Surgical treatment of diplopia in Graves' Orbitopathy patients
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CHAPTER 9

GENERAL DISCUSSION
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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\textsuperscript{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 $\leq 2^\circ$ 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 compared outcomes of measurements of the Maddox tangent screen, the motility meter and the Goldmann perimeter. We found a difference of $\leq 8^\circ$ of duction in 92% of the patients comparing the last two devices. Remarkably, this finding is in complete agreement
with the literature, defining a change of ≥ 8° as a significant sign of disease activity\textsuperscript{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 \textit{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\textsuperscript{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 \textit{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\textsuperscript{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. \textbf{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 on 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\textsuperscript{8, 9}. The impaired depression in downgaze is supposed to activate the superior oblique muscle, which then causes an A-pattern\textsuperscript{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\textsuperscript{10, 12}, which however might induce incyclodeviation\textsuperscript{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\textsuperscript{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\textsuperscript{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\textsuperscript{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 $\leq 3^\circ$ 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 \textit{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’ \textsuperscript{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\textsuperscript{9, 19-21} or the use of absorbable sutures\textsuperscript{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\textsuperscript{18}. Esser \textit{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\textsuperscript{23}. Nevertheless, further research has to confirm the preliminary results\textsuperscript{23}.

\section*{OUTCOME PARAMETERS}

\subsection*{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.

\subsection*{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\textsuperscript{24}. In contrast, Dagi \textit{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\textsuperscript{25}. Besides the CT as quantitative instrument to measure muscle volume, recently, muscle thickness was evaluated with enhanced depth OCT\textsuperscript{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\textsuperscript{27}. In later studies of Volpe \textit{et al.} (2012) and Kim \textit{et al.} (2013), no influence of a prior decompression surgery was found\textsuperscript{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\textsuperscript{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 criteria18. 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 overcorrections18. 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. The initial supposition that the GO-QoL does not correlate strongly with the severity of GO, has been contradicted by researches in Korea, Taiwan and Germany.

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. 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. 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. 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\textsuperscript{39}. As stated by Estcourt \textit{et al.} (2011), patients with GO have lower QoL compared to patients with other chronic conditions\textsuperscript{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\textsuperscript{41} will raise the overall quality of care for GO-patients\textsuperscript{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 \textit{et al.} (2011), additional attention has to be given to the quality of care\textsuperscript{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.
REFERENCES


