



Quality of Life in Patients Receiving Botulinum A Toxin Treatment for Symptomatic Anal Fissure

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Abstract

Aim: To quantify changes in quality of life of patients treated with Botulinum A for chronic anal fissure.

Background and Literature Review: Anal fissures represent about 10% of colorectal clinic referrals. Chronicity is defined as a fissure that has persisted for greater than 6 weeks despite medical treatment. The underlying hypothesis is that chronic fissures have a raised resting anal pressure from internal anal sphincter hyper tonicity. Medical treatment for anal fissures includes GTN 0.2%/Diltiazem paste [1]. Resistant cases may be offered Botulinum Toxin or lateral internal sphincterotomy if Botox treatment fails. Sphincterotomy produces good healing rates but is associated with incontinence to flatus in up to 30% in long term follow up [2]. Prior to surgery, anal manometry should be performed on all cases except males who have not had previous anal surgery. If sphincter resting pressure is low, these refractory cases have a better outcome following an advancement flap procedure [3]. Meta analysis suggests medical treatment is safe for chronic anal fissure and reserves surgery for treatment failure [4-7].

Methodology: This observational study includes patients treated for chronic anal fissure. Patients qualifying for the study, with a diagnosis of chronic anal fissure, were entered into a database over a period of 2 years. Details of procedure carried out were verified from individual operation notes, demographics, symptoms; diagnosis and treatment details were recorded. Outcome measures used were patient symptoms and QOL scores. The Quality of life scores were recorded before and after respective procedure at follow up. The cohort of patients was assessed using the SF 36 Quality of Life Assessment Form [8-11]. The dimensions on SF-36 response score scale of 100 (best) to 0 (worst) were analyzed. The data are presented as median (range).

Results: The cohort included 24 patients. Fourteen patients were male. The median age was 48 (28-77) years. 95.83% patients completed the SF-36 form. This revealed that their quality of life improved significantly in physical functioning, pain, social functioning and mental health.

Conclusion: QOL data is rarely acquired in surgery so adds new knowledge to the study by using available tools to assess quality of life in patients undergoing minor surgical treatment. Our study shows improvement in the quality of life in patients treated with Botox for chronic anal fissure at follow up.

Introduction

An anal fissure (fissure-in-ano) is a longitudinal split in the anoderm of the distal anal canal, which extends from the anal verge proximally towards but not beyond the dentate line [1]. A fissure-in-ano represents up to 10% of new referrals in a colorectal clinic. It is associated with pain on defecation, which persists for minutes to hours and is associated with per rectal bleed. Clinical examination usually demonstrates a sentinel skin tag or fibro epithelial polyp regardless of the duration of the symptoms. The fissure in most cases is single and anteriorly situated at 6 o'clock. In 10% of cases it is present at 12 o'clock [2]. In cases where patients present with multiple fissures, one should be suspicious of inflammatory bowel disease, tuberculosis, syphilis or HIV. Aetiology is multifactorial and is linked to constipation in 10%, straining during defecation in 30% and associated with childbirth in 10% [3].

The majority of fissure-in-ano is acute and resolve with conservative management. Treatment for anal fissures includes GTN 0.2%/Diltiazem paste [4]. Resistant cases may be offered Botulinum Toxin (Botox) or lateral internal sphincterotomy. The option of surgery is used when Botox treatment fails. Sphincterotomy produces good healing rates but is associated with incontinence

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to flatus in up to 30% in long term follow up [9]. Prior to surgery, anal manometry should be performed on all cases except males who have not had previous anal surgery. If the sphincter resting pressure is low, these refractory cases have a better outcome following an advancement flap procedure [13]. Meta analysis suggests medical treatment is safe for chronic anal fissures and reserves surgery for treatment failure [14,21].

A chronic fissure is one that has persisted for greater than 6 weeks despite medical treatment. The underlying hypothesis is that a chronic fissure has a raised resting anal pressure from internal anal sphincter hypertonicity [15]. It has been shown that agents used to relax the internal sphincters lead to fissure healing. The resting anal pressure returns back to pre-treatment state in terms of function, the local ischemia and the internal sphincter hypertonia set back to the previous level once the fissure has healed and the treatment discontinued. Lund *et al.* [17] showed that anal spasm does not respond to pain because application of topical local anaesthetics relieves pain but not the spasm [18]. Chronic fissures have also been linked to decreased blood flow leading to tissue hypoxia and further lack of healing of the tissues [19]. Other hypotheses put forward suggest an inflammatory process, Brown and colleagues suggest the inflammatory process leads to myositis which in turn progresses to fibrosis [20]. The tissue tethering from resultant fibrosis leads to lack of partial eversion of the anal canal during evacuation resulting in tearing of the mucosa [17].

Botox treatment is used when conservative medical treatment fails [22]. Botulinum toxin A is a protein and neurotoxin produced by bacterium *Clostridium Alan Scott*, an ophthalmologist and Edward Schantz were the first to work on a standardized Botulinum toxin preparation for therapeutic purposes in 1960 and used Botulinum toxin type A (BTX-A) in monkey experiments in 1970 [23]. In 1980, he officially used BTX-A for the first in humans to treat strabismus. In 1993, Pasricha and colleagues showed Botulinum toxin could be used for the treatment of achalasia, a spasm of the lower esophageal sphincter [24-25].

The mode of action of Botox is due to inhibition of the release of Acetylcholine at the neuromuscular junction competing and binding to presynaptic cholinergic nerve terminals.

The distressing symptoms caused by a chronic fissure-in-ano are very likely to affect the quality of life of a patient, Griffin *et al.* [31] have shown successful non surgical treatment of fissure (use of Diltiazem) in ano improves quality of life in patients. Our study replicates that although no average QOL score in healthy people to compare to due to the absence of a control group. The efficacy of Botulinum toxin A has been investigated and reported in a number of randomized clinical trials and meta-analysis of trials suggest it is significantly better [28]. The patients' perception of outcome has been assessed in only a hand full of studies. In this novel prospective study we have looked to compare the quality of life in such patients before and after treatment with Botox [26,27].

Aim

To quantify the change in quality of life scores of patients presenting with chronic anal fissure after treatment with Botox.

Material and Methods

Patients with symptomatic chronic anal fissure disease from a single consultant's practice at a University Hospital were included

in the study. This prospective observational study comprises of a single consultant's practice. The study was approved by the local ethics committee and registered with the in house clinical effectiveness team. The subjects included in the study were the patients diagnosed with chronic anal fissure symptoms due to be treated with Botox (Botulinum neurotoxin A). These were entered in a prospective database. The operation notes were reviewed to confirm treatment. Consecutive patients treated over a 3-year period by a single consultant were reviewed. Patients with chronic anal fissure symptoms to be listed for Botox treatment were given the questionnaire on consenting to inclusion in the study at the clinic visit. They were issued with a further questionnaire to be completed after the procedure and handed in when they returned for their follow up at 2 months interval.

Patient demographic, symptoms, procedure findings and treatment were recorded; these are illustrated in Table 1. The questionnaire used for recording the pre and post procedure "the Short Form 36" survey responses were in line with the generic Short Form -36 Health Survey (SF-36) (Figure 1), whose validity has been established in multiple countries i.e. in the Netherlands, USA, Japan and in a short form version SF-20 in Scotland [6,7,26,27].

Study Design

Inclusion criteria

1. Patients included were all those who were symptomatic after failed medical treatment with stool softeners and Diltiazem ointment for 8 weeks.
2. Patients consenting to the proposed study.

Exclusion criteria

1. Patients with allergies to medical treatment or non-compliance were excluded.
2. Patients with recurrent fissure-in-ano previously treated with Botox were also excluded.
3. Patients with inflammatory disease, hemorrhoids and abscess warranting surgery.

Each patient received examination under anaesthesia of the anus and an inter-sphincteric Botox injection. They were discharged with instructions to take a laxative for 2 weeks post procedure and a follow up was arranged in 2 months' time. Digital examination and proctoscopy at the follow up clinic was carried out to evaluate healing.

Health Assessment Tools

Quality of Life (QOL) was assessed by making use of the Short Forum 36 health survey (SF-36) 23 at index and post-operative follow up check. The questionnaire takes into perspective the dimensions of health and wellbeing from the patient's point of view. The survey incorporates physical functioning, symptoms, mental, emotional health and social functioning along with the patient's satisfaction of the procedure carried out. The proforma used is displayed in Figure 1. Items are scored on a 4-point scale with response categories consisting of very satisfied (100 points), somewhat satisfied (75 points), somewhat dissatisfied (50 points), and very dissatisfied (<25 points). The scale score is the unweighted mean of the scores from the individual items, ranging from 0 to 100 per item (with 100 being most satisfied). As a default the questionnaire was resent if the completed form was not handed in at the follow up clinic. In some cases there was a need to contact the patient by phone, on occasions a reminder

Area	Dimension	No. Of Questions
Functional status	Physical functioning	10
	Social functioning	2
	Physical limitations	4
	Emotional limitations	3
Wellbeing	Mental health	5
	Vitality	4
	Pain	2
Overall evaluation of Health	General Health perception	5
	Health change	1
		36

Figure 1: SF 36 Analysis data sheet Questionnaire [23].

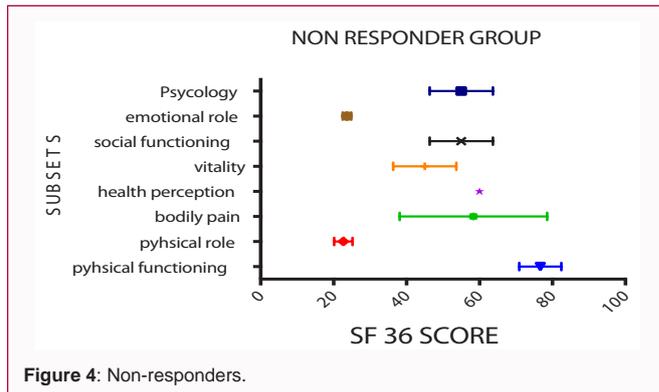


Figure 4: Non-responders.

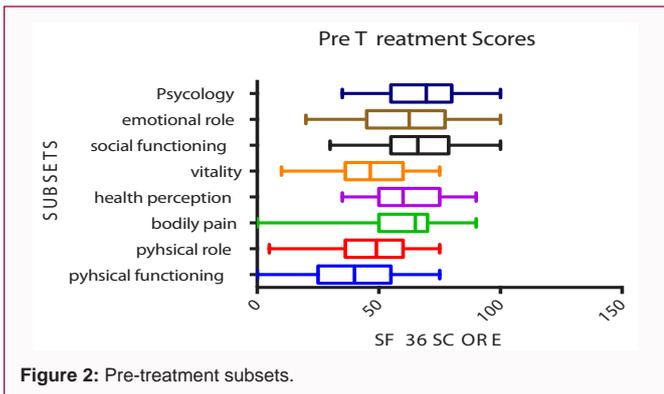


Figure 2: Pre-treatment subsets.

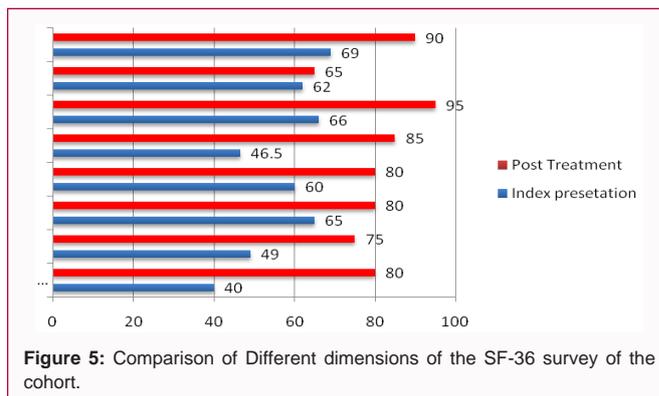


Figure 5: Comparison of Different dimensions of the SF-36 survey of the cohort.

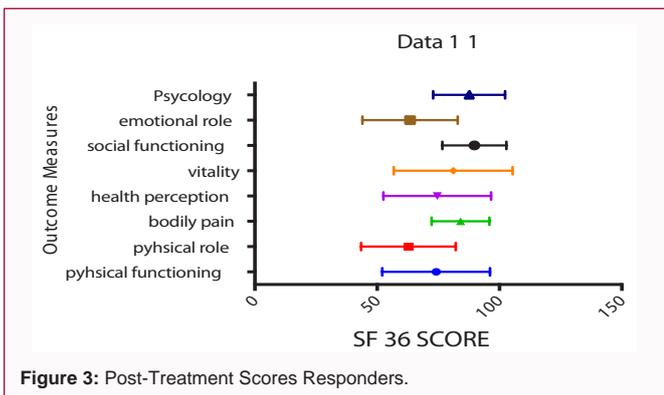


Figure 3: Post-Treatment Scores Responders.

by post had to be sent out where follow-up data was not available or incomplete. The SF-36 questionnaire used was a straightforward form measuring the functional status i.e. ability to physically perform routine work, ability to perform social functions, a measure of limitations at physical and emotional problems.

The wellbeing of patients was assessed using the outcome markers of symptoms, pain/discomfort, bleeding, discharge, mental health and vitality. The overall health evaluation was scored on perception of improved health symptoms as a result of health change post procedure.

To address the study weakness of a lack of a control group (this discussion and adjustment does not address the lack of a control group, it does address acceptability) and acceptability we arranged a consultation with colorectal/pelvic floor specialist nurse and educational supervisor and the clinical effectiveness team. Unfortunately time restraint meant we were unable to involve a control group and assess the retest reliability of the modified questionnaire.

The patients were asked to score themselves on all criteria in the

questionnaire at index clinic, subsequently they were asked to hand in their post procedure scoring sheets at the follow up clinic.

Statistical Analysis

Data are presented as medians (interquartile range or range as stated). The dimensions on SF-36 response score scale of 100 (best) to 0 (worst) were analyzed using Graph pad version 6 (GraphPad Software, Inc. 7825 Fay Avenue, Suite 230 La Jolla, CA 92037 USA). General symptoms were independent variables while age, sex, ASA were analyzed as additional co variants. Where statistical comparisons are made, non-parametric analyses are used and significance is accepted at the P at <0.05 level. Variables at index presentation and post procedure were compared using non-parametric tests. Multiple comparisons were made using Kruskal–Wallis test and contingency tables were analyzed by X² test incorporating Yates correction.

Results

The number of patients forming part of the study was 24. Fourteen patients were male. The median age was 48 (28-77) years. Treatment success rate (i.e. healing of the fissure) was 20(86.85%).

The demographics data, symptoms, site of fissure and corresponding units of Botox administered is illustrated in Table 1. One patient did not attend follow up clinic nor respond to reminders. Three patients complained of on-going symptoms of pain of which one subject attended accident and emergency for relief. He developed infection and a perianal haematoma. Treatment lead one subject having temporary incontinence to flatus, all subjects were continent at follow up at 2 months. 95.83% patients completed SF-36.

Symptoms before and at follow up are shown in Table 2, The scoring of severity of the symptoms at index presentation and follow up post treatment on a numerical scale ranging for 0-100;

Table 1: Demographic features of the Cohort.

		Median (range)
1	Age	48 (28-77)
2	Sex/ F/M	14/10
3	ASA	1 (1-3)
4	Pain	24 (100%)
5	Bleeding	17 (71%)
6	Irritation	15 (62.5%)
7	Position of fissure	
	Anterior	4
	Posterior	19
	Both	1
8	Botox	60 (40-100) units

Table 2: Pre-treatment vs. Post Treatment symptom scores.

Symptoms	Index presentation Median (range)	SEM	Follow up Median (range)	SEM
Bleeding	65 (25-100)	3.928	46.5 (0-75) ^A	3.695
Pain	80 (20-100)	4.398	40 (0-75) ^A	4.225
Pruritis	80 (60-100)	2.505	65 (0-90) ^B	2.961

Table 3: Scores of Short-forum 36 health survey, subscales before treatment.

Subscales	Median (range)
Number of patients	24
Physical functioning	40 (0-75)
Physical role	49 (5-75)
Bodily pain	65 (0-90)
Health perception	60 (35-90)
Energy (Vitality)	46.5 (10-75)
Social functioning	66 (30-100)
Emotional role	62.5 (35-100)
Mental health	69.5 (35-100)

this was categorized as 0 with no symptoms and 100 as worst, very distressing: (76-100 points), moderate (51-75 points), minimal (26-50 points), and occasional (0-25 points). Significant improvement seen in symptoms of pain and bleeding (p value 0.005), pruritis showed improvement but to a lesser degree yet significant (p=0.03). The Pre and Post treatment Quality of life scores are show in Table 3 and 4 respectively. The treatment resulted in healing of the fissure in 20 (87%) of cases, of which patients 17 were symptom free.

In our study the cohort was broken down into sub groups to see if age had any impact as a predictor for physical function. Age above 65 had a negative predictor for physical functioning, on regression analysis (variables included age, ASA grade and pain). SF-36 scores after treatment showed an improvement on outcome measures are seen in Figure 3.

Comparison of the pre and post treatment data showed significant higher scores on health perception, improvement in physical and social functioning along with mental health and Vitality. Pain score also showed an improvement in the healed cases. Of the Three patients who failed to respond to the treatment required further intervention of which 2 patients had a repeat treatment with Botox. Their follow up after 2nd treatment is not included in the study. The outcome measures of the non-responders are shown in Figure 4. SF-36 Scores in the Non responders after treatment have been illustrated in Table

Table 4: Scores of Short-forum 36 health survey, subscales after treatment.

Subscales	Median (range)
Number of patients	23
Physical functioning	80 (20-100)
Physical role	75 (23-100)
Bodily pain	80 (60-100)
Health perception	80 (0-100)
Energy (Vitality)	85 (0-100)
Social functioning	95 (50-100)
Emotional role	65 (23-100)
Mental health	90 (50-100)

Table 5: Follow up Results.

	NUMBER (n)	%
Pain free	17	73.91
Healing	20	87
Re Botox	2	8.6
Surgery	1	4.3
Continence	23	100%

Table 6: Median (range) scores of short-forum 36 health survey, subscales in non-responders after treatment.

Number of patients	3
Physical functioning	80 (60-80)
Physical role	23 (20-25)
Bodily pain	55 (40-80)
Health perception	60 (60-80)
Energy (Vitality)	40 (40-55)
Social functioning	40 (50-65)
Emotional role	50 (50-65)
Mental health	23 (20-25)

6. Non-responders were compared to responders, the results showed healed group had significant higher scores on physical functioning, mental health and bodily pain.

Comparisons of pre and post treatment SF-36 scores show significant improvement in 7 subsets. The data has revealed there was no significant change in the emotional status/scores/function in either of the groups. Physical functioning is directly related to the improvement in the pain score Table 2, (p value =0.001). On comparison higher scores where seen on 4 subsets of the Functional status. Overall the general health evaluation showed an improving score with decrease of symptoms (Figure 2).

Discussion

The study shows Botox treatment for chronic anal fissure is effective with minimal complications. The Quality of Life Scores show an improvement, which confirm the efficacy of the treatment. The mechanism of action of Botox affects the sympathetic nerve function leading to blockage of the myotonic tone of the internal anal sphincter thus decreasing the sphincter hypertonia. Theories suggest this in turn increases the local tissue vascular perfusion and accelerates the healing procedure. The effects of Botox last for up to 3 months allowing healing of the fissure.

Table 7: SF 36 Characteristic Functional Scoring Post-treatment: Median (Range).

	Number	Physical Function	Physical Limitation	Social Functioning	Emotional Limitations
Cohort	23				
Age					
<30	3	90 (25-100)	90 (85-100)	80 (65-90)	75 (65-80)
30-65	17	80 (20-100)	80 (60-100)	87 (23-100)	95 (60-100)
>65	3	70 (80-100)	70 (80-100)	90 (50-95)	60 (0-100)

Analysis of the SF36 pre and post scores showed (analysis doesn't change anything!) to a positive impact on mental, emotional and physical aspect of a patient. The study demonstrated that bodily pain was directly related to lower perception in general health. It shows pre treatment patients significant had more bodily pain. Quality of life in the cohort of patients showed significant improvement in all 8 scales of the SF-36 form.

In our study follow up was achieved for 23/24 patients. The results show health related QOL improved in scales; vitality, pain, physical role (role limitations), social functioning and physical functioning. The results show pain is a significant factor influencing the outcome by driving up the subscales scores. In our study analysis showed 5 scales to be influenced with symptoms of pain. A study carried out by Griffin and Scholefield *et al.* [28] reported symptoms of pain affected all the subscales. Ortiz *et al.* [8] looking at quality of life in chronic anal fissure cases undergoing lateral sphincterotomy indicated that 6 out of the 8 subscales of SF-36 showed significant improvement which was again directly related to ratio of post defecatory symptoms. Tsunoda A *et al.* [29], in his work showed that symptoms of chronic anal fissure (pain, pruritis and bleeding) were linked not only with bodily pain but also social functioning of an individual. Our study, although lacking a matched control group, has nonetheless answered the study question and quantified the (positive) change in quality of life scores after treatment with Botox. A further validation with a control group could add new knowledge and highlight the rare use of QOL data in Surgery. It is also important to highlight the fact that there is no disease specific tool for assessing the quality of life in patients with chronic fissure-in-ano disease. Due to the non-availability of a disease specific questionnaire, a standard generic instrument was used which was modified to address the disease investigated.

Given the host of potential confounding factors and absence of a control group it is important to acknowledge that the minor changes in health survey scores could go unnoticed. However, one permissible interpretation is that improvement in the bodily pain symptoms appears to influence the outcome of wellbeing and patient satisfaction.

Study Highlights

What is currently known?

Chronic anal fissures are a common problem with significant morbidity. QOL assessment in patients with chronic anal fissure after surgical intervention had been carried out (only a hand full published).

Meta-analysis suggests Botox is safe with minimal side effects. Late recurrence after Botox treatment is higher than after surgery, which is reserved for treatment failure.

What is new here?

A novel study assessing Quality of life in patients with chronic

anal fissure being treated with Botulinum A toxin.

Quality of life improvement is confirmed.

Conclusion

In conclusion, this study has reported the novel information on improvement in Quality of life with Botulinum A treatment in a well characterised cohort of patients with chronic anal fissure disease. The results show positive impact on mental, emotional and physical aspect of a patient an overall improvement in QOL of patients at their follow up.

The results from this group show that Botulinum A toxin is safe, acceptable and possibly effective but how does that compare to the other treatments? A larger trial could be helpful to validate QOL in patients treated with Botox alongside conservative medical treatment and patients requiring surgery.

Items are scored on a 4-point scale with response categories consisting of very satisfied (100 points), somewhat satisfied (75 points), somewhat dissatisfied (50 points), and very dissatisfied (25 points). The scale score is the unweighted mean of the scores from the individual items, ranging from 0 to 100 per item (with 100 being most satisfied). All patients gave informed consent to participate in this study when seen in clinic and after decision for Botox treatment made. Patients were follow up was incomplete were resent the questionnaire and some were contacted by phone, were follow-up data was not available.

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