The Effect of Ophthalmic Surgery for Graves' Orbitopathy on Quality of Life – A Systematic Review and Meta-analysis

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Abstract

Background

Graves' orbitopathy has a profound negative impact on quality of life. Surgery is undertaken to preserve vision, correct diplopia and improve aesthetics. We sought to quantify the effect of different surgical approaches on quality of life.

Methods

Electronic databases Ovid–MEDLINE, EMBASE were used from inception until 22nd March, 2021 to identify studies assessing quality of life pre- and post-surgical intervention for Graves' orbitopathy. Two reviewers independently extracted data and performed quality assessments. Random-effects and Bayesian models for meta-analyses were utilised.

Results

10 articles comprising 632 patients with a mean age of 48.4 years (range 16-85 years) were included. All used the Graves' Ophthalmopathy Quality of Life questionnaire (GO-QOL). For GO-QOL appearance, the pooled standardised mean improvement for patients after surgery was +0.72 (95% CI 0.50-0.94) I^2 69% (95% CI 52-80%). For GO-QOL visual functioning, the pooled SMD for patients after surgery was +0.41 (95% CI 0.25-0.58) I^2 60% (95% CI 36-74%).

For visual appearance, orbital decompression yielded the greatest improvement (SMD +0.84, 95% CI 0.54-1.13) followed by eyelid surgery (SMD +0.38, 95% CI 0.05-0.70), while strabismus correction had no significant effect (SMD +0.94, 95% CI -0.10-1.99). Conversely strabismus correction was associated with the greatest improvement (SMD +1.25, 95% CI 0.29-2.21) in visual

functioning, outperforming orbital decompression (SMD +0.29, 95% CI 0.15-0.43) and eyelid surgery (SMD +0.12, 95% CI -0.18-0.41).

A mean improvement in GO-QOL of greater than 10 points after orbital decompression surgery was achieved in 12/14 (86%) patient-groups for appearance and 5/14 (36%) patient-groups for visual functioning. A mean improvement of greater than six points was achieved in 5 of 6 (83%) patient groups for strabismus surgery for both appearance and visual functioning. A mean improvement of greater than six points after eyelid surgery was achieved in 2/3 (67%) patient-groups and 0/3 patient-groups for appearance and visual functioning respectively.

Conclusion

Ophthalmic surgery results in substantial improvements in quality of life in patients with Graves' orbitopathy, with greater perceived effects on appearance than visual function. Orbital decompression has particular impact on visual appearance, strabismus surgery benefits visual appearance and function equally whereas eyelid surgery benefits appearance alone.

Introduction

Graves' orbitopathy (GO), known also as Graves' ophthalmopathy or thyroid eye disease (TED), is a complex autoimmune disorder and has substantial morbidity (1, 2, 3, 4). Indeed GO has been shown to adversely affect quality of life, mental health, and economic activity (4, 5, 6). Its effects can be profound and include double vision, orbital disfigurement and even visual loss (3).

The vast majority of patients with GO have established Graves' disease and glucocorticoids are the mainstay of treatment for active disease although there is increasing use of additional agents such as mycophenolate and teprotumumab (3, 7). Surgery is frequently required and is usually performed during the inactive phase of disease with the goal of improving visual function and cosmesis, although emergency surgery is required in the setting of sight-threatening optic nerve compression (8). Options for surgical rehabilitation include orbital decompression, strabismus correction, eyelid-lengthening procedures and blepharoplasty (8). While treatment is often associated with objective improvements in clinical parameters, this may not necessarily translate into meaningful recovery in the patient's physical, emotional and social functioning (9).

In brief, orbital decompression is the mainstay of rehabilitation for surgery as it can be utilised for optic nerve compression, corneal exposure and to improve aesthetics. Common complications include double vision and scarring and rarely visual loss. It requires general anaesthesia but can be performed on an outpatient basis. Strabismus surgery which adjusts the extra-ocular muscles requires significant expertise in thyroid eye disease, but it can be done under general or twilight anaesthesia and again can be performed in an outpatient setting. A key complication is a slipped muscle and movement reduction. Lid surgery is often the final step in rehabilitative surgery and is used to improve lid retraction, it can be performed with twilight anaesthesia with scarring being a key complication.

Quality of life in GO is evaluated using general health-related questionnaires and disease-specific questionnaires. Disease-specific questionnaires are often less generic, permitting greater focus on relevant aspects of daily life affected by the disorder, and may be more sensitive to smaller changes in quality of life (9). The most widely described and validated GO-specific quality of life questionnaires, at present, include the Graves' Ophthalmopathy Quality of Life (GO-QOL) and the Thyroid Eye Disease Quality of Life (TED-QOL) (10). Briefly, the GO-QOL comprises two domains, one pertaining to visual functioning and the other to physical appearance, each made up of eight items (11). The raw score for each domain is then transformed to a total score out of 100 with higher scores reflecting better quality of life. The TED-QOL contains three subscales, including overall quality of life, the capacity to perform daily tasks, and satisfaction of appearance (12). For the GO-QOL, Terwee *et al*. proposed that a change in score of at least six points after minor therapy (such as strabismus correction, eyelid-lengthening procedures and blepharoplasty) or at least 10 points after major therapy (such as orbital decompression) is indicative of a minimal clinically important difference (MCID) (13). This MCID was established based upon the amount of GO-QOL score change in patients who reported moderate subjective improvement in their visual functioning, appearance, and overall quality of life post-procedure (13).

The aim of this systematic review and meta-analysis was to synthesise the existing literature on the impact of these different surgical interventions for the management of GO on patients' quality of life, as evaluated using these disease-specific questionnaires.

Methods

The systematic review and meta-analysis was performed in accordance with the Preferred Reporting Items for Systematic Review and Meta-analysis (PRISMA) guidelines. This study was registered with the International Prospective Registry of Systematic Reviews (PROSPERO; registration number CRD42021245615).

Search Strategy and Study Selection

Published articles were searched for in two major electronic databases via Ovid – MEDLINE and EMBASE. Keywords for the search are listed in Supplementary Table 1. The last search was performed on March 22, 2021. No restrictions were placed on the date or language of publication. Only original articles were included with exclusion of abstracts, commentaries and literature reviews. Articles without full text availability were also excluded. Replicates were identified and removed. Studies were considered relevant if they included patients undergoing rehabilitative surgery for GO, and whose quality of life was evaluated via an established disease-specific questionnaire before and after surgery (GO-QOL) which there is both substantial validity and reliability (Watt 2018). Articles providing primary data on pre- and post-operative questionnaire scores (mean and standard deviation) were eligible for quantitative synthesis. All papers yielded from the initial search were screened via title and abstract by two independent reviewers (CHL, TW) to determine relevance. Thereafter, articles were read in full and selected if they met the eligibility criteria by two reviewers independently. Any disagreement was resolved by discussion or recourse to a third reviewer (SG). The reference lists of eligible studies and review articles were also screened for additional relevant papers.

Data Extraction

Certain studies described more than one indication or surgical approach (either variations of the same procedure or different operations altogether) and GO-QOL scores have been reported according to these characteristics. These have therefore been summarised as individual patient groups (Table 1).

Relevant information from eligible studies were retrieved in accordance with a pre-specified protocol by two independent reviewers (TW, SG). These included the study's first author, publication year, country of origin, study design, sample size, inclusion and exclusion criteria, type of rehabilitative surgery performed, follow-up duration, disease-specific quality of life questionnaire used, pre- and post-operative quality of life questionnaire scores (or their differences), and post-operative complications. For the meta-analysis, the means and standard deviations for pre- and post-operative GO-QOL scores were extracted.

Quality Assessment

Eligible studies were assessed using the National Heart, Lung, and Blood Institute (NIH) Quality Assessment Tools for Before-After (Pre-Post) Studies with No Control Group and Controlled Intervention Studies by two independent reviewers (TW, CHL) (14). The overall quality of each study was rated as "good", "fair", or "poor". The final quality rating was determined upon agreement by both reviewers.

Statistical Analysis

Data analysis was performed using the R software with the "meta" package by two analysts (CHL, SG) (15). A conventional meta-analysis was mainly employed in this study. Subsequently, a Bayesian meta-analysis was performed to reaffirm the findings of the conventional meta-analysis. The "brms" package was used to fit Bayesian regression models (Burkner 2017). We utilised a random effects model and weakly informative prior distributions to inform the study effect size (mean of 0, variance of 1 was set) and between study heterogeneity variance (where the half Cauchy distribution with scaling factor of 0.5) was used (Williams 2018). Bayesian methods produce credible intervals and a 95% credible interval for an effect size is that region in which we believe the effect size to lie with probability 95%. This cannot be done with the classical meta-analysis. Bayesian approach is also particularly advantageous for random-effects analysis of among study variation where numbers of studies are small such as 10 studies or less (Turner 2012).

Standardised mean differences (SMD) in GO-QOL scores pre-operatively and post-operatively were calculated by Hedges' g. Standardised mean differences were utilised due to the heterogeneity of studies and also due to the relative difference in changes for the visual appearance and visual functioning domains from their baseline.

The random effects model was used to pool effect sizes and mean differences in GO-QOL scores. Restricted maximum likelihood was used to derive the estimator for heterogeneity τ^2. Subgroup analysis was performed to determine the effects of different types of surgery and follow-up durations on the outcome. Standard error of difference between subgroup effect sizes was also calculated and compared (16). Meta-regression was used to predict the effect of pre-operative GO-QOL appearance and visual function scores with the individual-study effect sizes generated from ophthalmic surgery. These are shown as bubble plots where individual bubbles represent individual study weightage.

A funnel plot and Egger test were used to detect potential publication bias augmented by the Duval and Tweedie trim-and-fill procedure which suppresses the most extreme results (**Supplementary Figures 1 and 2**). Results were considered statistically significant if the p value was <0.05.

Results

Study Characteristics

The search yielded a total of 158 articles across the databases (**Figure 1**). After removal of replicates, 95 articles were screened from which 32 were deemed relevant to the study. These were examined fully and 10 were selected for meta-analysis after meeting the eligibility criteria. For included papers no author contact was required for clarification of the data or study criteria, or availability of full text.

The 10 articles comprised 632 patients with a mean age of 48.4 years ranging between 16 and 85 years. The majority of patients were female (74.9%). The studies encompassed the three main categories of surgery - orbital decompression (n=410), strabismus correction (n=148), and eyelid procedures (n=47). Amongst the 10 studies, there were 23 different groups of patients. In general, patients were eligible for rehabilitative surgery if they were euthyroid with stable clinical activity scores typically for at least three months. All studies were prospective or retrospective observational studies with the exception of one randomised controlled trial (Sellari-Franceschini *et al*.), and all employed the GO-QOL questionnaire to evaluate disease-specific quality of life although one (Fayers *et al*.) also reported using the TED-QOL (20, 24). The post-operative follow-up duration ranged from two months up to at least 37.9 months with a median of 4 months.

Post-operative complications were sporadically reported, and all pertained to adverse effects of orbital decompression, the most common being induction of diplopia (19, 21, 24). Other described complications (which varied depending on the precise surgical approach) included eyelid oedema and chemosis, maxillary sinus obstruction, hypoaesthesia of trigeminal nerve branches, and cosmetic dissatisfaction. Cerebrospinal fluid leak was a rare complication."

Orbital Decompression

Orbital decompression was evaluated in seven studies encompassing 14 patient groups. The most common indication for orbital decompression was correction of disfiguring proptosis. Less frequently decompression was performed for compressive optic neuropathy, chronic conjunctival congestion, exposure keratopathy, and relief of retrobulbar sensation. A range of surgical methods were reported, varying by number and location of orbital walls removed with or without concomitant removal of adipose tissue, encompassing both open and endoscopic approaches. Cheng *et al*. also reported a technique consisting solely of fat decompression with preservation of orbital walls (18). The change in mean GO-QOL scores following orbital decompression ranged between 1.8 and 40.3 for the appearance domain (median=19.6, interquartile range [IQR]=14.9-23.5), and -1.7 and 34.6 for the visual function domain (median=8.0, IQR=2.5-13.2). A mean improvement of greater than 10 points (i.e. greater than the MCID for major intervention as proposed by Terwee *et al*.) after orbital decompression surgery was achieved in 12 of 14 (86%) patient groups and 5 of 14 (36%) patient groups for appearance and visual functioning domains respectively (13).

Strabismus Correction

Four studies involving six patient groups reported on the use of strabismus correction, most commonly performed for improvement of constant diplopia. The change in mean GO-QOL scores after strabismus correction ranged between 2.6 and 88.2 for the appearance domain (median=13.1, IQR=9.8-18.8), and 2.8 and 89.1 for the visual functioning domain (median=24.2, IQR=19.3-29.1). A mean improvement of greater than six points (i.e. greater than the MCID for minor intervention) after surgery was achieved in 5 of 6 (83%) of strabismus correction patient groups for both appearance and visual functioning domains.

Eyelid Procedures

Eyelid procedures including eyelid lengthening and blepharoplasty, performed for cosmetic indications such as eyelid retraction, were reported in two involving three patient groups. Mean GO-QOL scores changed between 4.2 and 18.4 for the appearance domain (median=10.2, IQR=7.2-14.3), and 0.2 and 4.4 for the visual functioning domain (median=3.7, IQR=2.0-4.1). A mean improvement of greater than six points after eyelid surgery was achieved in 2 of 3 (67%) patient groups and none (0 of 3) patient groups for appearance and visual functioning domains respectively.

Quality Assessment

The overall quality of studies were rated by two independent reviewers (TW, CHL) based on the NIH Quality Assessment Tools for the corresponding study designs (**Table 1**, **Supplementary Table 2**). Of the 10 studies 1 study was felt to be of poor quality, 5 of fair quality and 4 of good quality (**Supplementary Table 2**)

There was some weak evidence of publication bias. Publication bias was assessed using a funnel plot, which did not show significant asymmetry for GO-QOL appearance score (p=0.126) but demonstrated significant asymmetry for GO-QOL function ($p=0.0493$). However, upon application of the Duval and Tweedie trim-and-fill procedure, which removed the effect size from Sarici *et al*., the p-value achieved non-significance ($p=0.661$ and 0.564 with SMD of 0.684 and 0.392 respectively) (23).

Meta-analysis of the Effect of Surgery on Quality of Life

Patients who had undergone surgery experienced significant improvements ($p<0.05$) in both appearance and function domains compared to their baseline pre-operatively (**Figures 2 and 3**). For the improvement in GO-QOL appearance, the pooled SMD for patients after surgery using conventional (frequentist) meta-analysis was 0.72 (95% CI 0.50-0.94) and the I^2 was 69% (95% CI 52-80%) (**Figure 2**). For the improvement in GO-QOL visual functioning, the pooled SMD for patients after surgery was 0.41 (95% CI 0.25-0.58) and the I^2 was 60% (95% CI 36-74%) (**Figure 3**). A Bayesian random-effects meta-analysis was also performed (**Supplementary Figures 3 and 4**) which demonstrated a more conservative but significant improvement in GO-QOL scores for both domains. Using the study-level mean GO-QOL change (a change of 10 points or more for all types of surgery was considered a clinically meaningful difference), the odds of a clinically meaningful difference was 3.6 (95% CI 1.34-9.70) for GO-QOL appearance score and 0.769 (95% CI 0.34-1.75) for visual functioning score.

The Effect of Different Types of Surgery on Quality of Life

Subgroup analysis based on type of surgery indicated a trend towards a difference on the improvement in the GO-QOL scores for both appearance (Q=4.62, p=0.1) and visual functioning domains (Q=5.12, p=0.08) (**Figures 4 and 5**). Eyelid surgery (SMD 0.12, 95% CI -0.18-0.41) had the smallest effect on improving visual function followed by orbital decompression (SMD 0.29, 95% CI 0.15-0.43). Strabismus correction had the greatest effect on improving visual functioning (SMD 1.25, 95% CI 0.29-2.21) and significantly outperformed eyelid surgery and orbital decompression. By contrast, orbital decompression (SMD 0.84, 95% CI 0.54-1.13) yielded the greatest improvement in appearance, with a lesser effect from eyelid surgery (SMD 0.38, 95% CI 0.05-0.70). Strabismus correction had no significant effect on improving appearance (SMD 0.94, 95% CI -0.10-1.99).

The Effect of Different Follow-up Durations on Quality of Life Post-surgery

Most studies reported a follow-up duration of within 6 months post-operatively for the completion of the GO-QOL. Two studies had a long duration of follow-up beyond 6 months, with a mean of 37.9 months and 32.7 months respectively (**Table 1**). In one study there was no information on the duration of follow-up (18, 20, 23).

The different duration of follow-up among the studies (up to 6 months versus more than 6 months versus no information) did not significantly impact on the overall changes in the GO-QOL scores for both appearance (Q=1.14, p=0.57) and visual functioning (Q=0.92, p=0.63). The improvement in GO-QOL scores for both appearance (SMD 0.70, 95% CI 0.44-0.96) and visual function (SMD 0.39, 95% CI 0.22-0.57) remained significant after Cheng et al., Sarici et al.

(both more than 6 months follow-up) and Fayers et al. (no information on follow-up) were excluded from the analysis (Supplementary Figures 5 and 6) (18, 20, 23).

Relationship between Pre-operative Quality of Life and Improvement following Surgery

Meta-regression demonstrated a significant negative correlation ($p<0.001$) between pre-operative GO-QOL scores and the effect size. The lower the pre-operative GO-QOL score, the greater the improvement for both appearance and visual function after surgery (**Supplementary Figures 7 and 8**).

Discussion

To our knowledge, this is the first meta-analysis quantifying the effect size of surgical interventions for GO on quality of life measures. Primarily, we established there was a significant effect of all forms of surgical procedures on GO-QOL appearance and visual function scores using both frequentist and Bayesian approaches. For appearance, the pooled standardised mean improvement for patients after surgery was 0.72 (95% CI 0.50-0.94) and for visual functioning, the pooled SMD for patients after surgery was 0.41 (95% CI 0.25-0.58). Using the study-level mean GO-QOL change, the odds of a clinically meaningful difference was 3.6 (95% CI 1.34-9.70) for GO-QOL appearance score and 0.769 (95% CI 0.34-1.75) for GO-QOL visual functioning score.

The effect of surgery is important to quantify as although it is well established that clinical parameters such as total eye score, diplopia and ophthalmopathy index do improve with time and following surgery, these metrics may not necessarily correlate well with patients' physical and psychosocial wellbeing (3, 9, 26). The value of evaluating quality of life as part of routine clinical assessment of patients is therefore increasingly advocated to guide their management in a holistic manner (9). Our meta-regression also indicated that patients with lower quality of life at baseline were more likely to repeat more substantial improvements following surgery (Supplementary Figures 7 and 8). Furthermore, it is important to indicate where the most substantial improvements may be found with regard to both appearance and function. It would therefore be of interest to delineate whether visual function improves to a greater extent when orbital decompression is performed for optic neuropathy rather than proptosis. There was insufficient data to demonstrate this as GO-QOL scores for this indication was quoted in only ten patients in one study (13). The development and validation of disease-specific quality of life measures including the GO-QOL to evaluate these aspects have allowed interventional studies to define improvement from a more patient-centred point of view. Hence, quantitative synthesis of the effects of surgery on these end-points provides important information to guide clinical decisions while balancing the overall risks of surgical treatment.

Subgroup analysis showed that orbital decompression was associated with the greatest improvement in appearance, with a standardised mean improvement of 0.84 (95% CI 0.54-1.13). This dramatic effect on visual appearance is not surprising given orbital decompression is the mainstay of rehabilative surgery and also provides substantial benefits to visual function.

Meanwhile, strabismus correction had the strongest effect on improving visual function with a standardised mean improvement of This was unsurprising, since the primary goals for orbital decompression and strabismus correction are amelioration of disfiguring proptosis and diplopia respectively (8). Similarly, eyelid procedures which are performed to enhance cosmesis did not demonstrate a significant improvement in visual functioning (8).

For both domains, a moderate degree of statistical heterogeneity was observed. This is likely attributable to the varying surgical approaches studied, each associated with its own clinical objectives and complications, as well as the use of multiple different techniques of a type of surgery. Procedural outcomes are operator-dependent and this may introduce further discrepancies between studies, with all but one being performed in a single ophthalmological centre often by a solitary surgeon. A lack of standardised selection criteria may also contribute to the variability, given that some patients had already undergone a prior operation for GO or had received other forms of treatment which in turn may influence their baseline quality of life scores. In keeping with this, meta-regression demonstrated a significant negative correlation between baseline GO-QOL score and the effect size of surgery. Another explanation for the heterogeneity observed may be the subjective perception of quality of life amongst different individuals from a diverse spread of localities. Quality of life changes following surgery may also reflect differences in cultural norms play a role in determining one’s expectations of their quality of life (25, 27). There were also disparities in the follow-up duration of patients, however, this was not found to significantly influence changes in GO-QOL scores.

A major strength of this study was the concomitant use of a Bayesian meta-analysis to affirm the findings of the conventional meta-analysis. Bayesian analysis allowed us to integrate prior knowledge and assumptions when calculating meta-analysis and despite producing a more conservative effect size compared to frequentist approaches, the effect size remained considerable. An additional advantage in this study is the use of the GO-QOL itself, which was adopted relatively early in studies of GO and this enabled a smoother meta-analyses and clear conclusions. Indeed, this meta-analysis also provides further evidence of the validity and utility of the GO-QOL as the surgical procedures had the expected effects on GO-QOL with regard to their relative impact on visual appearance and functioning. We observed that orbital decompression influenced both appearance and function with a greater effect on appearance, strabismus surgery also had benefits on appearance and functioning but to a lesser degree whereas lid surgery had an impact on appearance but not visual function.

Nonetheless, there were several limitations in this study. As the GO-QOL scores extracted were averages of the cohort undergoing a given procedure, we were unable to comment on the effect sizes on an individual patient level and whether individual patients had attained a clinically meaningful improvement (hence study-level data SMD and odds were analysed). Moreover, this analysis was not based on controlled trials aside from one study (Sellari-Franceschini *et al*.), which was a randomised controlled trial and therefore effects observed may have benefited from a placebo effect or improvement in quality of life over time. Our studies utilised were often retrospective in nature and thus prone to selection, information and publication biases. In particular, Sarici *et al*.'s study reported a very small sample size with a large effect size (23). The strikingly low pre-operative GO-QOL scores amongst their cohort limits the generalisability of this study. We also did not incorporate unpublished conference papers or audits which may have resulted in bias against studies with unremarkable findings. We were limited in our ability to access two potentially eligible studies by the scope of our institutional search engine and a lack of author response when contacted. Finally, certain translations of the GO-QOL, originally published in Dutch and English, had yet to be formally validated *a priori* in their respective populations.

To confirm the efficacy of surgery, future studies should involve comparisons with a matched control population which may be challenging to conduct. With the emergence of promising novel therapies such as teprotumumab it would also be interesting to evaluate how surgery performs against the latest medical interventions. Additionally, GO patients often require more than one operation as part of a wider rehabilitative plan, and therefore it would be of value to assess whether quality of life continues to improve and to what extent. Future studies using individual patient level data could be undertaken to determine the likelihood of individual patients achieving a clinically meaningful improvement, and to identify predictive factors that correlate with responsiveness to surgery in the context of quality of life. In turn these could assist in guiding clinical decision-making and informing the likelihood of improvement amongst surgical candidates.

Conclusion

Graves' orbitopathy can be highly debilitating with substantial long-term negative connotations for patients' psychosocial wellbeing and quality of life. A multidisciplinary approach is often required to manage this condition. Rehabilitative surgery can substantially improve disease-specific quality of life in these patients although the choice of operation impacts on different aspects of quality of life to a varying extent.

Authors' Contributions

Conceptualisation, C.M.D.; study search and selection, C.H.L., T.W.; data extraction, S.G., T.W.; data analysis, C.H.L., S.G., T.W.; manuscript preparation, C.H.L, S.G., T.W.; manuscript review and editing, C.H.L., S.G., T.W., R.R., J.U., R.W.J.L., C.M.D., P.N.T.; supervision, C.M.D., P.N.T.

Author Disclosure Statement

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Table Heading

Table 1. Characteristics of studies.

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