SURGICAL TREATMENT OF DIPLOPIA IN GRAVES' ORBITOPATHY PATIENTS

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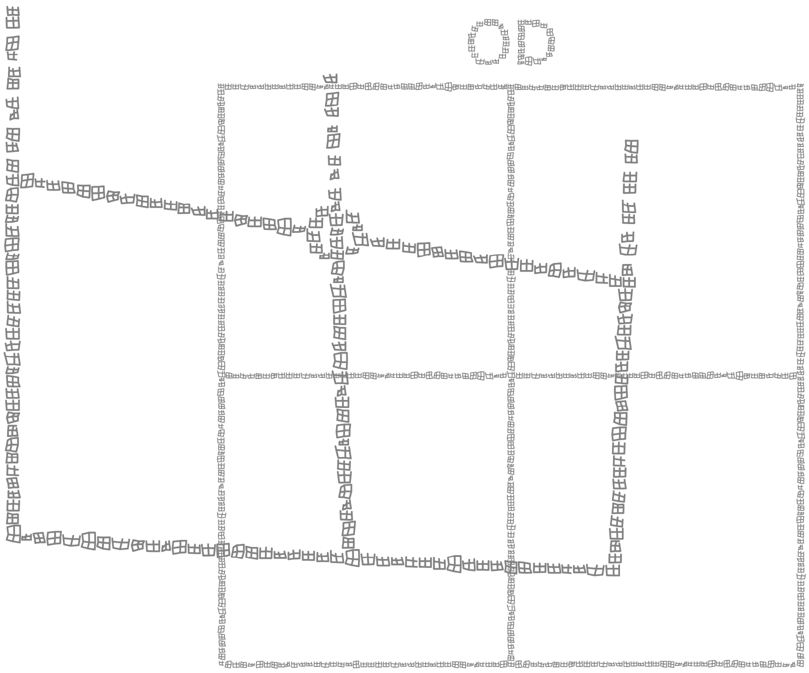


CHAPTER 1

GENERAL INTRODUCTION

AIMS AND OUTLINE OF THIS THESIS

GENERAL INTRODUCTION

A 45-year-old lady presents with the following complaints: Since eight months she feels agitated, she easily loses her temper and she has lost weight. Her eyelids have become swollen, her eyes are red, irritated and often teary and above all bulging. She hardly recognizes herself looking in the mirror. Her marriage broke down and now she faces the possible loss of her job as a teacher at a primary school as well, due to the recently developed double images. She cannot drive a car anymore. She becomes more and more isolated. When we explain to her that we she will need a long rehabilitation process, she starts crying……. This patient typically presents with symptoms of Graves' Orbitopathy.

Graves' Orbitopathy (GO) is an auto-immune disease that affects women four times more often than men. Besides the aesthetic changes, GO causes a number of functional impairments with a great impact on daily life activities. Therefore, it is understandable, that quality of life studies show that GO-patients consider themselves severely afflicted by their disease. More severely, for instance than insulin-dependent diabetes mellitus patients[1].
A major cause of GO-induced changes in quality of life is the development of double images as a result of inflammation of the extraocular muscles. In the treatment of these double images (diplopia), the orthoptist plays a significant role. This thesis will focus on the surgical treatment of the diplopia and on the psychosocial impact of this treatment.

ORTHOPTICS

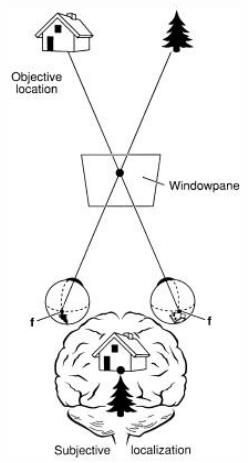
WHAT IS ORTHOPTICS?

Orthoptics is a paramedic profession complementary to ophthalmology. Orthoptists focus on diagnosis and non-surgical treatment of strabismus, visual development problems, refraction errors and eye motility disorders, in both children and adults. Orthoptists have a close working relationship with ophthalmologists, especially with oculoplastic surgeons, and neuro- and pediatric ophthalmologists. The word orthoptics is originally a junction between the Greek words ὀρθός *orthos*, 'straight' and ὀπςείν, 'sight'.

HISTORY

Orthoptics

From ancient times on, philosophers were puzzled by the concept of space. During the course of history, the idea of real or physical space evolved, filled with measurable objects, the so-called objective space. Another definition of space is a psychological process, a mental perception of the observer based on sensorimotor information. This is also referred to as subjective space[2]. For example, the *location* of an object (objective space) is different compared to the *localization* (subjective space) of an object[3]. This is shown in Figure 1: both foveas have the same subjective direction (the window plane) and the objects are seen in a common visual direction. This phenomenon is the foundation of binocular fixation e.g. binocular single vision. Descartes was the first to mention the concept of a sensorineural system in a theory of vision[2].



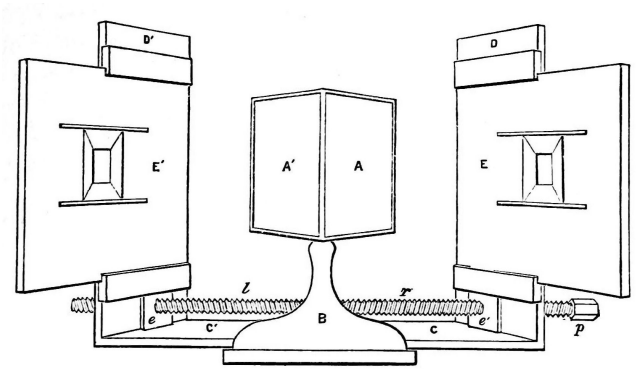


Figure 1. (left) Hering's fundamental experiment about the discrepancy between objective and subjective localization From: Campos and von Noorden (2002)[3].

Figure 2. (right) Wheatstones' stereoscope (1938). The right eye sees plate E reflected in a mirror A. The left eye sees E' via A'. The two images are combined into one (in depth). From: Crone (2003)[2].

The insights into the neuroanatomic and neurophysiological backgrounds of binocular single vision and stereopsis developed about a hundred years later, after the invention of the stereoscope (Fig. 2) by Wheatstone (1802 – 1875) and the successive application of this instrument in the treatment of squint by Javal (1839 – 1907). Javal showed that binocular single vision was often recoverable by stereoscopic exercises and his pupils Priestly Smith and Worth took it upon themselves to revise treatment of squint in England. In fact, Worth (1869 – 1936) – in spite of his insistence that a defect of the (central) fusion faculty was the

underlying cause of squint – contributed a great deal to the development of orthoptic training and from then several schools of orthoptics were founded in England[2, 4 5].

Ernst Maddox (1860 – 1933) had a great interest in orthoptic treatment of squint in children. He invented among others, the Maddox rod, the Maddox double prism and the Maddox wing, all devices which measure deviations of the eyes. His daughter Mary Maddox worked with him; she was probably the first woman to take up orthoptic treatment in the capacity of a 'medical auxiliary'. Maddox and his daughter inspired many others in England to study the orthoptic investigation and treatment of strabismus[4-6].

However, in 1938 Chavasse resisted against the orthoptic training of squint. He emphasized that the motor aspect of binocular vision was more significant to restore the straight eye position[7]. His exercises focused on the motor aspects of strabismus complemented by strabismus surgery. In the 1970's it became apparent that both aspects were important to achieve or regain normal binocular vision[4].

Orthoptics in the Netherlands

To confirm or dismiss the theory of the origins of squint of Chavasse, Zeeman (1879 – 1960) (Fig. 3) promoted the conservative treatment of strabismus and founded a strabismus clinic at the Wilhelmina Gasthuis in Amsterdam in 1940 (later the Academic Medical Center)[8]. Members from this clinic (Hagedoorn, Keiner, Velseboer, Roelofs, Crone and others) were leading researches interested in the physiology and pathophysiology of binocular vision and ocular motility disorders. For example, Crone (1918 – 2012)(Fig. 3), published his magnus opus 'Diplopia', a highly informative book on motility disturbances and binocular vision.

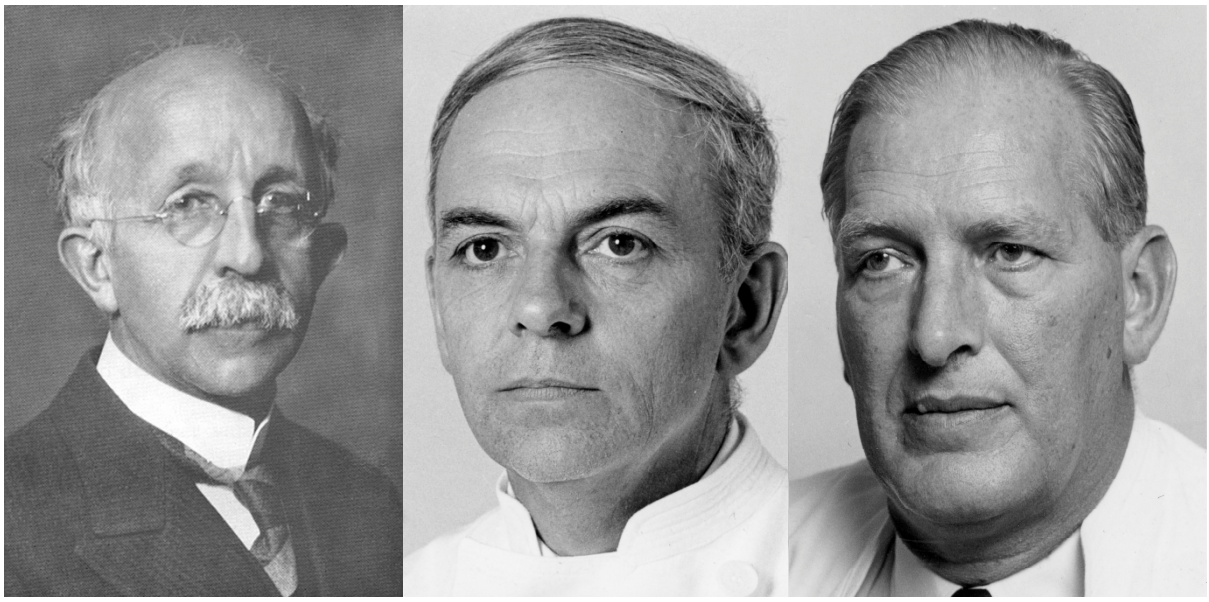


Figure 3. Left: Prof. Zeeman (1879-1960); Middle: Prof. Crone (1918-2012); Right: Prof. Bleeker (1915-1997)

As a result of this interest in strabismus the 'Dutch School for Orthoptic Assistants' was started in Amsterdam in 1956. Robert Crone was greatly involved as a teacher and as medical director of the school. Together with Joan Hagedoorn, patient care was combined with scientific work on fixation disparity, heterophoria, normal and abnormal binocular vision. Crone contributed significantly to the standard of the orthoptic profession in the Netherlands and the Dutch orthoptists honored him with an honorary membership of their association. In 1958, the first 8 orthoptists graduated and founded the Dutch Orthoptic Association. Nowadays, orthoptists have a Bachelor of Science degree after following a four year fulltime program at the University of Applied Health Science in Utrecht and the Dutch Orthoptic Association counts over 350 members.

Alongside the strabismic part of the clinic, Amsterdam founded their first orbital center of the Netherlands in the early 60's. Due to the sharp increase of orbital fractures caused by mopeds and the turbulent 60's, Bleeker (1915 – 1997) (Fig. 3) and later Koornneef (1945 – 2001) focused their treatment and research on the orbital part of ophthalmology. The first international orbital symposium held in Amsterdam in 1968 gained an enormous interest and by now, the orbital center treats a wide variety of orbital diseases, of which Graves' Orbitopathy is a significant one.

Surgical treatment

In ancient times, a squinting eye was seen as an 'evil' eye[2]. In the 7th century, eye masks were advised to correct this evil eye and encourage the eyes to look straight (Fig. 4)[9]. Until the late 18th century, the surgical interventions on the eye muscles were not yet possible. The first person who tried to correct strabismus by means of surgery was Taylor (1703 – 1772). He made an incision of the conjunctiva of the deviated eye and covered the straight eye. Of course, this therapy was not successful. It was Dieffenbach (1792 – 1847) in Germany who actually changed the eye position by unfastening the muscle from the eye[2, 10].

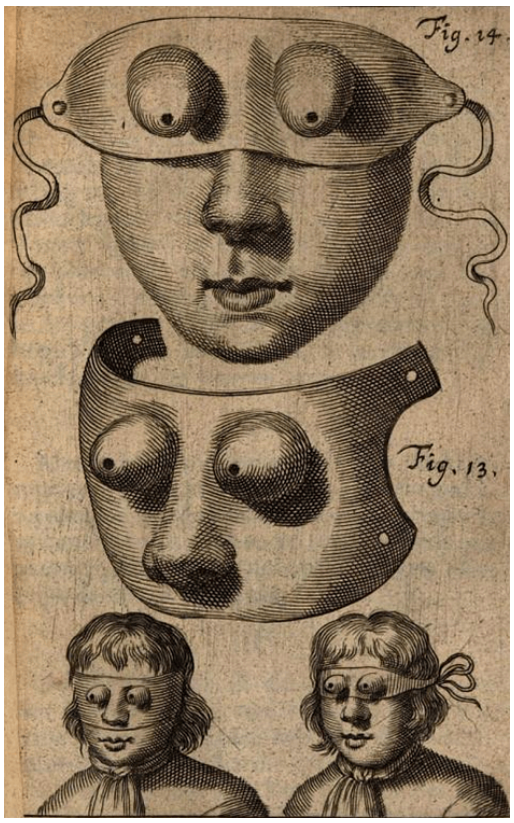


Figure 4. Masks to correct strabismus.[9]

Franciscus Cornelis Donders (1818 – 1889), father of ophthalmology in the Netherlands, stressed in his work 'On the anomalies of accommodation and refraction of the eye' (1864) the relation between accommodation and convergency and the co-relation between hypermetropia and esotropia[2, 11]. However, prescribing hypermetropic glasses only cures patients with a specific type of esotropia. The surgical techniques developed further and during the end of the nineteenth century, both weakening procedures (tendon weakening, recession) and strengthening procedures (tendon tucking, resection) were invented. During the 20th century, surgery on the oblique muscles and transposition procedures became feasible to correct the deviation[12].

BASICS OF ORTHOPTICS RELEVANT TO THIS THESIS

Normal binocular vision and diplopia

Binocular vision is the ability to see with two eyes simultaneously. Double vision (diplopia) proves that a patient at least has a sensory input into both eyes. To perceive only one image with two eyes (binocular *single* vision), the image in both eyes has to fall on identical spots in each retina (corresponding points) (Fig. 5, left).

However, if an image falls on retinal points with a small horizontal separation (disparity), depth perception is perceived. When the disparity between the retinal points is too large, it is impossible to see one image and diplopia occurs (Fig. 5, right).

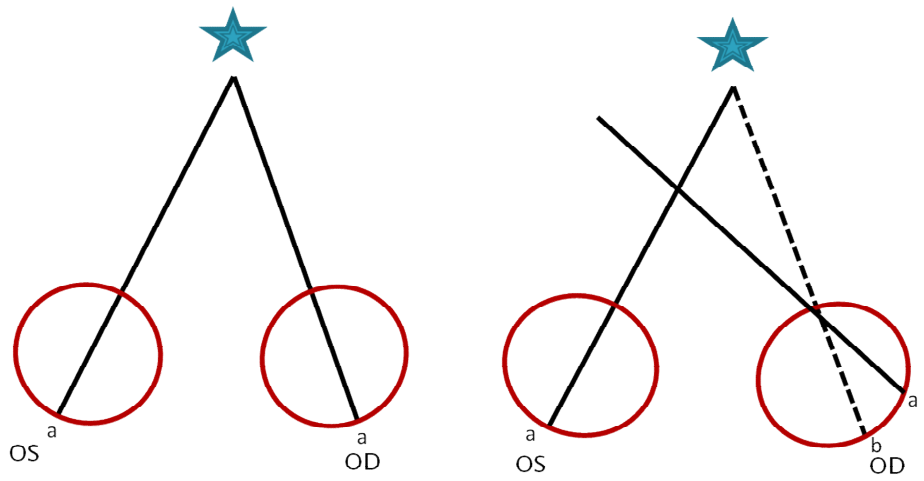


Figure 5. Left: Normal binocular single vision. The image (star) falls on corresponding retinal points and is perceived as a single image. Right: Esotropia in the right eye with normal retinal correspondence. The image (star) falls on non-corresponding retinal points (a and b) which causes a double image.

The development of binocular single vision takes place during early childhood. Only when both eyes are aligned, binocular single vision can develop. If a constant misalignment between both eyes (strabismus) occurs during early childhood, the visual cortex suppresses the image of the deviated eye. This process (amblyopia) is irreversible in time, but helps the patient to function in daily life.

Measurements

binocular vision

The first quote of the famous orthoptic textbook of Campos and von Noorden states under the heading of ”the eyes as an sensorimotor unit”: ”The two human eyes with their adnexia and nervous system connections form an indivisible entity”[3].

To measure the quality of this binocular system, several orthoptic tests are available. Some tests focus on the sensory and other on the motor aspects of the oculomotor system. To get the most reliable results, it is important to test the patient’s system of binocular single vision under circumstances as natural as possible and on different viewing distances. *Bagolini striated glasses* are most frequently used to test the quality of binocular vision (Fig. 6)[13]. It gives information about the presence of binocular single vision, diplopia or suppression, both at near and distance fixation.

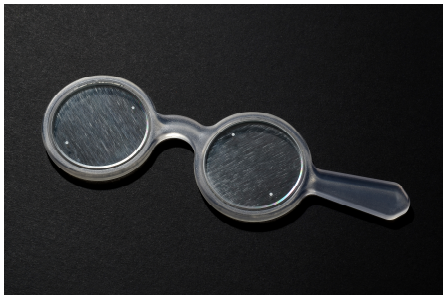


Figure 6. Bagolini striated glasses.

Figure 7. Prims bars.

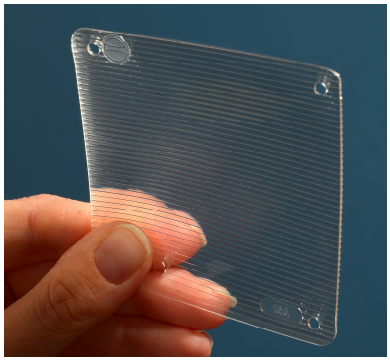


Figure 8. Fresnel prims.

With help of the additional prism bars (Fig. 7), the orthoptist can analyze if prisms can be of help in correcting the double vision (Fig. 8).

The part of the objective visual space in which the patient has single vision is called the *field of binocular single vision* (BSV). Measurement of this field gives information about the daily life situation of the patient. In case of lack of fusion, the field of perceived BSV can be limited[14]. The Maddox screen and Harmswand are suitable to measure this field[13, 15] although in limited gaze directions. A larger field can be tested with the Goldmann perimeter (Fig. 9).

Figure 9. Goldmann perimeter.

Figure 11. Motility meter.

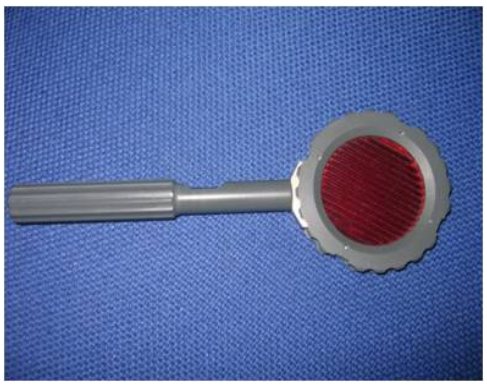


Figure 12. Cycloforometer of Franceschetti.

strabismus

It is of great importance to measure the squint angle at both distance and near. Differences in angles between both distances could influence the surgical treatment plan. The amount of strabismus can be measured objectively and subjectively. In general the best test to measure the angle objectively in GO patients is with help of the *prism cover test* (PCT)[15-31]. With the prism bars the amount of horizontal and vertical deviation can be accurately measured at near and distance up to 40^. In case of a larger angle of strabismus, additional prisms have to be used. Care has to be taken to hold the prisms in the Prentice position rather than in the frontal plane, otherwise measurement errors occurs easily[32].

To test the angle of strabismus subjectively, the Lancaster Hess chart[16, 23, 33-38], the Maddox screen[39] and Harmswand at 2½ meters[15, 40-42] are used in patients with GO. All three tests measure the deviation in nine positions of gaze. The results in the nine positions can be drawn schematically and give information about the involved eye muscles, the stability of the disease and is of help when making a surgical plan for strabismus correction (Fig. 10).

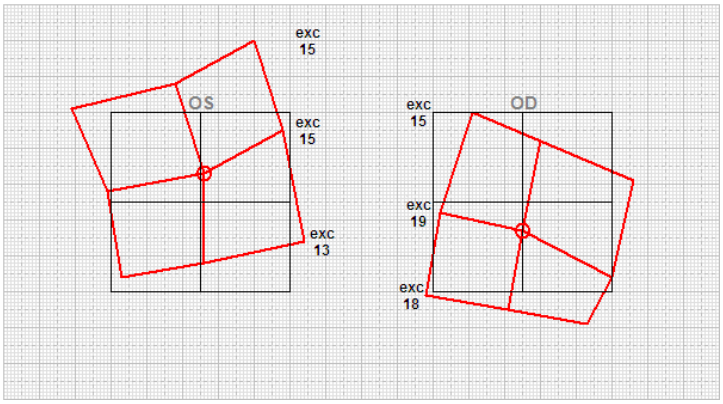


Figure 10. Amsterdam motility diagram showing the eye position in nine directions of gaze including the cyclodeviation of the eyes in primary position, up- and downgaze (exc = excyclodeviation).

motility

In testing ocular motility, distinction between binocular (version) and monocular (ductions) eye movements must be made. In patients with GO, ductions are often impaired due to the restrictive eye muscles due to inflammation. To monitor the progress of the disease and to make the best choice of therapy, ductions have to be measured carefully. In general, abduction, adduction, elevation and depression are all important to measure. This can be done semi-quantitatively by ranking the ductions from 0 – 4, with 0 indicating full ductions and 4 no movement possible in that direction[20, 43]. For more accuracy, Flanders and Hastings (1997) divided the ductions in 7 steps[44]. Quantitatively, the most appropriate device is the Goldmann perimeter[45-47] or the motility meter[48] (Fig. 11).

cyclodeviation

Four out of the six eye muscles cause a primary or secondary amount of a rotary eye movement (incyclo- or excyclodeviation) (Table 1). To perceive and/or maintain binocular single vision, the amount of cyclodeviation may not exceed 8°[49]. To restore the field of BSV in GO-patients, it is important to know if any bothersome cyclodeviation exists. Furthermore, eye muscle surgery can change the amount of cyclodeviation. Both pre- and postoperatively, accurate measurement in primary position, up- and downgaze is necessary. However, measuring the secondary gaze positions with the Maddox Double Rod test can give measuring errors[50]. For that reason, the Harmswand or the cycloforometer of Franceschetti (Fig. 12) are preferred.

Table 1. Action of external eye muscles in primary position

Nerve	Muscle	Primary action	Secondary action	Tertiary action
III	Inferior rectus	depression	excyclo	adduction
III	Superior rectus	elevation	incyclo	adduction
III	Medial rectus	adduction	—	—
VI	Lateral rectus	abduction	—	—
IV	Superior oblique	incyclo	depression	abduction
III	Inferior oblique	excyclo	elevation	abduction

GRAVES' ORBITOPAHTY AND DIPLOPIA TREATMENT

GRAVES' ORBITOPATHY

Graves' disease is an auto immune disease affecting the thyroid gland, the orbits and the legs. In patients with eye involvement, the disease is called Graves' Orbitopathy (GO). The most frequent sign of the disease is eyelid retraction, followed by protrusion of the eye (proptosis). This proptosis is a result of swelling of the eye muscles in an early stage of the disease and increase of the volume of the orbital fat in a later stage[51]. Due to the increased exposure of the anterior part of the eyeball, patients complain of tearing, photophobia, and/or a gritty sensation of the cornea. In addition, they may have eyelid swelling, chemosis and double vision. Sight loss appears in the severe cases, if the optic nerve becomes compressed[52].

Although the association between hyperthyroidism and exophthalmos was already described in the 12th century[53], it was the Irish doctor Robert James Graves in 1835[54] who was the first to publish the syndrome. Only 5 years later, the German doctor Karl Adolph von Basedow did the same, independently from Graves. For that reason, both the names of Graves and von Basedow are linked to the disease. Synonyms for GO are Graves' Ophthalmopathy (used by endocrinologists), Thyroid Associated Ophthalmopathy (TAO) (used in the UK), Thyroid Eye Disease (TED) (used in the USA) and Thyroid-Related Orbitopathy (TRO) (not frequently used).

GO is primarily associated with hyperthyroidism (80%), but patients can also be euthyroid (10%) or even hypothyroid. (10%)[55]. The disease primarily affects women (female : male ratio 4:1)[56] with the highest risk to develop GO around the age of 40 – 60 years[57]. In the USA, the prevalence of Graves' disease is 1:90, of whom about 50% develop GO. In contrast, the incidence of Primary Open Angle Glaucoma is 1:136 and of Age Related Macula Degeneration 1:175[58]. The severity, duration and expression of GO differs significantly between patients[57] as does the impact of the disease on the patients' quality of life [59-62]. Generally, the disease first tends to get worse (active phase), followed by a slow decrease in severity and ends with a stable stage (inactive phase)[63]. Treatment is fitted to this natural course of the disease. During the active phase, immunosuppressive treatment is aimed at prevention of progression of the disease. After the active phase, the inactive phase follows,

which is confirmed by a period of stability of 3 – 6 months[15, 57, 64]. During the inactive phase, functional and rehabilitative surgery is performed, starting with orbital decompression, followed by strabismus surgery and finally by eyelid corrections[57]. Decompression surgery can be required during the active phase of the disease when there is a threat of blindness and insufficient response to medical or radio therapeutic treatment.

Diplopia

Diplopia in GO patients is the result of a loss of elasticity of the swollen extraocular muscles following the inflammatory process. The extraocular volume increases due to edema formation following secretion of high amounts of glucosoaminoglycans by activated orbital fibroblasts[65]. This induces duction impairment in the contralateral gaze. Along with the levator muscle, the inferior and medial rectus muscles are most frequently involved. The belly part of the muscle is mainly affected, the tendon usually keeps its original shape[65]. This restrictive type of strabismus is often bilateral and asymmetric, which results in intractable diplopia. Any GO patient may develop diplopia, but in up to 64% GO-patients, diplopia develops after decompression surgery [66-68] [69-72] [73]. If the eye muscles are impaired asymmetrically, normal binocular single vision cannot be established.

DIPLOPIA TREATMENT

Torticollis

Patients with diplopia due to GO often try to compensate with an abnormal head position (torticollis). Due to the elevation impairment, the chin is elevated to avoid looking up. When the abduction impairment is predominantly on one side, a head turn can help to reach the field of BSV. Although a torticollis avoids diplopia, most patients suffer from neck pain. Therefore, this cannot be seen as a permanent solution.

Prisms

During the active phase or if the diplopia is mild, Fresnel press-on membrane prisms can be worn on glasses (Fig. 8)[15, 74-78]. The prism changes the direction of the image in the primary position to the correct retinal spot and the often large range of fusion makes it possible to regain single vision[15]. The incomitant aspect of the strabismus per se is not a contradiction for the use of Fresnels[74], however no optimal field of binocular single vision (BSV) can be achieved[78]. The Fresnel prisms are available in a range of strengths, which enables adjustments when the angle of strabismus changes. Nevertheless, strong Fresnel prisms

cause vision loss and distortion[74]. If long term stability is reached, the amount of prisms is low and the eye motility is the same in all directions of gaze, prisms can be grinded into the glasses. In many cases, the eye motility is highly incomitant and the deviation is too large to correct with prisms, therefore other measures are needed.

Occlusion

One of the most frustrating issues for patients with GO is the time needed to confirm stability of the disease. In the meantime, if prisms are not achievable, occlusion of an eye to overcome diplopia may be the only possible treatment. However, if one eye is occluded, the visual field is severely restricted and patients often suffer from a tired fixating eye. In some cases, occlusion is a permanent option, when all other efforts to gain a useful field of BSV, have failed. Eye patches, occluder contact lens or frosted glasses are examples of occlusion[79].

Surgery

The goal of strabismus surgery is to reach a useful field of BSV around primary position and down gaze[44, 80-84], but a wide variety of success criteria is mentioned in literature. To reach this goal, the orthoptic status must be stable for 3 – 6 months[33, 85-87]. A thorough surgical plan has to be established within a team of orthoptists and ophthalmologists, verifying ductions, eye motility, amount of cyclodeviation and contribution of secondary muscle actions. Due to the incomitant type of strabismus, additional surgery is often necessary to reach the desired goal[85].

The ideas about the cause of squint in GO-patients changed over time. In 1944, Rundle and Wilson reported a bilateral and symmetrical 'paralysis' of elevation, which they thought was caused by a dysfunction of the superior rectus muscle and potentially of the inferior oblique muscle[63, 88]. Following this conception, Miller treated these GO-patients with a single recession of the inferior rectus and adhesiolysis of the inferior oblique[89]. He also stated that if limitation in elevation was absent, a resection of the underacting muscle had to be performed. In all cases, the forced duction test was found to be essential in this process to identify the involved muscle[90]. In contrast to the 'paralytic hypothesis', Braley (1953)[91] and later Smith and Soll (1960) suggested that the inferior rectus muscle was the primary cause of restriction of elevation due to a fibrous infiltration[92]. We now know he was right. Smith and Soll suggested lengthening of the involved muscle instead of performing a strengthening procedure[88, 93].

Nowadays, surgery of the eye muscles is based on either one of two concepts: the duction concept or the deviation concept. In the duction concept, the surgeon evaluates at the time of surgery the position of the eye muscle during active or passive motility[21, 22, 88, 94-96]. The deviation concept is based on the measured squint angle prior to the surgery[84, 97-99]. Several modifications are based on these two concepts[98].

In general, resections of the eye muscles in GO are avoided and recessions are preferred[15, 85, 100, 101]. In some cases resection can be considered after preceding maximal recession surgery[102]. With regard to recession, different techniques are used, such as recession with fixed sutures[25, 98], adjustable sutures[20, 44, 76, 80, 87, 103-107], relaxed muscle technique[83, 108] and lengthening procedures with scleral graft or Tutopatch®[88, 109 110]. The most common complication is overcorrection, especially seen after inferior rectus recession[85, 104, 105, 111, 112]. However, the advantage of these lengthening procedures is that the arc of contact of the muscle with the eye remains. This would prevent duction impairment in the direction of the operated muscle postoperatively and lower the chance of overcorrection. Till present, randomized control trials are not available to confirm or counter this theory. Moreover, for each method chosen, the success and reoperation rate shows a wide variation[42, 44, 83, 84, 113, 114]. Furthermore, the effect of surgery can and should be measured both in an objective and subjective way. Measuring change in quality of life appears to be a major outcome in evaluation of surgery in this patient group[59].

Quality of life

After enduring all stages and treatments of the disease, eventually, patients with GO seem to acquiesce in their situation and again gain in their quality of life (QoL). Nonetheless, this process is long and with a lot of obstacles. A survey among 120 patients up to 17 years after diagnosis revealed that 52% found their appearance to be abnormal and 38% were unhappy as a consequence. Another third of the patients reported eye discomfort[115]. Obviously, GO is a chronic disease which permanently effects patient's QoL[116]. A disease specific questionnaire to measure the quality of life in GO-patients was designed by Terwee *et al.*(1998) [117] and another by Fayers and Dolman (2011)[118]. Both questionnaires are validated and are used in different countries[28, 119-122]. By now, only one study evaluated the change of QoL after strabismus surgery[121].

In addition to the disease specific QoL questionnaire, Yeatts *et al.* (2005) added mental health questions to evaluate mood en psychological factors of the disease[62]. This study

showed that social and vocational function was significantly impaired. Another study showed a psychological depressed mood in a group of moderate to severe GO-patients. This was especially significant in patients who suffered from proptosis and diplopia[60]. More recently, the same psychosocial characteristics were found in a patient group undergoing orbital decompression surgery[123]. Future studies are necessary to explore this area of the QoL more in depth.

AIMS AND OUTLINE OF THIS THESIS

The primary goal of this thesis is to evaluate the effect of different surgical procedures to correct diplopia in GO-patients. Additionally, analysis of the effect of treatment on the quality of life plays a major role in this thesis.

To make multicenter studies possible in this field, this thesis starts with a paper comparing the outcome of objective tools for measuring ductions and cyclodeviation (**chapter 2**). In **chapter 3, 4 and 5** we will analyze the outcome of bilateral inferior rectus muscle recession, uni- and bilateral medial rectus muscle recession and combined superior rectus and inferior rectus muscle recession. In addition, the effect of the surgery on outcome of ductions, cyclodeviation, squint angle and stability of the postoperative orthoptic status are evaluated. A review of success criteria in this patient group is necessary to present a proposal for success criteria (**chapter 6**). Finally, two prospective studies on the outcome of the QoL questionnaire and the field of BSV after strabismus surgery in this patient group will be discussed (**chapter 7 and 8**).

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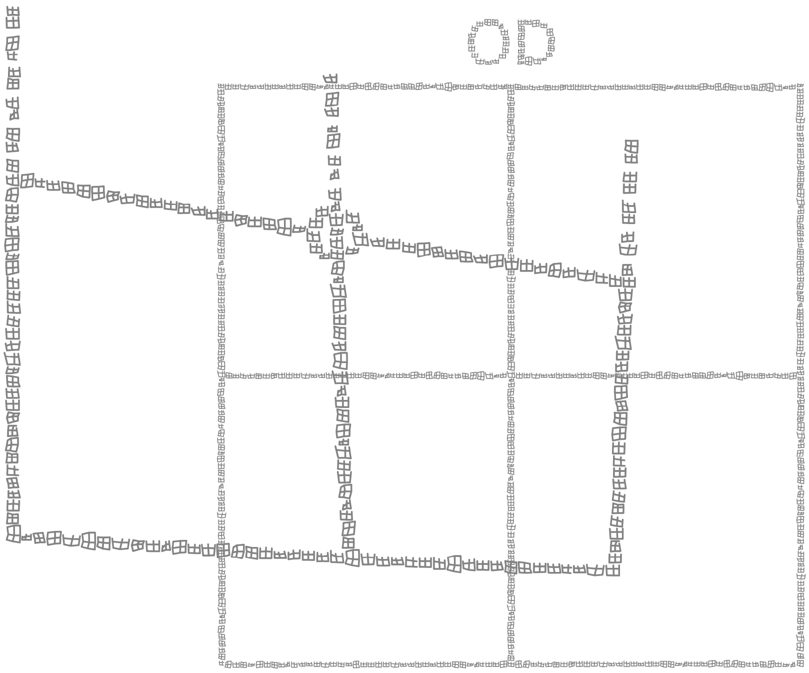

CHAPTER 2

COMPARISON OF CYCLODEVIATION AND DUCTION MEASUREMENT IN GRAVES' ORBITOPATHY PATIENTS USING DIFFERENT DEVICES

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ABSTRACT

Purpose: To compare measurement outcomes of different devices measuring cyclodeviation and ductions in Graves' Orbitopathy (GO) patients.

Methods and materials: Cyclodeviation in GO-patients was measured using the Harms tangent screen (HTS), the cycloforometer of Franceschetti and the synoptometer. Ductions were measured using the modified perimeter, the Goldmann perimeter and the Maddox tangent scale (MTS).

Results: In 13 patients, cyclodeviation in primary position, up- and downgaze was measured with the above mentioned devices. The mean differences ranged from 0.3° to 3.1° and were smallest between the HTS and the cycloforometer (89% of all measurements within 2° difference).

Measurement of abduction, adduction, elevation and depression using the modified perimeter, Goldmann perimeter and MTS were obtained in another 13 patients. The mean differences ranged from 1.2° to 12.9° and were smallest between the modified perimeter and the Goldmann perimeter (92% of all measurements $\leq 8°$).

Conclusions: The HTS and cycloforometer produce interchangeable measurement outcomes. The modified perimeter and the Goldmann perimeter are interchangeable as well. However, the synoptometer and the MTS are not suitable for comparative analysis.

INTRODUCTION

Graves' Orbitopathy (GO) is characterized by eyelid retraction, proptosis, double vision, restricted eye motility and reduced vision. Eventually, about 20% of GO-patients need surgery to correct diplopia (Sasim et al., 2008). Diplopia in GO is caused by the disease itself or develops or deteriorates after orbital decompression surgery. It can be horizontal, vertical or torsional. Thereby, restriction in eye movements, asymmetrical or symmetrical, severely reduces quality of life of GO patients (Ponto *et al.*, 2009). In order to set up an optimal treatment plan for surgery, accurate measurements of the strabismus angle, fusion range, cyclodeviation, ductions and the field of binocular single vision are mandatory.

Various devices are used to measure these components of ocular motility. For instance, to measure cyclodeviation, the synoptophore (Boyce, 2000; Capdepon *et al*., 1994; Davidson & Clearly, 2000; Georgievski & Kowal, 1996; Klainguti *et al.*, 1992), the synoptometer (Klainguti *et al.*, 1992; Kolling, 1982), the Harms tangent screen (HTS) (Capdepon *et al.*, 1994; Klainguti *et al.*, 1992; Kolling, 1982), the Maddox Double Rod (MDR) test (Boyce, 2000; Capdepon *et al.*, 1994; Garrity *et al.*, 1992; Georgievski & Kowal, 1996; Klainguti *et al.,* 1992;), the torsionometer (Boyce, 2000; Davidson & Clearly, 2000; Georgievski & Kowal, 1996), the Maddoxwing (Boyce, 2000; Georgievski & Kowal, 1996), the Awaya cyclotest (Boyce, 2000), Bagolini Striated glasses (Boyce, 2000; Johnson *et al.*, 1987;Kraft *et al.,* 1993) and the cycloforometer of Franceschetti (Gutter *et al.*, 2010; Klainguti *et al.*, 1992) are used. So far, few studies have been performed to assess whether these devices produce interchangeable results (Georgievski & Kowal, 1996; Klainguti *et al.,* 1992; Kolling, 1982). This knowledge, however, is indispensable for research. Georgievski & Kowal found no significant difference in outcomes measuring cyclodeviation in primary position using the torsionometer, the MDR test, the synoptophore or the Maddox wing (Georgievski & Kowal, 1996).

However, measurement of cyclodeviation is not only required in the primary position, but also in up- and downgaze. The cycloforometer of Franceschetti, the HTS and the synoptometer allow such measurements and are therefore suitable to be used in GO-patients (Klainguti *et al.,* 1992). These devices have not yet been studied in terms of their interchangeability.

Various devices are available to measure ductions in different directions in GO-patients: the cervical range of motion (CROM) (Kushner, 2000), the Maddox tangent scale (MTS)

(Gerling *et al.*, 1997; Gutter *et al.,* 2010), the HTS (Gerling *et al.*, 1997; Pitz *et al.*, 2005), the modified perimeter (Mourits *et al.,* 1994), the synoptophore (Gerling *et al.,* 1997), the Goldmann perimeter (Haggerty *et al.,* 2005; Gerling *et al.*, 1997;), the grading scale 0-5 (Kupersmith & Fazzone, 2004), the Kestenbaum limbus test (Kupersmith & Fazzone, 2004) and the Aimark (Hanif *et al.,* 2009). The synoptophore is considered inappropriate because maximal recordable elevation is limited (Hanif *et al.,* 2009). The Goldmann perimeter was found to be more convenient than the tangent screen and the synoptophore because the former has a telescope available (Gerling *et al.,* 1997). The grading scale Kestenbaum limbus test and CROM were found to be not suitable for research because of a low interobserver repeatability (Kupersmith & Fazzone, 2004). The Goldmann perimeter, the synoptophore and the Aimark have been compared and showed considerable measurement differences (Hanif *et al.,* 2009). In conclusion, the literature shows that some of the various devices are inappropriate for research, whilst other devices have not yet been studied. We undertook this study to find out whether the modified perimeter, the Goldmann perimeter and the MTS showed interchangeable duction measurement outcomes in GO-patients.

METHODS AND MATERIALS

The study was conducted according to the principles of the Declaration of Helsinki (seventh edition, October 2008, Seoul) and in accordance with the Medical Research Involving Human Subjects Act (WMO). Informed consent was given by each patient.

Study A: Cyclodeviation

We included consecutive GO-patients who visited the ophthalmology clinic in Mainz because of the availability of the HTS. Patients who accepted to participate in the study were asked about the presence of horizontal, vertical and/or torsional diplopia (no, yes). One orthoptist measured the cyclodeviation using the cycloforometer. Another orthoptist measured the cyclodeviation using the HTS or using the synoptometer. The measurements were performed in a random order.

Patients with intra-ocular pathology were excluded along with monocular patients, patients with uni- or bilateral vision < 1.0 LogMAR and patients with suppression. The tests were carried out binocularly without optical correction and with fixation of the right eye. Cyclodeviation in 25° up- and downgaze was only measured if the patient was able to fixate in those directions. In each device, each measurement was repeated four times, two times

started from the excyclo direction and two times from the incyclo direction as suggested by Klainguti *et al.* (1992).

During the examination with the cycloforometer at 2½ meter in front of the HTS (Fig. 1), a headlamp was used to secure the head position of the patient. The cycloforometer was held with the horizontal slits for the right eye in such a way that the patient perceived an almost vertical red line. The cycloforometer was then rotated until the patient perceived the line exactly vertical. The procedure was carried out in primary position and in 25° up- and downgaze.

The cyclodeviation with the HTS and the headlamp was measured as described by Klainguti *et al.* (1992). Cyclodeviation with the HTS was measured by holding a Maddox glass in front of the right eye of the patient, who thereby perceived a red line. The patient was instructed to adjust the red line exactly horizontal with help of a handheld device. To measure the cyclodeviation using the synoptometer, a Maddox slide (foveal size) with a circle and a cross was presented in front of the right eye. The examiner rotated the slide from 20° excyclo position to 0° and asked the patient to warn as soon as the cross was perceived in perfect horizontal and vertical position.

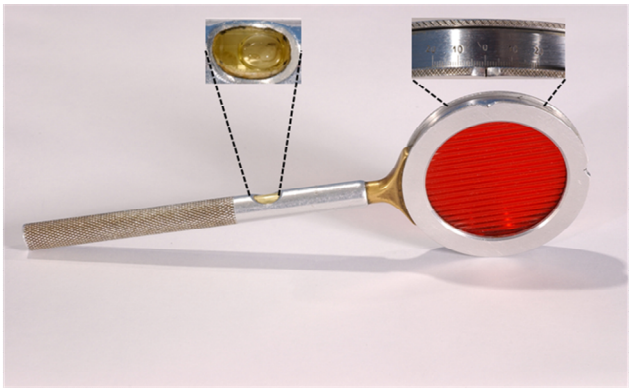

Figure 1. Cycloforometer of Franceschetti.

Figure 2. Modified perimeter as described by Mourits *et al.* (1994).

Study B: Ductions

For this study, we included consecutive GO-patients who visited the ophthalmology clinic at the University of Amsterdam. Ductions were measured with the modified perimeter, the Goldmann perimeter and with the MTS at 0.75 m. Only the right eye was investigated. Each time, ductions were measured in 0°, 90°, 180° and 270° gaze directions. Patients with a vision < 1.0 LogMAR of the investigated eye were excluded.

Ductions were measured using the modified perimeter by instructing the patient to fixate a spotlight which moves on a rotatable rail (Fig. 2). The observer assesses the amount of duction by observing when the light reflex on the cornea moves out of the centre of the pupil (Mourits *et al.*, 1994). In downgaze, the eyelid was held up by the investigator.

To measure ductions using the Goldmann perimeter we followed Gerling *et al.,* except for the fact that the ductions were only measured once in each direction (1997). In downgaze, a small alteration had to be made because the eyelid could not be held open by the investigator due to the large bowl of the Goldmann perimeter. If the spotlight could not be seen because it was covered by the upper eyelid, the patient was asked to hold up the upper eyelid. The non-investigated eye was occluded and the strongest spotlight was used (relative intensity 4e (1.0), object V (64 mm^2)).

To measure the ductions using the MTS, the MTS itself is used in combination with a headlamp. The patient fixates a fixation light in the center of the MTS, while the investigator turns the head of the patient in different directions and checks whether the corneal reflex of the light remains in the same place in the pupil. As soon as the reflex moves away from its place on the cornea, the duction can be read off on the tangent scale (the distance in degrees between the light on the wall and the reflex of the headlamp on the tangent scale). Normally, the patient is seated at a distance of 2½ meter in front of the tangent scale. But at that distance, the MTS is not big enough to record maximal duction (in which we are interested). In order to overcome this problem, we calculated a distance in which maximal recordable duction is possible. For this, we used the following formula: $b = \tan(X_{2.5}) / \tan(X_b) \cdot 2.5$, where $X_{2.5}$ = degrees when measuring at 2½ m distance from Maddox tangent scale; X_b = degrees when measuring at b (in meters) distance from Maddox tangent scale and b = distance (in meters) between the patient and the MTS. We calculated a distance of 0.75 m. With conversion of this formula we were also able to adjust the measurement of the screen to the distance used.

Statistical analysis

We calculated the sample size for both studies with help of the Query Advisor (equivalence of means). A sample size of minimal 7 patients was necessary in the cyclodeviation group to detect a difference in outcome between the devices of > 2° with an alpha of 0.05 and a power of 80% by using the SD as found in the cyclodeviation study of Georgievski & Kowal (1996). The 2° difference was chosen because we found this to be a clinical difference in measurement outcome. For the duction group, minimal 8 patients had to be recruited to detect a difference of 5° with an alpha of 0.05 and a power of 80% by using the SD as found by Haggerty *et al.* (2005). Again, the chosen detectable difference was found to be clinical significant, as also argued by Mourits *et al.* (1994).

Software package SPSS 17.0 was used for the statistical analysis. Each variable was checked with the Kolmogorov-Smirnov test to find out whether it met the requirements for normal distribution. If so, parametric tests were used. If not, non-parametric tests were used. To assess agreement between devices, Bland-Altman analysis was carried out (Bland & Altman, 1986; Chan, 2003).

Table 1. Measurement outcome differences between cyclodeviation devices

	HTS vs cycloforometer degrees ± SD [95% CI]		**HTS vs synoptometer degrees ± SD [95% CI]**		**Cycloforometer vs synoptometer degrees ± SD [95% CI]**	
primary position	0.5 ± 1.3	[-2.7 – 3.6]	2.1 ± 3.2	[-0.5 – 4.7]	1.7 ± 2.9	[-0.7 – 4.0]
upgaze	0.7 ± 1.6	[-2.5 – 3.9]	3.1 ± 3.4	[0.2 – 6.0]	2.4 ± 2.7	[-0.3 – 5.1]
downgaze	0.3 ± 1.8	[-2.7 – 2.0]	1.6 ± 2.8	[-3.4 – 1.0]	1.1 ± 3.3	[-2.8 – 1.1]

HTS = Harms tangent screen

Table 2. "Tolerance table"; absolute differences for each direction of gaze between cyclo measurement devices

Tolerance (degrees)	**HTS vs cycloforometer n (%)**			**HTS vs synoptometer n (%)**			**Cycloforometer vs synoptometer n (%)**		
	0	*25*↑	*25* ↓	0	*25*↑	*25* ↓	0	*25*↑	*25* ↓
≤ 1	9 (70)	5 (45)	6 (50)	6 (46)	4 (36)	6 (50)	7 (54)	5 (46)	7 (59)
> 1 ≤ 2	2 (15)	5 (45)	5 (42)	1 (8)	1 (9)	2 (17)	2 (15)	2 (18)	1 (8)
> 2 ≤ 3	2 (15)	0	0	2 (15)	1 (9)	1 (8)	1 (8)	1 (9)	1 (8)
> 3	0	1 (10)	1 (8)	4 (31)	5 (46)	3 (25)	3 (23)	3 (27)	3 (25)

HTS = Harms tangent screen

RESULTS

Study A: Cyclodeviation

Thirteen GO-patients, 6 male and 7 female, participated in this part of the study. Ten patients experienced horizontal and/or vertical diplopia, of which one experienced torsional diplopia as well. We were able to measure cyclodeviation in primary position in all patients, elevation in 11 patients and depression in 12 patients. We found a normal distribution for all cyclodeviation measurements (Kolmogorov-Smirnov test).

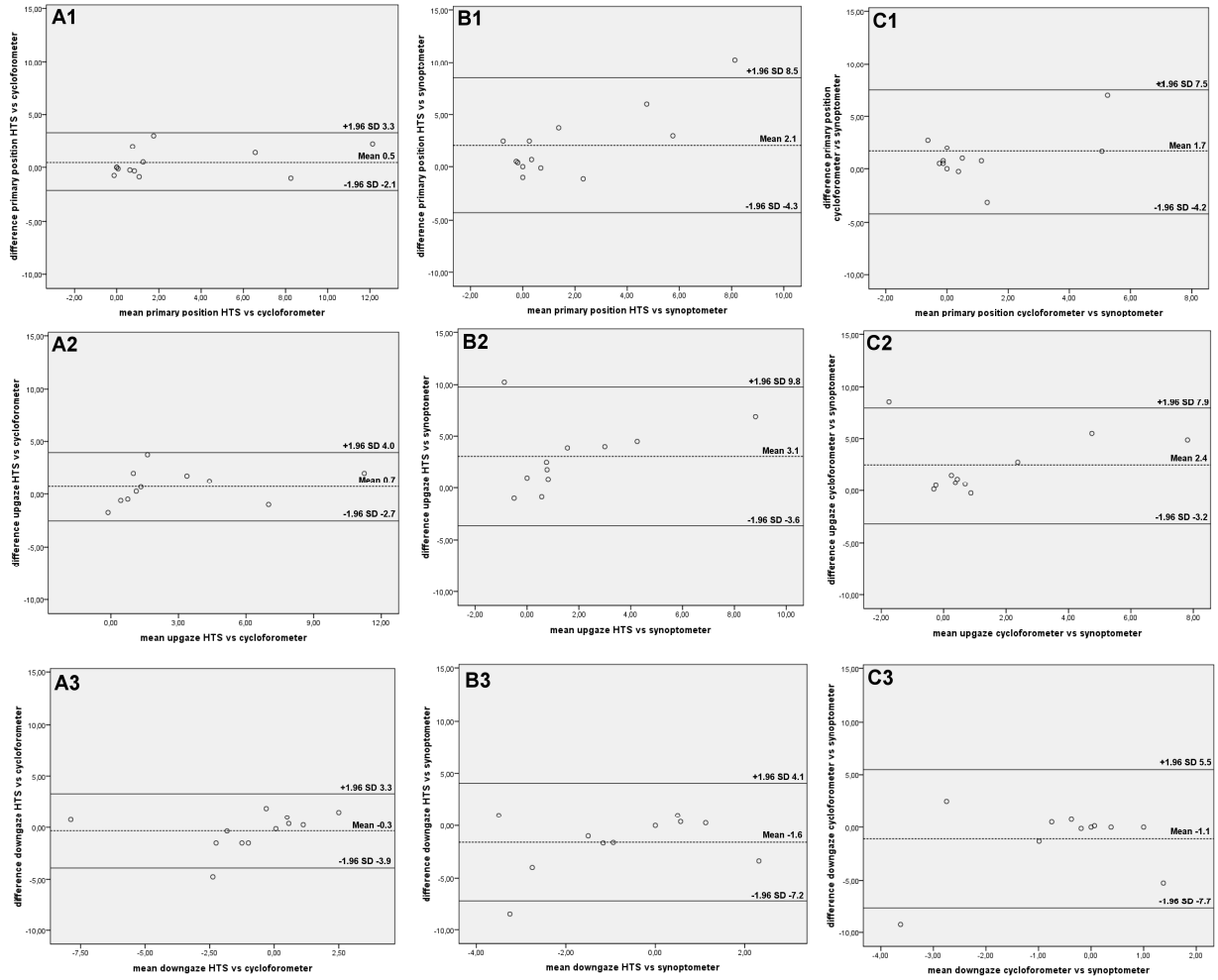

Figure 3. Bland Altman plots for the comparison of the different cyclodeviation measurements (A1) HTS versus cycloforometer in primary position; (A1) HTS versus cycloforometer in upgaze; (A3) HTS versus cycloforometer in downgaze; (B1) HTS versus synoptometer in primary position; (B2) HTS versus synoptometer in upgaze; (B3) HTS versus synoptometer in downgaze; (C1) cycloforometer versus synoptometer in primary position; (B2) cycloforometer versus synoptometer in upgaze; (C3) cycloforometer versus synoptometer in downgaze.
HTS = Harms tangent screen; - - - = Mean; – = ± 1.96SD.

The mean differences between the devices are listed in Table 1 showing that the differences between the HTS and the cycloforometer were smaller than the differences between the other devices. The Bland Altman plots (Fig. 3) show, that the upper and lower limits of agreement were smallest between the HTS and the cycloforometer. However, confidence intervals (CI) for all plots were large. Finally, Table 2 shows that the differences between two measurements were smallest (70% < 1° in primary position) when comparing HTS and the cycloforometer.

Study B: Ductions

Thirteen patients, 1 male and 12 female, participated in this part of the study. The mean age of the patients was 55 years (range 37 – 73). The duction measurements of all three tests in all directions, showed a normal distribution (Kolmogorov-Smirnov test).

The mean differences between the devices are listed in Table 3, showing the smallest differences when ductions were measured using the modified perimeter and the Goldmann perimeter, except for measuring elevation. The Bland Altman plots (Fig. 4) show, that the upper and lower limits of agreement were smallest between the modified perimeter and the Goldmann perimeter. However, CI for all plots was large. In total, 4 (8%) duction measurements using the modified perimeter and Goldmann perimeter exceeded 8° of difference (Table 4).

Table 3. Measurement outcome differences between duction devices

	Modified perimeter vs Goldmann degrees ± SD [95% CI]		**Modified perimeter vs MTS degrees ± SD [95% CI]**		**Goldmann vs MTS degrees ± SD [95% CI]**	
Abduction	3.1 ± 3.8	[-10.0 – 4.3]	4.5 ± 8.9	[-3.3 – 12.3]	7.6 ± 8.1	[0.0 – 15.2]
Adduction	1.2 ± 2.4	[-6.1 – 3.6]	7.0 ± 7.2	[-1.5 – 12.5]	8.2 ± 6.4	[2.6 – 13.8]
Elevation	3.8 ± 4.7	[-11.1 – 3.6]	2.2 ± 7.8	[-3.3 – 7.7]	6.0 ± 11.0	[-1.0 – 13.0]
Depression	3.4 ± 5.3	[-1.8 – 8.6]	12.9 ± 6.6	[5.0 – 20.1]	9.5 ± 8.8	[2.5 -16.5]

MTS = Maddox tangent screen

Table 4. "Tolerance table"; absolute differences for each direction of gaze between duction measurement devices

Tolerance (degrees)	**Modified perimeter vs Goldmann perimeter n (%)**				**Modified perimeter vs MTS n (%)**				**Goldmann perimeter vs MTS n (%)**			
	abd	*add*	*elev*	*depr*	*abd*	*add*	*elev*	*depr*	*abd*	*add*	*elev*	*depr*
≤ 3	6 (46)	10 (77)	7 (54)	6 (46)	3 (23)	1 (8)	4 (31)	0	2 (15)	1 (8)	4 (31)	4 (31)
4 ≤ 5	3 (23)	2 (15)	2 (15)	1 (8)	3 (23)	5 (38)	1 (8)	2 (15)	1 (8)	3 (23)	0	1 (8)
6 ≤ 8	4 (31)	1 (8)	3 (23)	3 (23)	3 (23)	0	2 (15)	1 (8)	5 (38)	2 (15)	2 (15)	1 (8)
≥ 9	0	0	1 (8)	3 (23)	4 (31)	7 (54)	6 (46)	10 (77)	5 (38)	7 (54)	7 (54)	7 (54)

abd= abduction; *add* = adduction; *elev* = elevation; *depr* = depression; *MTS* = Maddox tangent screen

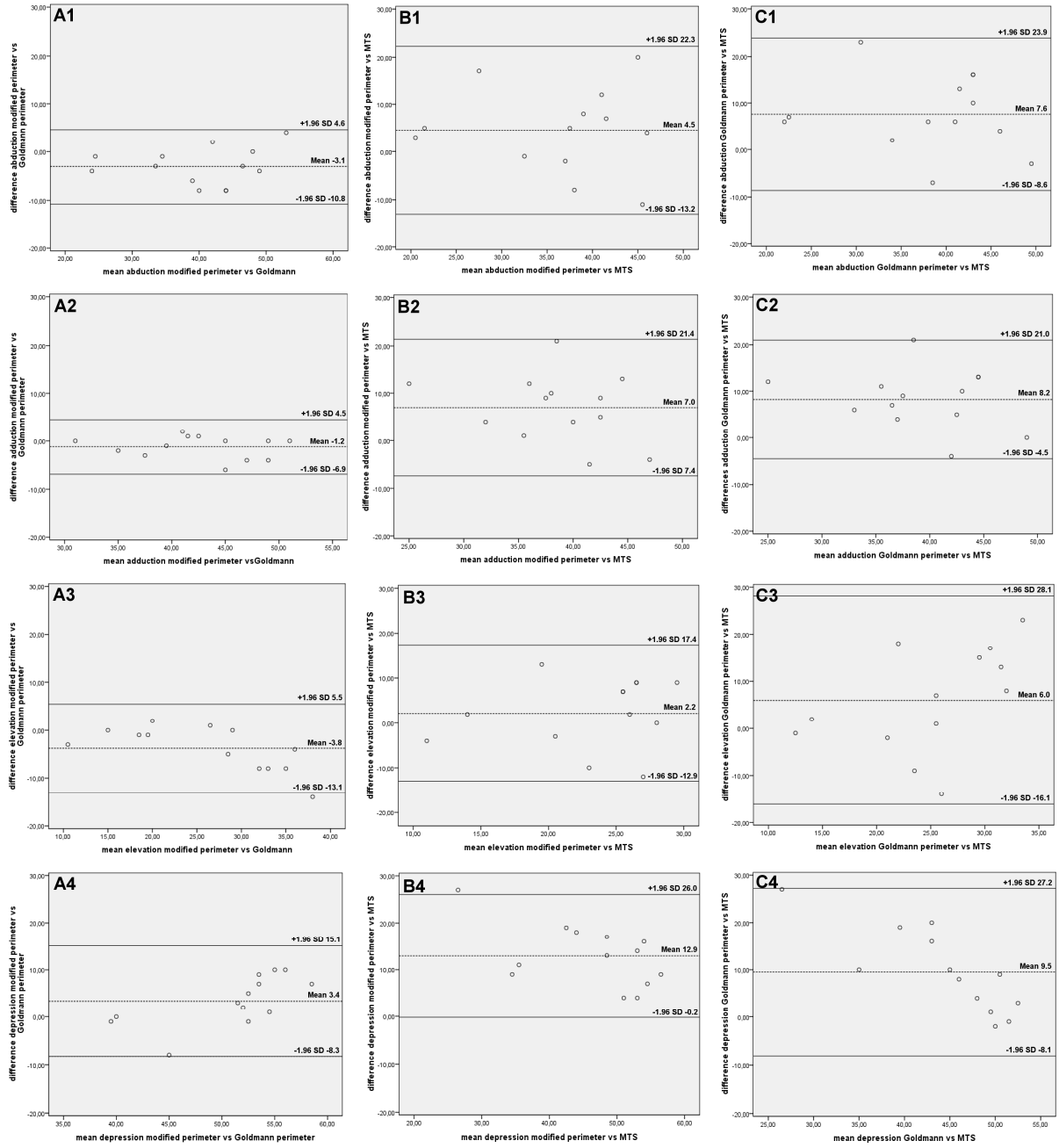

Figure 4. Bland Altman plots for the comparison of the different duction measurements (A) modified perimeter versus Goldmann perimeter; (A1) for abduction; (A2) for adduction; (A3) for elevation; (A4) for depression; (B) modified perimeter versus MTS; (B1) for abduction; (B2) for adduction; (B3) for elevation; (B4) for depression; (C) Goldmann perimeter versus MTS; (C1) for abduction; (C2) for adduction; (C3) for elevation; (C4) for depression.

MTS = Maddox tangent screen; - - - = Mean; – = ± 1.9 SD.

DISCUSSION

This study shows that, whereas the differences of measurements of cyclodeviation between the HTS / synoptometer and the cycloforometer / synoptometer are significant, the differences between the HTS / cycloforometer are 'negligible. Regarding the ocular ductions, the modified perimeter and the Goldmann perimeter showed the best corresponding outcomes. Comparison of both devices with the MTS showed significant differences. We, therefore, conclude that the synoptometer and the MTS are not interchangeable within multicenter and unicenter trials.

We cannot exclude the possible bias caused by differences in head position in our two sub studies. Using the HTS, the cycloforometer and the MTS, head movement is necessary, whereas in the other devices, eye movements are required for the measurement outcomes. However, we used a headlamp to correct for the head movements. Another shortcoming of this study is that we did not measure the interobserver variations. The explanation for this is that we limited ourselves to the technique with which each of us was most experienced.

Table 5. Studies regarding cyclodeviation devices

Study	Devices					Population (n)	Position of gaze	Results
Brown (1990)	Lees screen*					1 intermittent XT	9	less time consuming than synoptophore
Davinson and Cleary (2000)	torsiono meter	synopto-phore				20 normal subjects	PS, ↑, ↓	no correlation (r = < 0.25)
Georgievsky and Kowal (1996)	torsiono meter	synopto-phore	MDR	Maddox wing		33 torsional diplopia	PS and sometimes ↓	overall ICC 0.74 mean diff 2.4°±1.7°
Johnson and Harcourt (1987)	Lees screen*	synopto-phore	MDR	Awaya	Bagolini	1 large VD	PS	cyclo measurement only possible with Lees screen* because of large VD
Klainguti *et al.* (1992)	cycloforo-meter	synopto-phore	MDR	synopto-meter	HTS	30 normal subjects	PS	median all devices around 0°
Present study	cycloforo-meter			synopto-meter	HTS	13 GO-patients	PS, ↑, ↓	min mean diff 0.3° ± 1.8° (HTS – cycloforometer) max mean diff 3.1° ± 3.4° (HTS – synoptometer)

MDR = Maddox Double Rod; *HTS* = Harms tangent screen; *VD* = vertical deviation; *PS* = primary position; *diff* = difference ↑ = elevation; ↓ = depression; * = with linear pointer ;*min* = minimal; *max* = maximal; *GO* = Graves' Orbitopathy; *XT* = exotropia

It is well-known, that the devices used for cyclodeviation measurements cause dissociative effects and therefore enhance measurement results. One may argue that these dissociative effects are different for each device and that the synoptometer for this reason causes the largest excyclodeviation measurements (Kolling, 1982). However, our findings do not support this hypothesis and are in line with the study of Georgievsky and Kowal, who concluded that dissociation differences between the devices did not influence the outcomes (1996).

Other devices for the measurement of cyclodeviation have been proposed (Table 5). Klainguti *et al.* suggested using the same tool when comparing pre- and postoperative cyclodeviation in clinical use, although they found a corresponding outcome when comparing different tests. They stated, that the Maddox double rod test (MDR) is suitable for clinical trials in GO-patients (1992). Georgievsky and Kowal compared the cyclodeviation in primary position with the torsionometer, the MDR, the synoptophore and the Maddox wing. The measurements with these tests showed a good correlation (1996). However, the accuracy of the MDR decreases when the vertical deviation is more than 20 PD (Bland & Altman, 1986; Johnson *et al.,* 1987) and in other directions than primary position and is therefore not suitable for measuring cyclodeviations in GO-patients (Ansons & Davis, 2001; Bland & Altman, 1986; Brown, 1990; Capdepon *et al.*, 1994; Johnson *et al.*, 1987; Klainguti *et al.*, 1992). Moreover, the Maddox wing and torsionometer are not suitable to measure the cyclodeviation in up- and downgaze and the Maddox wing has a small range for measuring cyclodeviation in relation to the clinically observed range of cyclodeviation.

Davidson and Cleary consider the synoptophore as the golden standard for the measurement of cyclodeviation (2000), but Brown found this tool time consuming, tending to overestimate the deviation and therefore inaccurate (Brown, 1990). The cyclodeviation measured with the synoptophore simulates infinity fixation due to the +6.50 lenses (Gutter et al., 2010). Because of the induced impression of convergence, the synoptophore is thought to produce an *ex*cyclodeviation in normal subjects (Kolling, 1982), but Klainguti *et al.,* in contrast, found a tendency towards incyclodeviation (1992). In this study we also found a small tendency of *in*cyclodeviation in the synoptometer group, but this tendency was not significant (p = 0.142). In the literature, few studies compared duction measurements using different devices (Table 6).

Table 6. Studies regarding duction devices

Study	Devices			Assess-ment	Population (n)	Position of gaze	Results
Gerling *et al.* (1998)	Goldmann perimeter			objectively	100 normal subjects 36 GO-patients	0°, 90°, 180°, 270°	*GO population:* Intra and inter mean CV 0,7% to 2,3%
Hanif *et al.* (2000)	Goldmann perimeter*	synopto-phore	Aimark perimeter	subjectively	64 abnormal motility 50 normal motility	90°	Mean bias from -10 ±10.43° (Goldmann – Aimark) to -26 ±11.71° (synoptophore – Aimark)
Haggerty *et al.* (2005)	Goldmann perimeter*			subjectively	35 normal subjects 29 GO-patients	0°, 67°, 141°, 180°, 216°, 293°	*Normal population:* Intra OV within 4° Inter OV within 7.9° *GO population:* Inter OV within 7.8°
Mourits *et al.* (1994)	Perimeter*			objectively	40 normal subjects 18 GO-patients	0°, 90°, 180°, 270°	*GO population:* Intra OV within 6.9° Inter OV within 8.0°
Present study	Perimeter*	Goldmann perimeter	MTS	objectively	13 GO-patients	0°, 90°, 180°, 270°	Mean difference from 1.2 ± 2.4° (180° perimeter* – Goldmann) to 12.9 ± 6.6° (270° perimeter* – MTS)

MTS = Maddox tangent screen; *CV* = coefficient of variation; *OV* = observer variation; *diff* = difference; * = modified; *GO* = Graves' Orbitopathy

Hanif *et al.* compared the measurement of direct elevation using the Goldmann perimeter, the synoptophore and the Aimark (2009). The authors found a considerable variation among the three tests. They also stated that the synoptophore is limited in its use because of the ceiling-effect in upgaze (Hanif *et al.*, 2009). We found that this 'ceiling'-effect also occurs in depression. In our opinion this is one of the disadvantages of the synoptophore and therefore we do not favor this device for clinical use in GO-patients.

One could bring the accuracy of assessing the movement of the light reflex on the cornea up to discussion. However, this technique is used for all duction devices and our results show a low variance when comparing the modified perimeter with the Goldmann perimeter. Further research could be helpful to improve this technique.

Regarding the age of the patients, Haggerty *et al.* found no age-related decline in ductions when measuring ductions in 0°, 67°, 141°, 180°, 216° and 293°. In contrast, in a previous

study we found an age related decline when measuring abduction, adduction, elevation and depression. In this study, the age ranged from 37 – 73 years, but the study population was too small to divide the subjects in different age groups. In this study, test equipment was limited so duction measurement were only performed in 0°, 180°, 270° and 360°.

Differences between subjective and objective duction measurements are described (Haggerty *et al.,* 2005). Fatigue and discomfort during eye movement may influence the subjective measurement, particularly in GO-patients. Because of that fatigue component, we limited ourselves to objective duction measurement only.

The position of the upper eyelid in downgaze has been considered a disadvantage of objective measurement of duction in downgaze (Haggerty *et al.,* 2005). We have tried to overcome this disadvantage by holding the upper lid digitally up. Nevertheless, relatively large differences were observed in downgaze comparing the modified perimeter with the Goldmann perimeter. This is in agreement with a prior publication, in which the largest intraobserver variation was found in downgaze (Mourits *et al.,* 1994). Measurement in downgaze, therefore, remains an object of concern.

The measurement with the MTS could have been negatively influenced by the position of the patient in front of the MTS (height of the chair) and because of the head rotation and misalignment causing parallax errors. Nevertheless, we do not believe that, even when these shortcomings should have been corrected, the measurement outcomes between the modified perimeter / MTS and Goldmann perimeter / MTS will be interchangeable.

In conclusion, reproducible and objective measurements of cyclodeviation and duction are needed for proper patient care and for research. We recommend to, whenever possible, to use the same test to be utilized for follow-up. Thereby, we demonstrated that measurements of the HTS and the cycloforometer show least variations. The same holds true for duction measurements with the modified perimeter and the Goldmann perimeter. Although we measured the cyclodeviation and ductions in GO-patients, we believe that the outcomes of this study are also applicable to other patient groups.

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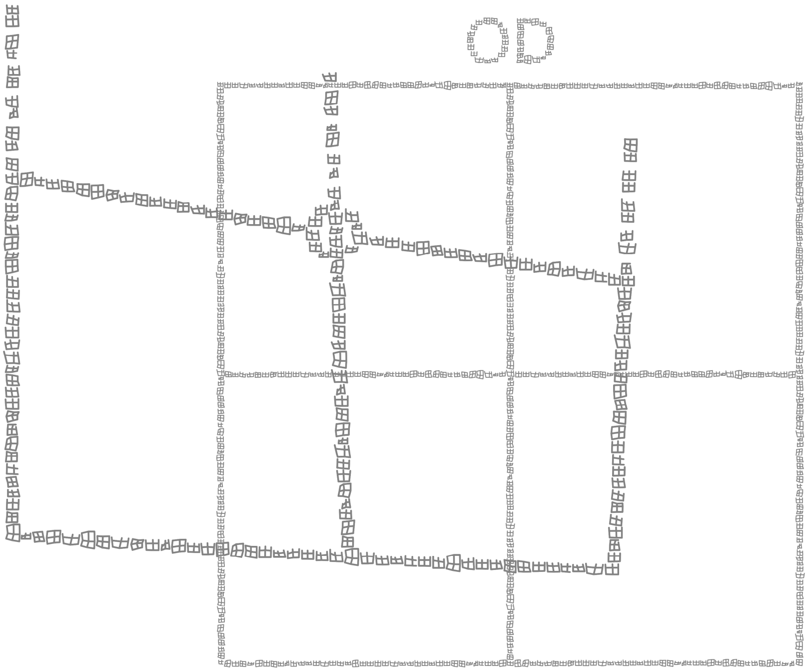

CHAPTER 3

BILATERAL INFERIOR RECTUS RECESSION IN PATIENTS WITH GRAVES' ORBITOPATHY: IS IT EFFECTIVE?

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ABSTRACT

Purpose: To evaluate the effect of bilateral inferior rectus recession regarding improvement of elevation, reduction of abnormal head tilt and vertical squint angle in patients with Graves' Orbitopathy (GO).

Method: Retrospective case series. Patients with GO who underwent symmetrical or asymmetrical bilateral inferior rectus recession were selected for this study. Effect on change of elevation, depression cyclodeviation and vertical squint angle was calculated 3 months and 6 to12 months postoperatively.

Results: Forty-three patient could be included, who underwent a recession of both inferior recti by 1 of our 5 surgeons. Three months postoperatively, the elevation changed from 12°±6.9° preoperatively to 19°±6.7° postoperatively (p = 0.000) and the depression from 54°±6.2° pre-operatively to 48°±9.2° postoperatively (p = 0.005). Total duction range remained stable (p = 0.728). Three months after surgery, motility did not change significantly anymore. The dose effect response on elevation was 1.7°±1.7°/mm and was higher in case of severe preoperative elevation restriction (r = -0.405). Three months postoperatively, the excyclodeviation changed from 6.4°±6.0° to 0.4°±6.0° in primary position (p = 0.000). However, in downgaze 4 patients developed a significant incyclodeviation of > 5°. Muscle volume, prior decompression surgery or performing surgeon did not influence the outcome.

Conclusion*:* Bilateral recession of the inferior rectus muscles in Patients with Graves Orbitopathy results in a shift of vertical duction range towards upgaze and a significant decrease of excyclodeviation. Overcorrection of cyclodeviation in downgaze has to be considered before planning this type of surgery. Poor preoperative elevation contributes to higher dose-effect responses. Concerning all variables, the orthoptic picture does not change anymore after 3 months since surgery.

INTRODUCTION

Graves' Orbitopathy (GO) is an auto-immune disease, which may present with proptosis, eyelid retraction, periorbital swelling, diplopia and vision loss[1]. Active orbitopathy is usually treated with intravenous methylprednisolone pulse therapy[2]. Depending on the wide variation in clinical presentation per patient, one or more of the following procedures are necessary in the quiescent stage of the decease: decompression surgery, strabismus surgery and/or if necessary, eyelid correction[1;3]. The primary goal of treatment regarding diplopia is to create a useful field of binocular single vision in primary position and downgaze[4;5]. The inferior rectus muscles are frequently affected by muscle enlargement due to inflammation, leading to fibrosis which causes impaired elevation and large excyclodeviation. In case of significantly impaired ocular elevation, bilateral inferior rectus recession is the first operation of choice in the authors' centre. So far, this surgical technique has been poorly represented in literature[6;7]. Therefore, this study is designed to strengthen the theoretical basis for this procedure. All consecutive patients with GO who were treated with a bilateral inferior rectus recession over the past 10 years were included in this study.

MATERIALS AND METHODS

The study was conducted according to the principles of the Declaration of Helsinki (seventh edition, October 2008, Seoul).

All patients who underwent recession of both inferior rectus muscles between January 2000 and June 2009 at the ophthalmology department of the Academic Medical Centre in Amsterdam were included in this study. The primary goal of surgery was ocular elevation improvement and reduction of abnormal head posture.

All patients had inactive GO with a stable orthoptic evaluation for at least 3 months prior to the squint surgery. Specific ophthalmic data were collected such as prior decompression surgery, muscle enlargement on CT scan, interval between decompression and strabismus surgery, type of squint surgery and the amount of recession of the inferior rectus muscles. The authors based the amount of our inferior rectus recessions in the first place on the severity of the elevation impairment. If elevation was less than 10°, 5 mm recession with or without a hang-back suture was carried out. When the elevation was between 10 - 15°, 4 mm recession was performed and when the elevation was > 15° the inferior rectus muscle

was recessed 3 mm. However, the authors also took into consideration the depression impairment and the vertical squint angle in primary position and downgaze to fine-tune the recession amount. In such a way, an individual approach for each patient was accomplished.

The operations were carried out by 5 different surgeons who all used fixed sutures with Vicryl 5.0. An asymmetrical recession of the inferior recti was performed in case of a manifest vertical deviation in primary position. The ductions were measured with a modified perimeter as described by Mourits *et al*.[8]. If ductions exceeded 25°, the vertical deviation in primary position and in eight directions of gaze was measured using the Maddox tangent screen at 2½ m. Cyclodeviation was measured with the cycloforometer of Franceschetti at 2½ m, in primary position, up- and downgaze as described by Klainguti *et al.*[9].

Patients with a history of strabismus, neuromuscular diseases, severe amblyopia, or retinal problems were excluded. Also patients who were simultaneously operated on the oblique muscles were excluded. Patient operated simultaneously on the medial or lateral rectus muscle were included. Muscle thickness was analysed, semi-quantitatively, for all available CT scans in coupes with a slice thickness of 1.3 mm and a slice increment of 0.7 mm. For interobserver variability, muscle enlargement was assessed 2 orbital surgeons (Peerooz Saeed and Maarten Mourits). They analysed the available CT scans independently and without prior knowledge concerning surgical outcome.

Analysed orthoptic data included orthoptic anamnesis and examinations less than 3 months preoperatively, within 3 months postoperatively and 6 – 12 months postoperatively. Statistical analysis was made with software package SPSS 17.0 (SPSS Inc., Chicago, IL, U.S.A.). Each variable was verified for normal distribution with help of the Kolmogorov-Smirnov test. If the data met the requirements for normal distribution, parametric tests were applied. If not, non-parametric tests were used. To uncover the main and interaction effects of categorical independent variables on an interval dependent variable ANOVA was used.

RESULTS

Between January 2000 and June 2009, 44 patients, 12 male and 33 female, with GO underwent recession of both inferior rectus muscles. Two patients were excluded because recession of the inferior recti was combined with an inferior oblique recession procedure. In 9 (21%) patients, the inferior rectus recession procedure was combined with horizontal squint correction. In 9 (21%) cases, a hang-back suture was carried out. Mean age was

54±12.8 years. Ten patients (24%) had undergone prior coronal decompression surgery, 23 patients (55%) underwent an inferomedial decompression. Nine patients (21%) did not have prior decompression surgery. Prior to the decompression surgery, only 8 (19%) patients experienced diplopia within the 20° field of binocular single vision. The interval between the decompression surgery and squint surgery was 12.7±10.4 months. The degree of muscle volume of both inferior rectus muscles and superior rectus muscles is shown in Table 1.

Table 1. Muscle enlargement

	Inferior rectus muscle	**Superior rectus muscle**
No	0	2
Mild	16	25
Moderate	36	28
Severe	16	13
Not available	14	14
	p* = 0.208	***p* = 0.796***

*Analysis of variance

Table 2. Pre- and postoperative measurements of elevation, depression and cyclodeviation

	< 3 months preoperatively degrees ± SD	**< 3 months postoperatively degrees ± SD**	***p***
Elevation	12° ± 6.9°	19° ± 6.7°	0.000
Depression	54° ± 6.2°	48° ± 9.2°	0.005
Cyclodeviation *primary position* *downgaze*	 6.4° ± 6.0° 4.2° ± 5.6°	 0.4° ± 5.6° -1.3° ± 6.1°	 0.000 0.000

- = incyclodeviation; *SD* = standard deviation

A symmetrical inferior rectus recession was performed on 18 patients (symmetrical group), with a mean recession of 3.6±1.0 mm per eye and an asymmetrical inferior rectus recession in 24 patients with a mean of 4.2±1.2 mm per eye (asymmetrical group). This difference in mm recession was significant ($p = 0.012$).

After bilateral recession of the inferior rectus, 27 (64%) patients needed no further strabismus surgery, 8 (20%) patients needed only 1 horizontal strabismus procedure and 7 (17%) patients needed one or more further vertical strabismus surgeries. At average, a patient needed 2 (range 1 – 6) operations.

Ductions

Both elevation and depression changed significantly after the bilateral inferior rectus recession procedure (elevation p = 0.000; depression p = 0.005, Table 2). No correlation was found between these changes (r = -0.009). Total pre-operative vertical duction range (sum of elevation and depression) was 66.4°±10.4° and postoperative 67.4°±11.4° (r = 0.728). No correlation between the duction change and duration of the disease was found (r = -0.127). No further changes of ductions were seen 6 – 12 months after the inferior rectus surgery (elevation p = 0.432; depression p = 0.968).

The dose-effect response of improved elevation per mm of recession was 1.7° ± 1.7°/mm. This dose-effect response was negatively influenced by the preoperative restricted elevation (r = -0.429, p = 0.000; Fig. 1).

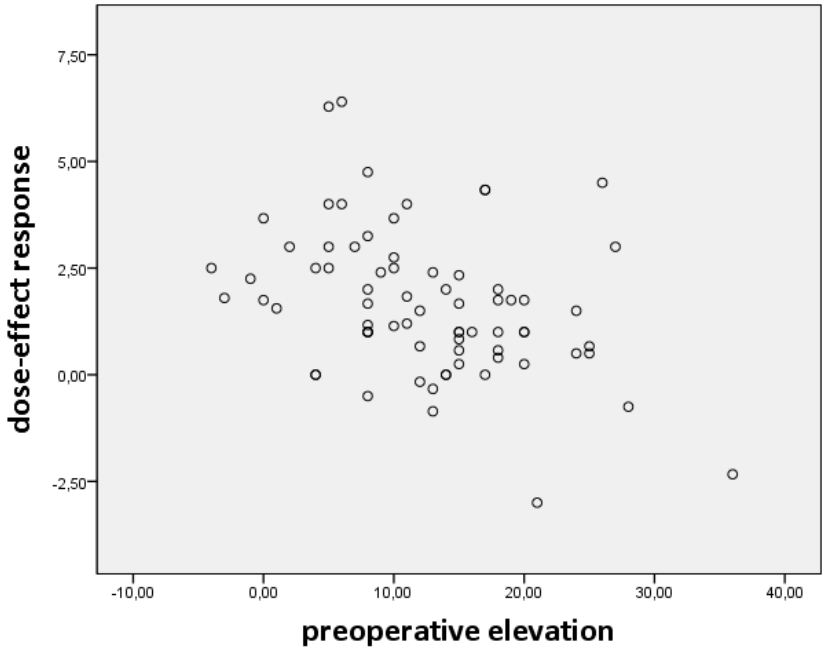

Figure 1. Preoperative elevation per eye correlated to the dose-effect response (r = -0.405).

Prior performed decompression surgery did not influence this outcome (p = 0.056). Because of the influence of preoperative elevation on the effect, no correlation was found between the amount of recession of the inferior rectus muscle and the improved elevation (r = - 0.101) or decreased depression (r = -0.288) because a small recession already has a large effect. Age did not influence this correlation (elevation r = 0.093; depression r = -0.196). When focussing on the group with diplopia prior to the decompression surgery, dose-effect response was not different compared to the group without diplopia prior to the decompression (p = 0.080).

Muscle volume analysed on CT scan did not influence outcome on dose-effect response either (inferior rectus muscle p = 0.208; superior rectus muscle p = 0.796). There were no discrepancies of surgical outcome between the performing surgeons (p = 0.114).

No significant differences were found between pre- and postoperative elevation, depression and cyclodeviations when comparing the inferior rectus recession with or without hang-back suture (p = 0.819; p = 0.507; p = 0.366).

Squint angle

The average vertical deviation in primary position was 1.4°±2.1° in the symmetrical group and 4.8°±3.1° in the asymmetrical group. In the latter group the vertical squint angle was significantly reduced after strabismus surgery to 2.3°±2.4° (p = 0.000). One patient in the asymmetrical group had a postoperative overcorrection in primary position. Nine to 12 months postoperatively, the vertical deviation remained stable (p = 0.685).

In downgaze, the angle of vertical squint did not change significantly postoperatively in the symmetrical group (p = 0.278).

In the group where no medial rectus recession was carried out, the horizontal squint angle reduced 1.0°±2.1° in primary position (p = 0.016) and 3.0°±4.2° in downgaze (p = 0.001).

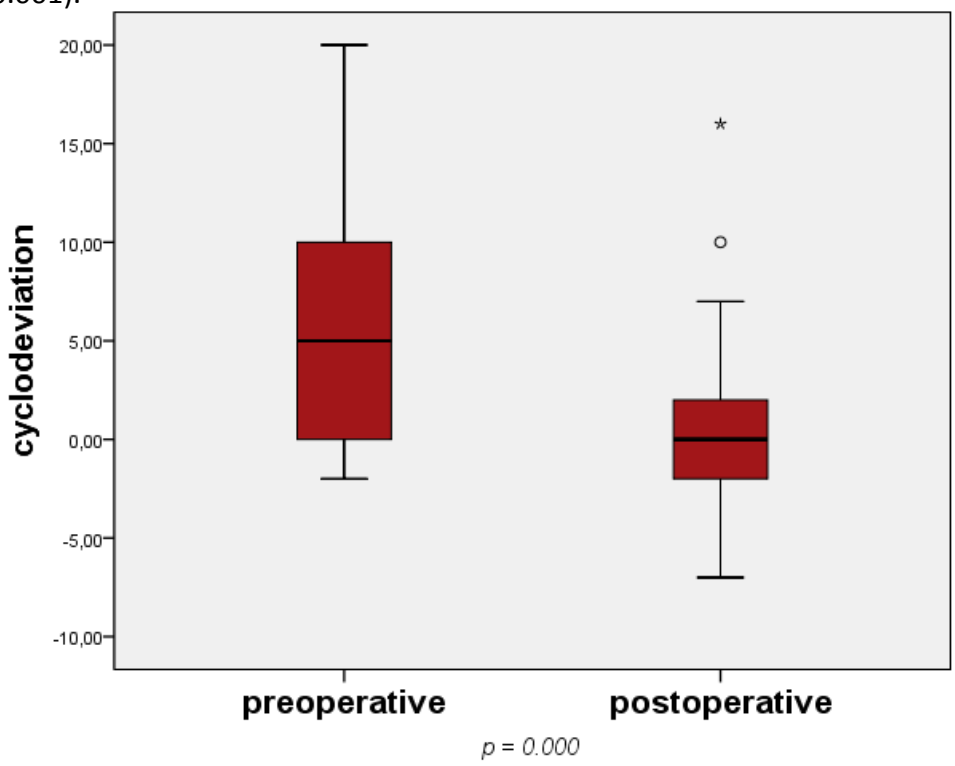

Figure 2. Pre- and postoperative cyclodeviation in primary position. * and o are outliers.

Cyclotorsion

In the majority of cases, cyclodeviation could only be measured in primary position and downgaze because of severely impaired elevation. Preoperative excyclodeviation diminished significantly postoperatively (Table 2 and Fig. 2). A case example is found in Figure 3. In 4 (18%) patients, incyclodeviation exceeded 5° 6 to 12 months postoperatively. Six to 12 months postoperatively, no significant changes of cyclodeviation were found (primary position $p = 0.547$; downgaze $p = 0.864$).

Dose-effect response for improvement of cyclodeviation per mm of recession was 0.74°±0.61°/mm in primary position and 0.7°±0.6°/mm in downgaze.

No correlation was found between the amount of recession and postoperative reduction of cyclodeviation in primary position ($r = 0.007$) or downgaze ($r = 0.067$).

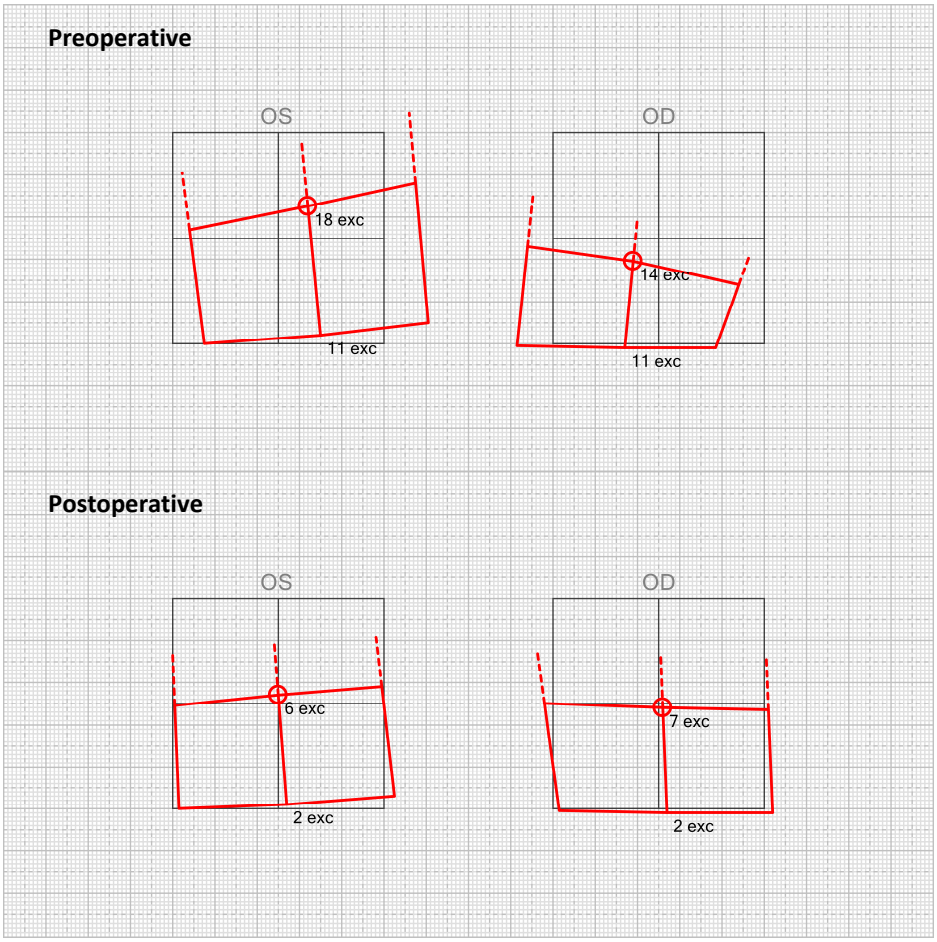

Figure 3. Above: preoperative large excyclodeviation due to secondary overaction of the inferior oblique. Below: after surgery: 3.5 mm OD and 3.0 mm OS recession of the inferior rectus muscle. Postoperative decrease of overaction of inferior oblique muscle because of decrease of restriction of elevation.

DISCUSSION

To the authors' knowledge, this is the first large case series describing the effects of the bilateral inferior rectus recession in patients with GO (Table 3). This treatment significantly improves elevation (with a mean of 37%), decreases depression (with a mean of 12%) and decreases excyclodeviation, unrelated to the amount of recession carried out. However, poor preoperative elevation was related to higher dose-effect response.

Table 3. Studies regarding inferior rectus recession in Graves' Orbitopathy patients

Study	Procedure			Population (n)	Limitation of depression	Results
Flanders and Hasting (1997)	unilateral	recession	5 – 10 mm	10	not measured	6/10 had BSV primary position and reading gaze
	bilateral	recession	5 – 10 mm	3	not measured	3/3 had BSV in primary position and reading gaze
Cruz and Davitt (1999)	bilateral	6 mm adjustable suture on hypotropic eye 2–3 mm other eye		8	2 Patients undercorrected	successful without overcorrection
Prendiville *et al.* (2000)	bilateral	recession	not specified	11	not measured	overall: 37/50 BSV in primary position with AHP in 4/37
	unilateral	recession	not specified	18	not measured	
Kose *et al.* (2002)	unilateral	recession + adjustable loop	4 + Loop	5	2	BSV in primary position and reading gaze. No measurement in downgaze
Eckstein, Schulz and Esser (2004)	unilateral	recession	1.5 – 8 mm	187	not measured	69% orthophore in primary position 24% undercorrection / 7% overcorrection
Schittkowski, Fichter and Gutthoff (2004)	unilateral	recession	2.5 – 10 mm	21	no change	76% – 88% BSV with prism
Dal Canto *et al*. (2006)	bilateral	recession until tendon rested on the globe in primary position	3.5 – 9 mm	8	not measured	no correlation between amount recession and preoperative angle (bilateral r = 0.448; unilateral r = 0.5583)
	unilateral	idem	4 – 8 mm	11		
De Hoog, Stravers and Kalmann (2009)	bilateral	recession	2 – 4 mm	24	37% (> 4° worse and < 55°)	
	unilateral	recession	2 – 4 mm	100		increased volume superior rectus predictor overcorrection
Present study (2012)	bilateral	recession	4 – 7 mm (> 5 mm; loop)	42	40% (> 4° worse and < 55°)	shift of ductionrange towards upgaze

BSV = Binocular single vision; *AHP* = Abnormal head posture

Postoperative changes in ductions were not influenced by prior decompression surgery, muscle volume, surgeon, surgical technique, or duration of the GO. The total vertical duction range remained stable. This vertical duction range is comparable to the range found by Gerling *et al.* who found a mean vertical duction range of 71.5° in patients with GO[10].

Late overcorrections in unilateral inferior rectus recessions are widely discussed in literature, as also the other side effects as proptosis, lower eyelid retraction, and iatrogenic deviations in downgaze due to depression impairment[4;11-19]. However, no clear data are available for bilateral inferior rectus recession cases. The assessment of the incidence of all these side effects was beyond the scope of the present study. De Hoog *et al.* described a series of 124 Patients with GO who underwent uni- or bilateral inferior rectus recession, of which 24 bilateral inferior rectus recessions. Depression impairment was found in 37% of all cases. De Hoog *et al.* did not record results of improved elevation, changes in cyclodeviation, or dose-effect response. They suggest that in case of a contralateral impairment of elevation, bilateral recession of the inferior rectus should be performed[16]. Cruz and Davitt described 8 patients who were treated with a bilateral inferior rectus recession for the correction of a vertical squint, with the use of an adjustable suture on the most hypotropic eye. They found no late overcorrections 6 – 40 months postoperatively. It must be mentioned that they only measured the vertical deviation without measuring ductions in downgaze[7]. Dal Canto *et al.* operated on 4 patients with GO on both inferior rectus muscles symmetrically (4 – 6 mm each eye) and 5 patients asymmetrically. They also found unlimited depression, but no depression measurement was recorded within the study[6]. With the authors' motility meter, small differences of depression can be easily measured and were indeed found in our case series. The authors did not find overcorrections in downgaze in the asymmetrical group. Possibly, the simultaneous recession of the fellow inferior rectus prevents this overcorrection. The authors thereby agree with Cruz *et al.* to recess both inferior rectus muscles in patients with GO with hypotropia, but not in all cases. Careful investigation of the ductions of both eyes, the preoperative angle in right-, left- and downgaze is important in properly planning the surgery. With regard to muscle volume, de Hoog *et al.* found that limited depression was significantly related to superior rectus muscle enlargement on CT-scan[16]. By reanalyzing the CT-scans in the present study, the authors too did not find statistical significant relations between ductions and muscle enlargement.

In the literature, the described dose-effect responses of unilateral recessions of the inferior rectus muscle, vary from 1.6° to 2.1°/mm[3;18;20]. To the authors knowledge no dose-effect responses are available of bilateral inferior rectus recession in relation to elevation improvement. The dose-effect response measured in this study on elevation improvement was 1.7°±1.7°/mm. A side-effect of this procedure is a reduction of the horizontal squint angle, especially in downgaze, without creating a real A pattern in the authors' series. This A pattern is described in literature as a complication of decompression or inferior rectus surgery[21;22].

Some studies suggest to correct contralateral eye muscles like the superior rectus or inferior oblique muscle to correct the hypotropia and cyclodeviation[23;24]. The authors' are, however, convinced that the cause of the hypotropia should be treated first by recessing the tight inferior rectus muscles. By doing this, excyclodeviation will reduce as a result of improved elevation as well as a reduction of inferior oblique muscle overaction (Fig. 3). As already described in literature, treatment has to be primarily focused on minimizing restrictions and differences in ductions[11]. A possible created incyclodeviation as arose in some of our patients can be treated with a superior oblique recession procedure. As previous suggested by Kushner, one could argue to simultaneously recess the inferior rectus muscles and superior oblique muscles to prevent this incyclodeviation[25].

The authors' found that within 3 months postoperatively, long term stability of squint surgery can be predicted, as supported by other authors[6;19].

The authors' are aware that this retrospective type of study creates bias. They regret that the abnormal head posture and the field of binocular single vision were not measured consequently to be included in this analysis. Also, it would have been interesting to relate the postoperative objective result to the subjective improvement most patients report. In addition, missing data and lack of a standard surgical plan influences the reliability of our results. However, the authors believe that the conclusions are strong enough to set a basis for future studies. In future studies, more attention should be given to the measurement of the field of binocular single vision and a quality of life questionnaire in this patient group[26]. These 2 outcomes would be more accurate in evaluating the effect of squint treatment in patients with GO.

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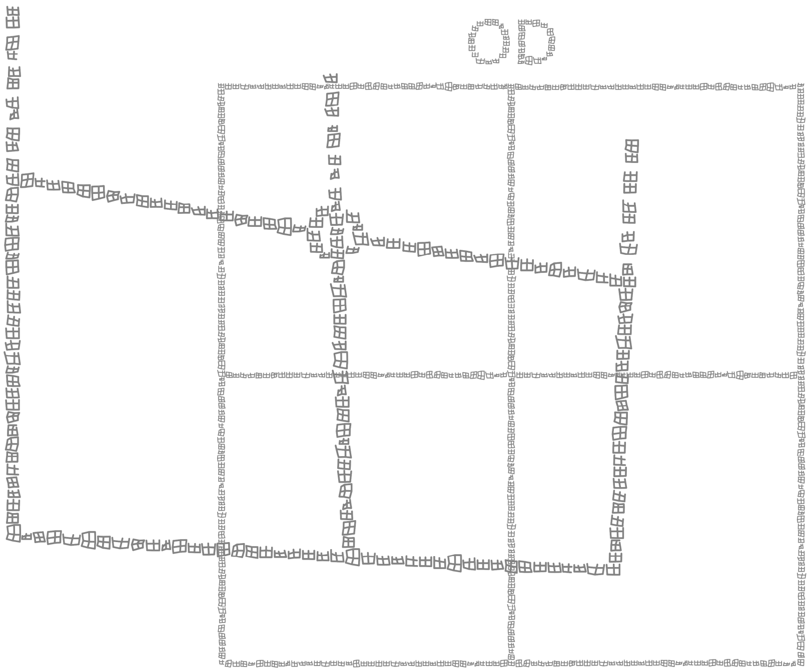

CHAPTER 4

UNILATERAL AND BILATERAL MEDIAL RECTUS RECESSION IN GRAVES' ORBITOPATHY PATIENTS

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ABSTRACT

Purpose: To evaluate the effect of uni- and bilateral medial rectus recession on squint angle and ductions in Graves' Orbitopathy (GO) patients.

Design: retrospective case series.

Materials and Methods: Consecutive GO-patients seen between January 2000 and March 2012 who were operated on one or both medial rectus muscles were selected for the study. Data regarding squint angle, abduction and adduction were collected starting 3 months before surgery and 3 and 6 – 12 months after surgery.

Results: 102 patients were eligible for inclusion. Of these, 24 patients were operated on one medial rectus and 78 on two medial rectus muscles. The dose-effect response was 1.0 [-0.6 - 3.8]°/mm in the unilateral and 1.4 [0.2 – 3.0]°/mm in the bilateral group (p = 0.000). In the bilateral group, the maximal ab- and adduction changed significantly (p = 0.000). However, the total duction range remained unchanged (unilateral: p = 0.525; bilateral: p = 0.137). The extent of the preoperative abduction did not influence the dose-effect response (r = - 0.234; p = 0.040), nor did the muscle volume (unilateral p = 0.989; bilateral p = 0.397). Twenty-three patients (23%) needed additional horizontal squint surgery.

Conclusion: In this large series of medial rectus recessions in patients with Graves' disease we found significantly lower dose-effect response ratios as compared to other studies. The amount of abduction deficit does not influence outcome.

INTRODUCTION

Approximately 50% of patients with Graves' Orbitopathy suffer from double vision, with a tremendous impact on daily life activities (Yeatts, 2005;Wiersinga *et al.*, 2004;Wiersinga, 2012;Gerding *et al.*, 1997). Diplopia in GO-patients is caused by enlarged and fibrosis of extra-ocular muscles; in particular the inferior rectus and medial rectus. GO often affects both orbits in an asymmetric manner. This asymmetric involvement is particularly responsible for the most complicated motility patterns. Several studies have focused on surgical treatment, primarily for vertical squint (Esser *et al.*, 2011;Esser, 1993;Coats *et al.*, 1999;Hoog de *et al.*, 2009;Sprunger & Helveston, 1993;Flanders & Hastings, 1997;Prendiville *et al.*, 2000;Dal Canto *et al.*, 2006;Baker & Ansons, 2001;Kalpadakis *et al.*, 2002;Kose *et al.*, 2002;Cormack *et al.*, 2007;Esser *et al.*, 2011). Until now, no consensus has been reached on how to treat this patient group. Variation exists in surgical approach (adjustable sutures (Scott & Thalacker, 1981;Lueder *et al.*, 1992;Flanders & Hastings, 1997;Russo *et al.*, 2004;Mocan *et al.*, 2007), fixed sutures, relaxed muscle positioning (Dal Canto *et al.*, 2006)), type of muscle surgery (recession or resection (Pitz *et al.*, 2005)), amount of recession and outcome criteria. Only a few studies focus on horizontal strabismus surgery. Most have small sample sizes and different surgical procedures and outcome criteria (Table 1)(Mocan *et al.*, 2007;Pitz *et al.*, 2005;Kalpadakis *et al.*, 2004;Eckstein *et al.*, 2004;Schittkowski *et al.*, 2004;Esser, 1993).

Table 1. Literature overview

	Mocan *et al.* (2006)	**Pitz *et al.* (2005)**	**Eckstein *et al.* (2004)**	**Kalpadakis *et al.* (2004)**	**Schittkowsky *et al.* (2004)**	**Esser (1993)**
Number of patients	31	26	81	11	11	26
Prior decompression	24	yes	no	not specified	2	no
Unilateral (degree / mm ± SD)	1.74°± 0.92° (near) 2.61°± 2.11° (distance) (n=9)*		1.70° (1.55° - 1.85°) (n=37)	11 81% fusion on day after surgery	5	1.92° ± 0.13° (n=10; distance)
Bilateral (degree / mm ± SD)	2.64°± 2.70° (near) 2.14°± 0.59° (distance) (n=22)		1.55° (1.43° - 1.67°) (n=44)	not specified	6	1.88° ± 0.17° (n=16; distance)
Not specified uni / bil (range, degree / mm ± SD)		0.9 – 2.7°			2,6 mm improvement abduction 0.1 mm improvement adduction	1.67° ± 0.55° (n=26; near)

* included vertical surgery; *n* = number of patients

The purpose of this study is to analyze the surgical effect / success rate of recession of the medial rectus muscle(s) in GO-patients with horizontal diplopia. Our goal is to present our results, to give recommendations when to perform a uni- or bilateral medial rectus recession and to present the effect of surgery on horizontal excursion.

MATERIALS AND METHODS

The study was conducted according to the principles of the Declaration of Helsinki (seventh edition, October 2008, Seoul) and in accordance with the Medical Research Involving Human Subjects Act (WMO). The ethical board has reviewed the study and concluded that no approval was needed.

Consecutive GO-patients operated for horizontal diplopia between January 2000 and March 2012 were included in this study. Patients who underwent simultaneous surgery for vertical diplopia were excluded, as well as patients with pre-existent strabismus, a history of previous surgery on the medial rectus muscles, suppression, and/or vision < 0.2 in one or both eyes. Data were taken from the records starting 3 months before surgery until 6 – 12 months after surgery. The horizontal deviation was measured in primary position with the Maddox rod glass using the Maddox tangent screen at 2½ meters (Gutter *et al.*, 2010). The abduction and adduction was measured with the modified perimeter as described by Mourits *et al.* (Mourits *et al.,* 1994).

Surgery was only performed when the orbitopathy was inactive. The definition of inactivity was based on the clinical ophthalmic exam (Clinical Activity Score) and stable orthoptic findings for at least 3 months. Fixed sutures were used for surgery and carried out by different surgeons. Dose-effect response was assumed to be 1.5°/ mm. Using this dose-effect response, unilateral recessions were generally performed if the horizontal squint angle was ≤10°. In patients with larger squint angles, a bilateral recession of the medial rectus muscles was performed. In cases where there was an asymmetrical restriction of abduction, a greater recession was conducted on the more restricted side. Muscle thickness (graded as normal, mild, moderate, severe) was analysed, semi-quantitatively, for all available CT scans by a team of orbital experts. Dose-effect response was calculated by dividing the 'preoperative – postoperative squint angle' by the amount of recession. Statistical analyses were done with SPPS 19.0 (Statistical Package for the Social Sciences, Version 19.0, Chicago, Illinois, USA). Each variable was verified for normal distribution with

the Kolmogorov-Smirnov test. If the data met the requirements for normal distribution, parametric tests were applied. If not, non-parametric tests were used. Results were considered statistical significant for $p < 0.05$.

RESULTS

In total, 157 patients underwent horizontal squint surgery. Fifty-five patients had to be excluded, 10 due to loss of follow up and 45 due to simultaneously performed vertical strabismus surgery. A total of 102 patients fulfilled the inclusion criteria. Thirty (29%) patients were male and 72 (71%) were female. Mean age was 52.5±9.4 years. Orbital wall decompression was performed in 90 (88%) patients before strabismus surgery of which 48 patients underwent a 3 wall, 30 patients an inferior-medial wall, 8 a medial-lateral wall and 1 a medial wall decompression. In 18 patients, the decompression was performed via the coronal approach. The others have been operated using a swinging eyelid approach.

Twenty-four (24%) patients underwent surgery of one medial rectus muscle and 78 (76%) of both medial rectus muscles. Mean duration of the GO prior to the strabismus surgery was 33 [8 – 120] months. Mean recession was 3.3 [2.0 – 5.0] mm in the unilateral group and 4.5 [2.5 – 7.0] mm per eye in the bilateral group ($p = 0.003$). Data regarding squint angle are listed in Figure 1 and Table 2.

Table 2. Pre- and postoperative orthoptic measurements

	Unilateral group mean in degrees±SD (n = 24)	**Bilateral group mean in degrees±SD (n = 78)**
Horizontal deviation		
Primary position		
preop	8.7 ± 4.9	18.1 ± 7.0
postop < 3 months	4.8 ± 4.2 (*p*=0.000)	5.1 ± 5.6 (*p*=0.000)
postop 6 – 12 months	2.9 ± 5.0 (*p*=0.423)	4.6 ± 5.0 (*p*=0.420)
Abduction		
preop	33.1 ± 8.1	29.4 ± 10.8
postop < 3 months	34.2 ± 7.8 (*p*=0.368)	33.5 ± 8.8 (*p*=0.000)
postop 6 – 12 months	33.9 ± 6.5 (*p*=0.745)	35.8 ± 7.5 (*p*=0.002)
Adduction		
preop	40.2 ± 5.9	42.9 ± 6.9
postop < 3 months	38.1 ± 6.8 (*p*=0.036)	37.5 ± 7.8 (*p*=0.000)
postop 6 – 12 months	38.4 ± 5.7 (*p*=0.425)	37.4 ± 7.3 (*p*=0.877)
Total duction range		
preop	73.43 ± 12.17	71.9 ± 14.2
postop < 3 months	72.48 ± 12.7 (*p*=0.525)	70.7 ± 14.1 (*p*=0.137)

SD = standard deviation; *n* = number

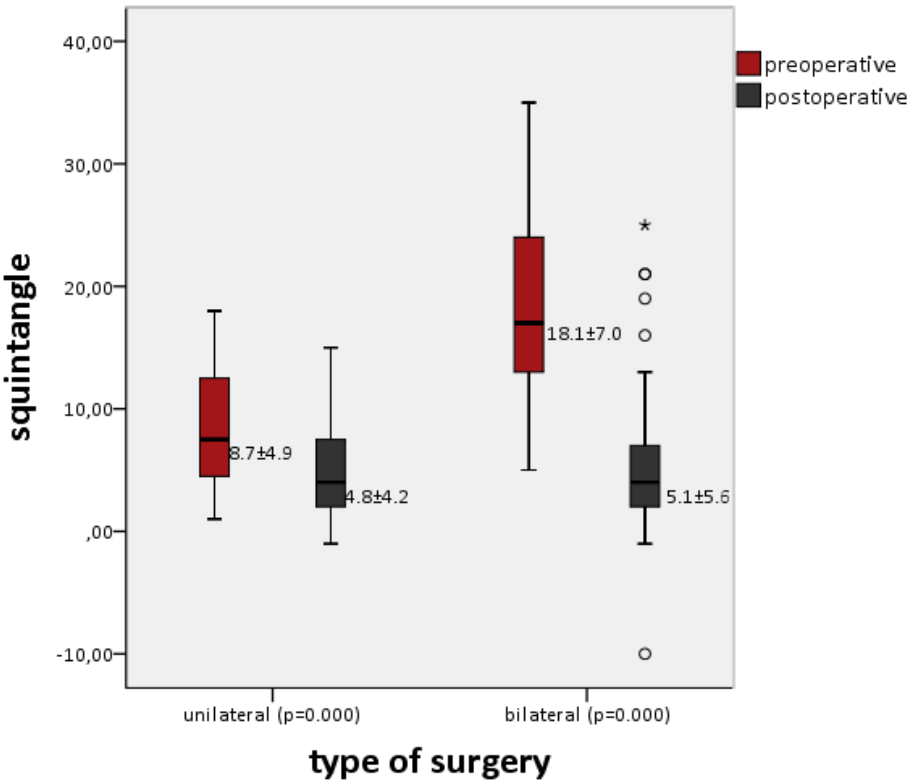

Figure 1. Squint angle measured with the Maddox rod glass at 2½ meter before and after surgery for unilateral (left boxplots) and bilateral (right boxplots) medial rectus recessions. *the outliers are two patients characterized by excessive squint angles (≥ 30°) and severe limited abduction (≤ 14°). This could be an explanation for their insufficient response to the surgery.

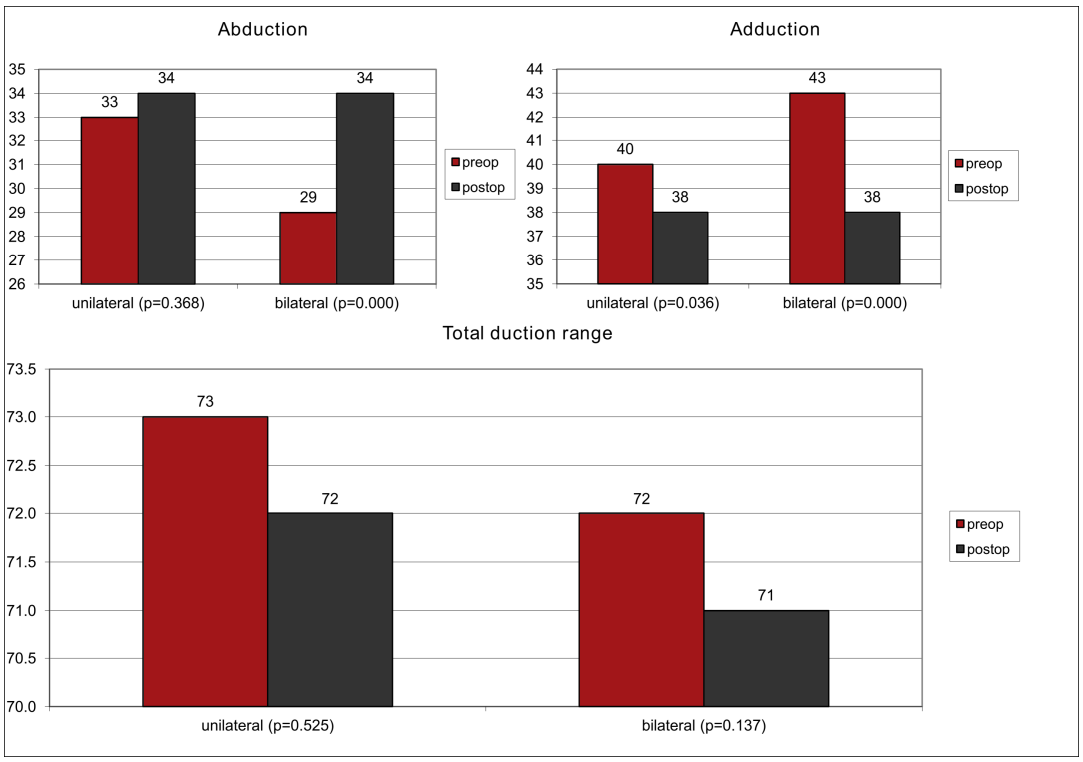

Figure 2. Mean abduction, adduction, and total duction range before and after surgery.

The preoperative squint angle was not influenced by the muscle volume (p = 0.361), nor by the decompression approach (coronal versus inferior-medial; p = 0.436). Dose-effect response was 1.0 [-0.6 – 3.8]°/mm in the unilateral group and 1.4 [0.2 – 3.0]°/mm in the bilateral group (p = 0.010). Overcorrection was observed in 3 patients. In 33% of the unilateral group and in 20% of the bilateral group a redo operation was considered necessary to correct the persisting horizontal deviation. Muscle volume did not influence the dose-effect response (unilateral p = 0.989; bilateral p = 0.397) nor the incidence of a redo operation (unilateral p = 0.921; bilateral p = 0.786).

As in the unilateral group only 2 patients underwent strabismus surgery without a preceding decompression, statistical evaluation of the influence of prior decompression surgery on dose-effect response was only possible in the bilateral group. We found no significant difference between prior decompression or no decompression (decompression n = 67, no decompression n = 11; p = 0.748). The type of decompression also did not influence the dose-effect response (p = 0.082).

In the bilateral group, the abduction increased after surgery (p = 0.000)(Fig. 2). No correlation was found between the dose-effect response and the preoperative abduction deficit (r = - 0.234; p = 0.040).

By 78 patients one operation was needed for their horizontal diplopia, 23 needed 2 and 1 needed 3 surgeries. With exception of the abduction of the bilateral group, all parameters were stable during the 6 – 12 months visit after surgery.

DISCUSSION

To the best of our knowledge, this study presents the largest case series of pure medial rectus recessions in GO-patients. The most intriguing question, e.g. how many patients benefitted from surgical intervention, cannot be answered, because till present no universally accepted definition of ‘success’ after squint surgery in GO-patients exists. However, in 77% of our patients one surgical procedure was sufficient to correct their horizontal diplopia. We found significant lower dose-effect responses compared to other studies, especially in the unilateral cases. Bilateral medial rectus recession was found to have higher dose-effect response than unilateral medial rectus recession. Although the ab- and adduction changed significantly after bilateral surgery, the total duction range remained unchanged.

No more than 3 – 6 studies so far addressed the effect of the medial rectus recession in GO-patients until now (Mocan *et al.*, 2007;Eckstein *et al.*, 2004;Esser, 1993;Pitz *et al.*, 2005;Kalpadakis *et al.*, 2004;Schittkowski *et al.*, 2004)(Table 1). In these studies, the dose-effect response in unilateral cases was markedly higher than found in this study. In Graves' patients, Mocan *et al.* found approximately the same relationship as we did for bilateral medial rectus recessions (Mocan *et al.*, 2007). However, in unilateral cases, we found no more than 1.0 degree per mm. This finding cannot be explained by the severity of the orbitopathy, because the choice for unilateral recession was based on a smaller squint angle, which most likely is associated with less severe GO. The discrepancy between our results and those of others, however, can be explained but not be compared by differences in inclusion criteria, operation technique, and differences in measuring the squint angle. In contrast to others, we calculated the amount of recession on the semi distance angle of 2½ meter as well as using a Maddox rod, both factors may influence the squint angle. This approach has no effect on the outcome of the dose effect response, because we measured the squint angle consistently, e.g. pre- and postoperatively in the same way. However, our way of assessing the squint angle does explain our relatively big residual esodeviation angle, as shown in Table 2, because the Maddox rod stimulates accommodation to which esodeviation is linked.

Following Eckstein *et al.* (2004), we excluded patients who underwent simultaneous vertical strabismus surgery because surgery in separate sessions gives less variability in outcome (Eckstein *et al.*, 2004). Mocan *et al.* (2007) combined horizontal and vertical strabismus surgery which creates bias of the results (Mocan *et al.*, 2007).

As observed in an earlier study about strabismus surgery in GO-patients we here again assessed that already 3 months after surgery the orthoptic status is stable (Jellema *et al.*, 2012). This is of importance in planning further surgery. Mocan *et al.* (2007) mentioned an improvement towards orthotropia during their final evaluation, but it is unclear what their time frame was from surgery to their final evaluation.

Just as in previous studies, we found no clinically relevant correlation between the dose-effect response and the preoperative abduction deficit (Pitz *et al.*, 2005;Nguyen *et al.*, 2002). Although a significant change in ab- and adduction was found, we could only assess such a relationship in the bilateral group and, moreover, the amount did not exceed the 'significant change of duction' (i.e. 8°) as referred in literature (Prummel *et al.*, 2004;Jellema

et al., 2011). As found in vertical squint surgery, the total duction range remains stable after surgery (Jellema *et al.*, 2012) which is very fortunate, because it creates a more centrally located field of binocular single vision.

The effect of preceding orbital decompression on squint surgery is unclear (Ruttum, 2000;Gilbert *et al.*, 2005;Mocan *et al.*, 2007). One study found more restriction of abduction if patients had a history of decompression (Mocan *et al.*, 2007). We cannot support this finding: the results after orbital decompression in our series were comparable to those without previous orbital surgery. Our more precise measurement of ductions (0 – 60°) compared to measurement of Mocan *et al.* (0 – 4 grade) can account for this difference.

There are limitations to our study. The retrospective nature of this study creates bias, such as assignment bias. In the future, a prospective randomized controlled study can avoid this. Another limitation is that we do not have data about the squint angle at internationally accepted standard distances for comparison nor do we have data on how the patient is coping with his double vision. We cannot supply information on the subjective outcome of our operations, because patients did not yet fill in a quality of life questionnaire. Future studies should not only evaluate the objective, but especially the subjective outcome for squint surgery. A quality of life questionnaire has to be incorporated in research about diplopia treatment in GO-patients.

In conclusion, the outcome of strabismus surgery in GO-patients can be reasonably predicted taking into account the differences in the dose-effect response between the uni- and bilateral procedures. In almost 80% of these patients horizontal diplopia was resolved after one strabismus operation.

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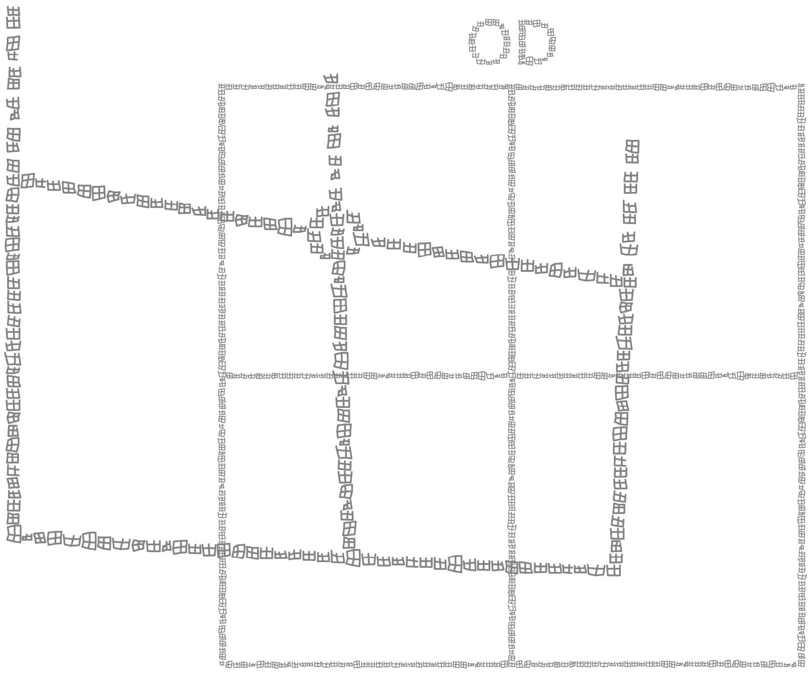

CHAPTER 5

OUTCOME OF INFERIOR AND SUPERIOR RECTUS RECESSION IN GRAVES' ORBITOPATHY PATIENTS

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ABSTRACT

Purpose: To evaluate the surgical effect of unilateral inferior rectus recession (IR-group) with or without a recession of contralateral superior rectus (IR/SR-group) on squint angle and motility restrictions in Graves' Orbitopathy (GO) patients.

Design: Retrospective case series.

Materials and Methods: Primary outcome parameters were the changes of squint angle 3 months and 6 – 12 months postoperatively. As in a previous study, success was defined as a postoperative vertical squint angle of ≤ 3° in primary position and on downgaze. Secondary outcome parameters were the influence of surgery on duction range and influence of muscle size on dose-effect response.

Results: Fifty-six patients were included in the study; 31 patients in the IR-group and 25 patients in the IR/SR-group. The amount of (fixed suture) recession ranged from 2 mm to 7 mm. Vertical deviations in primary position changed from 8.0° [95% CI 6.6 – 9.7°] to 1.0° [95% CI -0.4 – 6.5°] in the IR-group and from 17.0° [95% CI 15.7 – 20.0°] to 1.5° [95% CI 0.8 – 2.9°] in the IR/SR-group. The success rate was 74% in the IR-group and 64% in the IR/SR-group. In the IR group, depression significantly worsened (p = 0.000). Elevation significantly improved in both groups (IR-group p = 0.007; IR/SR-group p = 0.000). The volume of the inferior or superior rectus muscle as assessed on CT-scans did not influence the dose-effect response.

Conclusions: The highest success rate and highest reduction of depression was found in the IR-group. The total duction range remained stable after strabismus surgery (IR-group) or improved (IR/SR-group). Both squint angle and cyclodeviation remained stable during long time follow up (6 – 12 month after surgery).

INTRODUCTION

Double vision occurs in up to 48% of patients with Graves' Orbitopathy[1] and significantly interferes with daily life activities such as reading and driving a car[2-4]. Among types of diplopia seen in GO, vertical deviation is very common, which does not come as a surprise as the most frequently involved muscle in GO is the inferior rectus muscle. Success of strabismus surgery in GO varies from 44% to 100%[5-10], but there is no consensus as how to handle strabismus. Deviations up to 15° are corrected with a recession of only one muscle[11]. In large comitant vertical deviations, a tight inferior rectus muscle in combination with an enlarged contralateral superior rectus muscle is mentioned[12]. If then the angle exceeds 10-15°, it has been suggested to combine inferior rectus recession with a resection of the ipsilateral superior rectus muscle[13-15]. However, resection procedures are not the first choice of surgery in GO-patients. Volpe *et al.* (2012) categorized the strategy of adjustable surgery on the amount of vertical strabismus together with the limitation in upgaze[16].

Overcorrection after a recession of the inferior rectus muscle is common[13;14;17-24]. Previous studies showed that both restricted contralateral elevation and increased ipsilateral volume of the superior rectus muscle of the operated inferior rectus muscle are predictors of overcorrection[12;17;24].

The results of combined recession of the superior rectus muscle and the contralateral inferior rectus muscle for correction of the vertical deviation are poorly described[6;12;16;18;25]. Moreover, data regarding the influence of strabismus surgery on duction in this patient group are scarce. Therefore, we evaluated our Graves' patients with vertical deviations who were operated on the inferior rectus muscle with or without the contralateral superior rectus muscle and compared the outcome with the literature. Based on our findings, we present a kind of flow chart for strabismus surgery in GO patients with vertical deviations.

MATERIALS AND METHODS

The study was conducted according to the principles of the Declaration of Helsinki (seventh edition, October 2008, Seoul) and in accordance with the Medical Research Involving Human Subjects Act (WMO).This study was reviewed by the Ethical Board. No approval was needed for this retrospective study.

All consecutive GO patients in our tertiary referral center, operated between January 2000 and February 2012, who underwent a primary recession with fixed sutures of the inferior rectus muscle with or without recession of the contralateral superior rectus muscle, were included in this study. A simultaneously performed medial rectus recession procedure was no reason for exclusion. Both patients with disease induced strabismus and those who developed strabismus after orbital decompression were included. However, patients who also underwent oblique muscle surgery or myopexia procedures were excluded. In addition, patients with pre-existing strabismus, low vision which interfered with the orthoptic examination, or co-existing orbital pathology were excluded. Surgery was only performed when the orbitopathy was inactive and the orthoptic findings were unchanged for at least 3 months.

Unilateral inferior rectus recession (2 – 5 mm) was carried out when the vertical deviation was < 15°, and when the deviation was comitant or increased in upgaze. A combined procedure was carried out in large (mostly > 15°) comitant vertical deviations (2 – 6 mm), with typically an ipsilateral elevation impairment with a contralateral depression impairment. If an incomitance was present, then the recession was carried out asymmetrically (for instance 2 mm recession superior rectus and 6 mm recession inferior rectus on the other eye).

In general, the calculation was a dose-effect response of 1.5°/mm was Horizontal and vertical deviation was measured in primary position and in eight directions of gaze (if ductions exceeded 25°) using the Maddox tangent screen at 2½ meters.

The ductions were measured with the modified perimeter as described by Mourits *et al.*[26]. Duction impairment postoperatively was defined as limited if duction worsened ≥ 5°[24] and depression was ≤ 50°. Cyclodeviation was measured with the cycloforometer of Franceschetti at 2½ m, in primary position, 25° up- and downgaze as described by Klainguti *et al*.[27]. Surgery was performed by different orbital surgeons.

Success was defined as a vertical angle ≤ 3° of and under- or overcorrection was defined as a vertical deviation of > 3° after surgery. This criteria were set in addition to the criteria in a previous study[22]. Within this vertical deviation, fusion is often possible (with or without prism). Both success definitions apply for primary position and/or downgaze. Dose-effect response was calculated by dividing the 'preoperative – postoperative squint angle' by the amount of recession. Orthoptic data from within 3 months before and after surgery and 6 –

12 months after surgery were collected. The size of the extraocular muscles as seen on coronal CT-scans was semi-quantitatively assessed by two orbital specialists (PS and MM) independently and without knowledge of the orthoptic situation and surgical intervention. All available orthoptic data were collected, as well as data concerning onset and severity of the GO and previous decompression surgery. For statistical analysis, SPSS 19.0 software was used.

RESULTS

General

In total, 202 GO patients operated for their vertical strabismus could be identified. 129 patients were excluded because of a simultaneous myopexia procedure, oblique muscle surgery, unilateral superior rectus recession, bilateral inferior rectus recession or reoperation on the inferior rectus muscle. Another 17 patients were excluded due to reactivation of the GO after surgery (changes in Clinical Activity Score[28]), incomplete data, strabismus present before onset of the GO or a co-existing orbital tumor or a supernumerary extra-ocular muscle. Fifty-six patients could be included, of which 36 (64%) were female and 20 (36%) male. Mean age was 58±10 years. An accompanying medial rectus recession was performed in 7 patients of the IR-group and in 2 patients of the IR-SR-group.

Twenty-eight (50%) of all patients underwent an orbital decompression prior to the strabismus surgery. Twenty-one patients had a field of binocular single vision ≥ 20° in all directions of gaze prior to the orbital decompression. Mean time between the orbital decompression and strabismus surgery was 17±22 months.

Strabismus

Table 1 shows the general data before and after surgery for both groups and Table 2 gives an overview of success rate, including the number of over- and undercorrection.

In both the IR group and IR/SR-group, the success and failure rates were not influenced by the amount of recession (IR group $p = 0.394$; IR/SR-group $p = 0.363$).

Dose effect responses are listed in Table 3. No difference was found when comparing the success and failure group (IR-group $p = 0.234$ and IR/SR-group $p = 0.173$).

Table 1. Pre- and postoperative data

	IR-group (n = 31) mean°±SD [range]	***p-value***	**IR/SR-group (n = 25) mean° ±SD [range]**	***p-value***
Recession (mm)				
IR eye	2.9 ± 0.8 [2.0 – 5.0]	0.000	3.8 ± 1.2 [2.0 – 6.0]	0.000
SR eye		n.a	4.5 ± 1.0 [3.0 – 6.0]	n.a.
	° median [95% CI]		**° median [95% CI]**	
Vertical deviation				
Primary postion				
preop	8.0 [6.6 – 9.7]	0.000	17.9 [15.7 – 20.0]	0.000
postop < 3 months	1.0 [-0.4– 6.5]	0.000	1.5 [0.8 – 2.9]	0.000
postop 6 – 12 months	2.0 [-0.5 – 5.9]	0.132	2.0 [-0.2 – 4.5]	0.082
Downgaze				
preop	6.8 [5.4 – 8.1]		14.5 [11.5 – 17.4]	
postop < 3 months	3.0 [0.9 – 7]	0.000	1.5 [-0.5 – 6.1]	0.000
postop 6 – 12 months	1.0 [1.1 – 6.6]	0.796	3.7 [-1.4 – 10.3]	0.304
Cyclodeviation				
Primary postion				
preop	+3.0 [-0.4 – 8.9]		+5.0 [-1.8 - 10.8]	
postop < 3 months	0.0 [-3.3 – 8.1]	0.002	+2.5 [-0.7 – 3.7]	0.018
postop 6 – 12 months	0.0 [-3.0 – 7.6]	0.496	+0.0 [-2.0 – 3.3]	0.340
Downgaze				
preop	+1.0 [-4.2 – 7.9]		+4.0 [-0.8 – 9.5]	
postop < 3 months	0.0 [-3.4 – 5.7]	0.142	+0.5 [-3.9 – 4.2]	0.015
postop 6 – 12 months	0.0 [-5.2 – 6.1]	0.230	-0.5 [-6.0 – 4.3]	0.167

cyclodeviation + = excyclodeviation; *IR* = inferior rectus muscle operated; *SR* = superior rectus muscle operated

Table 2. Outcome

	IR group (n)	**IR/SR-group (n)**	***p-value***
Success (≤ 3°)	23	16	0.000*
Overcorrection (> 3°)	5	5	
Undercorrection (> 3°)	3	4	

IR = inferior rectus; *SR* = superior rectus; *= ANOVA

Table 3. Dose-effect response of vertical squint angle

	IR group median° / 95% CI (n = 31)	**IR/SR-group median° / 95% CI (n = 25)**	***p-value***
All patients	2.8 [2.3 – 3.1]	2.0 [1.7 – 2.3]	0.009
Success (< 4°)	2.8 [1.0 – 3.8] (n = 23)	2.0 [1.1 – 3.1] (n = 16)	n.a.
Failure (≥ 4°)	2.9 [1.0 – 6.4] (n = 8)	1.6 [0.4 – 3.6](n = 9)	
Difference success/failure group	*p* = 0.234	*p* = 0.173	

Dose-effect response: (preoperative-postoperative angle)° / mm recession
IR = inferior rectus; *SR* = superior rectus; *SD* = standard deviation; *n.a.* = not applicable

Nine patients were simultaneously operated on one or both medial rectus muscles. The dose-effect response did not differ between the patient with and those without a simultaneously performed medial rectus muscle recession (IR-group p = 0.314 and IR/SR-group p = 0.500). No changes in the horizontal deviation in primary position (p = 0.658) or downgaze (p = 0.233) were seen in the other 47 patients. No significant difference in change of strabismus angle was found between patients with disease induced strabismus and decompression induced strabismus (p = 0.501).

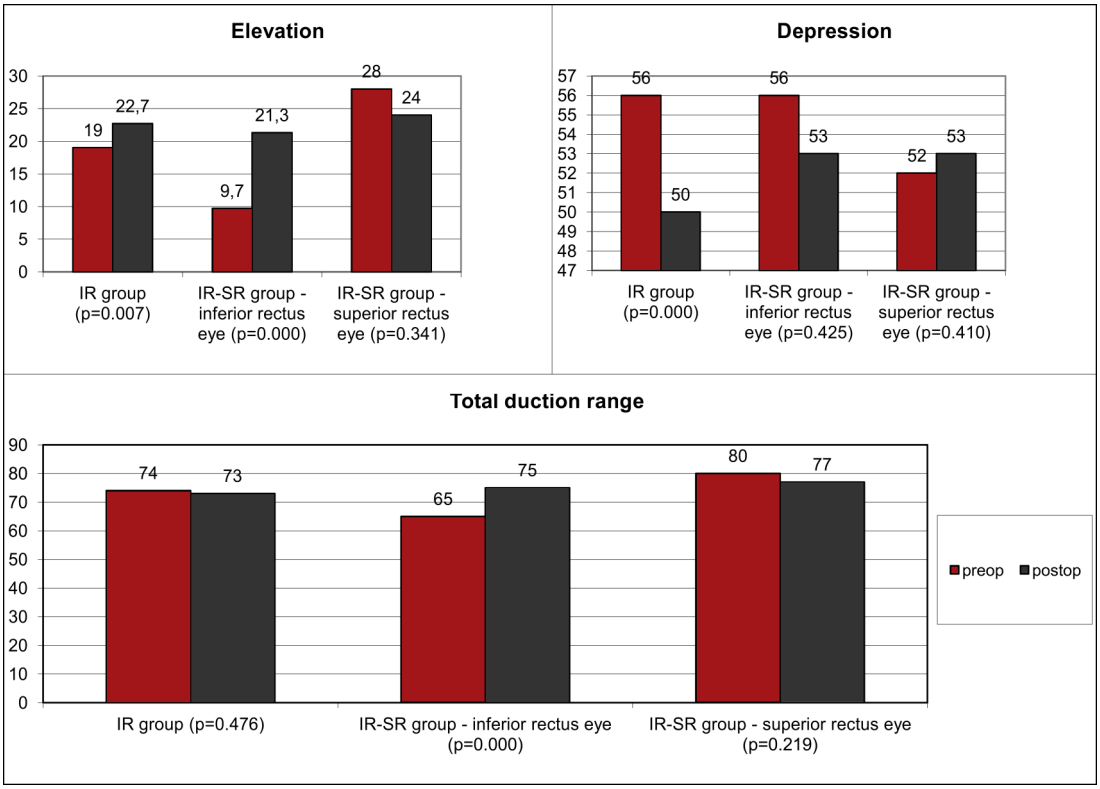

Figure 1. Elevation, depression and total duction range before and after strabismus surgery.

Duction

In general, elevation increased significantly after surgery when the inferior rectus muscle was recessed (Fig 1). Comparing the IR-group and IR/SR-group, the depression after surgery was significantly lower (p = 0.000) in the IR-group. However, smaller recessions were carried out in that group compared to the IR/SR-group (p = 0.011). No correlation was found between the amount of muscle surgery and the amount of depression (IR-group r = 0.034; IR/SR-group r = 0.029). When dividing the IR-group in a success and failure group, depression changed to 51.0±4.9 in the success group and to 44.6±9.3 in the failure group (p = 0.09). Total duction range increased only in the inferior rectus eye of the IR/SR-group. All other duction ranges remained stable (Fig. 1).

Cyclodeviation

Excyclodeviation in primary position diminished significantly in the IR-group (p = 0.000) and IR/SR-group (p = 0.015). Overall, no incyclodeviations were seen (Table 1).

Muscle enlargement

Table 4 shows the results of the muscle enlargement reassessed on the available CT-scans. No significant difference was found between the severity of muscle enlargement of the operated rectus muscle and outcome of the surgery.

Table 4. Muscle enlargement

	IR group (n)		IR/SR-group (n)			
	Operated IR	Ipsilateral SR	Operated IR	Ipsilateral SR	Operated SR	Ipsilateral IR
No	2	7	3	10	9	10
Mild	13	10	8	7	6	8
Moderate	9	8	10	5	7	4
Severe	2	1	5	0	0	0
Not available	5	5	3	3	3	3
Influence on success/failure	p = 0.446	p = 0.947	p = 0.184	p = 0.*328*	p = 0.137	p = 0.574

*Kruskal-Wallis test

DISCUSSION

After dysthyroid optic neuropathy, diplopia is one of the most serious quality of life threatening conditions within GO. Unfortunately, compared to decompression surgery, only a few studies are availably how to treat the diplopia. The present study tries to add to this subject and evaluates the largest series of combined inferior and contralateral superior rectus recessions in GO patients and presents the dose-effect response of this patient group. Success rate according to our stringent criteria of a postoperative strabismus ≤ 3° in primary position and downgaze varied from 64 – 74%. We assessed that the total duction range of the operated eye remained unchanged or even improved postoperatively. We found no differences in outcome between GO patients with primary strabismus (e.g. caused by the disease itself) and with decompression induced strabismus.

Only a few studies (with small numbers) describe the combined procedure of the inferior rectus muscle and the contralateral superior rectus muscle recession[6;12;18]. Success criteria within this group of strabismic patients were defined as amount of reoperations[12;18;25], binocular single vision in primary position and reading gaze[16] or postoperative orthotropia[6].

Most strabismus studies concern unilateral inferior rectus recessions[8;11;17;20;21;23;24;29-32]. Comparison with our results is hard to make, because we used other and more stringent criteria for success by including the downgaze position. In a comparable study by de Hoog *et al.* (2009), 37% of patients, operated on one or both inferior rectus muscles, a depression impairment and in 24% an overcorrection was found[24]. Eckstein *et al*. (2004) reported an overcorrection range of 7% – 56%, depending on the combined uni- or bilateral medial rectus recession procedure. They also found a significantly higher dose-effect response when the vertical strabismusprocedure was combined with a medial rectus recession. We did not find such a difference (IR-group $p = 0.314$ and IR/SR-group $p = 0.500$). Our dose effect responses of the IR-group are slightly higher compared to their dose-effect response[22]. No dose-effect response was found in the literature for the IR/SR-group.

Several explanations for overcorrection after inferior rectus recessions are described in literature.

1) The connection to the inferior oblique muscle with the capsulopalpebral fascia of Lockwood ligaments is said to cause a medial movement of the globe, when the muscle is not securely attached to the sclera[17].

2) A subtle *restriction in upgaze of the fellow eye* or an ipsilateral subclinical superior rectus restriction can create an overcorrection after surgery. By recessing the inferior rectus muscles bilaterally and asymmetrically on adjustable sutures, depression impairment can be prevented[12;17;24;30]. We agree with these studies that if the patient suffers from contralateral elevation impairment an (a)symmetrical bilateral inferior rectus recession has to be performed[33].

3) Excessive scarring which causes fibrosis and weakness of the inferior rectus muscle, especially in downgaze[23;30;34].

Overcorrection is often caused by restriction of depression postoperatively. Careful examination of the ductions is essential in this patient group. However, a lot of studies lack accurate measurement of ductions[6;12;16;21;23;25;30;32;35;35-37]. Schittkowsky *et al.* (2004) did measure ductions with the Kestenbaumbrille (0 – 10 mm), but found no depression impairment in their operated IR-group. In the present study, depression impairment after surgery exists but is not significantly different between the success and failure group. As said before, our stringent criteria for overcorrection also for duction make comparison with other

publications difficult. We emphasize that depression can be accurately measured with the performed modified motility meter (up to 58°)[26] or Goldmann perimeter[38].

The total duction range after surgery found in the present study was a little bit higher compared to the vertical duction range found by Gerling *et al.* (1997) (71.5°)[38].

Interestingly, no noticeable depression impairment arose in the IR-SR-group. This difference could be caused by the small patient group. Or one could assume that more muscles are enlarged in this group, but the diversity in muscle volume was not significantly different compared to the IR-group. Also, a lower volume of the superior rectus in the IR/SR-group could possibly account for this difference, but in our series we found no support for this assumption (p = 0.174). Possibly, subtle differences in muscle volume which cannot be seen on coronal CT-scans can count for this difference. Hopefully, exact muscle volume measurements in the future can give new keystones. It is also reasonable to think that the amount of recession was higher in the IR-group to explain the depression impairment in that subgroup. However, the amount of recession in the present study was higher in the IR/SR-group compared the amount in the IR-group (Table 1). This particular finding requires further research.

Recent experiments seem to indicate that tendon elongation can successfully be used to treat large vertical deviations without creating depression impairments[31]. Although the reported patient numbers are low and the results have to be confirmed by other studies, the technique may open new opportunities for the presented patient group.

It has been suggested that the nature of the strabismus induced by the decompression surgery differs from the strabismus induced by the orbitopathy itself. For that reason, we compared the subgroup that underwent a decompression with those who did not and we found no support for this hypothesis.

Although we now believe that the changes of the field of binocular single vision in combination with changes in quality of life questionnaires are the best outcome parameters for strabismus surgery, we did not use these parameters as there is no consensus yet as how to apply such parameters. Also, the retrospective nature of this study made it impossible to collect this data. Instead we used the change of strabismus and the duction range. Some previous studies have judged successful outcome only by the strabismus in primary position[5;17;23;36;37;39]. If we would have applied those criteria, our success rates would have been higher. However, we feel that such criteria do not justify the real life situations such as

reading or walking down on a flight of stairs. The field of binocular single vision is a good predictor for patients' quality of life, together with the GO-quality of life (GO-QoL) questionnaire of Terwee *et al*. (1998)[40]. Patients with GO often have increased vertical fusional amplitudes, which enables them to fuse small vertical angles. Future studies, like a recent study of our department[41], have to clarify if our measurement criteria for success match the patients' experience in daily life situations.

In conclusion, this study shows results and compares outcomes of two surgical approaches to correct vertical strabismus in GO-patients. Interestingly, less decrease of depression and lower dose-effect response was found in the IR/SR-group, despite the higher amount of muscle recession. Total duction range remains stable or even improves after surgery. The optimal surgical plan has to be made after careful evaluation of strabismus, ductions and ocular incomitance. A guideline for surgery, based on previous and present results, is presented in Figure 2[33].

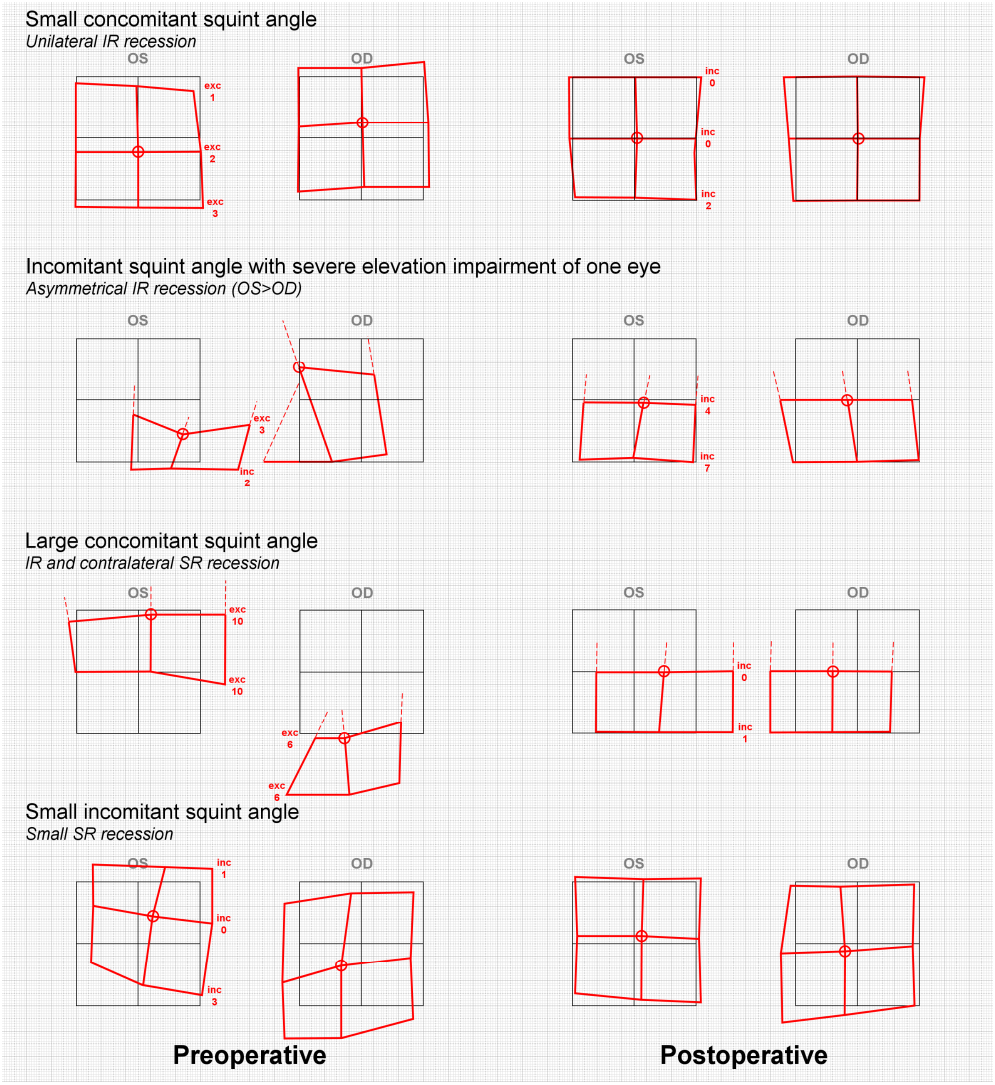

Figure 2. Surgical treatment plans for different motility problems shown on motility schemes. Motility schemes in nine directions of gaze measured with help of the Maddox rod en Maddoxcross on 2½ meter. Cyclodeviation measured in primary position, 25° downgaze and 25° upgaze. *IR*=inferior rectus; *SR* = superior rectus.

Small concomitant squint angle – in small concomitant squint angles a unilateral inferior rectus recession is surgery of choice. **Incomitant squint angle with severe elevation impairment of one eye** – with decrease of vertical deviation in downgaze; asymmetrical recession of the inferior rectus muscle is surgery of choice. **Large concomitant squint angle** – combined recession of the inferior rectus muscle of the hypotropic eye combined with a recession of the other eye is recommended. **Small incomitant squint angle** – incomitant angle with more vertical deviation in left or right downgaze a recession of the superior rectus muscle is preferred.

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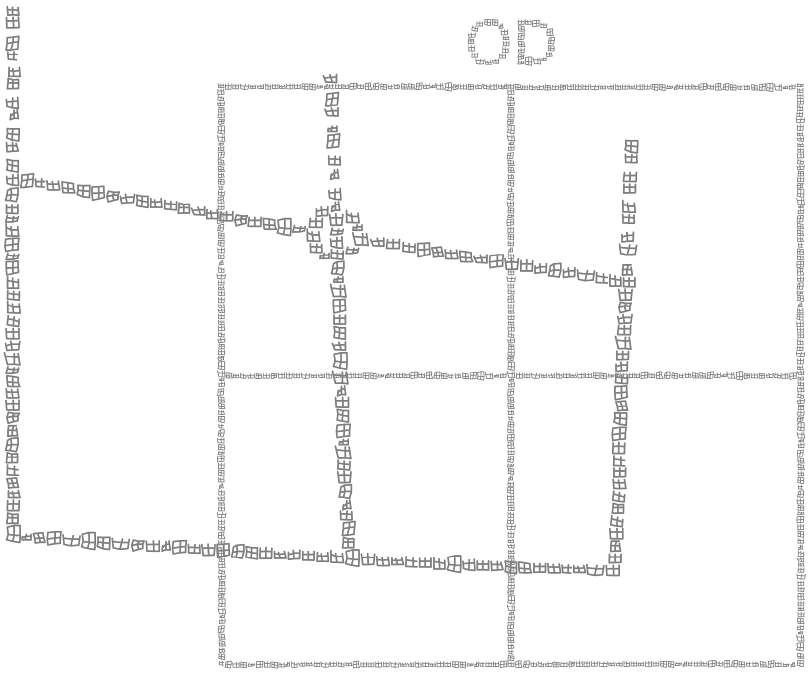

CHAPTER 6

PROPOSAL OF SUCCESS CRITERIA FOR STRABISMUS SURGERY IN GRAVES' ORBITOPATHY PATIENTS BASED ON A SYSTEMATIC LITERATURE REVIEW

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ABSTRACT

Purpose: To propose success criteria for strabismus surgery for patients with Graves' Orbitopathy (GO) based on a systematic review of the literature.

Methods: We performed a systematic search of OVID MEDLINE, OVID Embase, the Cochrane Central Register of Controlled Trials (CENTRAL) and the publisher subset of PubMed, to identify studies reporting on success criteria of strabismus surgery in GO. In addition, we handsearched several orthoptic journals and proceedings of strabismological congresses.

Results: Of the 789 articles retrieved, 42 papers described success criteria for strabismus surgery in GO. Most studies defined success in terms of a subjective diplopia free field in primary and down gaze. Almost half of the studies used a graded scale (excellent, good, acceptable, failure) to describe the outcome of surgery. Three of the eligible studies described a tool to quantify the field of single vision in detail. Quality of life was not reported as an outcome measure in any of the published studies.

Conclusion: Success criteria for strabismus surgery in GO-patients are poorly defined and no consensus is available. The lack of standardization hampers comparative studies and thus the search for the best surgical treatment for diplopia in GO-patients. Therefore, we propose strict success criteria including a tool for quantification of remaining diplopia plus a disease-specific quality of life questionnaire (the GO-QoL).

INTRODUCTION

Graves' Orbitopathy (GO) is characterized by swelling and retraction of the eyelids, proptosis, restricted motility and impaired vision. Restricted motility is caused by inflamed and less elastic extraocular muscles and causes head tilt and diplopia in up to 45% of all referred GO-patients (Sasim *et al.* 2008). Diplopia may be transient or permanent and may be limited to up- and side gaze or include all fields of vision. It limits the affected patient seriously in many daily life activities such as car driving, walking or reading (Gerding *et al.* 1997; Terwee 2000; Farid *et al.* 2005; Yeatts 2005; Bradley *et al.* 2006; Coulter *et al.* 2007). Specific quality of life questionnaires have been developed to assess the impact of these phenomena in patients with GO (Terwee *et al.* 1998; Fayers & Dolman 2011).

Diplopia can sometimes be corrected with prisms, but in more severe cases one eye has to be occluded. In the active phase of the disease, immunosuppressive or retrobulbar radiation may improve diplopia (Mourits et al. 2000; Prummel et al. 2004). However, when the disease and the motility pattern have become stable, there is consensus to treat residual diplopia surgically (Prummel *et al.* 2003; Bartalena *et al.* 2008; Nardi 2009; Lyons & Rootman 2010). Although a full field of binocular single vision (BSV) in patients with GO is difficult to obtain due to the incomitant type of strabismus typical for GO-patients, the goal of surgery is to reach a field of BSV as large as possible (Schotthoefer & Wallace 2007; Dickinson & Perros 2009; Dagi *et al.* 2010; Eckstein *et al.* 2012). There are many possible choices to reach this goal: recessions of the involved muscle with or without adjustable sutures (Flanders & Hastings 1997; Eckstein *et al.* 2004; Mocan *et al.* 2007; Jellema *et al.* 2012; Volpe *et al.* 2013), resection (Yoo *et al.* 2013), Faden procedures (Schittkowski *et al.* 2004) or interposition of spacers to lengthen the affected extraocular muscle (Esser *et al.* 2011). As restrictions may exist both in the vertical, as well as in the horizontal plane, corrections have to be performed in both planes. No guidelines are defined with regard to starting with one procedure or perhaps to combine corrections in both planes in one session. The existing treatment modalities cannot be compared as long as no consensus exists with regard to the definition of the outcome of these corrections. Success of strabismus surgery in GO-patients is defined in different ways. Kalpadakis *et al*. described a significant reduction of the squint angle as a good functional rehabilitation (Kalpadakis et al., 2004). Others used the presence of stereopsis (Mocan *et al.* 2007) or ability to fuse in primary position (Cruz & Davitt 1999) or also at distance and near and without an abnormal head posture (Coats *et al.* 1999) as a

criterion of success of strabismus surgery. Some authors define success as a residual deviation in prism dioptres (Sprunger & Helveston 1993) (Cruz & Davitt 1999; Prendiville *et al.* 2000; McCracken *et al.* 2008) (Yang *et al.* 2004; Zoumalan *et al.* 2011) in primary position [range 3 – 10^).

Usually success criteria are described in terms of improvement/changes of the field of BSV (Maillette de Buy Wenniger - Prick *et al.* 1986; Mourits *et al.* 1990; Fells *et al.* 1992; Lueder *et al.* 1992; Boergen 1993; Ellerton *et al.* 1995; Flanders & Hastings 1997; Oguz *et al.* 2000; Ruttum 2000; Tarrus-Montaner *et al.* 2000; Baker & Ansons 2001; Kalmann 2001; Yolar *et al.* 2001; Abrámoff *et al.* 2002; Ai *et al.* 2002; Del Monte 2002; Godts *et al.* 2002; Oguz *et al.* 2002; Kalpadakis *et al.* 2004; Schittkowski et al. 2004; Gilbert *et al.* 2005; Dal Canto *et al.* 2006; Paridaens *et al.* 2006; Pitchon & Klainguti 2007; Yan & Zhang 2008; Hoog de *et al.* 2009; Nassar *et al.* 2009; Nicholson *et al.* 2011; Volpe *et al.* 2013) . These criteria, however, differ significantly. For instance: e*xcellent* is described as no diplopia (Ruttum 2000; Baker & Ansons 2001; Kalmann 2001; Schittkowski et al. 2004; Paridaens *et al.* 2006; Pitchon & Klainguti 2007; Volpe *et al.* 2013) *or* no diplopia in primary position and downgaze (Lueder et al. 1992; Ellerton *et al.* 1995; Flanders & Hastings 1997; Kalmann 2001; Gilbert *et al.* 2005; Dal Canto *et al.* 2006) and *good* as no diplopia in primary position and down gaze with prisms (Lueder *et al.* 1992; Ellerton *et al.* 1995; Flanders & Hastings 1997; Baker & Ansons 2001; Gilbert *et al.* 2005; Dal Canto et al. 2006; Volpe *et al.* 2013) or without prisms (Pitchon & Klainguti 2007) *or* as gaze evoked diplopia (Kalmann 2001; Paridaens *et al.* 2006) *or* a no diplopia with prisms (Ruttum 2000) *or* $\geq$ 50% score of BSV with the score system of Sullivan et al. (Sullivan *et al.* 1992) and heterophoria in primary position (Nassar *et al.* 2009) or BSV with maximal 5^ prisms in primary position and reading gaze (Schittkowski *et al.* 2004). Although these criteria look quite uniform at first sight and the role of prisms being one of the most significant differences, at a closer look true differences appear which make these criteria not interchangeable. For instance, several systems do not quantify the change. Furthermore, terms as “extreme gaze” and “reading position/ downgaze” are often not specified. Changes in QoL scores can also be used to compare pre- and postoperatively status (Terwee *et al.* 2001; Wiersinga *et al.* 2004; Kashkouli *et al.* 2011). Terwee *et al.* developed a specific QoL for GO-patients (GO-QoL). This questionnaire contains two subscales: 1 for visual function (8 questions referring to limitations attributable to decreased visual acuity and/or diplopia) and 1 for appearance (8 questions referring to psychosocial

functions attributable to changes in appearance) (Terwee *et al.* 1998). Considering strabismus surgery, a change of at least 6 points on one or both subscales can be seen as an important change in daily functioning for the patient (Terwee *et al.* 2001). In conclusion, success criteria are preferred which contain both the field of BSV and incorporate parameters of QoL. No acceptable criteria exist as how to compare changes after strabismus surgery in GO-patients. To propose a definition of successful outcome, we studied the literature systematically about success criteria for strabismus surgery in GO-patients to create a starting point for consensus on this subject.

METHODS

To propose a definition of successful outcome, we studied the literature about success criteria for strabismus surgery in GO-patients to possibly create a starting point for consensus on this subject. Our review followed the PRISMA guidelines* for reporting (Liberati *et al.* 2009). A medical librarian (JL) performed a comprehensive search in the following electronic databases from inception till 2013 – 07 – 23: OVID MEDLINE, OVID Embase, the Cochrane Central Register of Controlled Trials (CENTRAL) and the publisher subset of PubMed to find publications not yet included in MEDLINE. Finally, we handsearched the indexes of the British and Irish orthoptic Journal (1990 – 2011), the proceedings of the European Strabismological Association (1990 – 2011), the International Strabismological Association (1990-2010), the International Orthoptic Association (1990 – 2012) and the American Orthoptic Journal (1982 – 2012). In electronic databases, we used both Subject Headings, such as MeSH (MEDLINE), and textwords, with no language restrictions. The search consisted of 3 components: 1. Graves' disease, 2. diplopia, strabismus or synonyms and related terms (i.e. depth perception) and 3. strabismus surgery (see Table S1 for the complete MEDLINE search strategy).

We also applied a methodological filter for secondary evidence to identify any systematic review on the topic. The search included an iterative process to refine the search strategy through adding search terms as new relevant citations were identified, i.e. by checking reference lists and citing articles using ISI Web of Science and handsearching. Reference Manager® software (version 12.0) was used to manage and de-duplicate all identified references (Liberati *et al.* 2009).

Table S1. Search strategy - online repository.

Database(s): **Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R)** 1946 to Present. Search Strategy: 2013-07-23

#	Searches	Results
1	exp Graves' Disease/	14186
2	(graves* or grave-s or basedow* or goiter* or hyperthyroid* or thyroid* or d?sthyroid).tw,ot,kw.	165119
3	(endocrine adj (eye or orbitopath* or ophthalm* or opthalm* or ocular)).tw,ot,kw.	445
4	(TED or GED or TAO or TRIO or EUGOGO or GO-QOL).tw,ot,kw.	3419
5	or/1-4	169614
6	exp animals/ not humans/	4001076
7	5 not 6	138742
8	(review or editorial or letter or comment).pt. not (Comparative Study.pt. or exp Cohort Studies/ or Cross-Sectional Studies/ or case-control studies/ or evaluation studies/ or case reports/ or exp treatment outcome/)	2623669
9	7 not 8	122751
10	(strabis* or optometr* or orthoptic).jw.	20683
11	Orthoptics/	1637
12	(orthopt* or pleoptic*).tw,ot,kw.	2747
13	exp Ocular Motility Disorders/ or exp Strabismus/	34085
14	(strabism* or squint or squinting or e?otropi* or hypertropi* or hypotropi* or cyclotropi* or heterophori* or e?ophori* or hyperphori* or hypophori* or cyclophori* or crossed-eye*).tw,ot,kw.	16268
15	Diplopia/	4118
16	(diplop* or polyop*).tw,ot,kw.	6450
17	Vision, Binocular/ or Vision, Monocular/	6836
18	((direction* or field* or position* or restrict*) adj2 (gaz* or upgaz* or downgaz*)).tw,ot,kw.	1752
19	((single or monocul* or double or doubling or binocul* or stereo* or horizontal* or vertical* or primary or secondar*) adj3 (gaz* or upgaz* or downgaz* or vision* or field* or position*)).tw,ot,kw.	21412
20	((binocul* or monocul*) adj2 (fusion or vision or perception or view or visual or field)).tw,ot,kw.	4635
21	((horizontal* or vertical*) adj2 deviation*).tw,ot,kw.	960
22	deviometr*.tw,ot,kw.	6
23	(orthophor* or orthotrop*).tw,ot,kw.	1090
24	diopter*.tw,ot,kw.	6451
25	duction*.tw,ot,kw.	480
26	(excyclodev* or cyclodev* or incyclodev* or excyclotors* or cyclotors* or incyclotors* or excyclo-tors* or cyclo-tors* or incyclo-tors*).tw,ot,kw.	269
27	exp Depth Perception/	9718
28	stereopsis.tw,ot,kw.	1804
29	((depth or space or spatial* or vis* or distance*) adj2 (percept* or discriminat*)).tw,ot,kw.	14886
30	exp eye movements/	39197
31	((eye or ocular) adj position*).tw,ot,kw.	2088
32	((cover or maddox or Hess*1) adj3 (screen* or test* or chart*)).tw,ot,kw.	825
33	(MDRT or covertest* or lancaster or AHS).tw,ot,kw.	1331
34	or/10-33	143253
35	Ophthalmologic Surgical Procedures/	8078
36	Ocular Motility Disorders/su or Diplopia/su or exp Strabismus/su or exp Ophthalmoplegia/su	5374
37	Oculomotor Muscles/su	3724
38	exp Graves Disease/su	1705
39	exp Suture Techniques/	38229
40	Muscle Relaxation/	11718
41	((extraocul* or extra-ocul* or muscle* or muscular or rectus or recti or IRM or tenon or strabism* or squint* or e?otropi* or hypertrop* or hypotrop* or cyclotrop* or orthotrop* or heterophor* or e?ophor* or hyperphor* or hypophor* or cyclophor* or orthophor* or diplop* or polyopsi* or prism* or e?odeviat* or deviat* or align* or malalign* or misalign* or duction or oculomotor or vision or binocular or orbipath* or opthalmopath* or restrict* or ortho) adj4 (surg* or operat* or preoperat* or pre-operat* or intraoperat* or intra-operat* or postoperat* or post-operat* or presurg* or pre-surg* or intrasurg* or intra-surg* or postsurg* or post-surg* or reoperat* or resurg* or resect* or reces* or positioning or repair* or correct* or overcorrect* or undercorrect* or restor* or adjust* or incis*)).tw,ot,kw.	36390
42	(adjustable or nonadj* or realign* or re-align*).tw,ot,kw.	12323
43	(Faden or Tenon or SSASS or MISS).tw,ot,kw.	6973
44	(surgical adj (treatm* or repair or intervention or alignment or realign* or management)).tw,ot,kw.	178711
45	((surg* or operat* or perioper* or postop*) adj2 (outcome* or approach)).tw,ot,kw.	53294
46	sutur*.tw,ot,kw.	56413
47	(no-decompression or NDG).tw,ot,kw.	99
48	or/35-47	362168
49	9 and 34 and 48	471
50	(meta-analysis.pt. or exp technology assessment, biomedical/ or exp Evidence-Based Practice/ or exp Databases, Bibliographic/ or exp guideline/ or guideline*.ti,ot. or (((hta or health technology) adj6 assessment*) or meta analy* or metaanaly* or meta?analy* or ((review* or search* or research) adj10 evidence) or ((review* or search* or research or evidence) adj10 (literature* or medical database* or systemat* or exhaustive)) or medline or pubmed or embase or cochrane or cinahl or psychinfo or psychlit or healthstar or biosis or current conten*).tw,ot,kw. or (cochrane or evidence or EBM or duodecim).jw.) not (comment or editorial or historical-article).pt.	509946
51	**7 and 34 and 48 and 50**	**14**

Studies addressing success criteria or goal of strabismus surgery in adult GO patients were eligible; studies only addressing outcome of dose-effect response were excluded. Two authors (HMJ and YBB) independently screened all titles and abstracts. Disagreement was solved by discussion.

RESULTS

The search identified 789 unique publications, of which 102 were selected for full text screening. In total, 42 papers reporting on success criteria were eligible (Fig. 1). We found one prospective case series (Prendiville *et al.* 2000). The other publications were either comparative or non-comparative retrospective case series (Table 1).

A number of criteria were found in defining success. These criteria are: outcome in primary position, differentiation between near and distance, outcome in reading gaze and other gazes (field of BSV), ability to fuse, prism required, present abnormal head posture (AHP), equipment used for measurement, level of outcome (good, fair, etcetera). Six studies included the number of surgeries (Mourits *et al.* 1990; Fells *et al.* 1992; Kraus & Bullock 1993; Yolar *et al.* 2001; Godts *et al.* 2002; Oguz *et al.* 2002) and one included the possible complications following strabismus surgery in their success criteria (Coats *et al.* 1999) (Table 2).

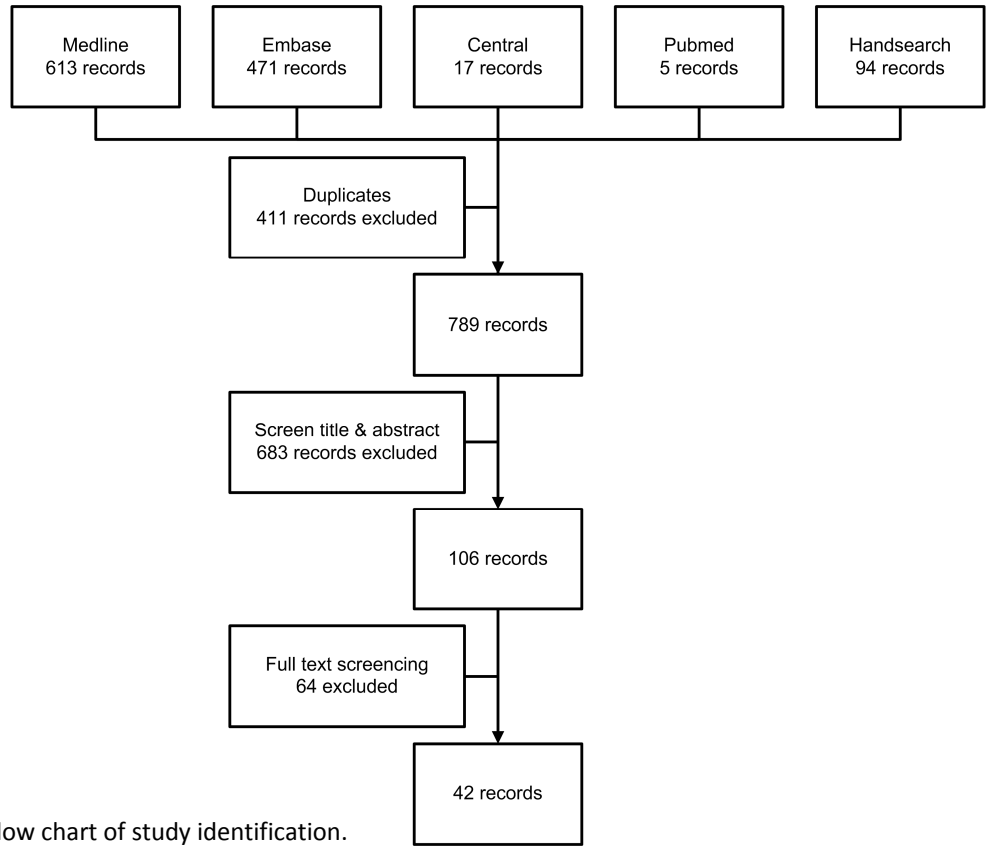


Figure 1. Flow chart of study identification.

Table 1. Overview of included studies

study	year	type of study	number patients	measurement*
Maillette de Buy Wenniger - Prick *et al.*	1986	1	22	not specified
Trokel *et al.*	1988	1	160	fuse with prisms
Mourits *et al.*	1990	1	38	field of BSV with Maddox screen
Fells *et al.*	1992	1	58	Hess, ductions, BSV not specified (score by Fitzsimons *et al.*[67])
Lueder *et al.*	1992	1	47	presence of diplopia
Nardi	1992	1	34	field of BSV - not specified device
Boergen	1993	1	74	field of BSV - not specified device
Kraus and Bullock	1993	1	52	Lee screen, Hess screen, binocular visual fields
Ellerton *et al.*	1995	1	67	ocular deviation (indirectly PCT), and muscle restrictions
Flanders and Hastings	1997	1	22	Worth four dot, biMaddox rod, ductions 0 / - 7, APCT near and distance
Coats *et al.*	1999	1	8	PCT 20 feet and14 inches, ductions – 1 /- 4
Cruz and Davitt	1999	1	8	APCT in primary and downgaze, 20 ft and 13 inches + ductions and versions
Oguz *et al.*	2000	not specified	27	not specified
Prendiville *et al.*	2000	2	31	PCT at distance in primary position, calculation of duction as described by Feldon (1984)
Ruttum	2000	1,4	55	not specified / presence of diplopia
Baker and Davis	2001	1	15	ocular motility assessment
Jacks and Adams	2001	1	44	not specified
Russo *et al*.	2001	1	44	not specified
Yolar *et al.*	2001	not specified	13	Krimsky test with far fixation, Worth four dot test, Hess screen
Ai *et al.*	2002	not specified	11	not specified
Del Monte	2002	1	135	not specified
Godts *et al.*	2002	1,4	30	APCT 33 cm and 6 m, synoptophore, Lancaster, Lees screen, Goldmann perimeter for BSV
Nguyen *et al.*	2002	1,4	137	PCT primary position
Oguz *et al.*	2002	1	23	diplopia in primary and reading gaze, Hess stability, indirect PCT
Schittkowski *et al.*	2004	1	26	ductions with Kerstenbaumbrille, field of BSV with Harmswand
Yang *et al.*	2004	1	25	APCT 6 m and 33 cm
Gilbert *et al.*	2005	1,4	50	not specified
Dal Canto *et al.*	2006	1	24	deviation in primary gaze and symptoms
Lu and Yan	2007	1	30	not specified
Mocan *et al.*	2007	1	32	PCT near and distance, MDR, ductions 0 /- 4, Worth four dot, Titmus
Pitchon and Klainguti	2007	1	21	Harmwand - eye position inclusive cyclodeviation and field of BSV
Schotthoefer and Wallace	2007	3		not specified
Thomas and Cruz	2007	1,4	86	PCT (indirectly)
Yan and Zhang	2008	1	25	APCT 6 m and 33 cm
Nassar *et al.*	2009	1	50	ductions with Goldmann (Haggerty *et al.*[73]), BSV with Goldmann (score by Sullivan *et al.*[68]), horizontal and vertical fusion range
Nardi	2009	3		perimeter ductions, versions, APCT
De Hoog *et al.*	2009	1	124	not specified
Nicholson *et al.*	2011	1	63	PCT primary position, presence of diplopia
Zoulaman *et al.*	2011	1	26	APCT at near and distance
Volpe *et al.*	2012	1	54	ductions 0 / - 4, PCT 6 m and 33 cm in nine positions of gaze, Maddox rod to test overcorrection > 20 degrees
Kim *et al.*	2013	1,4	56	PCT and APCT 6 m in primary position
Yoo *et al.*	2013	1	8	MDR, Titmus, ductions 0 / - 4, APCT 20 feet and 14 inches

1 = retrospective case series; 2 = prospective case series; 3 = overview article; 4 = comparative study; * including those to quantify success criteria if stated in the article; *PCT* = prism covertest; *APCT* = alternating prism covertest; *BSV* = binocular single vision; *MDR* = Maddox double rod

Table 2. Overview of description of success criteria		
success criteria	**number of studies**	**percentage (%)**
primary position	**42**	100
prism covertest	**8**	20
near/ distance	**3**	7
fuse / diplopia	**36**	86
prism added	**24**	57
abnormal head posture	**9**	21
reading gaze	**22**	52
quantification of reading gaze	**4**	10
field BSV	**8**	20
levels of success (excellent, good etc.)	**19**	45
able to drive	**1**	2
number of surgeries	**7**	
after one surgery	***4***	10
after one or two surgery	***2***	5
no visual threatening complication	***1***	2

Successful outcome was frequently described in terms of fusion or diplopia (n=36; 86%). All studies considered 'absence of diplopia in primary gaze'(Ruttum 2000; Russo *et al.* 2004) or diplopia only present in extremes of gaze'(Godts *et al.* 2002) as a successful outcome. Eight studies based the outcome of surgery on the change in outcome of the prism covertest (20%) (Sprunger & Helveston 1993; Cruz & Davitt 1999; Prendiville *et al.* 2000; Nguyen *et al.* 2002; Sharma & Reinecke 2003; Thomas & Cruz 2007; McCracken *et al.* 2008; Zoumalan *et al.* 2011). Prisms to gain single vision were regularly mentioned as part of the outcome description (n=24, 57%) (Mourits *et al.* 1990; Fells *et al.* 1992; Lueder *et al.* 1992; Flanders & Hastings 1997; Cruz & Davitt 1999; Oguz *et al.* 2000; Ruttum 2000; Baker & Ansons 2001; Del Monte 2002; Godts *et al.* 2002; Oguz *et al.* 2002; Schittkowski *et al.* 2004; Yang *et al.* 2004; Gilbert *et al.* 2005; Dal Canto *et al.* 2006; Lu & Yan 2007; Pitchon & Klainguti 2007; Yan & Zhang 2008; Nassar et al. 2009; Nicholson et al. 2011; Zoumalan *et al.* 2011; Kim *et al.* 2013; Volpe *et al*. 2013). The head position as part of the outcome was described in nine papers (Fells *et al.* 1992; Lueder *et al.* 1992; Coats *et al.* 1999; Jacks & Adams 2001; Del Monte 2002; Oguz *et al.* 2002; Gilbert *et al.* 2005; Yan & Zhang 2008; Nassar *et al.* 2009); the distinction between near and far distance fixation in three (Flanders & Hastings 1997; Coats *et al.* 1999; Zoumalan *et al.* 2011). It was not mentioned how the abnormal head position was assessed. Twenty-two (52%) studies considered single vision in primary gaze an

important aspect of the outcome of strabismus surgery (Trokel *et al.* 1988; Mourits *et al.* 1990; Fells *et al.* 1992; Lueder *et al.* 1992; Nardi *et al.* 1992; Boergen 1993; Kraus & Bullock 1993; Ellerton *et al.* 1995; Flanders & Hastings 1997; Ruttum 2000; Baker & Ansons 2001; Jacks & Adams 2001; Ai *et al.* 2002; Schittkowski *et al.* 2004; Dal Canto *et al.* 2006; Schotthoefer & Wallace 2007; Yan & Zhang 2008; Hoog de *et al*. 2009; Nardi 2009; Nassar *et al.* 2009; Nicholson *et al.* 2011; Kim *et al.* 2013). To assess the presence of single vision in different directions of gaze, the field of BSV was used in eight studies (20%) (Maillette de Buy Wenniger – Prick *et al.* 1986; Mourits *et al.* 1990; Boergen 1993; Ai *et al.* 2002; Godts *et al.* 2002; Schittkowski *et al.* 2004; Pitchon & Klainguti 2007; Nassar *et al.* 2009). Four studies specified how these directions should be measured (Godts *et al.* 2002; Schittkowski *et al.* 2004; Pitchon & Klainguti 2007; Nassar *et al.* 2009). In addition to the primary gaze, the majority of studies mentioned the reading gaze as an outcome parameter (n = 22; 52%) (Trokel *et al.* 1988; Mourits et al. 1990; Fells *et al.* 1992; Lueder *et al.* 1992; Nardi *et al.* 1992; Boergen 1993; Kraus & Bullock 1993; Ellerton *et al.* 1995; Flanders & Hastings 1997; Ruttum 2000; Baker & Ansons 2001; Jacks & Adams 2001; Ai *et al*. 2002; Schittkowski *et al*. 2004; Dal Canto *et al.* 2006; Schotthoefer & Wallace 2007; Yan & Zhang 2008; Hoog de *et al.* 2009; Nardi 2009; Nassar *et al.* 2009; Nicholson *et al.* 2011; Kim *et al.* 2013) of which four (9%) studies measured the reading gaze by means of the field of BSV (Mourits *et al.* 1990; Schittkowski *et al.* 2004; Pitchon & Klainguti 2007; Nassar *et al.* 2009) (Table 3). Other directions of gaze were specified in eight studies (20%)(Maillette de Buy Wenniger – Prick *et al.* 1986; Boergen 1993; Ai *et al.* 2002; Godts *et al.* 2002; Pitchon & Klainguti 2007; Hoog de *et al.* 2009; Nassar *et al.* 2009). In 45% of the studies, success criteria were described in terms of excellent, good, fair and poor (Fells *et al.* 1992; Lueder *et al.* 1992; Ellerton *et al.* 1995; Flanders & Hastings 1997; Ruttum 2000; Baker & Ansons 2001; Yolar *et al.* 2001; Del Monte 2002; Oguz *et al.* 2002; Schittkowski *et al.* 2004; Gilbert *et al.* 2005; Dal Canto *et al.* 2006; Pitchon & Klainguti 2007; Yan & Zhang 2008; Hoog de *et al.* 2009; Nassar *et al.* 2009; Nicholson *et al.* 2011; Volpe *et al.* 2013). Nassar *et al.*(Nassar et al. 2009), Pitchon and Klainguti (Pitchon & Klainguti 2007) and Schittkowsky *et al*. (Schittkowski *et al.* 2004) introduced a measurement tool to define the levels (Table 3).

A score sheet to quantify the field of BSV was used by Fells *et al.* (1992) and Nassar *et al.* (2009). One study focused on a subjective outcome criteria of strabismus surgery in terms of 'being able to drive after strabismus surgery'(Jacks & Adams 2001).

Table 3. Three examples of success criteria	
Study	**Success criteria**
Nassar *et al. (*2009)	Good – field of BSV > 50% and heterophoria in primary position Moderate – field of BSV 1% - 50% and heterotropia correctable with prism or AHP in primary position Poor – no field of BSV and intractable diplopia *Measurement: Goldmann perimeter and Sullivans scores system*[68].
Pitchon and Klainguti (2007)	Excellent – BSV in all directions of gaze Good – BSV in primary position and reading gaze without prisms Fair – BSV in primary position and reading gaze with prisms Failure – persistent diplopia in primary position and/or reading gaze with prisms *Measurement: field of BSV with Harmswand*
Schittkowski *et al.*(2004)	Excellent – in all directions of gaze free of diplopia. Very good – BSV without prisms in primary and reading position. Good – BSV with maximal 5^prisms in primary and reading position. Fair – diplopia in reading or primary position to much for prism. Failure – diplopia not correctable with prisms. *Measurements: field of BSV with Harmswand*

BSV = binocular single vision

DISCUSSION

This analysis reveals that binocular single vision in primary position and reading gaze is the most frequently used outcome measure of strabismus surgery in GO-patients. In addition, many authors modify the outcome criteria by using a grading system (excellent, fair, and poor). The assessment of the field of BSV, however, is rarely elaborated on and therefore not very accurate. Quantification of success criteria is lacking in almost all studies. We conclude that based on existing outcome criteria, adequate comparison of operation techniques is difficult.

The three most sophisticated studies (Table 3) base their outcome criteria on a graded system of the field of BSV and describe a tool how to measure this field. The tool used is either the Goldmann perimeter (Nassar *et al.* 2009) or the Harmswand (Schittkowski *et al.* 2004; Pitchon & Klainguti 2007). In contrast to the Harmswand, the Goldmann perimeter is well known all over the world and counts as the golden standard. Although the cervical range of motion (CROM) device measures the diplopia free zone in daily life condition (Holmes *et al.* 2005; Hatt *et al.* 2007) and a scoring system has been developed (Holmes *et al.* 2005), the device is not integrated in the orthoptic practice worldwide. Therefore, the **Goldmann perimeter** is the most suitable instrument to quantify the field of BSV. The existing grading systems mentioned in Table 3 reveal some shortcomings. Nassar *et al.*

distinguish good, moderate and poor outcomes and consider a field of BSV of ≥ 50% of normal as 'good' (Nassar *et al.* 2009). However, it matters in which direction of gaze single vision exists. Single vision in primary and reading position is far more important than in side gaze (Woodruff *et al.* 1987; Fitzsimons & White 1990; Sullivan *et al.* 1992). In addition, more subtle grades of outcome are to be preferred. Two studies applied a score sheet to quantify the field of BSV (Fells *et al.* 1992; Nassar *et al.* 2009). To compare surgery results, such a score system is essential. Fitzsimons and White (Fitzsimons & White 1990) applied a score sheet but did not weigh central and downgaze segments differently from peripheral ones. Woodruff *et al*. (Woodruff *et al.* 1987) and Sullivan *et al*. (Sullivan *et al.* 1992) proposed a weighted scoring system for the field of BSV. Higher scores are given to the field of BSV in primary and reading positions. This type of scoring is essential in diplopic patients. The total score of the field of Woodruff *et al.* was 124 and of **Sullivan *et al.*** 100 points. This latter score is to be preferred because a direct expression of a percentage of normal is possible.

Only one study within the timeframe mentioned in the method section quotes subjective outcome parameters like quality of life (Jacks & Adams 2001). In a previous paper, we found a significant improvement of the quality of life measured with the Graves' Orbitopathy specific QoL questionnaire (GO-QoL) after strabismus surgery, but no strong correlation between the field of BSV and the QoL outcome (Jellema *et al.* 2014). This finding supports the theory that the patients' quality of life encompasses more than the squint angle in primary position and reading gaze. So, apart from objective outcome criteria, it would be best to have subjective outcome criteria as well. The GO-QoL (Terwee *et al.* 1998) has shown to be of value in this respect, containing 16 questions; 8 items about visual functioning and 8 items about appearance. Especially the items about visual functioning (for instance: 'ability to drive, read and walk around the house) connect to the complaint of diplopia. The GO-QoL is validated and a Minimal Clinically Important Difference (MCID) was calculated (Terwee *et al*. 2001). Also, this questionnaire is translated in several languages and used in randomized clinical trials (Prummel *et al.* 2004; European Group on Graves *et al.* 2009). Another QoL questionnaire for GO was developed by Fayers and Dolman and composes three questions (TED-QoL). This questionnaire comprises two questions which are indirectly related to diplopia. Comparing the TED-QoL with the **GO-QoL**, it was found that the latter correlated better to the symptoms and signs of strabismus (Fayers & Dolman 2011). A questionnaire used for strabismus patients in general is the ASQ-20 (Hatt *et al.* 2009a,b). This questionnaire

is suitable for both diplopic and non- diplopic patients. Hatt *et al.* found a higher psychosocial score (below threshold) in the non-diplopic patients and higher function scores (below threshold) in the diplopic patients (Hatt *et al.* 2009a). However, comparing this ASQ-20 with the GO-QoL, the latter is a questionnaire spearheaded for patients with Graves' Orbitopathy and is generally accepted and implemented worldwide.

Successful outcome of strabismus surgery in GO-patients is a challenge and some studies express the amount of surgeries as their outcome criteria (Mourits *et al.* 1990; Fells *et al*. 1992; Kraus & Bullock 1993; Yolar *et al.* 2001; Godts *et al.* 2002; Oguz *et al.* 2002) . Recent studies (Sasim *et al.* 2008; Lyons & Rootman 2010; Jellema *et al.* 2012) showed that often **2 strabismus surgeries** are needed to create a useful field of BSV. At the same time, not only the outcome at the end is important, but also the amount of change is relevant. It is calculated as the difference between the post- and preoperative score of the field of BSV or QoL questionnaire. To define success, this gain in score can also be used as success criteria.

We conclude that several criteria for the definition of success criteria in GO patients undergoing strabismus surgery are already available in the literature, but one single reproducible and easy manageable system including all essential parts does not exist. Based on the discussion about the field of BSV, amount of surgeries and QoL questionnaires (both visual function and appearance) above, we suggest the following to define success of strabismus surgery in GO patients (Fig. 2):

(1) Measurement of the field of BSV with the Goldmann perimeter with the score system of Sullivan *et al.* (Sullivan *et al.* 1992) after one or two surgeries including the improvement per surgery.
(2) Quality of life questionnaire as developed and implemented by (Terwee *et al.* 1998) comprising both the visual function and appearance questions and after one or two surgeries including the change per surgery.

With this proposal primary outcome measurements can be quantitatively recorded from the field of BSV, the GO-QOL visual function and the GO-QoL appearance questionnaire. Changes over time in the field of BSV can also be used together with the other available tools like CAS score, Hertel measurement, ductions, eye position, etcetera, to evaluate if GO is still active or to plan surgery. We hope to have produced a practical and useful score system for both clinical and scientific use to create a foundation for future studies including the ability to compare outcomes between studies.

A: Score system for the field of binocular single vision (BSV) measured with the Goldmann perimeter (Sullivan *et al.* 1992). Each segment is scored if the central dot is within the field of BSV.

First surgery

Preoperative score (Pre-score) __ __ __ __ __ __ points = %

Postoperative score (Post-score) __ __ __ __ __ __ points = %

Change (Post-Pre score) __ __ __ __ __ __ points = %

Second surgery

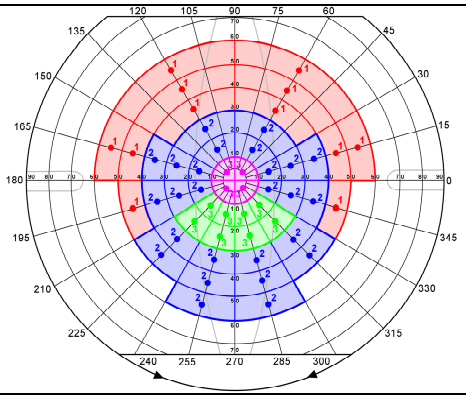
Preoperative score (Pre-score) __ __ __ __ __ __ points = %

Postoperative score (Post-score) __ __ __ __ __ __ points = %

Change (Post-Pre score) __ __ __ __ __ __ points = %

Final Outcome score BSV: __ __ __ __ __ __ points = %

Permanent prism glasses are accepted



B: Questions about quality of life in Graves' Orbitopathy (adapted from Terwee, 2000).

VISUAL FUNCTIONING

The following questions deal specifically with your thyroid eye disease. Please focus on the past week while answering these questions. During the past week, to what extent were you limited in carrying out the following activities, because of your thyroid eye disease (with your (prism) glasses)? Tick the box that matches your answer. The boxes correspond with the answers above them. Please tick only one box for each question.

		Yes, seriously limited	Yes, a little limited	No, not at all limited
1. Bicycling	[never learned to ride a bike O]	O	O	O
2. Driving	[no driver's licence O]	O	O	O
3. Moving around the house		O	O	O
4. Walking outdoors		O	O	O
5. Reading		O	O	O
6. Watching T.V.		O	O	O
7. Hobby or pastime i.e.....		O	O	O
8. During the past week, did you feel hindered from something that you wanted to do because of your thyroid eye disease?		O	O	O

APPEARANCE

The following questions deal with your thyroid eye disease in general

	Yes, very much so	Yes, a little	No, not at all
9. Do you feel that your appearance has changed because of your thyroid eye disease?	O	O	O
10. Do you feel that you are stared at in the streets because of your thyroid eye disease?	O	O	O
11. Do you feel that people react unpleasantly because of your thyroid eye disease?	O	O	O
12. Do you feel that your thyroid eye disease has an influence on your self-confidence?	O	O	O
13. Do you feel socially isolated because of your thyroid eye disease?	O	O	O
14. Do you feel that your thyroid eye disease has an influence on making friends?	O	O	O
15. Do you feel that you appear less often on photos than before because of your thyroid eye disease?	O	O	O
16. Do you try to mask changes in appearance caused by your thyroid eye disease?	O	O	O

All GO-QoL questions are scored as `severely limited' (one point), `a little limited' (two points), or `not limited at all' (three points). The questions 1 – 8 (visual functioning) and questions 9 – 16 (appearance) are added up to two raw scores from 8 to 24 points, and then transformed to two total scores from 0 to 100 by the following formula: total score = ((raw score – 8)/16 x 100). For both total scores holds that higher scores indicate better QoL. For questions 1 and 2, the answers `no drivers' license' or `never learned to ride a bike' can be scored as a missing value. When there are missing values for some items, total scores are calculated for the remaining completed items. The transformation is then adjusted to: total score = ((raw score – *)/ (2 x *) x 100) where * is the number of completed items (Terwee *et al*., 2001).

First surgery		
Preoperative score (Pre-score)	VF __ __ __ __ __ points = %	AP__ __ __ __ __ points = %
Postoperative score (Post-score)	VF __ __ __ __ __ points = %	AP__ __ __ __ __ points = %
Change (Post-Pre score)	VF __ __ __ __ __ points = %	AP__ __ __ __ __ points = %
Second surgery		
Preoperative score (Pre-score)	VF __ __ __ __ __ points = %	AP__ __ __ __ __ points = %
Postoperative score (Post-score)	VF __ __ __ __ __ points = %	AP__ __ __ __ __ points = %
Change (Post-Pre score)	VF __ __ __ __ __ points = %	AP__ __ __ __ __ points = %
Final Outcome score QoL:	VF __ __ __ __ __ points = %	AP__ __ __ __ __ points = %

Permanent prism glasses are accepted. *VF* =visual functioning questions / *AP* = appearance questions

Figure 2. Proposal of success criteria for strabismus surgery in Graves' Orbitopathy patients.

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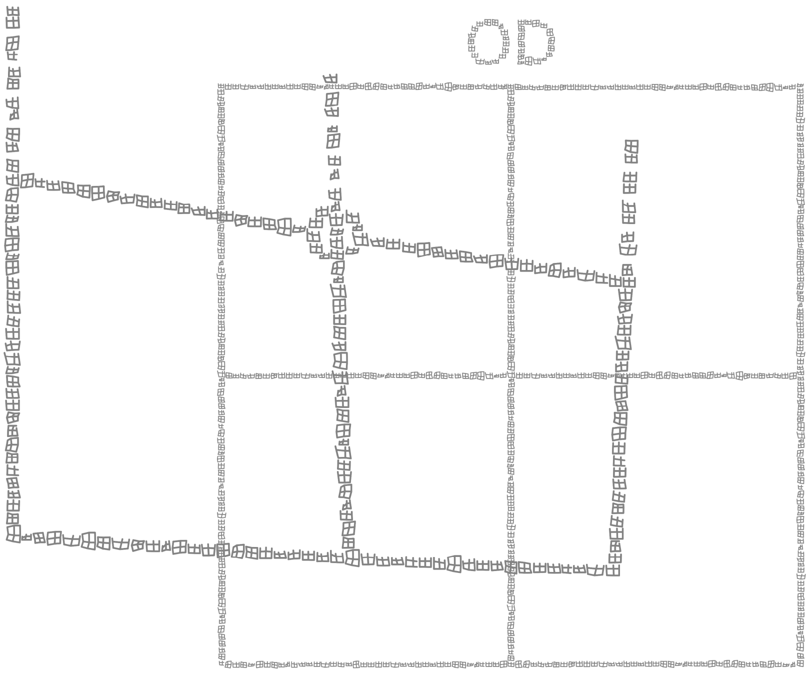

CHAPTER 7

QUALITY OF LIFE IMPROVES AFTER STRABISMUS SURGERY IN PATIENTS WITH GRAVES' ORBITOPATHY

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ABSTRACT

Objective: To evaluate the influence of strabismus surgery on quality of life (QoL) in Graves' Orbitopathy (GO)-patients.

Design: Prospective study of case series

Methods: Consecutive GO-patients who were scheduled for their first strabismus surgery were included into the study. Patients completed the GO Quality of Life questionnaire (GO-QoL) within 3 months before surgery and 2 – 4 months after surgery. A complete orthoptic examination, including the field of binocular single vision (BSV), was performed. Clinically relevant response (CRR) of the QoL was also evaluated.

Results: In this study, 28 patients were included. The GO-QoL score for visual functioning was 46.3±24.2 before surgery and 65.7±30.5 after surgery (p = 0.009). The GO-QoL score for appearance changed from 60.6±25.9 to 69.5±24.2 (p = 0.005). After surgery, the field of BSV increased from 24.3±34.8 to 68.5±36.0 points (p = 0.000). A weak correlation was found between the field of BSV and the visual functioning score after surgery (r = 0.417;p = 0.034). CRR was found in 20 (71%) of the patients. Those with a CRR showed a larger field of BSV (p = 0.002) and better GO-QoL scores (p = 0.008).

Conclusions: GO-QoL score increases significantly for both visual functioning and appearance after the first strabismus surgery in GO-patients, showing the highest improvement for the visual functioning questions. Both the GO-QoL and field of BSV outcome correlate well with the CRR.

INTRODUCTION

At least 40% of patients with Graves' Orbitopathy (GO) suffer from diplopia, which severely interferes with the activities in daily life like working, driving a car or reading[1-4]. To assess the impact of the disease on functioning and appearance, the GO quality of life (QoL) questionnaire was developed in Dutch and English, validated and translated into six other languages (www.eugogo.eu)[1-5]. For both functioning and appearance, a total of 100 points can be scored. Terwee *et al.* (2001)[6] studied the effect of different surgical treatments on GO-QoL outcome and concluded that for strabismus surgery a minimum of 6 points of change has to be considered as minimal important change. However, to our knowledge, this minimum clinically important difference was not confirmed by other studies.

The importance of QoL in evaluating the outcome of treatment has been extended by the EUGOGO group and the Amsterdam declaration[7;8]. Similarly, the goal of the present study is to quantify the QoL before and after strabismus surgery in GO-patients. Approximately 170 new GO-patients are referred to our hospital each year and about 50 (29%) patients require strabismus surgery. This percentage is almost comparable to the numbers assessed in a previous study and a comparable setting[1]. Improvement of QoL for the functional part can be established by creating the largest possible field of binocular single vision (BSV)[9]. In the literature, this measurement is scarcely used as outcome criteria[10-14]. However, in the clinical setting, this instrument is the best available equipment for testing BSV in directions other than the primary position. The purpose of this study is to evaluate the effect of strabismus surgery on the QoL and to investigate the correlation between the GO-QoL and the field of BSV.

SUBJECTS AND METHODS

The study was conducted according to the principles of the Declaration of Helsinki (seventh edition, October 2008, Seoul) and in accordance with the Medical Research Involving Human Subjects Act (WMO).This research did not receive any specific grant from any funding agency in the public, commercial or not-for-profit sector. Our local ethical committee reviewed the research protocol. No approval was needed, because all interventions are normally carried out within the daily routine. Between December 2011 and September 2012, all consecutive GO-patients (clinically and biochemically euthyroid) in our tertiary referral center who

needed a first strabismus surgery for diplopia were asked to participate into the study. Patients with pre-existent strabismus, suppression and/or vision < 0.2 in one or both eyes were excluded. An informed consent form was signed by patients who could be included. Data regarding, gender, date of first diagnosis of GO, prior treatment for their thyroid and eye disease and diplopia complaints before the strabismus operation were recorded. A full orthoptic exam was performed within 3 months before and 2 – 4 months after surgery. This examination included the following: prism covertest at near (30 cm) and distance (5 m), cyclodeviation on 2½ m using the Maddoxscreen and the cycloforometer of Francheshetti[15], measurement of ductions by a motilitymeter[16], eye position measured in 9 directions of gaze with the Maddoxglass and Maddoxscreen (Amsterdam motility scheme) and the field of BSV at 2½ m with help of the Maddoxscreen[17]. A stable orthoptic examination during the last 3 months was part of the inclusion criteria. The choice of surgery procedure was based on the full orthoptic exam[17]. There were no restrictions about the type of surgical procedure. Patients were operated by three orbital surgeons (RK, PS and MM).

Patients completed both subscales within the GO-QoL; the visual functioning and the appearance questions[2]. Questionnaires were self-administered, without supervision, following verbal and written instructions.

Table 1. Modified diplopia / BSV score sheet (18). Diplopia is scored in all 13 standardized positions by analyzing the field of BSV. Total score ranges from 0 (constant diplopia everywhere) to 25 (no diplopia). The score can be multiplied by 4 to give a value between 0 and 100 if this is necessary for comparison with other instruments.

Gaze position using the Maddox cross	**Score of BSV (points)**	**Score**
primary position	6	
up 5°	1	
up 10°	1	
up15°	1	
up 30°	1	
down 10°	2	
down 30°	3	
right 10°	2	
right 20°	2	
right 30°	1	
left 10°	2	
left 20°	2	
left 30°	1	
	Total	

BSV = binocular single vision

All the questions in the GO-QoL were scored as `severely limited' (one point), `a little limited' (two points), or `not limited at all' (three points). The questions 1 – 8 and questions 9 – 16 were added up to two raw scores from 8 to 24 points, and then transformed to two total scores from 0 to 100 by the following formula: total score = ((raw score – 8)/16 x 100). For both total scores holds that higher scores indicate better QoL. For questions 1 and 2, the answers `no drivers' license' or `never learned to ride a bike' were scored as a missing value. When there were missing values for some items, total scores were calculated for the remaining completed items. The transformation was then adjusted to: total score = ((raw score – *)/ (2 x *) x 100) where * is the number of completed items[6].

The outcome of the field of BSV was scored with help of a modified score system for diplopia by Holmes *et al.* (2005)[18](Table 1). The original system is a subjective score system containing the questions about double vision during “reading” (4 points) and in “any position” (1 point). Also, the question if a person can get rid of the double vision (-1 point) is part of the score list. Those 3 questions were deleted and gaze position up 5°, right 20° and left 20° were added. Score points were reformatted and the score system was objectively used.

Two orthoptists (HMJ and EMT) independently defined the clinical relevant response (CRR) in each patient. Patients who showed clinical sufficient improvement on the Amsterdam motility scheme were called responders.

Statistical analyses were done with help of SPPS 19.0 (Statistical Package for the Social Sciences, Version 19.0, Chicago, Illinois, USA). Each variable was verified for normal distribution with help of the Kolmogorov-Smirnov test. If the data met the requirements for normal distribution, parametric tests were applied. If not, non-parametric tests were used. To uncover the main and interaction effects of categorical independent variables on an interval dependent variable ANOVA was used.

RESULTS

In this study, 28 patients were included, and 21 patients were excluded because 13 of them needed a reoperation, two had suppression and thus no diplopia complaints and for six of them the data were incomplete. Of the included patients, 8 were male (29%) and 20 were female (71%). Mean age was 54.5±11.2 year. All general data can be found in Table 2. The type of surgery is listed in Table 3.

Table 2. General data		
Gender	8	male
	20	female
Age	54.5	±11.2
Diagnosis of GO	36.5	±37.9 [7 – 216 months]
Prior treatment GTD	I 131	4
	Thyriodectomy	1
	Anti thyroid drugs	24
Prior treatment GO*	Lubricants	11
	Selenium	2
	Steroids	2
	Radiotherapy	3
	Other immunosuppressive treatment	8
	Decompression	16
Diplopia complaints	Intermittent diplopia	6
	Gaze dependent diplopia	12
	Constant diplopia	9
	Abnormal head posture	1

GO = Graves' Orbitopathy; *GTD* = Graves thyroid disease; * more therapies per patients possible

Table 3. Surgical procedure	
	n (%)
Inferior rectus recession unilateral	6 (19)
Inferior rectus recession bilateral	11 (36)
Medial rectus recession unilateral	4 (13)
Medial rectus recession bilateral	5 (16)
Superior rectus recession	3 (10)
Superior oblique recession	2 (6)

The field of BSV changed from 24±35 points to 68±37 points (p = 0.000) (Fig. 1). The GO-QoL for visual functioning before surgery was 46±26 points and increased to 66±31 points after surgery (p = 0.009). The questions about appearance scored 61±26 points before and 71±22 points after surgery (p = 0.005)(Fig. 2). A decompression that was performed earlier did not influence the outcome (p = 0.224).

Between the diplopia groups (e.g. intermittent, gaze dependent, constant or abnormal head posture), no different outcome in the score of the preoperative field of BSV (ANOVA p = 0.111) or the score of the GO-QoL for visual functioning (p = 0.430) was found.

A weak correlation was found between the field of BSV and the GO-QoL for the visual functioning score after surgery (r = 0.417; p = 0.034)(Fig. 3), but not for appearance (r = 0.180; p = 0.374).

CRR was found in 20 (71%) patients. The responders showed significant larger fields of BSV (p = 0.002) after surgery and better outcome on GO-QoL for visual functioning (p = 0.008) compared to the non-responders.

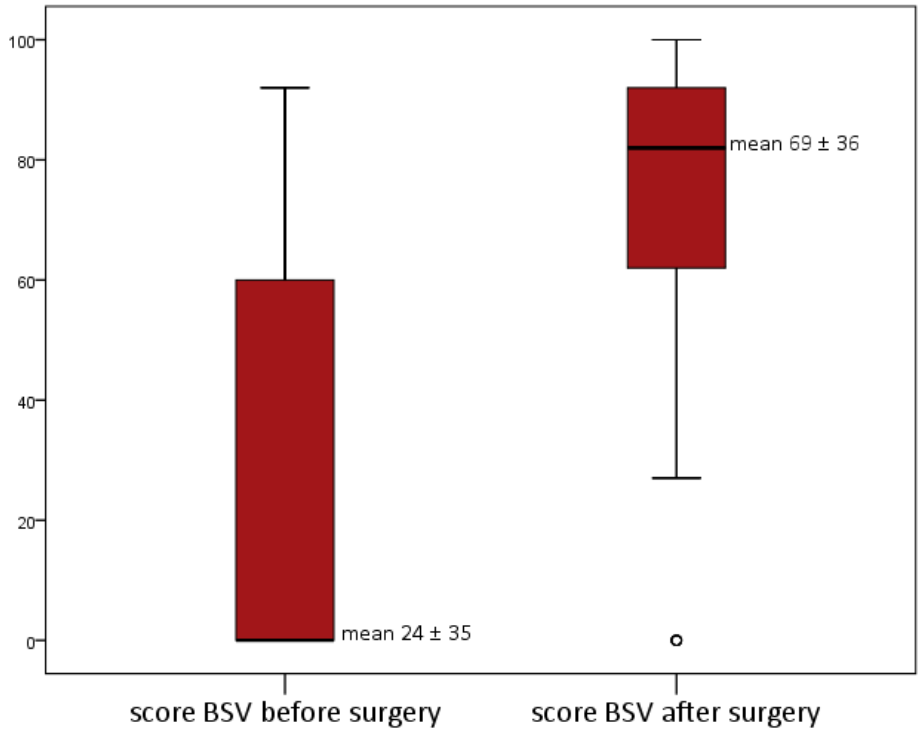

Figure 1. The score of the field of binocular single vision before surgery (left boxplot) and after surgery (right boxplot)(p = 0.000).

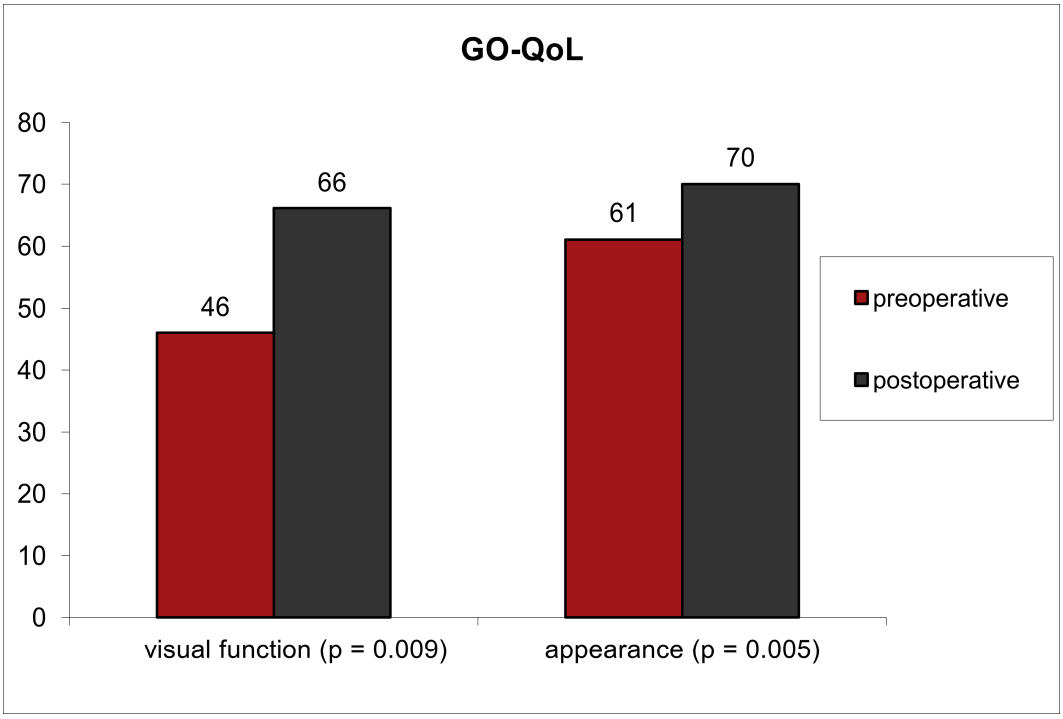

Figure 2. GO-QoL questionnaire score for visual functioning (left two bars) and appearance (right two bars) before and after surgery.

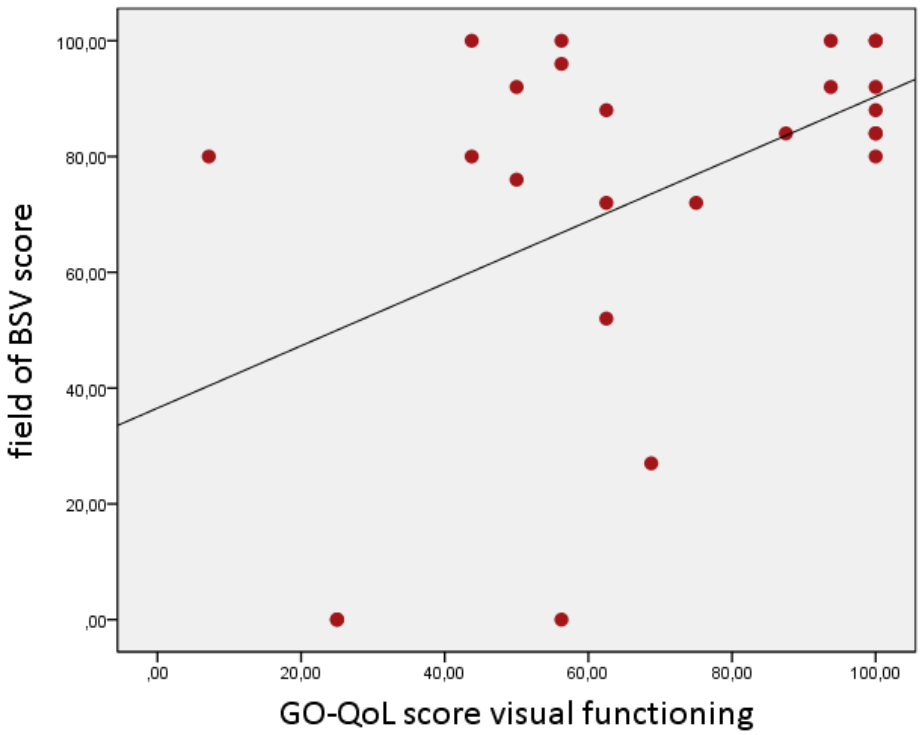

Figure 3. Correlation between the score of the field of BSV and the score for visual functioning of the GO-QoL after surgery (r = 0.417; p = 0.034).

DISCUSSION

The present study is, to the best of our knowledge and inspired by the Amsterdam declaration, the first prospective study focusing on the QoL after strabismus surgery in GO-patients. After this strabismus surgery, a significant improvement of the GO-QoL score for both visual functioning and appearance occurs. Both the field of BSV and GO-QoL score after surgery are significantly higher in the responders group.

In contrast to a previous study, we found a significant higher GO-QoL score for the visual functioning after surgery (mean improvement 19.4±34.5 in the present study compared to mean 2.8±25.4 in the study of Terwee *et al.* (2001))[6]. The improvement is also higher as the mentioned 6 points of minimal clinically important difference(MCID)[6]. The hospital setting, duration of the GO, the mean age, sex distribution and number of participating patients (n = 31 vs present study, n = 28) are comparable in both the studies. The improvement of the subjective score we found in this study is more in line with what clinicians would expect. Terwee *et al.* could not clearly explain why the improvement of the subjective score in het study was rather modest[6]. Explanations for the differences of results between her and our studies are the following: i) Terwee *et al.* sent questionnaires 3 months after the operation

via mail, while our questionnaires were embedded in the treatment protocol; ii) As the questionnaire was embedded in the protocol, the response rate was 100% compared to 80% in Terwee's study. The 20% difference may be because of the non-responders who were asymptomatic, which had a negative influence on the total score; iii) For the last five years strabismus surgery in GO-patients has been a focus of research in our institute, which might have improved the outcome of strabismus surgery and thus the outcome of the subjective evaluation. To ratify this, the CCR rate in the study of Terwee *et al.* was 50% as we found 71% of patients responding to the strabismus surgery; iiii) In the present study only primary strabismus surgeries were included, in the study of Terwee *et al.* this item is not specified. This could also clarify the difference between the visual functioning score before surgery which is lower at baseline in the present study.

Terwee *et al.* (2001)[6] suggested that the surgery is part of a larger surgery plan and that this minor invasive strabismus surgery does not change the outcome significantly. However, in our study group 16 patients underwent decompression surgery which counts as a major invasive surgery. GO-QoL was not different between the group with or without prior decompression surgery (p = 0.224).

In general, one should take into account that changes of the GO-QoL score can be influenced by the side-effects, costs and possible available alternative treatments like prism therapy. Also, total score changes in the lower end of the score scale may be less important than changes to the higher end of the score[6]. However, in contrast to the results of Terwee *et al.* (2001) we had a lower baseline GO-QoL score (due to stricter inclusion criteria) and despite that there was a higher treatment effect. The side effect aspect may explain the weak correlation found between the GO-QoL for visual functioning and the field of BSV after surgery. The field of BSV is a clinical measurement in a setting wherein the head of the patients is being moved slowly which is different from movements in daily life (question 4 of the visual functioning questionnaire).

Another aspect which can influence the outcome of the GO-QoL is the regression to the mean phenomenon[19]. However, by merely asking the patients to fill in the GO-QoL one time before and one time after the surgery, we cannot distinguish between the influence of the surgery and that of the regression of the mean.

It would be interesting to see if the GO-QoL outcome also applies to the results 6 – 12 months after surgery for orthoptic stability, as was found in our previous results[20 13]. Hatt *et*

al. (2012)[21] found no changes in the health related quality of life questionnaire (HR-QoL) one year after surgery in both the diplopic and non-diplopic patients following successful strabismus surgery. A future study may reveal if this is also applicable for the GO-patient group.

We are aware of the fact that we evaluated the GO-QoL and BSV scores after one strabismus surgery and that for many patients multiple strabismus surgeries are needed[20;22;23], and therefore undervalue the final outcome. For that reason, a future study will focus on the effect after 2 surgeries.

In conclusion, the GO-QoL and the field of BSV outcome both add in their own way to the information for the clinician regarding CRR in GO-patients who undergo strabismus surgery.

DECLARATION OF INTEREST

All authors state that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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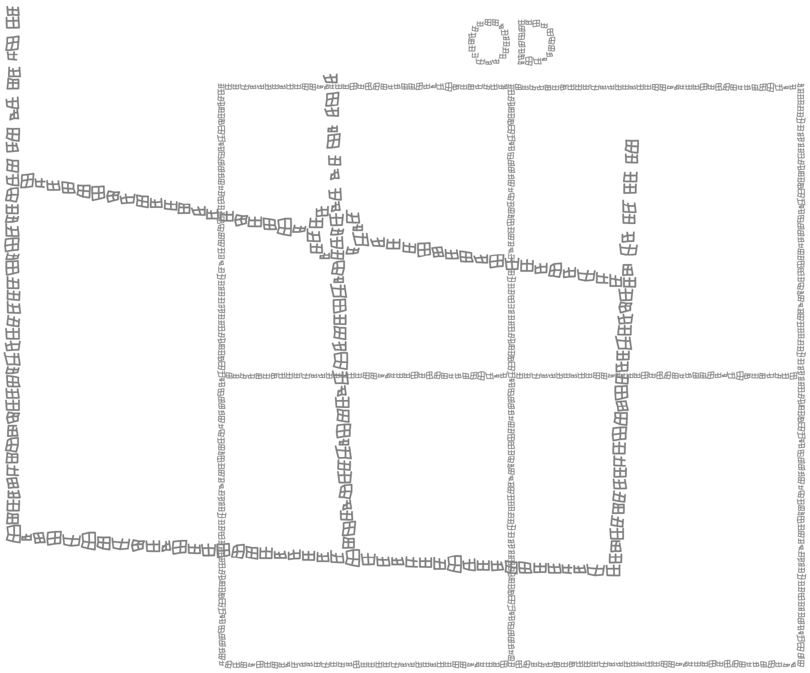

CHAPTER 8

OBJECTIVE AND SUBJECTIVE OUTCOMES OF STRABISMUS SURGERY OF IN GRAVES' ORBITOPATHY: A PROSPECTIVE MULTICENTER STUDY

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ABSTRACT

Objective: To assess the change and interrelationship of the field of binocular single vision (BSV) and the quality of life (QoL), tested with two different tools, after one or two strabismus surgeries in patients with Graves' Orbitopathy (GO).

Design: Prospective, observational, multicenter cohort study

Participants: Consecutive patients with GO scheduled for their first strabismus surgery, recruited from 5 clinical centers specializing in the treatment of GO.

Methods: One week pre-operatively and 3 months after the last operation, a full ophthalmic and orthoptic exam was performed. Change in field of BSV, GO-QoL and Thyroid Eye Disease-QoL was recorded.

Results: 59 met all the eligibility criteria of whom 15 (25%) needed two strabismus operations. In 89% of cases, a muscle recession was performed. The median (interquartile range) preoperative score of the field of BSV was 0 (0 – 0), which improved to 73 (53 – 85) after the correction(s) ($p < 0.001$). A moderate correlation was found between the score of the field of BSV and the GO-QoL visual functioning (VF) questionnaires ($r = 0.485$; $p < 0.001$). Both the GO-QoL and TED QoL for VF and appearance (AP) showed significantly higher scores postoperatively ($p < 0.001$). Smoking ($p = 0.74$), prior orbital decompression surgery ($p = 0.43$) or time of onset of the GO ($p = 0.13$) did not influence the outcome.

Conclusions: Strabismus surgery significantly expands the field of BSV and the quality of life. In a quarter of the patients, an additional strabismus surgery is required. No parameters were found which influenced the outcome.

INTRODUCTION

Motility impairment causing diplopia and/or head turn/tilt is a frequent manifestation of Graves' Orbitopathy (GO) that seriously affects quality of life and has profound socio-economic consequences [1-3]. Orbital decompression may be associated with a worsening of motility in 2 – 66% of cases [4-6]. Approximately 20% of GO-patients seen in a tertiary referral center are not adequately treated with prisms alone and require strabismus surgery[7]. Oftentimes GO, presents with both a horizontal and vertical restriction of ocular motility, occasionally with a torsional component. Therefore, more than one correction may be required to reach the desired outcome[8 9] – an adequate field of binocular single vision (BSV) in primary and downgaze. The field of BSV and the Quality of Life (QoL) are among recently published criteria defining successful treatment[10], in which the patient reported outcome is complementary to the clinically measured outcome[11]. At this time, two specific questionnaires for GO are available which have been tested under different circumstances [12-14]. To-date, the outcome of different techniques of strabismus surgery in GO has not been investigated in a systematic way using strict criteria and QoL measurements. The aim of this study is to assess that outcome objectively using success criteria for the field of BSV as proposed by Jellema *et al.*[10] and subjectively with the use of the GO-QoL and Thyroid Eye Disease (TED)-QoL questionnaires.

METHODS

Design and patients

We conducted a prospective observational cohort study and recruited patients from 5 tertiary referral centers specializing in orbital surgery in the United States, Canada, Belgium and the Netherlands. The study was conducted according to the principles of the Declaration of Helsinki (seventh edition, October 2008, Seoul). Each center obtained Institutional Review Board or Ethics Committee approval. Patients were prospectively recruited over a period of 12 months. Individuals diagnosed with GO without prior strabismus surgery and candidates for surgical correction were eligible for the study if they met the inclusion criteria. These criteria included: clinically and biochemically euthyroid for at least three months; a stable orthoptic examination for at least three months e.g. no greater than 5 prism diopters change in primary position and no greater than an 8° change in duction[15-17]. Patients with

suppression, previously diagnosed and/or treated strabismus not related to the thyroid, and/or with best corrected visual acuity (BCVA) less than 20/100 in one or both eyes were excluded. Written informed consent was obtained from all patients. At the initial visit, medical and ophthalmic history was taken. Data regarding gender, race, age at surgery, date of first diagnosis of GO, prior treatment for the Graves thyroid disease (GTD) and GO, smoking status (current smoking or stopped < 1 year ago) and history of diplopia were recorded. The study collected data from the ophthalmic and orthoptic exams that were performed one week preoperatively, and 3 months postoperatively. At both study visits, the patients were asked to complete the GO-QoL and TED-QoL questionnaires. If a second procedure was required, the 1-week preoperative visit was scheduled at least 3 months after the first procedure.

Procedures

The following measurements were performed 1 week before and 3 months after surgery: distance BCVA; interpalpebral distance including the Marginal Reflex Distance 2 (MRD 2), ;abnormal head posture recorded as 'yes' or 'no'; the test was performed prior to the alternating Prism Cover Test (PCT) at near (30 cm) and distance (5 – 6 m);ductions measured with the modified motility meter[16] or Goldmann perimeter[18] in abduction, adduction, elevation and depression; cyclodeviation tested with synoptophore, Maddox Double Rod or cyclophorometer of Franceschetti (torsion in the primary position and 25° up- and downgaze was recorded); the field of BSV with Goldmann perimeter using a III4e light target[19] was scored as suggested by Sullivan *et al.* [20] on a score-sheet of 0 – 100%; GO-QoL questionnaire designed by Terwee *et al.*[21] and TED-QoL by Fayers and Dolman were administered[13].

All GO-QoL questions were scored as `severely limited' (one point), `a little limited' (two points), or `not limited at all' (three points). The questions 1 – 8 for visual functioning (VF) and questions 9 – 16 for appearance (AP) were summed to produce two raw scores from 8 to 24 points, and then transformed to two total scores from 0 to 100 by the following formula: total score = [(raw score – 8)/16 x 100]. In both cases higher total scores indicate better QoL. When there were missing values, total scores were calculated for the remaining completed items. The transformation was then adjusted to: total score =[(raw score – *)/ (2x*) x 100] where * is the number of completed items[21].

The score of the TED-QoL (0 – 10) was multiplied by 10 and then subtracted from 100, which gave a quality of life score as a percentage. Each of the three variables (QoL overall, ability to function (VF), change in appearance (AP)) was reported independently.

The surgical procedure was determined by the surgeon and the orthoptist. The surgeon was free to choose the approach and technique. Surgery was performed under local or general anaesthesia. Detailed data were recorded about the procedure and complications.

Statistical analysis

Statistical analysis was performed with software package SPSS 19.0. Both categorical and continuous data were analysed quantitatively with the appropriate statistical tests.

Changes between baseline and 3 months after treatment were tested statistically using a paired samples t-test or Wilcoxon Signed Ranks test. To detect differences between patient subgroups the independent samples t-test or Mann-Whitney test was used. Correlations were analysed with the Spearman Rang correlation test. The influences of prior treatment on outcome were investigated with linear regression analysis.

RESULTS

At screening, 77 patients were found eligible for the study. Two patients withdrew consent and 4 patients were excluded due to changes in motility or suppression. A total of 12 patients were lost to follow up. The remaining 59 patients with complete data at baseline and exit study visits were analyzed (Fig. 1). The majority of patients were female (66%) and the mean (±SD) age at the time of the operation was 57±11.5 years. Table 1 shows the patient population baseline characteristics. Of the included patients, 15 (25%) required two strabismus procedures.

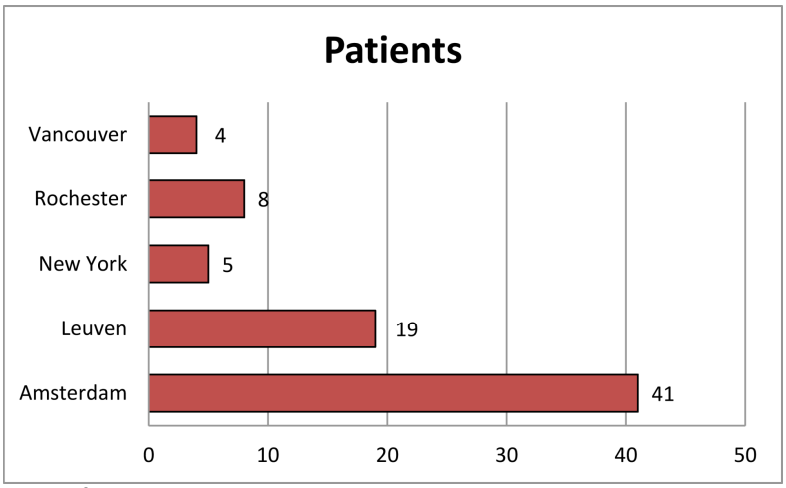


Figure 1. Recruited patients from participating centers.

Table 1. General data		
Gender	Male	20
	Female	39
Age	57	± 11.5 [35 – 81 years]
Race	Caucasian	55
	Asian	4
Diagnosis of GO	26	± 18 [6 – 98 months]
Prior treatment GTD*	I 131	17
	Thyroidectomy	4
	Anti-thyroid drugs	40
	None	11
Prior treatment GO*	Lubricants	37
	Botulinum toxin	2
	Selenium	21
	Steroids (oral / iv)	19
	Radiotherapy	17
	Other immunosuppressive treatment	10
	Decompression	40
	None	4
Diplopia complaints	Intermittent diplopia	7
	Gaze dependent diplopia	4
	Constant diplopia	48
	Abnormal head tilt	9

GO = Graves' Orbitopathy; *GTD* = Graves thyroid disease; * more therapies per patients possible

Table 2. Surgical procedure		
muscle	n	(%)
Inferior rectus	49	(36)
bilateral	12	(9 recession, 1 resection)
Medial rectus	66	(49)
Lateral rectus	7	(5)
Superior rectus	10	(7)
bilateral	1	
Superior oblique	2	(1.5)
Inferior oblique	2	(1.5)
procedure		
Recession	123	(79)
Resection	7	(4)
Loop	4	(3)
Recession + loop	1	(0.5)
Readvancement	3	(2)
Adjustable	1	(0.5)
Transposition (nasal or temporal)	8	(5)
inferior rectus	6	
superior rectus	2	
Tenon's recession (Zoumalan *et al.*, 2011)	3	(2)
Muscle elongation (Esser *et al.*, 2011)	5	(3)

Surgical procedure

Most procedures were performed on the inferior rectus and medial rectus muscles (85%). Muscle recession was the first choice of treatment (89%), followed by resection (5%) (in 2 centers). The latter procedure was carried out as second surgery in 3 out of 4 cases. Of all 15 patients who needed a second surgery, in 13 patients it concerned an additional procedure of the initial deviation. Two 2 (3%) patients needed a second surgery due to an overcorrection (consecutive deviation) after the first surgery. In some cases, muscle lengthening was performed with Tutopatch[22] or fascia lata. This technique was used twice on the medial rectus muscle, twice on the inferior rectus muscle and ones at the superior rectus muscle. A muscle transposition was performed in 8 cases and a Tenon recession in 3 cases[23]. Local anesthesia was used in 17% of the patients. No complications were recorded. All surgical procedures are summarized in Table 2.

Strabismus surgery did not significantly influence the amount of proptosis (preoperative 18.7±4.1 and postoperative 18.3±4.1; p = 0.07) nor the MRD 2 in cases were the inferior rectus muscle was recessed (preoperative 4.4±2.0 and postoperative 4 p = 0.38).

Strabismus

Table 3 illustrates the degree of strabismus. Both horizontal and vertical strabismus changed significantly (p < 0.001) after surgery with a mean postoperative angle in straight gaze of < 5 prism diopters. The mean initial size of vertical strabismus was smaller compared to the horizontal deviation (p < 0.001). No difference was found in the initial amplitude of vertical strabismus between patients who needed or two surgeries (p = 0.35). We did demonstrate the difference to be true for the initial amount of horizontal strabismus i.e. the larger the horizontal deviation, the greater the chance of a second surgery (p = 0.04).

Table 3. Pre- and postoperative prism covertest measurements at 5 / 6 m

	< 1 week preoperatively ^ ± SD	**3 months postoperatively ^ ± SD**	**p-value***
Horizontal 1th	17 ± 18	2 ± 5	0.000
2nd	13 ± 13	5 ± 8	0.165
total	**15 ± 18**	**2 ± 5**	0.000
Vertical** 1th	13 ±13	2 ± 2	0.000
2nd	4 ± 7	3 ± 3	0.297
total	**13 ± 13**	**2 ± 3**	0.000

1th = first surgery / 2nd = second surgery; Horizontal deviation for patients required horizontal surgery; Vertical deviation of patients required vertical surgery; *paired t-test; **symmetrical vertical muscle surgeries were excluded

Field of BSV

The preoperative score (median (IQR)) of the field of BSV was 0 (0 – 0) and improved to 73 (53 – 85) postoperatively ($p < 0.001$). The preoperative score of the field of BSV was not significantly associated with the number of required surgeries ($p = 0.98$). However, the score of the field of BSV after the first surgery was significantly lower for the group who needed two surgeries 0 (0 – 63) compared to the group who needed one surgery 76 (60 – 86) ($p < 0.001$). After the second surgery, the field of BSV improved to 62 (40 – 76) ($p = 0.05$). The correlation between the postoperative field of BSV and the postoperative GO-QoL VF was moderate[24] ($r = 0.49$; $p < 0.000$) as was its correlation with the TED-QoL VF ($r = 0.39$; $p = 0.013$).

Quality of life

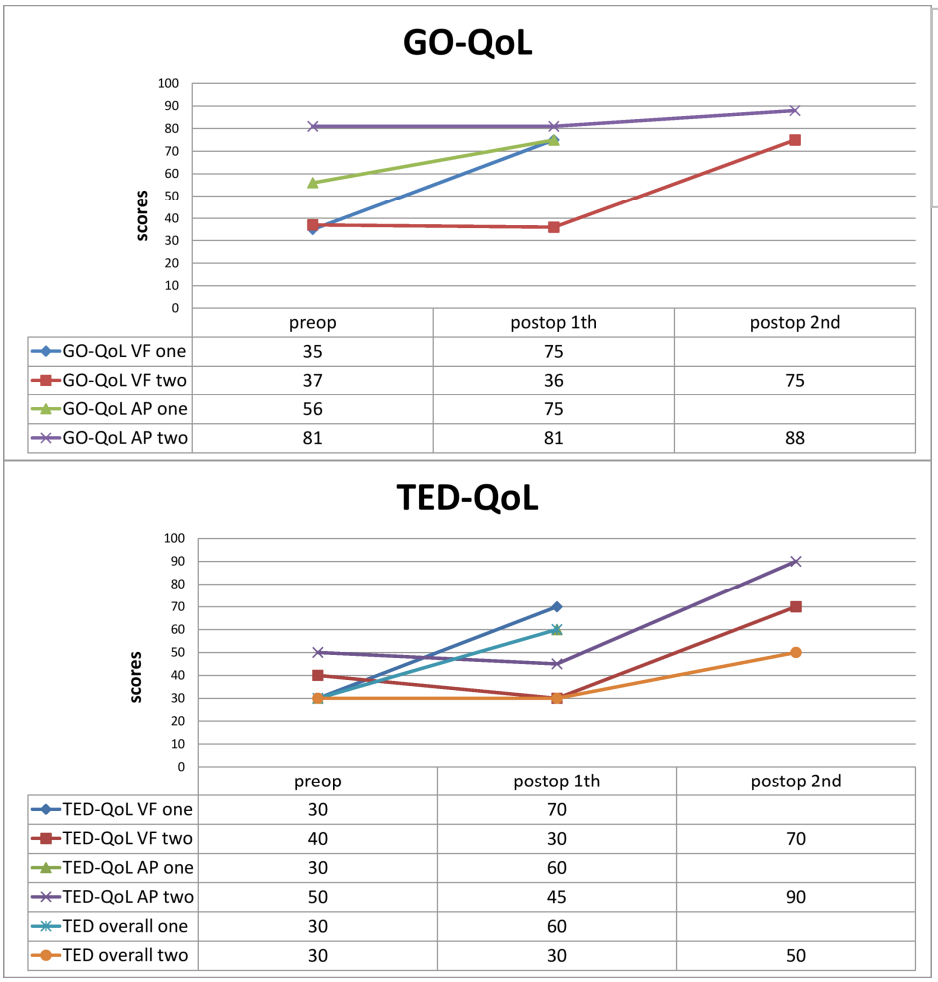
The quality of life as measured by both the GO-QoL and TED-QoL improved significantly after one or two surgeries ($p < 0.001$). No difference was noted between the baseline scores of patients who needed one or two surgical interventions (GO-QoL VF $p = 0.91$; TED-QoL VF $p = 0.20$). No difference was found in the final result of either (both VF and AP). Changes in QoL are visualized in Figure 2.

The median (IQR) GO-QoL VF increased 54 (36 – 90) points and the TED-QoL VF with 40 (30 – 70). The score of QoL was not influenced by gender ($p = 0.71$ GO-QoL VF; $p = 0.34$ GO-QoL AP). The correlation between the change of GO-QoL VF and the duration of the GO ($r = 0.06$; $p = 0.66$) was not statistical significant.

There was a strong[25] and statistically significant correlation between the postoperative GO-QoL VF and the TED-QoL VF ($r = 0.67$; $p < 0.001$) (Fig. 3) and between the postoperative GO-QoL AP and the TED-QoL AP ($r = 0.72$; $p < 0.001$).

Previous treatment

Previous anti-thyroid drugs or I^{131} were not significantly associated with the GO-QoL VF score after strabismus surgery ($p = 0.68$; $p = 0.64$), nor was the time of onset of the disease ($p = 0.13$) neither did smoking ($p = 0.74$). Among patients with a history of decompression surgery, 8 out of 40 (20%) needed a second strabismus surgery compared to 7 out of 19 (37%) patients in the non-decompression group ($p = 0.94$). The previous decompression procedure had no impact on the final outcome of the GO-QoL VF ($p = 0.43$).



	preop	postop 1th	postop 2nd
GO-QoL VF one	35	75	
GO-QoL VF two	37	36	75
GO-QoL AP one	56	75	
GO-QoL AP two	81	81	88

	preop	postop 1th	postop 2nd
TED-QoL VF one	30	70	
TED-QoL VF two	40	30	70
TED-QoL AP one	30	60	
TED-QoL AP two	50	45	90
TED overall one	30	60	
TED overall two	30	30	50

Figure 2. Changes in QoL after one or two surgeries. Only significant differences were found between GO-QoL VF one (75) versus GO-QoL VF two (36) (p = 0.000) and between TED-QoL VF one (70) and TED-QoL VF two (30)(p = 0.004) after the first surgery.

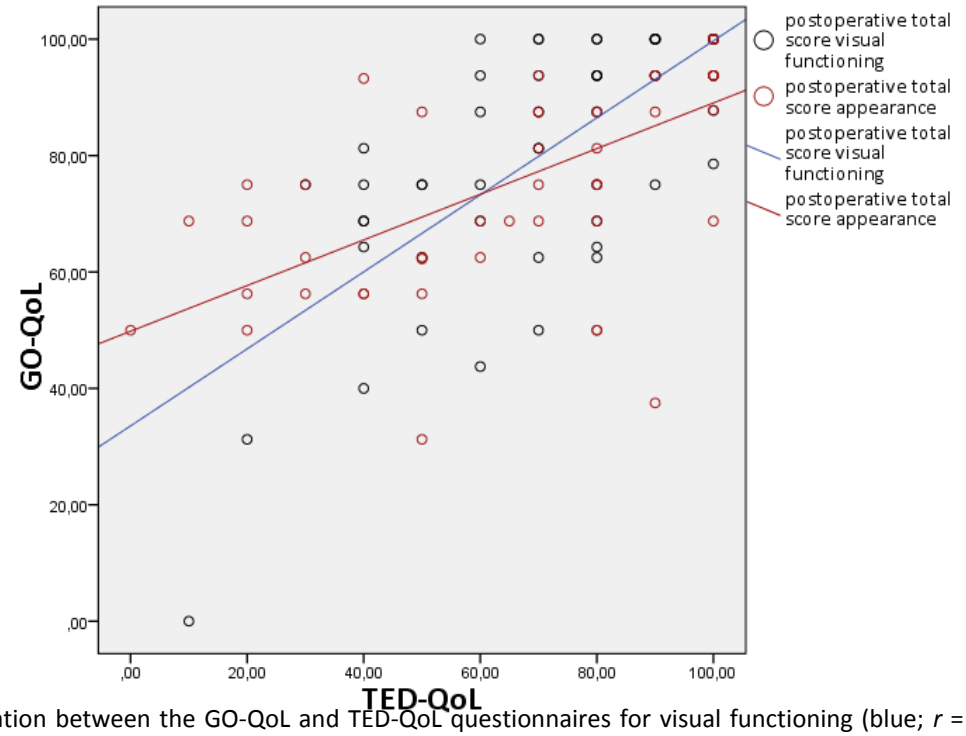


Figure 3. Correlation between the GO-QoL and TED-QoL questionnaires for visual functioning (blue; r = 0.67) and appearance (green; r = 0.72).

DISCUSSION

This multicenter prospective study shows that the field of BSV increases significantly (from median 0% to median 73%) after strabismus surgery in GO-patients. In a quarter of the patients an additional or second procedure is required. Both the GO-QoL and TED-QoL for visual functioning and appearance show significant improvement after strabismus surgery and show high correlation with each other.

Similar to the literature, this study shows that also in our group of surgeons a recession is most frequently performed for patients with GO. Other types of surgery were too small in number to meaningfully compare the outcomes. In a few patients, an elongation was performed as previously described by Esser *et al.* (2011)[22]. Similarly to previous studies [26 27] we found no differences in surgical frequency or outcome of QoL between patients who had had a prior decompression surgery and those who had not.

Inherent to the multicenter design, we encountered some intercontinental differences. The travel distance in the United States of America and Canada did result in a few drop outs. One might wonder whether those patients had poor outcomes and sought care elsewhere and the missing data may have inflated the estimates of success. Another shortcoming could be the lack of objective criteria for a second surgery. However, despite the differences in surgical techniques and measurements across sites and continents, the results of the study have an overwhelming significance, be it in statistical or clinical outcome. Only 2 (3%) patients needed a second surgery due to an overcorrection after the first surgery, an extremely low percentage compared to the literature (2% – 42%)[28 29]. The frequency of an additional surgery in our study (25%) is consistent with the literature (8% – 45%)[27 30-32].

Compared to a pilot study on QoL with comparable age and gender distribution, operated for strabismus after one procedure[12], our cohort showed a higher outcome of the GO-QoL for VF after one surgery (pilot study mean 70; present study median 86). The mean change of outcome of the visual functioning (VF) questionnaire for the GO-QoL in the pilot study was 19 points compared to ≥ 50 points in the present study. The difference can possibly be explained by the contribution of the second procedure (Fig. 2). Additionally, the present study contains a larger cohort (59 compared to 28 in the pilot study), which enhances the analyses power. Moreover, both changes are much higher than the aforementioned 6 points of minimal clinically important difference found in the study of Terwee *et al.*[33]. Several reasons for this high discrepancy are explained in our previous

study (strict inclusion criteria, etc)[12]. As mentioned in that study, the measurement of the field of BSV with Goldmann perimeter does not reflect daily life experiences and can overestimate diplopia[34]. This could lead to a lower correlation between QoL and BSV scores. However, diplopia was only overestimated in patients with fragile fusion or suppression[34], which is not the case in the present population. In the pilot study about QoL and the present one, a moderately strong correlation was seen between the field of BSV and the GO-QoL. Correlation coefficients between objective and subjective outcomes are often small-medium in magnitude. QoL is not only influenced by biological and physiological variables and symptom status, but also by psychological factors, patient values and expectations, social factors, demographics and adaptation to changing health[35]. These factors have been addressed in other studies concerning GO-patients[1]. Because of the numerous factors that may influence QoL, correlations between objective clinical outcomes and QoL are inevitably not very strong. This issue has also been recognized in other areas of ophthalmology, such as in the evaluation of dry eyes[36].

The correlation between the GO-QoL and TED-QoL was good in the present study. Both contribute to clinical practice. For screening purposes and when time is constrained, the TED-QoL is preferred. However, more detailed research about subareas within the visual functioning or appearance topics can be analyzed with the GO-QoL. Future studies can focus on this particular area.

In the present cohort, the mean time between onset of the GO and initial strabismus surgery was 26 months (range 6 – 98 months). With such a long duration of the disease patients may have adapted to their illness by changing the internal standards by which they evaluate their QoL, and /or the values and conceptualization of QoL, i.e., response shift[11 37]. In the present study, we did not find different GO-QoL VF outcomes related to the length of the GO (p = 0.13). In future studies, special attention could be given to this subjective shift.

In conclusion, different surgical techniques are used internationally to gain a maximally functional field of BSV in patients with GO. Both outcome of TED-QoL and GO-QoL significantly improve after one or two strabismus surgeries. While both the objective (field of BSV) and subjective (QoL) outcomes improve in great measure, only a moderate correlation was found between them. This relative discrepancy highlights the need for both to be assessed. Each in their specific way adds to the clinical management of this disease.

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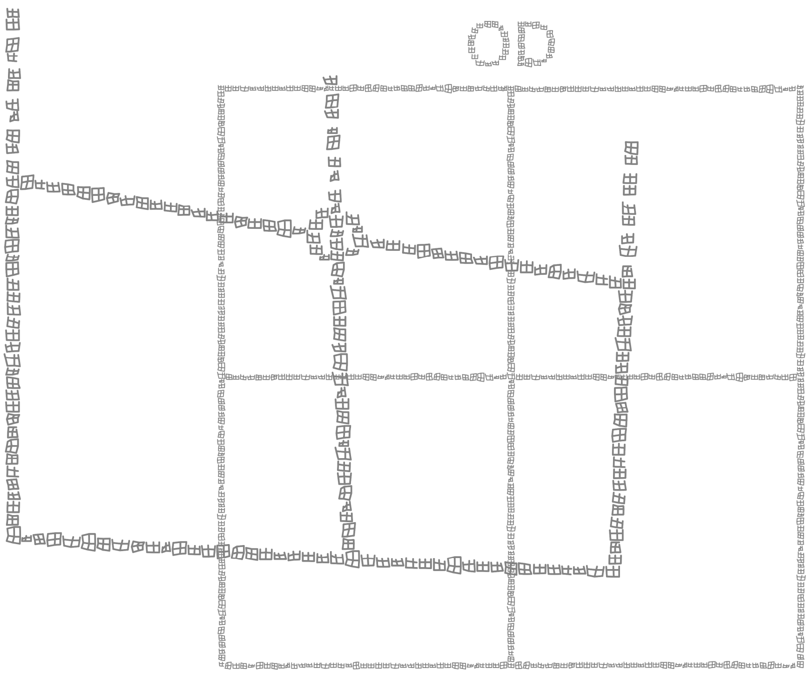
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CHAPTER 9

GENERAL DISCUSSION

GENERAL DISCUSSION

Diplopia is one of the most debilitating expressions of Graves' Orbitopathy (GO) and yet surgical treatment of diplopia has gained little attention in the literature as compared to other surgical treatments of GO such as orbital decompression and eyelid lengthening.

After it became apparent that the nature of diplopia in GO is mechanic rather than paralytic, several different surgical techniques to restore the field of binocular single vision (BSV) were introduced. Even today, it is unclear which technique is best, because comparison of outcome of these surgical techniques is impossible as long as each author uses his or her own outcome parameters. Moreover, even the tools to assess diplopia differ in various countries. For the assessment of ductions, for instance, different devices are used and it is unknown whether the outcomes of these measurements are interchangeable. More importantly, in present times, we are not only interested in objective but especially in subjective outcome parameters. Therefore questionnaires to evaluate the quality of life have been developed and validated. The GO-QoL is such a questionnaire for GO. Up to today these questionnaires have not been systematically applied before and after strabismus surgery.

In this thesis, therefore, we explore these topics in order to provide a better and more contemporary approach to the GO-patient with diplopia.

MEASUREMENTS AND DOSE EFFECT RESPONSE

There are few reports on the measurement of cyclodeviation[1-3]. In GO-patients, cyclodeviation differs in different directions of gaze. For this reason, cyclodeviation in GO-patients has to be measured in secondary gaze directions in order to compose an optimal surgical plan. In **chapter 2**, we compared the outcome of cyclodeviation assessments, measured with the Harms tangent screen, the cycloforometer of Franceschetti and the cyclo measurement in the synoptophore in different gaze directions. A difference of ≤ 2° was found between the Harms tangent screen and the cycloforometer. Comparison of these two devices with the synoptophore revealed significant differences and are not interchangeable. Next, we compaired outcomes of measurements of the Maddox tangent screen, the motility meter and the Goldmann perimeter. We found a difference of ≤ 8° of duction in 92% of the patients comparing the last two devices. Remarkebly, this finding is in complete agreement

with the liturature, defining a change of ≥ 8° as a significant sign of disease activity[4, 5]. When comparing the motility meter and the Goldmann perimeter with the Maddox tangent screen, significant differences were found. We conclude that measurements of the motility meter and the Goldmann perimeter are the only two which are interchangeable. This observation has consequences for the set-up of future multicenter studies. Dolman *et al. (*2015) compared outcome of duction changes by performing the 'best guess', the light reflex and the ruler technique with the Goldmann perimeter, objectively and subjectively. They concluded that the light reflex was as reliable as the Goldmann perimeter, but less time consuming[6]. In our opinion, the light reflex test basically is a semi-quantitative technique and not as accurate as the Goldmann perimeter and the motility meter. This is reflected by the fact that Dolman *et al.* (2012) needed a change of 12° as a significant difference, while with a more accurate approach a change of 8° already appeared to be of clinical relevance. Duction measurement in downgaze is very difficult due to position of the upper eyelid and all studies report the largest variation of motility in downgaze[4, 6, 7]. For future studies, it would be beneficial when an improved measurement for downgaze becomes available.

In chapter 3, 4 and 5, we evaluated our own results of strabismus surgery in GO-patients. **Chapter 3** presents the results of a retrospective case series operated on both inferior recti muscles. Eighteen patients underwent a bilateral inferior rectus recession and 27 an asymmetrical inferior rectus recession. Effects on duction, cyclodeviation and squint angle were observed. The more severe the preoperative elevation impairment proved to be, the more effect of surgery on elevation was found. The mean dose-effect response was 1.7°/mm on increased elevation in the total group. In this study, we found that patients needed at average 2 surgeries to reach an acceptable field of BSV. The excyclodeviation found in primary position prior to the surgery, diminished with a mean of 6°. That amount is significant and can be of influence in planning further surgery.

Not a single postoperative A-pattern was found in our series. This finding was striking, because the existence of an A-pattern is often found after bilateral inferior rectus recession and a topic of discussion in literature[8, 9]. The impaired depression in downgaze is supposed to activate the superior oblique muscle, which then causes an A-pattern[10, 11]. The fact that we did not find an A-pattern in our patients might be explained by our relatively small number and size of depression impairment as compared to the literature.

To prevent an A-pattern, the inferior rectus muscle can be inserted medially during surgery[10, 12], which however might induce incyclodeviation[13, 14]. An A-pattern is also seen when the recession of both inferior recti is combined with a bilateral medial rectus recession. To avoid this, the medial rectus muscle can be shifted upward or the medial rectus muscle recession can be scheduled as a second procedure[15]. In 9 of our patients, a simultaneous medial rectus recession was performed without superior or inferior displacement. An advantage of separate sessions is that the dose-effect response is more predictable[16]. In conclusion, to prevent an A-pattern, it is important to evaluate cyclodeviation and ductions in secondary gaze positions preoperatively.

In **chapter 4** we investigated the effect of another type of strabismus surgery in GO-patients, namely the uni- and bilateral medial rectus recession. We specifically looked for the effect of surgery on horizontal ductions as well as on squint angle. A group of 102 fulfilled the inclusion criteria, of which 78 were operated on both medial recti. We found a smaller dose-effect response in the unilateral group with regard to the esodeviation (1.0°/mm compared to 1.4°/mm in the bilateral group). In total, 3% of the patients were overcorrected and 23% of the patients needed additional horizontal surgery. Especially for the unilateral medial rectus recession, we found a lower dose-effect response compared to that found in the literature[16, 17]. However, no recent and/or prospective studies are available to compare our results. Prospective studies have to be performed to confirm our findings.

Chapter 5 evaluates the inferior rectus muscle (IR) surgery and the combined inferior rectus-superior rectus muscle (IR/SR) surgery retrospectively. In a total of 56 patients the effect of surgery on vertical ductions, cyclodeviation and squint angle was analysed. A postoperative squint angle of ≤ 3° in primary position and downgaze was defined as successful. This was achieved in 74% of the IR-group and in 64% of the IR/SR-group, although the former had a higher incidence of depression impairment. The amount of recession did not negatively influence this impairment. Al Qahtani *et al.* (2015) used adjustable sutures and found a success percentage of 64% after one operation for the vertical deviation. They defined success as a satisfactory field of BSV in primary position at distance and near. However, no criteria were given how the field of BSV was measured, nor what is perceived as 'satisfactory' [18].

The dose-effect response in chapter 5 was 2.8°/mm in the IR-group and 2.0°/ mm in the IR/SR-group. The cyclodeviation did not significantly change after surgery. These findings are

useful for planning future surgery. We found an overcorrection in 18% of patients. In the literature, an induced force of the ipsilateral superior rectus is mentioned as a cause of this overcorrection[9, 19-21] or the use of absorbable sutures[20 22]. However, the operations in our study were performed with fixed sutures. Moreover, the muscle volume did not correlate with overcorrection. An asymmetrical inferior rectus recession can avoid this increased force of the superior rectus muscle[18]. Esser *et al.* (2011) performed a muscle elongation with Tutopatch on the inferior rectus muscle in 10 patients. They found an identical dose-effect response as for recessions without Tutopatch and no overcorrections. Muscle elongation may be the first choice of treatment in a large vertical squint angle[23]. Nevertheless, further research has to confirm the preliminary results[23].

OUTCOME PARAMETERS

Time frame

It is generally accepted that the orthoptic parameters should be stable for at least 6 months before surgery is planned, although this has never been properly investigated. We compared the orthoptic measurements of strabismus surgery 3 months and 6 – 12 months postoperatively in 3 separate studies (chapter 3, 4 and 5). We found no significant differences in all but one parameter; the abduction improved further after 6 – 12 months after recession of the medial rectus muscle (chapter 4). However, although this was a significant change (2.3°), the increase fell within the 8° of duction change mentioned earlier. The results of our 3 retrospective studies contradict the common knowledge that surgical treatment in GO-patients has to be postponed until a stable situation is reached after 6 – 12 months. This is very fortunate for patients who can now be planned for surgery in an earlier stage, which decreases the duration of time in which they are forced to cope with their handicap.

Muscle volume

The muscle volume, assessed in a semi-quantitative way, was another parameter which was investigated in 3 studies (chapter 3, 4 and 5). In our series, we found no influence of the muscle volume on the amount of strabismus, dose-effect response, or outcome on range of ductions. Hudson and Feldon (1992) were the first to mention the influence of muscle volume of the superior rectus muscle on the outcome of strabismus surgery in patients, who

were overcorrected after a recession of the inferior rectus muscle. Their observations were confirmed by others[24]. In contrast, Dagi *et al.* (2011) found the relationship between muscle diameter and motility weak, especially in the younger age population (< 40 years). Reflecting on our retrospective cohorts, we realize that we did not analyze the outcome according to age. Moreover, our analysis of muscle volume was semi-quantitative. In the meantime, a validated tool to calculate soft tissues in the orbit has been developed using CT[25]. Besides the CT as quantitative instrument to measure muscle volume, recently, muscle thickness was evaluated with enhanced depth OCT[26]. We believe that these new techniques may give a definite answer to the question whether a relationship between muscle volume and outcome of strabismus surgery really exists.

Decompression surgery

A third parameter, studied in these case series, was the influence of preceding decompression surgery (chapter 3, 4 and 5). The dose-effect response was not affected in patients who had undergone prior decompression surgery. In contrast, Ruttum (2000) found lower success rates in a group of 50 patients of whom 17 had undergone prior decompression surgery. Also, more muscles were operated on compared to those who did need an orbital decompression[27]. In later studies of Volpe *et al.* (2012) and Kim *et al.* (2013), no influence of a prior decompression surgery was found[28, 29]. Their observation could be confirmed by our prospective studies in chapter 7 and 8 about the QoL after strabismus surgery.

Duction

If a recession of a muscle is performed in GO-patients, its contraction effect becomes less and its as a result the duction more limited. The contralateral muscle, however, shows an increase in duction. For instance, a recession of the medial rectus muscle decreases the adduction and increases the abduction of the involved eye. This phenomenon is confirmed in chapter 3, 4 and 5. Of great interest is that the total duction range in horizontal and vertical gaze remained stable. For that reason, the duction range may be a better indicator for stability compared to unidirectional duction alone due to less inadvertent differences in head position[30].

SUCCESS CRITERIA

During our studies described in chapters 3, 4 and 5, we realized that comparing our findings with other studies was difficult, because no generally accepted outcome parameters and success criteria of strabismus surgery exist. Therefore, we reviewed the literature in **chapter 6** to overview attempts that have been made to describe these success criteria. Of the 789 hits obtained, eventually 42 articles were eligible. A wide range of criteria were reported, such as the ability to fuse, the number of surgeries or 'single vision in primary position and downgaze'. Only 3 studies quantified these positions with a measurement tool. No more than 1 study mentioned the subjective outcome. Based on these findings, we proposed success criteria for GO-patients having had strabismus surgery. This proposal includes both a score sheet for the field of BSV and a suggestion to use the GO-QoL questionnaire and recommends to measure the outcome after one or if needed, two operations.

A recent study on strabismus surgery in GO patients was performed after publication of our proposal of success criteria[18]. The authors stated that a scored field of BSV helped to illustrate the goals of surgery. However, the success criteria they formulated were only a 'satisfactory field of BSV in primary position at near and distance'. We believe that such criteria are not detailed enough to make comparison with other studies possible.

In **chapter 7 and 8**, we prospectively evaluated the surgical results after 1 and 2 surgeries. We found that 25% of the patients needed an additional correction. However, care must be taken with regard to this number, as different centers participated in this study (chapter 8), each with their own guidelines. Al Qahtani *et al.* (2015) showed a success rate of 84% (horizontal surgery) vs. 66% (vertical surgery) success after the primary operation using adjustable sutures and a cumulative success rate of 94.1% after the second procedure. A third correction further improved the overall success rate to 98.6%. Their success was defined as 'a satisfactory field of BSV in primary position at near and distance' which makes comparison with our series very difficult. They also found significantly higher reoperation rates for the vertical deviation (33%) compared to the horizontal deviations (16%)[18]. In our study, we did not separate the surgical outcome between horizontal and vertical surgeries. Al Qahtani *et al.* (2015) recorded that 15% of re-operations were caused by overcorrections[18]. In contrast, our overcorrection rate was 3%. This remarkable difference

may be due to the low amount of adjustable sutures in our group (1 %). Another explanation could be that our dropout rate was high (17%), mainly due to weather conditions in the USA preventing adequate follow up. However, one cannot rule out the possibility that those patients suffered from an overcorrection and therefore did not show up for their appointments.

QUALITY OF LIFE

As stated at the beginning of this chapter, it is the opinion of the patient that matters most. In chapter 7 and 8 we used the GO-QoL and the Thyroid Eye Disease (TED)-QoL to evaluate disease-specific QoL. Both visual functioning and appearance items showed significant improvement after one or two strabismus surgeries. The GO-QoL questionnaire contains 8 items regarding visual functioning and 8 items about appearance. A point of concern regarding the GO-QoL is the question about cycling and outdoor walking, which is not applicable in every country[31]. The initial supposition that the GO-QoL does not correlate strongly with the severity of GO[32], has been contradicted by researches in Korea, Taiwan and Germany[33 34, 35].

Apart from the GO-QoL, several other QoL questionnaires for GO are available and one may question which questionnaire is most applicable. The TED-QoL is a 3-item questionnaire and less time consuming[36]. However, a detailed analysis of visual functioning or appearance is not possible. Kahaly *et al.* (2005) and others have suggested that not only visual and appearance items but also social elements should be part of a valuable disease specific GO-QoL. They used a questionnaire including items regarding mental depression and anxiety. They showed that 45% of the GO-patients suffer from anxiety, depression or both. In comparison to healthy controls, GO-patients report 72% more problems related to professional activities, more financial difficulties and/or more family conflicts[37]. This mood disorder could explain the moderate relationship found in chapter 7 and 8 between the objective outcome of the field of BSV and the subjective GO-QoL outcome. Yeatts *et al.* (2005) developed a QoL questionnaire containing these elements in relationship to general and mental health, self-perception and social functioning together with items regarding disease-specific visual function. This GO-Quality of Life Scale (QLS) contains 9 items[38]. Especially the social factors add to the outcome. Another study showed that patients with moderate to severe GO experience significant mood disturbances, especially those who

suffer from disfiguring changes[39]. As stated by Estcourt *et al.* (2011), patients with GO have lower QoL compared to patients with other chronic conditions[40]. In conclusion, the implementation of the GO-QoL in the outcome assessment of strabismus surgery in GO-patients is an important one, but more elements need to be added. Referral to specialized GO-clinics and optional psychosomatic treatment[41] will raise the overall quality of care for GO-patients[40].

CONCLUSIONS AND RECOMMENDATIONS

In this thesis, a few major issues are discussed. One of those is that the time frame pending surgery can be shortened to 3 months. Patients could gain from this shorter waiting span. Prospective studies digging further into the stability of the disease e.g. a stable orthoptic situation within 3 months can shorten the treatment process of the patient in future.

Different assessment tools may generate values that are not always interchangeable. This should be taken into consideration in setting up future multicenter studies. Regarding the analyzing process of study results, it is important to focus on change of duction range instead on change of unidirectional duction. The former method is less liable to the subtle changes of position of the head. Moreover, two surgeries should be regarded as a normal set-up for GO-patients instead of assigning the second procedure as a failure of the first. This is not perceived as common knowledge yet and should be criticized or adopted by other centers.

Of course one has to take into consideration that the success criteria developed in this thesis need further foothold in prospective, preferably multicenter, studies about dose-effect responses of different treatment strategies. Each technique has its own goals and evaluating these goals with embedded criteria helps the final outcome of strabismus surgery in this patient group.

The most important question raised by this thesis is the issue of quality of care. As already written in the Amsterdam declaration and acknowledged by Estcourt *et al.* (2011), additional attention has to be given to the quality of care[40, 42]. Future studies that will include this parameter in their protocol, can help to specifically improve the patients' quality of life. Validation of the GO-QLS in other countries could be the first step, followed by prospective research of this questionnaire in patients undergoing strabismus surgery.

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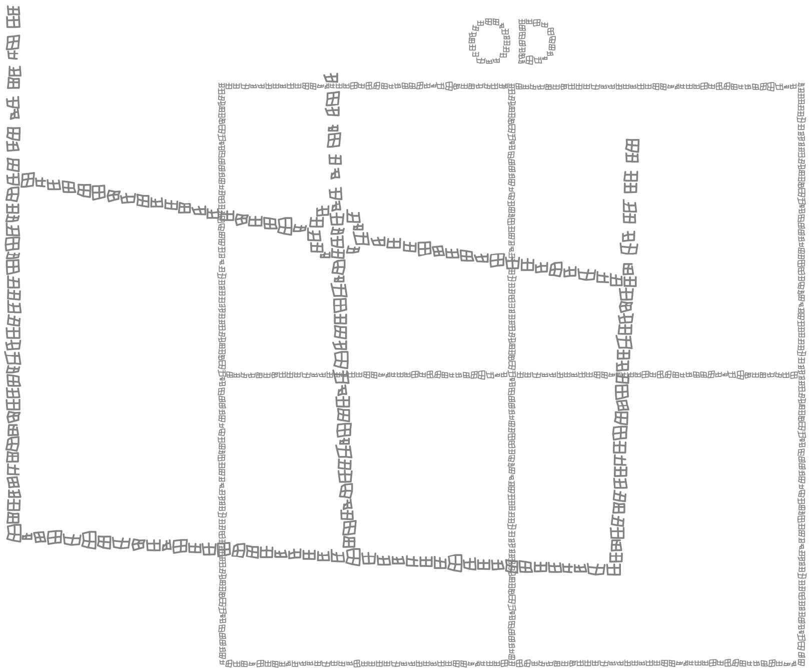
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CHAPTER 10

SUMMARY / SAMENVATTING

SUMMARY

This thesis addresses several aspects of the surgical treatment of diplopia in patients with Graves' Orbitopathy (GO).

Chapter 1 starts with a definition and a historic overview of the profession of orthoptics. A few basic principles of the binocular system are discussed and a couple of tests to measure diplopia and strabismus are described. Furthermore, Graves' Orbitopathy disease and diplopia treatment are discussed, with special attention given to the surgical treatment.

We wanted to know which devices for measuring ductions and cyclodeviation gave a comparable outcome so multicenter studies could be performed. Accordingly, in **Chapter 2** we compared 3 tests for cyclodeviation and 3 for duction measurements. A total of 13 patients were recruited to investigate the cyclodeviation and measurements were repeated 4 times. The Harms tangent screen, the cycloforometer of Franceschetti and the cyclomeasurement in the synoptophore were compared. A difference of ≤ 2° was found between the Harms tangent screen and the cycloforometer, which is clinically not significant. Ductions were measured in another group of 13 patients and the motilitymeter, the Goldmann perimeter and the Maddox tangent screen were compared. A difference of ≤ 8° was found in 92% of the measurements when comparing the motility meter and the Goldmann perimeter. We concluded that several instruments (Harms tangent screen / cycloforometer and motilitymeter / Golmann perimeter) generated interchangeable outcome, which is important for coming multicenter studies.

In addition, we evaluated our surgical outcome of strabismus surgery in our tertiary referral center. Chapter 3, 4 and 5 presents results of these retrospective analyses. **Chapter 3** demonstrates the results of GO-patients operated on both inferior rectus muscles to improve elevation and eye position. Of the total group, 18 patients underwent a bilateral inferior rectus recession and 27 an asymmetrical inferior rectus recession. Effects on ductions, cyclodeviation and squint angle were observed. We found a significant improvement on elevation and a decrease on depression. However, the total duction range remained stable. The more severe the preoperative elevation impairment proved to be, the more effect of surgery on elevation was found. A prior performed decompression surgery, muscle volume or duration of the disease did not influence the postoperative ductions. The excyclodeviation found in primary position preceding surgery, diminished with a mean of 6°.

No A-pattern was found postoperatively. We compared the orthoptic changes 3 months after surgery with 6 – 12 months postoperatively, and found no significant change in data. This indicates that already 3 months after surgery orthoptic stability is reached. We also found that patients needed 2 strabismus surgeries at average. **Chapter 4** evaluated the uni- and bilateral medial rectus recession. We specifically looked for the effect on horizontal ductions and squint angle. A group of 102 fulfilled the inclusion criteria, of which 78 were operated on both medial recti. Regarding the ductions, the abduction increased and the adduction decreased after surgery, but the total duction range remained stable. However, this was only significant in the bilateral group. We found a smaller dose-effect response in the unilateral group with regard to the esodeviation. In total, 3% of the patients were overcorrected and 23% needed additional horizontal surgery. Again we found no influence of the muscle volume on the squint angle or on the dose-effect response and also a preceding decompression surgery did not have impact on these outcomes. Six to 12 months after surgery, all but one item showed stability; the abduction showed further improvement. The last study mentioned in this thesis, evaluating strabismus surgery retrospectively is presented in **chapter 5.** It assesses the inferior rectus muscle (IR) surgery and the combined inferior rectus-superior rectus muscle (IR/SR) surgery. In a total of 56 patients the effect on vertical ductions, cyclodeviation and squint angle was analysed. A postoperative squint angle of ≤3° in primary position and downgaze was defined as successful. This was achieved in 74% of the IR-group and 64% of the IR/SR-group, although the former had a higher incidence of depression impairment. The amount of recession did not influence this impairment and the total duction range remained stable or increased (IR/SR-group). With regard to the strabismus we found an overcorrection in 18% of patients. The cyclodeviation did not significantly change after surgery. All three retrospective studies report stable duction ranges and orthoptic stability already 3 months after surgery for all parameters compared to 6 – 12 months postoperatively.

In these retrospective studies we were faced with the fact that no proper success criteria for strabismus surgery in GO exist. In **chapter 6,** we therefore, present the outcome of a systematic review of literature, in which we searched for success criteria for strabismus surgery in GO-patients. The goal of the review was to construct success criteria for this treatment in GO-patients. Of the 789 hits, eventually 42 articles were eligible. A wide range of criteria were reported, such as the ability to fuse, number of surgeries or single vision in

primary position and downgaze. Only 3 studies quantified these positions with a measurement tool. There was one study that mentioned the subjective outcome. These findings resulted in a proposal of success criteria for GO-patients by presenting a score sheet for the field of binocular single vision and suggesting using the GO-quality of life (QoL) questionnaire.

To evaluate the effect of strabismus surgery on this QoL, **chapter 7** prospectively evaluates the effect after one strabismus surgery on QoL and field of binocular single vision (BSV). In a group of 28 patients we evaluated the GO-QoL and field of BSV 3 months preoperatively and 3 months postoperatively. Both visual functioning and appearance questions showed a significant improvement after surgery. The correlation between this subjective outcome of the QoL and the more objective outcome by means of the field of BSV was moderate. The same moderate correlation between objective and subjective outcome was found in **chapter 8** in which in the framework of a multicenter study, patients were evaluated using these outcomes after one or two strabismus corrections. Both the GO-QoL and the Thyroid Eye Disease (TED)-QoL questionnaire were used to analyze the subjective outcome. By allowing the participating centers to perform a second surgery if necessary, a greater change in outcome of QoL was found. The correlation between outcomes between the GO-QoL and TED-QoL was good.

In this thesis we present useful information regarding interchangeable tools and therefore their outcome on ductions and cyclodeviation. For future research, this knowledge helps to set up further multicenter studies more easily. The results of our retrospective studies on strabismus surgery show that the duction range remains stable after surgery and dose-effect responses differ per chosen eye muscle. Another important finding is that orthoptic stability can be reached as soon as 3 months after surgery. With the presented proposal for success criteria given in this thesis future multicenter studies can become more constrained to evaluate both objective and subjective outcome in GO-patients undergoing strabismus surgery.

SAMENVATTING

Het proefschrift onderzoekt verschillende aspecten van de oogspieroperatie ter behandeling van dubbelzien bij patiënten met Graves' Orbitopathie (GO).

Hoofdstuk 1 begint met een definitie van het beroep orthoptist en geeft daarna een historisch overzicht van haar ontstaan. Er worden een aantal basisprincipes van het binoculaire systeem besproken waarna testen om het dubbelzien en de oogstand te meten worden beschreven. Vervolgens wordt de ziekte GO en de behandeling van het dubbelzien bij deze ziekte, aan de orde gesteld. Speciale aandacht is besteed aan de chirurgische kant hiervan.

Om te komen tot multicenter studies, wilden we weten welke meetinstrumenten voor het bepalen van de ducties en cyclodeviatie te vergelijken waren. Daarvoor hebben we in **hoofdstuk 2** een studie opgezet en zijn 3 testen voor het meten van de cyclodeviatie en 3 voor het meten van de ducties vergeleken. In totaal werden 13 patiënten gerecruteerd om de cyclodeviatie te meten. De metingen werden gedaan met de Harmswand, de cycloforometer van Franceschetti en de synoptofoor en werden vier keer herhaald. Tussen de metingen met de Harmswand en de cycloforometer bleek het verschil in cyclodeviatie ≤ 2° te zijn, wat klinisch niet significant is. Bij een ander groep van 13 patiënten werden de ducties gemeten. De ducties zijn gemeten met de motiliteitsmeter, de Goldmann perimeter en het Maddoxkruis. In 92% van deze metingen werd een verschil van ≤ 8° gevonden tussen de motiliteitsmeter en de Goldmann perimeter. De uitkomsten van deze testen zijn uitwisselbaar voor toekomstig multicenter onderzoek. Het Maddoxkruis en de synoptofoor zijn hiervoor niet geschikt.

Daarnaast wilden we in ons academisch ziekenhuis de uitkomst van de oogspieroperatie bij deze patiëntengroep retrospectief evalueren. De volgende 3 hoofdstukken laten uitkomsten hiervan zien. **Hoofdstuk 3** presenteert de resultaten van GO-patiënten die aan de musculus rectus inferior van beide ogen werden geopereerd om de elevatie en de oogstand te verbeteren. 18 patiënten werden symmetrisch aan beide spieren geopereerd en 27 asymmetrisch. Het effect van de operatie op de ducties, cyclodeviatie en oogstand werd geanalyseerd. We vonden een significante verbetering van de elevatie en tegelijkertijd een verslechtering van de depressie. De totale verticale ductiebeweging bleef stabiel. Tevens vonden we dat hoe ernstiger de elevatie beperking pre-operatief was, des te meer effect de

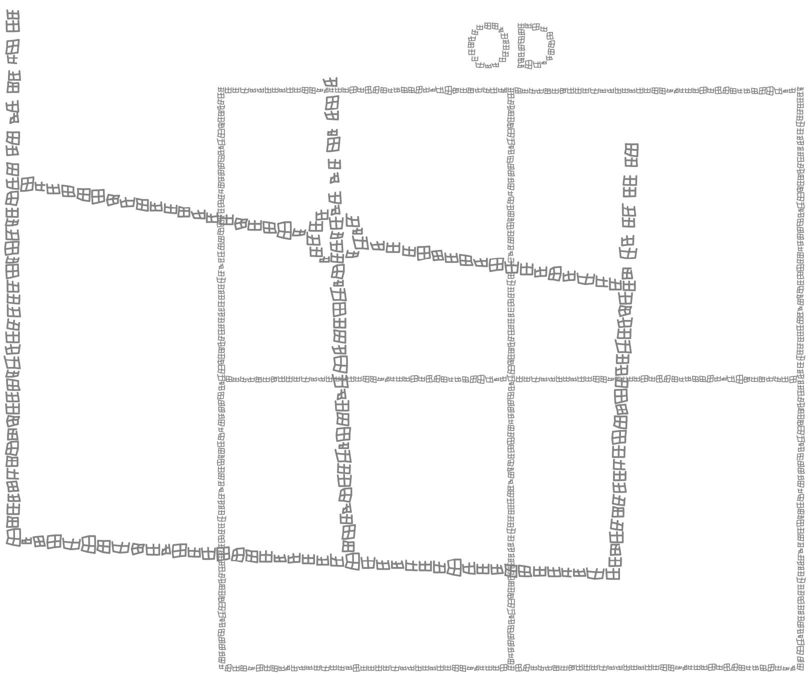
operatie had op de verbetering van de elevatie. Zowel een eerder uitgevoerde decompressie-operatie, als het volume van de oogspier of de duur van de ziekte, hadden allemaal geen invloed op de post-operatieve uitkomst van de ducties. De excyclodeviatie in primaire stand die we pre-operatief vonden, verminderde gemiddeld met 6° na de operatie. We zagen geen A-patroon post-operatief. Bij de vergelijking van de metingen 3 maanden postoperatief met die van 6-12 maanden post-operatief, vonden we geen significante veranderingen. In deze studie bleken patiënten gemiddeld 2 oogspieroperaties nodig te hebben. **Hoofdstuk 4** evalueert de resultaten van de uni- en bilaterale recessie van de musculus rectus medialis. We keken specifiek naar de effecten op de horizontale ducties en de oogstand. Er werden 102 patiënten geïncludeerd, waarvan er 78 geopereerd werden aan beide ogen. De abductie verbeterde na de operatie en de adductie nam af, waarbij de totale horizontale ductiebeweging stabiel bleef. Dit verschijnsel was aanwezig bij beide groepen, maar alleen bij de bilateraal geopereerde groep statistisch significant. De dose-effect respons op de esodeviatie was kleiner in de unilaterale groep dan in de bilaterale groep. In totaal werd er bij 3% van de patiënten een overcorrectie gevonden. Bij 23% van de patiënten was een tweede operatie nodig ter correctie van het horizontale oogstand. Net als in de vorige studie vonden we dat noch een eerdere decompressie-operatie noch het volume van de oogspier effect hadden op de uitkomst. 6-12 maanden na de operatie waren de metingen stabiel vergeleken met de uitkomsten na 3 maanden. Alleen de abductie verbeterde nog wel na 3 maanden. De derde en laatste retrospectieve studie over de effecten van de oogspieroperatie is gepresenteerd in **hoofdstuk 5.** We onderzochten de resultaten van de recessie van de musculus rectus inferior (IR) en die van de gecombineerde recessie van de musculus rectus inferior met de contralaterale musculus rectus superior (IR/SR). Er werden 56 patiënten geïncludeerd waarbij de effecten op de verticale ducties, de cyclodeviatie en de oogstand werden gemeten. Een operatie werd als succesvol gezien als de post-operatieve oogstand ≤ 3° in primaire stand en benedenblik betrof. Dit zagen we bij 74% van de IR- en bij 64% van de IR/SR-patiënten. In de IR-groep troffen we een hogere incidentie van een depressiebeperking aan, de hoeveelheid verrichtte recessie was hierop niet van invloed. De totale verticale ductiebeweging was post-operatief stabiel of verbeterde zelfs (in de IR/SR-groep). Bij 18% van de patiënten was de verticale oogstand overgecorrigeerd. De 3 retrospectieve studies (hoofdstuk 3, 4 en 5) concluderen dat de totale ductiebeweging stabiel blijft en dat de orthoptische status 3 maanden na de operatie al stabiel is.

We werden in de retrospectieve studies geconfronteerd met het feit dat er geen eenduidige succescriteria voor de oogspieroperaties bij GO-patiënten bestaan. **Hoofdstuk 6** is een systematische literatuur studie naar de beschreven succescriteria van deze oogspieroperaties. Er werden 789 artikelen gevonden over dit onderwerp, waarvan uiteindelijk 42 geschikt bleken. We vonden een grote variatie in beschrijving van de succescriteria, zoals 'de mogelijkheid de dubbelbeelden te fuseren', het benodigde aantal oogspieroperaties of 'binoculair enkelzien in primaire stand en benedenblik'. We vonden maar 3 studies die deze blikrichtingen kwantificeerden met een meetinstrument en 1 studie noemde de subjectieve uitkomst als succescriterium. Deze bevindingen resulteerden in een voorstel om succes criteria bij GO-patiënten te definiëren en analyseren. Hierbij werd ook gebruikt gemaakt van een scoreformulier om het veld van binoculair enkelzien (BEZ) te meten en een 'kwaliteit van leven' vragenlijst.

Om het effect op de kwaliteit van leven te laten zien na een oogspieroperatie toont **hoofdstuk 7** de prospectieve resultaten van de oogspieroperatie op de score van het veld van BEZ en de kwaliteit van leven vragenlijst. 28 patiënten werden gerekruteerd waarbij 3 maanden pre- en 3 maanden post-operatief het veld van BEZ werd gemeten en de vragenlijst werd afgenomen. Zowel de positieve effecten op het visueel functioneren als op het uiterlijk waren significant na de operatie. We vonden een matige correlatie tussen deze subjectieve uitkomst en de verbetering van het veld van BEZ. In **hoofdstuk 8** zien we dezelfde matige correlatie tussen de objectieve en subjectieve uitkomsten. In de multicenter studie werden patiënten geëvalueerd na 1 of 2 oogspieroperaties. Zowel de GO-kwaliteit van leven vragenlijst (GO-QoL) als de Thyroid Eye Disease kwaliteit van leven vragenlijst (TED-QoL) werden gebruikt om de subjectieve score vast te leggen. Na een tweede operatie steeg de uitkomst van de kwaliteit van leven verder. In dat geval steeg de uitkomst van de kwaliteit van leven verder. De beide vragenlijsten hadden een goede onderlinge correlatie.

In dit proefschrift is aangetoond en kunnen we concluderen dat verschillende testen voor het meten van de ducties en de cyclodeviatie uitwisselbaar zijn. Dit geeft handvatten voor het opzetten van verder toekomstig multicenter onderzoek. De resultaten van de retrospectieve studies naar de effecten van de oogspieroperaties dragen daaraan bij. Het is belangrijk om te realiseren dat de dose-effect respons afhankelijk is van de beoogde te opereren oogspier. De totale ductiebeweging blijkt een stabiele parameter na de

oogspieroperatie. Daarnaast vonden we 3 maanden na de operatie al een stabiele orthoptische status. Gecombineerd met een voorstel voor succescriteria voor toekomstige prospectieve multicenter studies geeft dit proefschrift meer houvast om zowel objectieve als subjectieve uitkomstmaten te gebruiken bij het evalueren van oogspieroperaties in deze patiëntengroep.



DANKWOORD

DANKWOORD

Dit proefschrift was niet tot stand gekomen zonder de steun en belangstelling van alle mensen om me heen die door de jaren heen interesse toonden in de voortgang ervan. Het proces ging niet zonder slag of stoot, maar uiteindelijk is het af. Graag zou ik een aantal mensen bij naam willen bedanken.

Allereerst een woord van dank aan de patiënten, die bewust en onbewust mee hebben gewerkt en dit proefschrift mogelijk hebben gemaakt. Patiënten met Graves' Orbitopathie zijn bijzondere patiënten, waar we als orthoptist vaak een intensieve band mee opbouwen. Ik dank hen ook voor alle gesprekken, die mij meer inzicht hebben gegeven in de overige (niet medische) facetten van deze ziekte.

Maarten, mijn promotor, zonder jou was dit boek er niet (of veel later) gekomen. Bedankt dat je op die zonnige dag in mei 2008 opperde of ik interesse had om te promoveren op de behandeling van dubbelzien bij patiënten met Graves' Orbitopathie. Je had ook al een einddatum, 12 12 2012, maar het werd iets later... Bedankt voor alle correcties op de concept artikelen, de ideeën die ontstonden tijdens onze gesprekken op de vrijdagochtend, het bieden van de mogelijkheid om op vele congressen te spreken en de niet aflatende steun en het vertrouwen op een goede uitkomst!

Peerooz, mijn copromotor, dank voor al je tijd op vrijdagmiddagen als ik op de rode bank neerplofte voor advies. Wat begon als samenwerking tijdens de tumoren spreekuren op de vrijdagmiddag is uitgemond in een zeer prettige werkrelatie, waar ook menig sociaal aspect ter sprake kwam. Jij was het ook die me leerde om de einddatum te relativeren. Hopelijk kijk je nog vaak in de orthoptische spiegel!

Ook de leescommissie wil ik zeer hartelijk bedanken voor hun kritische beoordeling van het manuscript van dit proefschrift. Ik waardeer het zeer dat iedereen zich direct bereid toonde zitting te nemen in de commissie.

Professor Wiersinga, hartelijk dank voor kritische vragen en feedback tijdens diverse fasen van dit proefschrift. Dit heb ik als zeer prettig ervaren.

Elly, Yvette en Linda, wat een topteam vormen wij! Ik ben zo blij dat ik jullie collega mag zijn. Hoe vaak hebben jullie me niet gevraagd of jullie iets van me over konden nemen? Elk van jullie heeft op haar eigen manier een substantiële bijdrage geleverd aan dit proefschrift.

Yvette, je hebt alle artikelen (soms meermaals) inhoudelijk en op Engels gecorrigeerd, waarvoor dank. En wat te denken van die ruim 1000 te screenen abstracts voor het review artikel. Zoals je zelf al zei: jij hebt dit proefschrift echt helemaal van voor tot achter gelezen!

Linda, jij bent degene geweest die het uitpluis werk van me heeft overgenomen, door alle patiënten door te spitten op uitgevoerde operaties. Maar dat ging op de jouw kenmerkende supersnelle manier, waarvoor enorme dank!

Elly, jij stond en staat bijna letterlijk naast me als ik weer eens spreek over dubbelzien bij patiënten met Graves' Orbitopathie. Naast onze gezamenlijke congresreizen naar Mainz, Brugge, Toronto, Groningen, Marseille en Venetië ben je ook een erg dierbare vriendin. Ik hoop nog heel wat gezamenlijke orthoptische jaren samen mee te maken en ik ben er trots op dat je mijn paranimf wilt zijn!

Orthoptie collega's vanuit het regio-overleg, werkgroepen, commissies, opleiding en werkveld, dank voor jullie belangstelling, kritische vragen en patiënt-overleggen. Ik hoop dat we het orthoptisch werkgebied op diverse manieren verder kunnen ontwikkelen, zowel wetenschappelijk als inhoudelijk.

Alle medewerkers van de afdeling Oogheelkunde, oogartsen, TOA's, dokters-assistenten, secretaresses, Oculenti en medewerkers van het research bureau, samen vormen we een apart geheel, maar ondanks alles zijn we wel een team. Een speciale dank gaat uit Carola, die me in de eindfase van het proefschrift als een soort moeder begeleidde en hielp, top! Dick, bedankt voor het maken van de foto's die ik nodig had voor mijn presentaties en proefschrift, altijd het liefst op korte termijn. En Monique, je leerde me de fijne kneepjes van het vak als het gaat om het schrijven van een goed onderzoeksprotocol en het verzinnen van afkortingen voor de studies inclusief de kleur van de mapjes! Bijzonder vormt ook de samenwerking met Gerrit Burger, die altijd snel ter plaatse is om de orthoptische apparatuur/motiliteitsmeter, te smeren/repareren. Jij maakte de Amsterdamse cycloforometer en samen ontwikkelden we de meer mobiele hoofdlamp.

Roel, als orbitoloog heb je ook menig patiënt uit de studies geopereerd. Jij bent altijd zeer betrokken bij het operatievoorstel en in voor elk (wild) idee van ons! Sinds we samen in het kernteam Oogheelkunde zitting hebben, heb ik je beter leren kennen en zie ik nog beter hoe je je ingezet hebt voor een werkbaar nieuw EPD. Als je 'PA' ga ik deze samenwerking straks missen!

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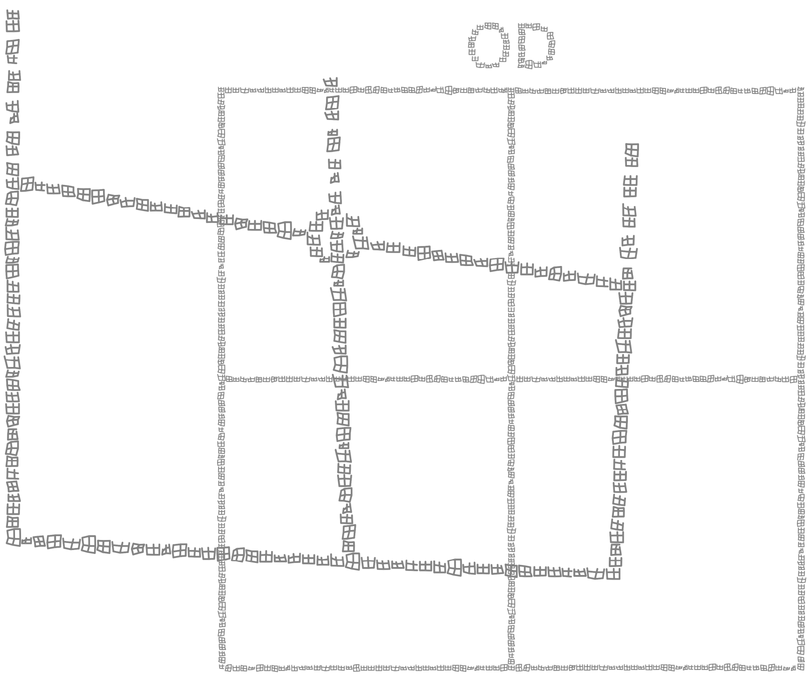

CURRICULUM VITAE

CURRICULUM VITAE

Hinke Marijke Jellema werd 5 december 1977 geboren te IJlst in Friesland. Ze deed het atheneum op het Bogerman College te Sneek en ging daarna naar Utrecht om de opleiding Orthoptie aan de Hogeschool Utrecht te volgen. Na het cum laude afronden van deze opleiding kreeg ze een baan aangeboden in het Academisch Medisch Centrum te Amsterdam als orthoptist. Ze had naast haar orthoptiewerk ook belangstelling voor het doceren en volgde hiervoor de tweejarige docentenopleiding tot eerstegraads docent aan de Vrije Universiteit te Amsterdam. Parallel hieraan werkte ze vanaf 1999 – 2008 als praktijkdocent en later als hogeschooldocent bij de opleiding Orthoptie aan de Hogeschool Utrecht. In deze periode ontwikkelde ze diverse delen van het onderwijsprogramma en was ze intensief betrokken bij de overgang van de driejarige naar de vierjarige opleiding Orthoptie. In 2004 begon ze aan de Master of Medical Science in Orthoptics aan de Universiteit te Sheffield in Engeland. Deze rondde ze cum laude af met als afstudeerscriptie de dose-effect response van de musculus rectus medialis recessie bij patiënten met Graves‘ Orbitopathie. Met deze opleiding was de interesse in het doen van onderzoek gewekt. Naast haar werk als orthoptist was ze tussen 2008 en 2011 bestuurslid kwaliteit van de Nederlandse Vereniging van Orthoptisten en van 2008 – 2015 bestuurslid van de landelijke Stichting Kwaliteitsregister Paramedici (KP). Tevens is ze betrokken (geweest) bij diverse werkgroepen, waaronder de kwaliteitsregistratie commissie van het KP en de Congress Scientific Program Comittee ter voorbereiding van het Internationale Orthoptische (IOA) Congres in Rotterdam in 2016.

PHD PORTFOLIO

Name PhD student: Hinke Marijke Jellema PhD period: December 2008 – February 2016 Name PhD supervisor: Prof. M.P. Mourits		
	Year	**Workload (Hours/ECTS)**
General courses		
Better use of Pubmed	2008	0.1
Reference manager	2009	0.1
Clinical Data Management	2009	0.5
Clinical Epidemiology	2009	0.8
Endnote	2013	0.1
Presentations at (Inter)national conferences		
• *Quality of life after strabismus surgery in Graves' Orbitopathy patients: a multicenter study.* Presentation at the annual European Strabismological Association (ESA) congress	2015	1.25
• *Strabismus surgery in patients with Graves' Orbitopathy.* Presentation at the annual Donders Gezelschap meeting	2015	0.75
• *Outcome of strabismus surgery in patients with Graves' Orbitopathy: a prospective multicenter study.* Presentation at the meeting of the annual Dutch Ophthalmology Society (NOG)	2015	1.0
• *Thyriod and Orthoptics.* Presentation at the annual meeting of Ophthalmic assistants	2015	0.5
• *Quality of life of orthoptic patients*. Presentation at the ESA congress	2013	0.5
• *Quality of life after strabismus surgery in Graves' Orbitopathy patients, a pilot study*. Presentation at the annual NOG meeting	2013	0.75

Presentations at (Inter)national conferences		
• *Strabismus surgery in patients with Graves' Orbitopathy: do measurements count?* Presentation at the meeting of the Dutch Orthoptic Association (NVvO)	2013	0.5
• *Outcome of strabismus surgery in patients with Graves' Orbitopathy: a prospective multicenter study.* Presentation at the International Thyroid Eye Disease Symposium (ITEDS)	2013	1.0
• *Results of strabismus surgery in Graves' Orbitopathy patients*. Presentation at the annual NOG meeting	2012	0.75
• *Uni- or bilateral inferior rectus recession in Graves' Orbitopathy patients?* Presentation at the ESA congress	2011	1.25
• *Standardized orthoptic assessment as proposed by the EUGOGO.* Presentation at the 2nd SWISS congress	2010	1.0
• *Criteria to evaluate motility disorders and outcome of therapy in Graves' Orbitopathy patients.* Presentation at the annual meeting of the National Graves' association	2009	0.5

LIST OF PUBLICATIONS

	Year
Peer reviewed	
• Jellema HM, Braaksma-Besselink Y, Limpens J, von Arx G, Wiersinga WM and Mourits MP. Proposal of success criteria for strabismus surgery in patients with Graves' Orbitopathy based on a systematic literature review. *Acta Ophthalmol.* 2015 Nov;93(7): 601-9.	2015
• Jellema HM, Saeed P, Groenveld A, Kloos R and Mourits MP. Outcome of inferior and superior rectus recession in Graves' Orbitopathy patients. *Orbit*. 2015;34(2): 84-91.	2015

• Jellema HM, Saeed P, Braaksma-Besselink Y, Schuit A, Kloos R and Mourits MP. Unilateral and bilateral medial rectus recession in Graves' Orbitopathy patients. *Strabismus* 2014;22(4): 182-7.	2014
• Jellema HM, Merckel-Timmer E, Kloos R, Saeed P and Mourits MP. Quality of life improves after strabismus surgery in patients with Graves' Orbitopathy. *Eur J Endocrinol.* 2014 Apr;170(5): 785-9.	2014
• Jellema HM, Saeed, P, Everhard-Halm, Y, Prick L and Mourits MP. Bilateral inferior rectus muscle recession in patients with Graves' Orbitopathy: is it effective? *OPRS.* 2012 Jul-Aug;28(4): 268-72.	2012
• Jellema HM, Baader A, Pitz S, Prick L and Mourits MP. Comparison of cyclodeviation and duction measurement in Graves' Orbitopathy patients using different devices. *Strabismus.* 2011;19: 43-51.	2011
Other	
• Jellema HM. Success criteria and protocol of assessment of the motility disorders in Graves' Orbitopathy patients according the EUGOGO. In: Genol Saavedra I. TFN, ed. *Thyroid eye disease* [Orbitopatía de Graves]. 1 ed. Barcelona: Editorial Glosa; 2011; 120-127.	2011
• Gutter M, van Petegem-Hellemans J, van Wijnen-Segeren I and Jellema HM. *Orthopics: Handbook of Practical Skills*. 2010 1th ed. Ridderkerk: Luiten Publishing.	2010
• Gutter M, Petegem van JC, Van Wijnen-Segeren I and Jellema HM. *Handleiding Praktische vaardigheden Orthoptie.* 2008 Ridderkerk, Uitgeverij Luiten.	2008