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THERAPEUTIC IMPACT OF GLYCERYL TRINITRATE IN SOME BENIGN ANAL CONDITIONS

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PURPOSE: *Internal anal sphincter hypertonia plays a role in the etiology of pain associating fissure in ano (F.I.A), thrombosed external haemorrhoids (T.E.H), and in the post operative period for minor anal procedures such as hemorrhoidectomy, excision of anal warts or polyps or even after fissurectomy. Nitric oxide is found to be the neuro-transmitter that mediates relaxation of IAS in response to recto-anal inhibitory reflex. This report documents a therapeutic role for nitric oxide in the treatment of such painful benign anal conditions.*

METHODS: *The study included 230 patients with painful anal conditions. In group (A), including 170 patients with chronic anal fissure (76 patients), T.E.H (26 patients), & post-operative (68 patients). Treatment consisted of topical glyceryl tri-nitrate. In group (B), including 60 patients with C.A.F (20 patients), T.E.H (10 Patients) & post-operative (30 patients). They received the usual local anaesthetic and antibiotic creams. Manometric studies were performed before, during and after treatment with the evaluation of maximum resting pressure (MRP), maximum squeeze pressure (MSP),& recto-anal inhibitory reflex (RAIR).*

RESULTS: *In group (A), all patients reported marked relief of anal pain within 3 - 5 minutes following local application of glyceryl tri-nitrate cream. Pain relief lasted from three to six hours. Pain control was achieved in 92.11% of patients with C.A.F, 84.61% of patients with T.E.H and 88.23% of patients in postoperative period within 4 days. Healing had occurred in 78.94% of patients with chronic anal fissure, 88.46% of patients with T.E.H & 79.41% of postoperative patients within four weeks of glyceryl tri-nitrate therapy. These results were significantly superior to that obtained in patients in group (B), as pain control was achieved in 70% in patients with anal fissure, 60% in patients with C.A.F & 60% in postoperative patients within 4 days of therapy. Also healing had occurred in 40% of patients with F.I.A, 60% of patients with T.E.H & 70% of patients in the postoperative period within 4 weeks .Manometric studies in patients in group (A) showed significant decrease in MRP , MSP & RAIR values while patients in group(B) showed no significant changes .*

CONCLUSION: *Topical application of glyceryl tri-nitrate appears to have a powerful relaxing effect on IAS with a significant decrease in MRP and hence help healing and relief of pain associating painful anal conditions.*

INTRODUCTION

High pressures in the anal canal are primarily due to the myogenic properties of the internal anal sphincter (IAS) smooth muscle [1].IAS plays a significant role in recto-anal continence and relaxes in response to defecation and recto-anal inhibitory reflexes [2].

Recent evidence suggests that IAS is innervated by nitric oxide releasing nerves.Stimulation of these nerves releases the chemical mediator Nitric Oxide (N.O) which causes the IAS to relax. Exogenous (N.O) will cause a similar response[3]. Organic nitrates such as glyceryl tri-nitrate, a NO donor, is commonly used as a sublingual drug or as a topical gel in the treatment of angina pectoris[4]. Passive diffusion through normal skin leads to therapeutic plasma levels, mediating relaxation of smooth

muscles after a few minutes [5]. Fissure in ano (F.I.A) and acutely thrombosed external haemorrhoids(T.E.H) are common benign anal conditions usually characterised by severe anal pain that is probably of an ischaemic origin, internal anal sphincter hypertension or spasm[6]. So that, treatment of these conditions has logically focused on relieving the spasm of the internal sphincter[7].

Anal dilatation and lateral internal sphincterotomy are effective treatments for Fissure in ano. Both procedures may result in permanent incontinence of varying severity[8]. However, reversible chemical sphincterotomy using topical glyceryl trinitrate seemed likely to relief pain associated with thrombosed external hemorrhoids and anal fissure and possibly promote healing of anal fissure[9].

The aim of this study is to determine the effect of topical glyceryl tri-nitrate on manometric studies & patient acceptance in management of some benign anal conditions.

PATIENTS AND METHODS

From 1995 to 1999, a series of 230 patients with painful benign anal conditions in the form of chronic anal fissure, thrombosed external haemorrhoids & postoperative for minor anal procedures haemorrhoidectomy or fissurectomy were treated in the Colo-Rectal Surgery Unit, in Mansoura University Hospital, Mansoura, EGYPT.

Patients were randomized using the closed envelope method into two groups:

*** GROUP (A): GTN TREATED GROUP;***

Consisted of 170 patients (100 males & 70 females); ages 5-63 years with mean ages (31.76 ± 11.27 years) presented by anal pain and were diagnosed as chronic anal fissure (76 patients), external thrombosed hemorrhoids (26 patients) and 68 postoperative patients for minor anal procedures. Treatment consisted of local application of GTN super cream, which was prepared by a qualified pharmacist. It is formed of a 0.5% concentration GTN in a water base. It was given in a dose of about 0.5 gram every 4 - 6 hours applied to the anoderm and inside the anal canal for about 2 - 6 weeks. Patients were instructed to keep the cream in the refrigerator and to note any side effects such as headache, flushes or allergic reactions.

*** GROUP (B): CONTROL GROUP;***

Consisted of 60 patients (40 males & 20 females) ; ages 10-50 years (mean: 28.81 ± 8.04 years) presented by chronic anal fissure (20 patients) , ETH (10 patients) and 30 postoperative patients. They were treated with the ordinary local anaesthetic (xylocaine 2% gel or lignocaine cream) and antibiotic creams (gentamycin cream). Patients were instructed to use the local anaesthetic cream inside the anal canal fifteen to twenty minutes before defecation while using both types after defecation.

All patients were subjected to thorough clinical and laboratory investigations including mainly, manometric studies. Manometry was performed with the patients lying on the left side using a water- perfused catheter applying a continuous and a stepwise pull-through technique (SANDHIL BIOLAB CENTERAL UNIT MANOMETRY). Evaluation of maximum resting pressure (M.R.P), maximum squeeze pressure (M.S.P), and recto-anal inhibitory reflex (RAIR), was done with and without local application of GTN.

All results were recorded using a computerized recording device. Thereafter, the program of therapy was started. All patients were interviewed and examined both clinically and manometrically 3-4 days, one week, two weeks, then every two weeks thereafter untill either healing or eight weeks of therapy had passed.

Statistical analysis was performed using non parametric test for comparison. For Qualitative data, Chi-square or Fisher's exact probability test (2 samples, unpaired) or Mc Nemar test (2 samples paired) was used. For the quantitative data ,Wilcoxon`s signed Rank test (two samples, paired) with correction for ties was used. Two sided value ≤ 0.05 were considered significant.

RESULTS

GROUP (A)

All patients in group (A), treated with GTN reported marked subjective relief of anal pain within 3-5 minutes after local application. Pain relief lasted 3-6 hours thereafter. In 70 (92.11%) patients with chronic anal fissure, pain control was achieved within 3-4 days and complete healing which was characterized by re-epithelialization of the anal canal has occurred in 60 (78.94%) of them within 4 weeks of therapy.

-22 (84.61%) Patients with ETH also reported marked relief of pain within 4 days after GTN therapy & resolution was complete in 23 (88.46%) patients after about 2-4 weeks.

-60 (88.23%) of postoperative patients who received GTN therapy experienced relief of pains specially that followed defecation & healing has occurred in 3-4 weeks in 54 (79.41%) of them.

Patients in group (A), showed a significant decrease in MRP as regards the values recorded before therapy; (mean value: 125.81 ± 25.39 mm Hg) to (96.17 ± 18.79 mm Hg) immediately after GTN local application then, continuous reduction was achieved throughout the period of therapy to reach (98.22 ± 19.88 mm Hg) which presented 21.92% reduction after 6 weeks (Fig. 3).

As regards to the MSP, there was also a significant decrease from a mean 217.54 ± 46.57 mm Hg to 203.47 ± 45.05 mm Hg which presented a 6.46 % reduction after 6 weeks.

Also, our patients showed a significant decrease in the values of recto-anal inhibitory reflex in the form of decrease in maximum excitatory pressure, maximum inhibitory pressure and recovery time (Fig. 4, 5,6,7).

Side effects were limited to headache in 20 (11.76%) patients. Headache was transient lasting for about 15 to 20 minutes and was mild in nature that did not interfere with patient activities so that they completed the course of treatment Infection had occurred in only one patient (0.58%) with chronic anal fissure & in five other patients (2.94%) of the postoperative group.

GROUP (B)

In patients who were treated with the ordinary local anaesthetic and antibiotic therapy, 14 (70%) patients with anal fissure, 6 (60%) patients with ETH, & 18 (60%) postoperative patients reported relief of pain within 4 days.

Healing occurred in 8 (40%) patients with anal fissure & 21(70%) of postoperative patients within 3-4 weeks of therapy. Also, resolution has occurred in 6 (60%) patients with TEH within 2-4 weeks of therapy. Manometric studies in this group showed no significant changes in maximum resting pressure, squeeze pressure or in the values of recto-anal inhibitory reflex. Infection has occurred in one (1.67%)patient with anal fissure & three (5%) postoperative patients.

Table – 1 : ***Pain control and healing in patients in group (A)***

	No. of	*Pain control*			*Healing / Resolution*			*Infection*	
	Patients	*Days*	*No.*	*(%)*	*Weeks*	*No.*	*(%)*	*No.*	*(%)*
Fissure	76	4	70	(92.11%)	4	60	(78.94%)	1	(0.58%)
ETH	26	4	22	(84.61%)	4	23	(88.46%)	0	
P.O	68	4	60	(88.23%)	4	54	(79.41%)	5	(2.94%)
Total	170		152	(89.41%)		137	(80.58%)	6	(3.52%)

Table – 2: ***Pain control and healing in patients in group (B)***

	No. of	*Pain control*			*Healing / Resolution*			*Infection*	
	Patients	*Days*	*No.*	*(%)*	*Weeks*	*No.*	*(%)*	*No.*	*(%)*
Fissure	20	4	14	(70%)	4	8	(40%)	1	(1.67%)
ETH	10	4	6	(60%)	4	6	(60%)	0	0
P.O	30	4	18	(60%)	4	21	(70%)	3	(5%)
Total	60		38	(63.3%)		35	(58.3%)	4	(6.67%)

Table – 3: ***MAXIMUM RESTING PRESSURE***
(Mean value in mm Hg)

	Before treatment	*Immediate*	*After 4 hours*	*After treatment*
Group (A)	125.81±25.39	96.17±18.79	98.14±18.62	98.22±19.88
P- value		0.000	0.000	0.000
Group (B)	113.80±16.26			112.78±16.40
P- value				0.734

P-value ≤ 0.05 is significant

Table –4: ***MAXIMUM SQUEEZE PRESSURE (Mean value in mmHg)***

	Before treatment	*Immediate*	*4 hours*	*After treatment*
Group (A)	217.54 ± 46.57	208.82 ± 46.47	220.93 ± 16.25	203.47± 45.05
P – value		0.004	0.001	0.000
Group (B)	205.93 ± 28.43			204.55 ± 27.28
P – value				0.560

P-value ≤ 0.05 is significant

RECTO-ANAL INHIBITORY REFLEX:
Table –5 : ***MEAN EXCITATORY PRESSURE (mm Hg)***

	Before treatment	*Immediate*	*4 hours*	*After treatment*
Group (A)	139.62± 27.69	102.84± 22.18	101.03± 10.20	101.37± 17.29
P- value		0.000	0.000	0.000
Group (B)	124.03± 28.43			124.45± 15.05
P- value				0.390

P-value ≤ 0.05 is significant

RECTO-ANAL INHIBITORY REFLEX:
Table –6: ***MEAN INHIBITORY PRESSURE (mm Hg)***

	Before treatment	*Immediate*	*4 hours*	*After treatment*
Group (A)	50.64± 6.22	43.09± 2.54	49.14± 4.55	41.64± 1.19
P- value		0.000	0.907	0.020
Group (B)	47.88± 4.12			47.78± 4.11
P- value				0.765

P-value ≤ 0.05 is significant

RECTO-ANAL INHIBITORY REFLEX:
Table –7: ***MEAN RECOVERY TIME (Sec.)***

	Before treatment	*Immediate*	*4 hours*	*After treatment*
Group (A)	7.71±1.19	11.51± 1.03	11.21± 0.75	10.89± 0.70
P- value		0.000	0.000	0.000
Group (B)	7.86± 0.62			8.03± 0.44
P- value				0.102

P-value ≤ 0.05 is significant

DISCUSSION

Our study presents the results of the first clinical application of G.T.N in the treatment of painful benign anal conditions in our locality. Clear and convincing data indicate that endogenously secreted neuronal N.O. mediates relaxation of the human IAS [10]. Exogenous N.O. such as that produced by cellular metabolism of organic nitrates will also produce IAS relaxation in normal humans [11].

The aim of our study was to evaluate the clinical and manometric changes of short-term use of GTN in a randomized trial in patients with painful benign anal conditions.

In our series, GTN treated patients experienced marked relief of pain with marked decrease (21.92 %) in the mean MRP that started few minutes after local application of GTN

and continued throughout and after the course of treatment and this is the first report on manometric studies measuring MRP immediately after GTN application although, some series reported a 27 % reduction in the mean MRP after 14 days following local application of GTN [11]. This explains the role of internal anal sphincter hypertonia in the etiology of pain associating benign anal diseases.

Also, we found a significant reduction of the mean Maximum Excitatory Pressure and Maximum Inhibitory Pressure with significant increase in the recovery time of recto-anal inhibitory reflex and in our openion, this could reflect the functional influence of GTN on IAS relaxation in humans. On the other hand, we had a significant and high (80.58 %) healing rate within 2-4 weeks in GTN treated patients versus (58.33 %) healing rate in patients in group(B). Several authors reported 83 % & 91.6 % healing rates in patients treated with local application of organic nitrates respectively [6, 12], while others reported a healing rate of 56% in 27 patients treated with topical GTN [7]. We think that our series is the biggest one so we with the reports of high success rates of healing after GTN application.

On the other hand, this is the first trial to use topical GTN therapy in patients who were in the post operative period specially following haemorrhoidectomy or fissurectomy and interestingly, they had shown similar results as regards the relief of pain, the manometric changes as well as the increase in the healing rate following GTN therapy compared with those in group (B). Increased healing rates observed in patients treated with GTN probably derive from a combination of improved vascular perfusion and a reduction of IAS pressure.

Headache is the most frequently reported side effect with the topical application of GTN that occurred in 11 to 58 percent of patients [12,13]. The headaches in general were reported to be mild and transient in nature and were most frequent in the first week of therapy [14]. GTN was well tolerated topically in most of our patients but 11.76% experienced headache which was self limited lasting about 15 minutes and did not interfere their lives. The other well known side effects of GTN such as hypotension, syncope and hypersensitivity reactions has rarely occurred in our patients as it seem to be dose dependent.

In conclusion, we were able to demonstrate that the effect of topical application of GTN on the healing rate and pain relief is going hand in hand with the resulting effects on the manometric studies in painful anal conditions as well as in postoperative period and hence convalescence. So, we recommend this kind of therapy in such circumstances.

REFERENCES

1. Culver J , and Rattan S,Genesis of anal canal pressure in the opossum.Am J physiol 251 (gastrointest. Liver physiol. 14:Gut 765 - 771, 1986
2. Rattan S, Chakder S,Role of nitric oxide as a mediator of internal sphincter relaxation.Am . J. physiol. 1992 ; 262: G 107-12.
3. Guillemot F, Leroi H, Lone YC, Rousseau CG, Lamblin MD, Cortot A, Action of in situ nitroglycerine on upper anal canal pressure of patients with terminal constipation: a pilot study.
4. Savonitto S, Motolese M, Agabiti Rosei E,Anti-anginal effect of transdermal nitroglycerine and oral nitrates given for 24 hours a day in 2,456 patients with stable angina pectoris.Int J Clin pharmacol Ther 1995 ; 33 : 194 – 203.
5. Romanelli M, Katz MH, Alvarez AF, Eaglstein WH, Falanga V,The effect of topical nitroglycerine on transcutaneous oxygen.Br. J. Dermatol. 1991 ; 124 : 354- 7.
6. Bacher H MD, Mischinger H J MD , Werkgartner G MD , Gerwinka MD , EL- Shabrawi A MD, et al .Local NTG for treatment of anal fissures : An alternative to lateral sphincterotomy.Dis. Colon Rectum 1997;40 (7) : 840 - 845.
7. Dorfman G, Levitt M, Platell C,Treatment of chronic anal fissure with topical glyceryl trinitrate.Dis. Colon Rectum 1999; 42(8) : 1007 - 1010.
8. Khubchandani I, Reed J,Sequalae of internal sphincterotomy for chronic fissure in ano.Br J Surgery 1989 ; 76 : 431 – 4.
9. Kennedy ML, Sowter S, Nguyen H, Lubowski DZ,Glyceryl trinitrate ointment for the treatment of chronic anal fissure: results of a placebo- controlled trial and long term follow up.Dis. Colon. Rectum 1999. 42;8 : 1000 -1009.
10. O`kelly T, Brading A, Mortensen N,Nerve mediated relaxation of the human internal anal sphincter: the role of nitric oxide .Gut 1993 ;34 : 689 - 93.
11. Loder P, Kamm M, Nicholls R, Phillips R,Topical glyceryl trinitrate (GTN): reversible chemical sphincterotomyDis Colon Rectum 1994; 36: P 22 .
12. Gorfine SR,Treatment of benign anal disease with topical nitroglycerine.Dis. Colon Rectum 1995 ; 38 : 453 - 5.
13. Lund JN, Scholefield JH,Glyceryle trinitrate is an effective treatment for anal fissure .Dis Colon Rectum 1997 ; 40: 468-70.
14. Herxheimer A, Glyceryle trinitrate ointment for chronic anal fissure. (Letter ; comment) Lancet 1997; 349: 573.