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Response Rate to Glyceryl Trinitrate as First Line Therapy in Patients with Chronic Anal Fissure in Kirkuk City

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Abstract Chronic anal fissure is common perianal condition. Surgical sphincterotomy is very successful at healing these fissures but requires an operation with associated morbidity. Temporary reduction in sphincter tone can be achieved on an outpatient basis by applying a topical nitric oxide donor (glyceryl trinitrate) 0.4% twice daily for four week duration. A total of 120 patients with chronic anal fissure were collected randomly from Kirkuk general hospital and private surgerical clinic prospectively from September 2014 till December 2015. Whether pharmacological treatment or surgical treatment is the best first line options in the treatment of chronic anal fissure will be the main issue of this study. **Results:** A total of 120 patients with chronic anal fissure were enrolled in this study. All patients received (GTN) as first line therapy for 4 week. 100 patients were able to complete medical treatment, while the remaining twenty patients were unable to complete medical treatments due to side effects caused by the drug. Regarding medical treatment outcome: 65 of patients(from total 100) (45 male, 23 female) achieved complete recovery and only 35 of patients (23 male, 12female) failed to reach complete recovery even after 4 week of treatment and undergoing sphincterotomy as second line options. About 91%(n=59) of patients achieved complete recovery within 2-3 week from the start of (GTN), and 9% (n=6) of patients recovered with complete 4 week administration of (GTN). **Conclusions:** digital application of glyceryl trinitrate as first line therapy for chronic anal fissure was the best choice for majority of patients, with treatment course of 4 week.

Keywords: *anal fissure, innovation therapy, glyceryl trinitrate, lateral internal sphincterotomy, Kirkuk*

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1. Introduction

Chronic anal fissure is a common benign disorder that causes severe, sharp anal pain during defaecation. Fissures are generally associated with raised resting anal pressures, and treatments are aimed at reduction of these pressures. [1] Most anal fissures are idiopathic with no identifiable underlying disease process. There is no simple and unified theory to explain their genesis though constipation and lack of dietry fibre are implicated. Most fissures occur in the posterior midline; this may be anatomically related as there is a lack of tissue support posteriorly within the anal canal. Fissures associated with pregnancy are commonly located anteriorly and are often associated with low anal canal pressures. Other causes of fissures include Crohn's disease, syphilis, human immuno-deficiency virus (HIV) or tuberculosis. [2] Lateral internal sphincterotomy (LIS) is considered the 'gold standard' therapy for chronic anal fissure (CAF) and relieves symptoms with a high rate of healing and less than 10% long term recurrence. [3] This optimal therapy has, however, been associated with the development of a period of transient postoperative impairment of anal continence in 30% (or even more) patients which can become permanent. [3] In all the examined studies, a long (>6 weeks) duration of symptoms was considered a sufficient inclusion criteria irrespective of fissure appearance. [4] Standard surgical treatment even though available, may require long hospital stay and sometimes have worrying complications like anal incontinence. So non-surgical treatment, Glyceryl Trinitrate has been shown to be an effective for chronic anal fissure. It decreases anal tone and ultimately heals the anal fissure. [5] Chemical sphincterotomy has been tried using a variety of novel agents including topical glyceryl trinitrate (GTN), calcium channel blockers such as nifedipine or diltiazem and botulinum toxin. Some of these agents were found to be effective in healing chronic anal fissure with negligible side effects and are now considered as first line treatment for chronic anal fissure. [6] Observations with respect to relief of pain, no bleeding and healing were recorded at 2, 6 and 12 weeks of duration. Lateral sphincterotomy remains effective but should be reserved for the patients who fail to respond to initial chemical sphincterotomy or GTN therapy. GTN is good alternative mode of therapy for patients who refuse surgery and prefer medical line of treatment. [5] In a prospective cohort study using topical isosorbide dinitrate Schouten et al. [4] found that fissure healing rate increased

with treatment duration. Healing rate was 35% at 6 weeks and 88% at 12 weeks. Higher healing rate at 10 weeks (89%) vs. 5 weeks (67%) is also documented in a randomized trial of sphincterotomy vs. isosorbide dinitrate. [7] This systematic review of seven trials validates and strengthens the finding of a previously published meta-analysis of two randomized trials. Both DTZ and GTN are equally effective in the management of CAF. However, DTZ is associated with a lower incidence of headache and recurrent fissure. Therefore DTZ should be the preferred first line of treatment for CAF. [8] Initial treatment is centred on conservative management with general measures, such as topical analgesics, increasing dietary fibre, laxatives and maintaining appropriate fluid intake. Medical management utilises topical glyceryl trinitrate (GTN) 0.4% and diltiazem 2% creams, whilst Botulinum toxin (Botox) has also been shown to be effective. Surgical treatment is often necessary if conservative and medical managements are ineffective. A variety of procedures are employed including lateral sphincterotomy, fissurectomy and anal advancement flap.

2. Patients and Methods

This study was carried out in Kirkuk general hospital and private clinic. A total of 120 patients with chronic anal fissure were collected randomly from both center prospectively from September 2014 till December 2015. Symptoms (especially pain) had been present in each patient continuously for at least 3 months. Full physical examination and digital rectal examination performed for each patient at time of admission and thereafter. The treatment program consisted of digitally self application of glyceryl trinitrate 0.4% two times each day for four weeks as first line therapy, with evaluation of patient regarding pain, bleeding, anal tone and fissure healing in every week end in order to observe patient response to medical treatment. Sphincterotomy was assigned as second line therapy after failure of medical treatment (A total 4 week course of GTN) or patients intolerance to medical treatment. Patients with comorbid disease (hypertension, diabetic, and heart disease) were excluded from this study.

3. Statistical Analysis

All patients' data entered using computerized statistical software; Statistical Package for Social Sciences (SPSS) version 17 was used. Fishers exact test was used for categorical variables.

4. Results

Cases were diagnosis AS follow: age 40-49 (23.3% male (n=28), 15% female(n=18)), age30-39 (male 18.3%(n=22), female 10% (n=12), age 20-29(male 13.3%(n=16), female 5%(n=5), and only 8.3% of male (n=10) and 6.7% of female (n=8) were at age ≥ 50 year old at diagnosis. As showed in (Table 1).

A total of (76) male and (44) female were involved in this study. fissure locations were: posterior fissure in male (n= 58, 73.31%) and female (n= 6, 16.63%), anterior fissure in male (n= 13, 17.1%) and in female (n= 36, 81.8%), combined (anterior and posterior) in male (n= 5, 6.57%) and in female (n= 36, 81.8%). Pain was present in all cases with anal fissure while bleeding account for (n= 14, 31.81%) in female and (n=30, 39.47%) in male. Half of male and female patient had sentinel skin tag, one fifth of them had hypertrophied anal papillae, and about one third of them had combined or other type of anal fissure. As showed in (Table 2).

Table 1. Age Distributions for patients with Chronic Anal Fissure according to Gender

Age of patients	Male		Female	
	n	%	n	%
20-29 Y	16	13.3%	6	5%
30-39 Y	22	18.3%	12	10%
40-49 Y	28	23.3%	18	15%
≥ 50 Y	10	8.3%	8	6.7%
Fisher exact =13.2		**P-value=0.0432**		

Table 2. Patient Characteristic of Anal Fissure according to Their Gender

	Male		Female	
	n	%	n	%
Patients (*n*)	76	100%	44	100%
Location of Fissure				
Posterior	58	73.31%	6	13.63%
Anterior	13	17.1%	36	81.8%
combined	5	6.57%	2	4.54%
Symptoms				
pain	76	100%	44	100%
Bleeding	30	39.47%	14	31.81%
Feature of Chronicity				
1. Sentinel Skin Tag	37	48.68%	23	52.27%
2. Hypertrophied Anal Papillae	12	15.78%	7	15.9%
3. Combined of 1&2	7	9.21%	3	6.81%
4. Others	20	26.31%	11	25%

About (83%) of patients (n=100) were able to complete the medical treatment, while (17%) of patients (n=20) were unable to complete the medical treatment. As showed in (Figure 1).

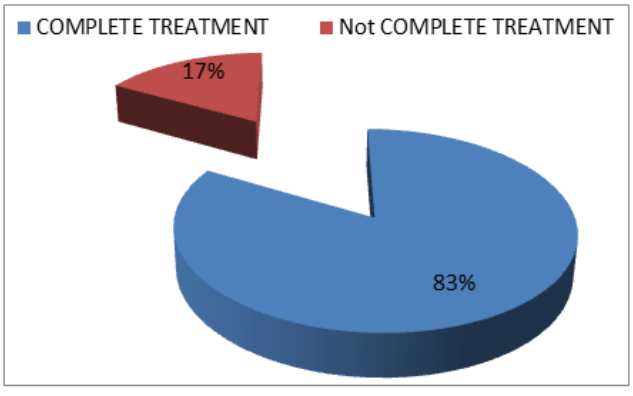

Figure 1. Distributions of Patients according to completions of Medical Treatment (GTN)

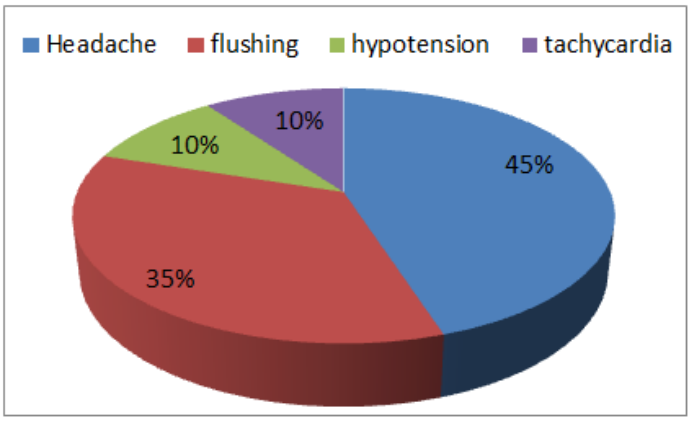

Figure 2. Patients Distributions according to Causes of Medical Treatment Cessation

The major causes for stopping the medical treatment was because of headache 45%, flushing 35%, hypotension 10%, and tachycardia 10%. As showed in (Figure 2).

About two third (n=65) of the cases respond to the medical treatment with (GTN), and one third (n=35) of the cases failed to respond to the medical treatment. A 42% of male and 23% of female were in responding arm, while 23 % of male and 12% of female were in non responding arm. As showed in (Table 3) there was significant association between patient respond to medical treatment and degree of anal fissure chronocity (especially Sentinel Skin Tag) with p value of 0.0005.

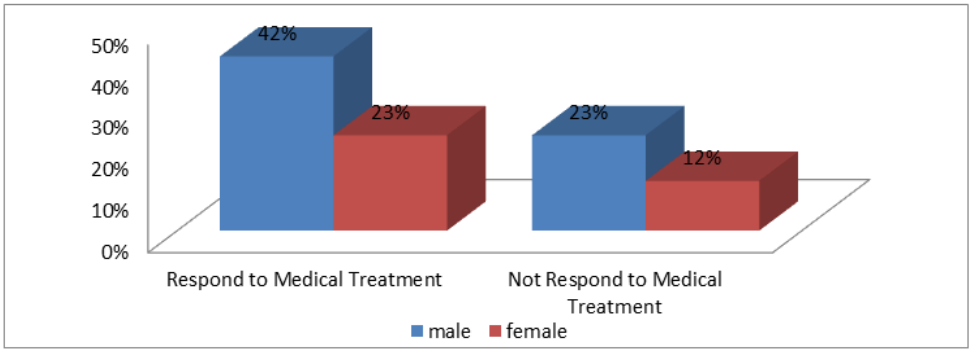

Figure 3. Distribution of Patients according to Gender and Response to Medical Treatment (GTN)

Table 3. Distribution of Patients according to Degree of anal fissure chronocity and Their Response to Medical Treatment(GTN).

Features of Chronocity	Respond to Medical Treatment		Not Respond to Medical Treatment	
	n	%	n	%
1. Sentinel Skin Tag	49	49%	5	5%
2. Hypertrophied Anal Papillae	10	10%	5	5%
3. Combined of 1&2	5	5%	3	3%
4. Others	1	1%	22	22%
Fisher exact = 113			**P-value= 0.0005**	

A 35.5% (n=23) of male and 20% (n=13) of female achieved recovery within 2 week with use of GTN, 23% (n=15) of male and 12 %(n=8) of female recover within 3 week with use of GTN, 6.15% (n=4) of male and 3 % (n=2) of female recover within 4 week with use of GTN. And no patients achieved recovery in the first week of the starting the medical treatment. As showed in (Figure 4).

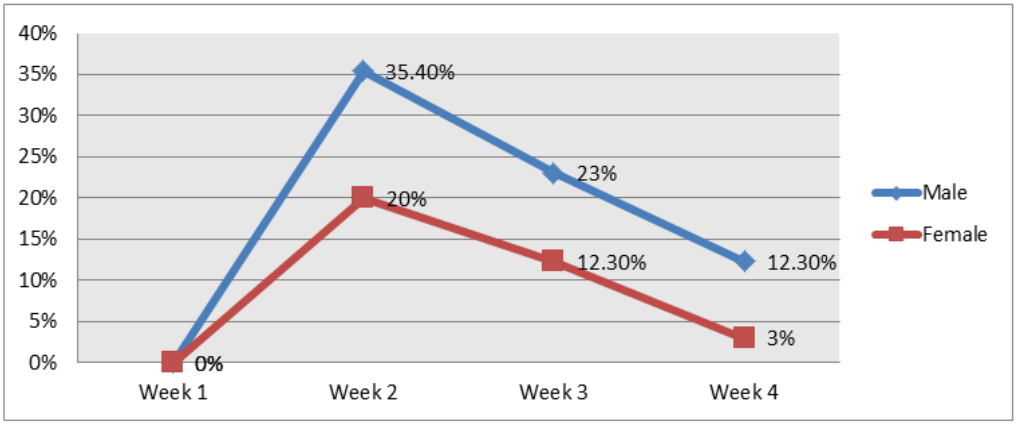

Figure 4. Male and Female Distributions according to Recovery Time

5. Discussions

The peak incidence of chronic anal fissure for both male and female in this study occurs at age 40-49 years (38.3%) followed by age group 30 -39 years (28.3%), and only 15% occur at age ≥ 50 years. This is in disagreement with population based cohort study that show increase in incidence with older age group especially for male patient. [9] The incidence of chronic anal fissure is more common in male than in women (63.3% vs 36.7%) in this study, this is in disagreement with another study done in 2011 which shows slight female predominance to this disease. [9,10] About three quarter of patients were able to complete the medical treatment and only 17% discontinued the medication due to side effect of drug and underwent surgery as second line therapy. This is higher than the study done in Erbil where only 60% of patients were able to complete the medical treatment. [11] The most common side effect of the drug was headache (45%). This is also in agreement with the previous study done by Ansar Latif and Fenton C [12,13] Fissure healing rate was 65% in medical group (use of GTN), and failure rate was 35% in medical group (use of GTN). This is in agreement with other studies. [12,13,14] There was asignificant association between degree of anal fissure chronocity and responce rate to GTN (p value = 0.0005). This was in agreement with a study done in 2003. [15] The maximum time required for complete recovery was 4 weeks with majority of the cases reaching the complete recovery in the second and fourth week from starting of GTN treatment (90%). This is in disagreement with other studies may be because majority of our patient show early signs of anal fissure chronocity, using of higher dose of (GTN), and different treatment course in those studies [10,15,16,17].

6. Conclusions

Majority of patients with chronic anal fissure were middle aged. Digital application of glyceryl trinitrate in adose of 0.4% as first line therapy for chronic anal fissure was the best choice for majority of patients with best response rate, and treatment course of 4 weeks.

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