RESEARCH PROTOCOL

RETROSPECTIVE REVIEW OF THREE & FOUR MUSCLE SURGERY FOR CORRECTION OF LARGE ANGLE ESOTROPIA IN CHILDREN

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CONTENTS

ABSTRACT

Large angle esotropia is still a frequently encountered problem in the developing world, although no epidemiological studies exist to quantify the burden of disease. The Red Cross War Memorial Children's Hospital (RCWMCH) ophthalmology service regularly assesses patients with this condition. Currently, the accepted form of treatment is a 2-stage surgical approach, with 2 horizontal muscles operated as the initial stage, and then either 1 or 2 horizontal muscles operated as the second stage 3-12 months later. There is some evidence reporting a single-stage strabismus surgery involving 3 or 4 horizontal extra-ocular muscles. This retrospective review intends to add to the body of evidence surrounding the single-stage procedure. A surgical dosage table to guide three and four muscle surgery will be devised.

INTRODUCTION

PROBLEM

It has been known for some time that congenital esotropia is the commonest form of strabismus. Large angle esotropia (in this study defined as >40 prism diopters, PD) is frequently encountered in the developing world, although no formal audit has been published detailing the precise burden of this disease, and the experience of the RCWMCH paediatric ophthalmology service supports this. Once identified, management must be directed at correcting the deviation so as to optimize vision early and prevent disability. There is currently no guideline for a four horizontal muscle procedure.

The clinical spectrum of congenital esotropia is variable. The Congenital Esotropia Observational Study found that 49% of the 175 infants enrolled exhibited large angle esotropia (>40 PD) and that the majority of these were constant deviations, therefore indicating the need for corrective surgery.[1] Currently, surgery for large angle esotropia is not uniform. Available techniques include graded bilateral medial recessions, bilateral medial recessions plus lateral rectus resection, bilateral medial recessions plus administration of botulism toxin, and bilateral medial recession plus posterior fixation suture.

A surgical dosage table for a three muscle procedure has been devised and validated by the same principle author[2,3], but there is no evidence in the literature of similar tables to add to the reliability of this tool. Additionally, Gole measured all medial rectus recessions from the limbus, as opposed to the preoperative muscle insertion. This method does not allow for the calculation of degrees according to millimetres of change of the muscle insertion. Another weakness of the Gole tool is that the mean age at surgery was 12.6 months.[2] In this study the mean age will be higher. Angle measurements for near and distance are more easily obtained in older children, therefore contributing to more accurate calculations and greater validity. The proposed weakness of this study is the shorter post-operative follow-up time as compared to Gole.

JUSTIFICATION

Historically, large (>6.5mm) bilateral medial rectus recessions was the preferred technique for the management of large angle esotropia. However, surgical success varied, with rates reported between 40% and 83.5%.[4,5] Gole also reports that this technique "frequently results in residual esotropia when used for angles of greater than 55 PD."[3]

An early 1985 paper by Goldstein suggested that for large-angle esotropia (defined as ≥80 PD) "if the surgery induces no limitation of movement or incomitance, there is an excellent likelihood that four-muscle surgery in one operation will result in a residual deviation between 15 PD of convergent strabismus and 15 PD of divergent strabismus."[6] Since Goldstein's paper, a number of studies have reported on the short-, medium- and long-term success rates of patients undergoing 3 or 4 horizontal muscle surgery for correction of large-angle esotropia, with most reporting favorable outcomes.

An early study by Scott et al. compared two different approaches to surgical management of large-angle congenital esotropia, namely the uniform approach, in which surgery is restricted to two extraocular muscles (bimedial recessions or monocular recession-resection), and the selective approach, in which bimedial recessions are combined with resections of one or both lateral rectus muscles. The average time to follow-up was 2.6 years, with surgical success defined as orthophoria ± 10 PD. The percentage of successful surgeries in the selective group was significantly higher than the uniform group: 64.5% compared with 37.3%, respectively.[7] Furthermore, "[o]nly three of the 48 patients in the selective group required a second procedure, compared with 17 of 59 patients in the uniform group."[7]

A more recent retrospective analysis by Thomas and Guha also used 10 PD as a measure of success. Although the study found no significant difference between success rates for two muscle and three muscle repairs (success rates of 57.58% and 64.71%, respectively), the latter did yield better surgical outcomes.[8] Interestingly, there was no statistically significant difference between the success rates of various age groups, suggesting that age is not a

predictive factor for positive outcomes.[8] This, in turn, that there is no need to delay surgery in a young paediatric population, which holds other benefits as discussed below.

A 2013 retrospective analysis by Chatzistefanou et al. assessed short-term and long-term success rates (again defined as ± 10 PD) of graded bilateral medial rectus recession and lateral rectus resection. At 8-weeks post-operatively 79.4% of patients were successfully aligned, with success at final follow-up (median time of 4.5 years) falling to 62.4%.[9] The higher rate of late versus early exotropic drift (24.1% vs 5.15%) was attributed to "the presence of inferior oblique overaction and the magnitude of preoperative esodeviation" as opposed to the total amount of millimeters of surgery.[9] Thus, the progressive failure is independent of the surgical dose, implying that a guideline in this regard is still a worthwhile tool.

Bayramlar et al. assessed the medium-term outcomes of three-horizontal muscle surgery for large angle infantile esotropia. They assessed 18 patients at a median follow-up of 32 months. Success was achieved, with the mean preoperative deviation of 68.8 ± 9.54 PD being reduced to a mean of 1 PD at the postoperative assessment. Four of the 18 patients had residual esotropia requiring additional surgery.[10] The favorable outcomes of this study support the use of three muscle surgery.

Gole et al. devised a surgical dosage table based on a study assessing a cohort of 49 patient undergoing three horizontal muscle surgery for infantile large angle esotropia. They followed this up with a second interventional case series and, using the surgical dosage table, reproduced the success of the first cohort. Large angle was defined as ≥60 PD and surgical success to orthotropia was defined as ±10 PD. Surgical success was achieved in 100% of cases at 2 months and 73.6% at 8 years. At 4 years, the surgical success for the first and second cohorts was 77.1% and 77.8%, respectively, thereby validating the proposed surgical dosage table.[2,3] However, as mentioned above, there is no other literature validating or replicating this tool.

In a 2015 study from Switzerland, Sturm et al. proposed an effect of 1.63°/mm for combined three muscle horizontal surgery.[11] However, this study was conducted on 27 patients with a mean preoperative deviation of 30.2°, therefore not qualifying as large angle esotropia, as defined by other papers.

The proposed benefits of a single corrective surgery include: the potential for earlier bifoveal fusion and prevention of amblyopia; fewer anaesthetics and therefore reduced anaesthetic risks; reduced economic cost to state and patient; fewer clinic follow-up visits, with overall reduced patient inconvenience and discomfort; and psychosocial benefits for children of school-going age.

Although not specific to large angle esotropia, a study by Shrestha et al. reviewed surgical outcomes of strabismus surgery in a population of whom only 3 cases (7.5%) were children under the age of 8 years. Although post-operative deviation was <10 PD in 77.5% of cases, it was noted that only 3% of cases showed an improvement in binocular single vision, advocating for the need for corrective surgery in a younger population with cortical plasticity.[12] A single-stage procedure allows for earlier correction by eliminating the interoperative delay.

Aside from the standard anaesthetic risks, evidence from a meta-analysis by Zhang et el. showed that "[t]he current evidence suggests a modestly elevated risk of neurodevelopmental disorders exists in children near 3 years of age."[13] Therefore, efforts to reduce cumulative anaesthetic time may reduce adverse neurological outcomes in young patients. Due to the need for early corrective surgery in large angle esotropia, one measure to reduce cumulative anaesthetic time is to reduce the number of operations required, as is the case with the single-stage approach.

Socially, children perceive esotropia as more disturbing than exotropia[14], leading to potential for ostracism of patients demonstrating this deviation. Therefore, it is important to address strabismus before social interaction is affected. This also advocates for the use of a single procedure approach, thereby decreasing the time to orthotropia and avoiding repeat surgery at a pre-school going age or later. Wong promotes evidence that surgery could be considered as early as 10 months of age or before.[15] In fact, a 2004 paper by Hutcheson advocated for the surgical correction of constant large angle esotropia within four months of onset, as these patients had better sensory outcomes due to early improvement in binocular visual input.[16]

OBJECTIVES

The aim of this study is to review the short-term and long-term motor and clinical outcomes of single procedure three and four horizontal muscle surgery for patients with large angle esotropia.

The objectives of this study are:

1. To create a surgical dosage table for three horizontal muscle surgery.
2. To compare the above table with existing tables.
3. To create a surgical dosage table for four horizontal muscle surgery.

METHODS

STUDY DESIGN

The study is a retrospective case series review.

CHARACTERISTICS OF STUDY POPULATION

This study will include 40 patients.

Inclusion criteria:

- Paediatric patients with large angle esotropia, defined as a deviation >40 prism diopters
- Undergoing 3 or 4 horizontal surgery between 01/10/2012 and present
- Assessed until most recent follow-up, with follow-up intervals of one week, two months, 6 months and 6-monthly thereafter

Exclusion criteria:

- Inadequate follow-up, defined as follow-up less than 2 months post-surgery

The study is based on data gained from a vulnerable population, specifically minors.

The inclusion of minors is essential to the study because the surgical intervention under review is specific to a paediatric population.

The study is based at the S21 eye clinic at Red Cross War Memorial Children's Hospital in Cape Town, South Africa.

RECRUITMENT AND ENROLLMENT

Due to the retrospective design, recruitment strategy and enrollment procedure is not applicable to this study. The Department of Ophthalmology has been granted approval to compile a database, HREC reference number R048/2014.

RESEARCH PROCEDURES AND DATA COLLECTION METHODS

Due to the retrospective design of this study, no procedures will be carried out. However, it is worth noting that the data under review was collected using a standard angle assessment technique by an ophthalmologist experienced in the use of this tool. This routine measurement is considered standard of care in order to assess response to surgery.

Data has been collected as per approval from the Human Research Ethics Committee. Data has been captured at one week, two months and six months post-surgery, and six monthly thereafter. A computer-based data collection form was used for capture, using folder numbers as index references. This information was then transcribed to an Excel spreadsheet where identifying data was removed. Only the principal investigator and co-investigator have access to these data sheets.

DATA SAFETY AND MONITORING PLAN

The retrospective collection of routine data has little potential for adverse events and harm to the patient.

The principal investigator will have exclusive access to the data sheets until the collection is complete, at which point both the principal investigator and co-investigator will have access during data analysis.

No interim analysis will be performed. Early stopping rules are not applicable to this study.

PILOT STUDY

A pilot study is not applicable to this research.

ANALYSIS

DATA COLLECTION AND ENTRY

Data will be collected by the principal supervisor, eliminating observer variation. Measurements will be recorded using a standard technique with an instrument that requires

no calibration, therefore ensuring accuracy and reliability throughout the data collection process.

Data will be captured on computer-based data collection forms. Data will then be transcribed from the data collection forms to a Microsoft Excel spreadsheet.

DATA ANALYSIS

Data analysis will be performed by the principal investigator and co-investigator.

Data will be analysed using Kaplan-Meier life-table analysis. Percentages for categorical data will be calculated. Measures of association between categorical variables will include Chi^2 test and prevalence ratios with 95% confidence interval.

Patient factors recorded are preoperative deviation and age at surgery.

The millimeters of recession/resection for each muscle will be recorded at surgery.

The post-operative outcome measured is deviation at one week, two months, 6 months and 6-monthly thereafter, correlating to short-term, medium-term and long-term rates of successful postoperative alignment, as well as overcorrection and undercorrection.

Change in angle will be compared to change in muscle insertion in order to devise a surgical dosage table.

ETHICS AND COMMUNICATION

ETHICS

This proposal will be submitted to the University of Cape Town Human Research Ethics Committee. Permission to conduct the study will be obtained from the relevant Medical Superintendent at the Red Cross War Memorial Children's Hospital.

RISKS AND BENEFITS

Due to the retrospective nature of this research, there are no physical, psychological, social, economic or legal risks to the participants.

There is no direct benefit to the patients whose data will be used for the study. Benefit lies in the management of future patients in this paediatric population. This equates to physical, psychological and social benefit through earlier corrective surgery and reduced anaesthetic risks. Economic benefit lies in reduced hospitalisation costs.

INFORMED CONSENT

All patient caregivers received thorough counselling prior to surgery to ensure informed consent for the procedure. This informed consent as administered by the principal investigator. No informed consent was taken for specific participation in this study, since approval had been granted for the existing database.

PRIVACY AND CONFIDENTIALITY

Patient confidentiality will be ensured and maintained during the study. Folder numbers will be used when retrieving patient records. Patient names will only be seen by the investigators and will be removed from the database after the information has been accessed from their records. After this all information will be used anonymously. No identifying data will be published in the study.

CONFLICT OF INTEREST

The investigators declare no conflict of interest.

REIMBURSEMENT FOR PARTICIPATION

No reimbursement was discussed as this was not applicable to the study design.

EMERGENCY CARE AND INSURANCE FOR RESEARCH-RELATED INJURIES

Not applicable.

STAKEHOLDERS

Patients
Red Cross War Memorial Children's Hospital

REPORTING AND IMPLEMENTATION

The completed study will be submitted for publication in a printed or online journal. The results of the study will be used alongside best current evidence to guide patient management at Red Cross War Memorial Children's Hospital, with potential for implementation at other tertiary ophthalmology services across Southern Africa and further afield.

LOGISTICS

TIMETABLE

The timeframe for the study involves four phases:

1. Writing and submission of research proposal: March 2016 to June 2016
2. Collection of data: July 2016
3. Analysis of data and formulation of tools: July 2016 to August 2016
4. Completion and submission of study: September 2016 to October 2016

BUDGET

The budget for the study will be the responsibility of the principal investigator. No additional funding is required.

REFERENCES

[1] Paediatric Eye Disease Investigator Group. 2002. Congenital Esotropia Observational Study. *American Journal Of Ophthalmology*. 133(1): 102-108.

[2] Forrest MP, Finnigan S, Finnigan S, Gole GA. 2003. Three horizontal muscle squint surgery for large angle infantile esotropia. *Clinical & Experimental Ophthalmology*. 31(6): 509-516.

[3] Camuglia, J.E., Walsh, M.J., Gole, G.A. 2011. Three horizontal muscle surgery for large-angle infantile esotropia: validation of a table of amounts of surgery. *Eye*. 25(11): 1435-1441. Doi: 10.1038/eye.2011.185.

[4] Assaf, A.A. 1997. Original papers: Large bimedial rectus recession (6.5 mm or more) in the management of large-angle esotropia. *Strabismus*. 5(2): 59-66. Doi: 10.3109/09273979709057388.

[5] Nelson, L.B. 1987. Surgical management of large angle congenital esotropia. *British Journal of Ophthalmology*. 71(5): 380-383.

[6] Goldstein, J.H. 1985. Management of large-angle esotropia. *Annals of Ophthalmology*. 17(11): 677-678.

[7] Scott, W.E., Reese, P.D., Hirsh, C.R., Flabetich, C.A. 1986. Surgery for Large-Angle Congenital Esotropia: Two vs Three and Four Horizontal Muscles. *Archives of Ophthalmology*. 104(3): 374-377. Doi: 10.1001/archopht.1986.01050150074030.

[8] Thomas, S., Guha, S. 2010. Large-angle strabismus: Can a single surgical procedure achieve a successful outcome? *Strabismus*. 2010(18): 129–136. Doi: 10.3109/09273972.2010.525778.

[9] Chatzistefanou, K.I., Ladas, I.D., Droutsas, K.D., Koutsandrea, C., Chimonidou, E. 2013. Three Horizontal Muscle Surgery for Large-Angle Infantile or Presumed Infantile Esotropia: Long-term Motor Outcomes. *JAMA Ophthalmology*. 131(8): 1041-1048. Doi: 10.1001/jamaophthalmol.2013.704.

[10] Bayramlar, H., Karadag, R., Yildirim, A., Öçal, A., Sari, Ü., Dag, Y. 2014. Medium-Term Outcomes of Three Horizontal Muscle Surgery in Large-Angle Infantile Esotropia. *Journal of Pediatric Ophthalmology and Strabismus.* 51(3): 160-164. Doi: 10.3928/01913913-20140318-02.

[11] Sturm, V., Menke, M.N., Jaggi, G.P. 2015. Three Horizontal Muscle Surgery for Infantile Esotropia and Decompensated Microtropia. *Klinische Monatsblätter Für Augenheilkunde*. 232(4): 446-451. Doi: 10.1055/s-0035-1545812.

[12] Shrestha, S., Manoranjan, A., Shrestha, S. 2013. Surgical outcome of strabismus. *Medical Journal of Shree Birendra Hospital*. 12(2): 23-26. Doi: 10.3126/mjsbh.v12i2.12921.

[13] Zhang, H., Du, L., Du, Z., Jiang, H., Dong, H., Li, Q. 2015. Association between childhood exposure to single general anesthesia and neurodevelopment: a systematic review and meta-analysis of cohort study. *Journal of Anesthesia*. 29(5): 749-757. Doi: 10.1007/s00540-015-2030-z.

[14] Mojon-Azzi, S.M., Kunz, A., Mojon, D.S. 2011.The perception of strabismus by children and adults. *Graefe's Archive for Clinical and Experimental Ophthalmology*. 2249(5):753-757.

[15] Wong, A.M.F. 2008. Timing of surgery for infantile esotropia: sensory and motor outcomes. Canadian Journal of Ophthalmology. 43(6): 643-651.
Doi: http://dx.doi.org/10.3129/i08-115.

[16] Hutcheson, K.A. 2004. Childhood esotropia. *Current Opinion in Ophthalmology*. 15(5): 444-448.

APPENDICES

Consent for surgery

Data collection form