Surgical treatment of diplopia 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\textsuperscript{15}, measurement of ductions by a motilitymeter\textsuperscript{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\textsuperscript{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\textsuperscript{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\textsuperscript{2}. Questionnaires were self-administered, without supervision, following verbal and written instructions.

<table>
<thead>
<tr>
<th>Gaze position using the Maddox cross</th>
<th>Score of BSV (points)</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>primary position</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>up 5°</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>up 10°</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>up 15°</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>up 30°</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>down 10°</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>down 30°</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>right 10°</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>right 20°</td>
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<td>right 30°</td>
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<tr>
<td>left 10°</td>
<td>2</td>
<td></td>
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<tr>
<td>left 20°</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>left 30°</td>
<td>1</td>
<td></td>
</tr>
</tbody>
</table>

\textit{BSV} = binocular single vision

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.
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.

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 SPSS 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 | 131 Thyroidectomy | 4 Anti thyroid drugs |
| | | 1 |
| 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.
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 her 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.

\(r = 0.417; p = 0.034\)
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; iii) 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) 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. 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. 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.
al. (2012)\textsuperscript{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\textsuperscript{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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