventing the release of acetylcholine, causing a reversible paralysis of striated muscle and fibrosis.[3] The reversibility is due, in part, to sprouting of new nerve terminals.[4] Success rates with BNT as primary therapy vary from 33% to 89%.[5,6] BNT is also used intraoperatively as an adjunct to surgery for large-angle esotropia, with reported satisfactory outcomes of 60%-80%.[7-9]

To address unmet needs for early intervention for infantile esotropia at our institution and to establish the role of BNT as primary intervention in these cases, in a recent randomized clinical trial (RCT) comparing BNT to surgery as a primary treatment, we reported a satisfactory outcome of 37% with BNT, better in subgroups with preoperative angle of esotropia of <50$^{\Delta}$ and age <21 months (52%).[10] BNT for large-angle infantile esotropia (>30$^{\Delta}$) has been less well studied. De Alba Campomanes and colleagues[5] reported satisfactory outcome with BNT in 36% of children

Table 1. Demographic and clinical characteristics of children with infantile esotropia treated with botulinum neurotoxin therapy

Study parameter	Overall (N = 117)	Group 1 (n = 54)	Group 2 (n = 63)	*P* value[a]
Age, months, mean ± SD	30.3 ± 18.8	27.9 ± 15.5	32.1 ± 21.1	NS
Deviation, PD, mean ± SD				
Baseline	62.5 ± 13.1	51.4 ± 8.4	73 ± 7.5	
Final	28.0 ± 18	19.9 ± 14.1	35.7 ± 17.8	
% angle change from baseline	55.2 ± 26	61.3 ± 27.3	51.1 ± 24.8	0.04
Success, no. (%)	30 (25.6)	20 (37)	10 (15.9)	0.02
BNT injections, mean	2.2	2.1	2.3	NS
No. injections				
1	21	13	8	
2	53	24	29	
3	43	18	25	
Mean change after injections (% angle change from baseline)				
1 injection	37 (59)	31 (57.4)	43 (60.5)	NS
2 injections	36 (57.4)	32 (61.7)	39 (53.0)	NS
3 injections	33 (50)	31 (53.6)	34 (46.2)	NS

BNT, botulinum neurotoxin therapy; *NS*, not significant; *PD*, prism diopters.
[a]group 1 vs group 2,

with esotropia >30$^{\Delta}$. BNT procedures required mean operating room time of 11 minutes compared with 72 minutes for standard surgery,[10] potentially allowing 20 more children per operating room list and the opportunity for earlier intervention, which is crucial for the development of fusion and stereopsis.[11]

Published data on the effect of BNT injections on change of angle relative to baseline esotropia are sparse. In small-angle infantile esotropia, Campos and colleagues[6] reported a change of 30$^{\Delta}$ with 1 injection in 60 children with a mean baseline angle of 35$^{\Delta}$ after 5 years' follow-up. Similarly, McNeer and colleagues[12] showed a mean change of 40$^{\Delta}$ after 3 years' follow-up. Isaho and colleagues,[13] in their meta-analysis of 9 studies of infantile esotropia treated with BNT, showed an average change in angle of 37$^{\Delta}$ from a mean baseline of 38$^{\Delta}$. However, it remains unclear whether the change in the degree of esotropia depends on the size of the baseline deviation. Moreover, there are few reported data on the effect of the number of BNT injections on the change in angle[13] and the outcome with subsequent surgery in children with an unsatisfactory response to BNT. The purpose of this study was to explore the outcome of one or more BNT injections in children with large-angle infantile esotropia, not only for success in alignment but also the effect of variable number of injections on the reduction from baseline deviation. A secondary aim of the study was to investigate outcome of surgery in children with residual infantile esotropia following BNT.

Subjects and Methods

This study was approved by the Human Research Ethics Committee of the University of the Witwatersrand. We conducted a longitudinal prospective study of children <10 years with large-angle infantile esotropia of >30$^{\Delta}$, treated with BNT between 2015 and 2019 at St John Eye Hospital. Diagnosis of infantile esotropia was based on a history of onset of esotropia before 6 months of age. Children underwent full orthoptic examination and cycloplegic refraction prior to BNT injections. All children with hyperopic correction > +2.00 DS were prescribed appropriate spectacle correction, and if after 2 months no change in angle of deviation was measured with glasses, the diagnosis was accepted. Study children were examined by an experienced orthoptist, and angle was measured for distance and near using prism and alternate cover testing in the majority of cases and Krimsky test for a few children on occasions. For this study, near deviation angles were used for analysis for all visits. Exclusion criteria were significant pattern deviation, hyperopic correction > +5.00 DS, >10$^{\Delta}$ difference between near and distance measurements, and neurological disorders. The study population included children from the RCT study comparing BNT to surgery in infantile esotropia[10] and children treated in an open-label study of BNT for infantile esotropia. Included in the RCT were children ≤6 years of age, randomized to either the BNT or surgery arms with angle of >30$^{\Delta}$.

In the BNT arm, a maximum of 3 injections of BNT were administered. Repeat injections were given if residual esotropia >10$^{\Delta}$ was measured at follow-up visits. In the case of the open-label cohort of <10 years of age, a variable number of 1-3 injections were administered, with an option of either repeat injections or surgery, based on parental preference. In all cases, 5 IU (0.1ml) of BNT was injected in both medial rectus muscles as initial therapy. Subsequent injections were given/offered at any of the follow-up visits at 6, 12, and 24 weeks. At these visits, 5 IU for angle >30$^{\Delta}$ and 3 IU for ≤ 30$^{\Delta}$ were administered bilaterally. The cohort was further divided into two subgroups: those with esotropia ≤60$^{\Delta}$ (group 1) and those with esotropia >60$^{\Delta}$ (group 2). Success was defined as alignment within 10$^{\Delta}$ of orthotropia. BNT injections were started within 1 month of enrollment (6 weeks after initial presentation, except for children given a trial of hyperopic glasses, in which case injections were given 2 months after a trial with glasses with no significant change from baseline deviation).

Table 2. Linear regression analysis of predictors of change in angle of esotropia from baseline to last visit

Variable	Univariate linear regression		Multivariate linear regression	
	β coefficient (95% CI)	*P* value	β coefficient (95% CI)	*P* value
Age	−0.18 (−0.35 to 0.01)	0.04	−0.21 (−0.37 to 0.04)	0.02
Baseline deviation	0.33 (0.15 to 0.89)	0.004	0.39 (0.15 to 0.64)	0.002
BNT injections	−2.14 (−10.4 to 1.4)	NS	−4.53 (−8.78 to −0.28)	0.04

BNT, botulinum neurotoxin; *CI*, confidence interval; *NS*, not significant.

Final deviation was assessed 6 months after the last injection. Mean change from baseline angle expressed as a percentage was calculated using the formula (baseline deviation − final deviation)/(baseline deviation) ×100 for each child and a mean calculated for each group. Adverse events were recorded in the RCT cohort.

Surgical intervention included unilateral or bilateral medial rectus muscle recession, depending on the residual angle. In children requiring surgery after BNT, surgery was performed after a stable deviation was documented on two consecutive visits, the first at 6 weeks after the last injection, the second, 1 month later and following repeat cycloplegic refraction. Children included in the analysis were followed up for a minimum of 6 months after surgery.

Statistical Methods

The χ^2 test or, where applicable, the two-tailed Fisher exact test was used to compare categorical variables between groups; the *t* test for paired samples was used to compare continuous variables between groups. Univariate and multivariate linear regression analyses were performed to evaluate potential associations of outcome (change in angle of deviation) with age of onset, baseline angle, and number of injections. Data were analyzed using STATA 16.1 (Statacorp, College Station, TX). A *P* value of < 0.05 was considered significant.

Results

The clinical characteristics, BNT details, and post-injection changes in angle are summarized in Table 1. The 117 children included in the study, 54 from the RCT and 63 from the open-label cohort, had a mean age (with standard deviation) of 30.3 ± 18.8 months (range, 7-100) and baseline angle of 62.5^{Δ} ± 13.1^{Δ} (range, 35^{Δ}-90^{Δ}). Mean baseline angle was 51.4^{Δ} ± 8.4^{Δ} for group 1 and 73^{Δ} ± 7.5^{Δ} for group 2.

Mean reduction in angle from baseline was 34.5^{Δ} (55.2%) for the overall cohort, and 31.5^{Δ} (61.3%) and 37.3^{Δ} (51.1%) for groups 1 and 2, respectively ($P = 0.04$ for percent reduction). Successful outcome was achieved in 30 (25.6%) of the overall cohort, 20 (36.4%) in group 1 and 10 (16.2%) in group 2 (OR = 2.65; 95% CI, 1.13-6.21; $P = 0.02$). Only 5 children (2 in group 1 and 3 in group 2) reverted to baseline angle, that is, had no improvement. Mean number of BNT injections was 2.2 ± 0.7 for the overall cohort, not significantly different between the two groups. Of the 117 children, 11 had dissociated vertical deviation and 6 had latent nystagmus.

Linear regression analysis for predictors of change in angle from baseline to last visit is shown in Table 2. Age, baseline deviation, and number of BNT injections were independent predictors of change of angle. An increase with each month in age was associated with 0.21^{Δ} less reduction from baseline angle ($P = 0.02$); an increase in baseline angle of 1^{Δ} was associated with 0.39^{Δ} greater reduction ($P = 0.002$). Scatterplots for the two groups are shown in Figure 1. With every additional injection, there was a mean decrease in the amount of correction of 4.5^{Δ}, which was marginally significant ($P = 0.04$).

Adverse events seen were ptosis in 16.7%, vertical deviation in 5.6%, and consecutive exotropia in 24.1%. All of these resolved by 12 weeks.

Of the 87 children who did not meet the criteria for success, 32 underwent surgery, with 5 undergoing only one medial rectus muscle recession and 27 requiring two-muscle recession. All 32 required less muscle recession than would have been required to treat their baseline deviations. The remaining 55 patients were either awaiting surgery or refused further intervention. Of the 22 children who were followed for a minimum of 6 months (mean, 9.6; range, 6-28), 20 were aligned within 10^{Δ} of orthotropia, 17 within the monofixation range, after a single

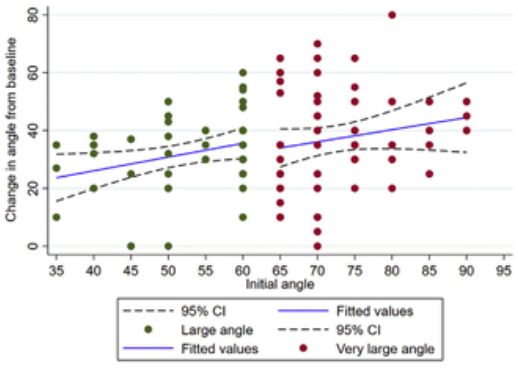

FIG 1. Scatterplot showing linear correlation between baseline esotropia and change of angle for large-angle (green) and very large-angle esotropia (red).

Table 3. Outcome of surgery after botulinum neurotoxin injection with minimum post-surgery follow-up of 6 months

Patient	Baseline angle, PD	Number of injections	Post-injection angle, PD	Recession, dosage	Outcome	Post-surgery follow-up, months
1	35	2	25	UMR, 6 mm	Ortho	6
2	40	3	20	UMR, 5 mm	Ortho	12
3	50	3	30	BMR, 4 mm	Ortho	12
4	60	3	35	BMR, 4.5 mm	6 PD ET	10
5	60	3	30	BMR, 4 mm	5 PD ET	12
6	60	3	20	UMR, 5 mm	Ortho	10
7	60	3	30	BMR, 4 mm	5 PD ET	9
8	65	3	40	BMR, 5 mm	Ortho	10
9	65	3	30	BMR, 4 mm	10 PD ET	10
10	65	1	30	BMR, 4 mm	10 PD ET	6
11	70	3	28	BMR, 3.5 mm	8 PD ET	28
12	75	2	45	BMR, 5.5 mm	6 PD ET	6
13	75	2	40	BMR, 5 mm	5 PD ET	6
14	75	3	40	BMR, 5 mm	Ortho	8
15	75	3	20	UMR, 5 mm	10 PD ET	13
16	80	2	60	BMR, 7 mm	Ortho	12
17	80	3	50	BMR, 6 mm	10 PD XT	8
18	85	1	50	BMR, 6 mm	Ortho	12
19	85	2	45	BMR, 5.5 mm	Ortho	6
20	85	3	45	BMR, 5.5 mm	15 PD ET	6
21	90	2	45	BMR, 5.5 mm	Ortho	6
22	90	2	40	BMR, 5.0 mm	Ortho	10

BMR, bilateral medial rectus recession; *ET*, esotropia; *Ortho*, orthotropia; *PD*, prism diopters; *UMR*, unilateral recession; *XT*, exotropia.

operation (Table 3). Consecutive exotropia was seen in one child, and another required an additional resection of the lateral rectus muscle to correct the residual esotropia. Surgery for dissociated vertical deviation was not required in any of the cases.

Discussion

In this prospective study of large-angle infantile esotropia, mean reduction of the baseline angle of deviation was 55.2% for the overall cohort following a mean of 2.2 BNT injections. All but 5 children (4.3%) had a reduction in deviation following BNT. Not surprisingly, relative (percent) reduction in deviation from baseline was less in cases of very large-angle esotropia, even though the absolute magnitude of change in deviation was larger for larger baseline deviations. Previous studies of BNT for infantile esotropia, with mean baseline angle of 33^{Δ} and 43^{Δ}, with similar sample sizes and mean number of injections, have shown reductions in angle of 45.8% and 40.0%.[14,15]

Both age and baseline deviation are known to affect response to BNT in infantile esotropia generally, as was the case in the present study for both large-angle and very large-angle infantile esotropia. Irrespective of angle, younger children responded better in our study than older children. Consistent with our findings, in previous reports, 88% of infants with a mean age of <7 months achieved alignment with a single injection,[6] compared to only 38% of children with a mean age of 36 months receiving a single injection, despite similar mean baseline deviations.[16]

Mean number of BNT injections (2.2) was similar for large and very large-angle infantile esotropia groups. There was a marginally significant inverse relationship betweenchange in angle from baseline and total number of BNT injections, reflecting the fact that additional injections were only given when there was a residual deviation after prior injection(s). Metaanalysis of other studies indicates a relationship between the number of BNT injections and total reduction in angle. Issaho and colleagues[13] cited mean changes in angle of 17^{Δ}-18^{Δ} with single BNT injections in two studies (mean ages 22-36 months, baseline angles 26^{Δ} -34^{Δ}), and 31^{Δ}-42^{Δ} with means of 2.0 to 2.2 injections in 4 studies (mean ages 7-25 months, baseline angles 36^{Δ} -43^{Δ}).

Although assessing success rate was not the major objective of the study, a quarter of children achieved successful outcome, 33% of the children with large pre-injection angle and 15.9% of those with very large angle. Compared with surgery, this is a relatively poor response; however, in the context of long waiting lists for surgery there is a role for BNT in children treated by ≤24months of age and with baseline angle of $\leq 60^{\Delta}$. A third could potentially develop binocular vision who otherwise would not, waiting for surgery.

Given that BNT reduced the pre-injection angle for very large angles by more than 50%, our findings indicate that less muscle recession may be needed to achieve alignment in children in whom surgery augmented with simultaneous BNT is planned. This is at odds with recommendations of some authors for maximal muscle recessions in combination with BNT.[7,17] Our results may support the findings

of Wan and colleauges,[9] who suggest a revised surgery nomogram incorporating 1.7$^{\Delta}$ additional effect per millimeter of recession with BNT in combination with surgery than with surgery alone.

The response to surgery in failed BNT cases has not been reported in the literature. In the present study, successful motor outcomes in these children were achieved in 20 of 22 children after a single procedure, and alignment was stable after 6 months' follow-up. This is comparable to surgery as a primary treatment, as evidenced by the results of the RCT (in the surgery arm), where 33 of 47 patients were aligned with one procedure.[10] A notable benefit of BNT treatment was that subsequent recessions were smaller than they would have needed to be with surgery as a primary treatment, and three-muscle surgery was unnecessary. The fact that some children required only a single muscle recession again implies less operative time and less discomfort.

There are several limitations of our study, including the variable age of presentation, our inability to assess higher functions of binocular fusion and stereopsis in children that achieved alignment, and the relatively short follow-up of 6 months after final intervention. We also did not separately analyze the contribution of each incremental dose of BNT on outcome as has been suggested by others.[18] A possible limitation of BNT is the protracted period to alignment compared with surgery; however, the long surgery waiting period justifies BNT use in our setting.

In conclusion, BNT was associated with successful outcomes in a quarter of our patients with infantile esotropia with large pre-injection angles of deviation. These results suggest that BNT is a viable alternative intervention in such cases in the context of constrained surgical resources. Young children and larger baseline angles of deviation showed larger absolute reductions in angle of esotropia with BNT. Children with smaller baseline angles were more likely to have a successful outcome. Moreover, children who did not achieve a successful outcome solely with BNT required less muscle recession at surgery than would have otherwise been necessary to correct the original deviation.

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Appendix E – consent from authors

Declaration: Student's contribution to article(s) and agreement of co-author(s)

I, Ismail Mayet, student number 8610918, declare that this Thesis/Dissertation/Research Report is my own work and that I contributed adequately towards research findings published in the article(s) stated below which are included in my Thesis/Dissertation/Research Report.

Signature of Student ..... **Date**: 10/12/2021.

Name of Primary Supervisor.....Professor Mohammed Tikly

Signature of Primary Supervisor .....**Date**.....

Agreement by co-authors: By signing this declaration, the co-authors listed below agree to the use of the article(s) by the student as part of his/her Thesis/Dissertation/Research Report. In cases where the student is not the 1st author of a published article, the primary supervisor must explain (under comments) why the student is entitled to use the paper for his/her degree purposes.

Article 1: **Title:** Botulinum Neurotoxin in Essential infantile esotropia

Journal name Eye, year 2021 volume and page numbers: .....

Authors	Name	Signature	Date
1st author	Ismail Mayet		
2nd author	Naseer Ally		06/12/2021
3rd author	Hassen D Alli		
4th author	Mohammed Tikly		
5th author	Susan Williams		04/01/2022
6th author			

Comments by primary supervisor:

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Article 2: Title: Cost comparison between botulinum neurotoxin and surgery in the treatment of infantile esotropia

Journal name BMJ (Open) Ophthalmology, year 2021, volume and page numbers:

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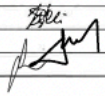
Authors	Name	Signature	Date
1st author	Ismail Mayet		
2nd author	S McGee		12/12/2021

1

3rd author	Naseer Ally		06/12/2021
4th author	Hassen D Alli		
5th author	Mohammed Tikly		
6th author	Susan Williams		04/01/2022

Comments by primary supervisor:

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Article 3: **Title**: temporal response to botulinum neurotoxin in large angle infantile esotropia- a post hoc analysis

Journal name JAAPOS, year 2022, volume and page numbers:

.....

Authors	Name	Signature	Date
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2nd author	Naseer Ally		06/12/2021
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Comments by primary supervisor:

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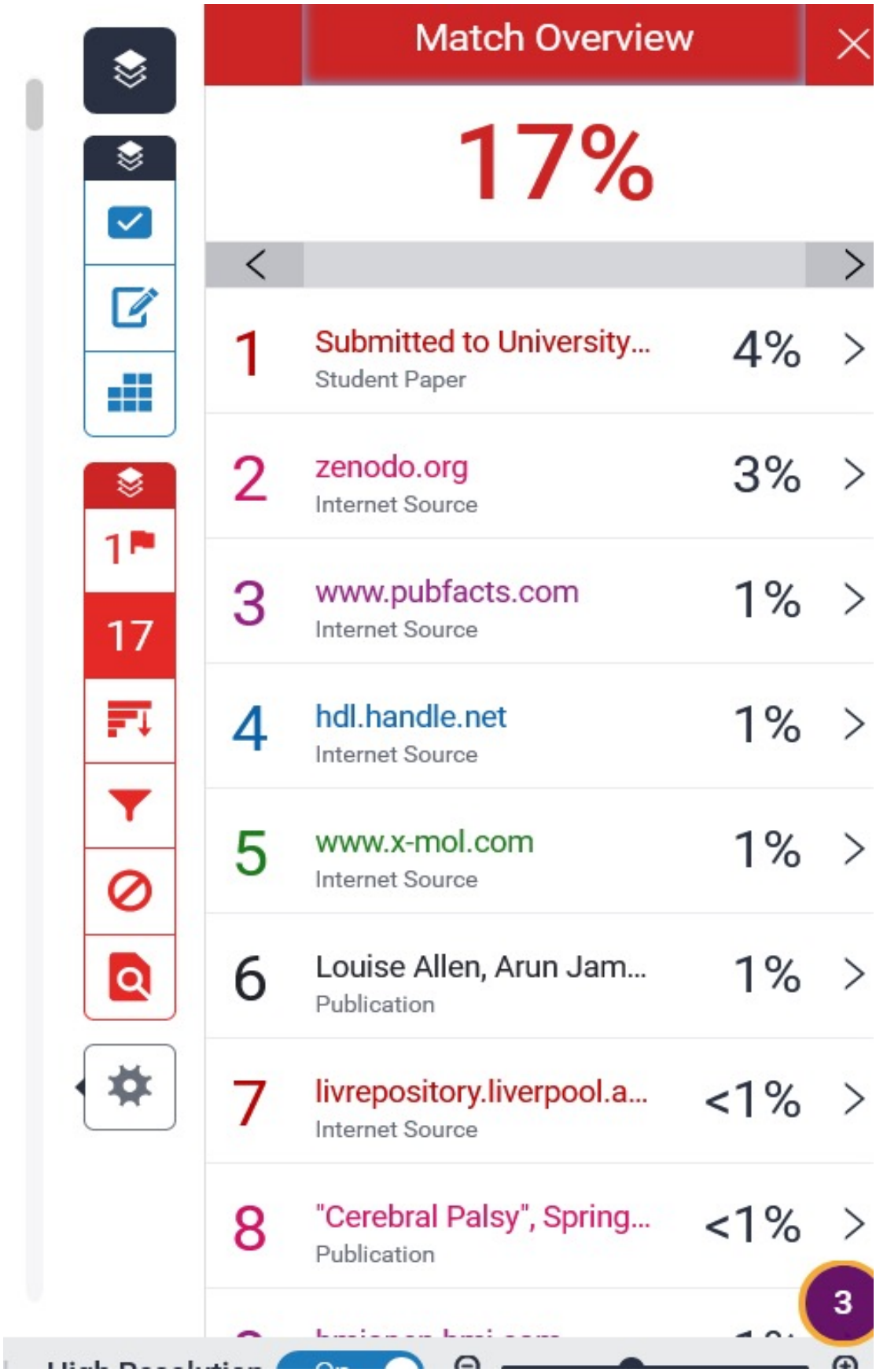
Appendix F Turnitin



Appendix G Declaration regarding Plagiarism

FACULTY OF HEALTH SCIENCES

SCHOOL OF CLINICAL MEDICINE

DEPARTMENT OF NEUROSCIENCES

Neurology; Neurosurgery; Ophthalmology; Otorhinolaryngology (ENT)

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Plagiarism declaration for written work

I, ***Ismail Mayet*** as a postgraduate student registered for a PhD at the University of the Witwatersrand declare the following:

- I am aware that plagiarism is the use of someone else's work without their permission and or without acknowledging the original source.
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- I confirm that this written work is my own work except where I have stated otherwise.
- I have followed the required conventions in referencing the thoughts and ideas of others.
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