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ORIGINAL ARTICLE

TOPICAL PAPAVERINE VERSRUS NITROGLYCERINE; A PROSPECTIVE RANDOMIZED TRIAL IN TREATMENT OF CHRONIC ANAL FISSURE.

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Aim: *Is to investigate topical papaverine (PAP), a phosphodiastase (PDE) inhibitor as an alternative agent for chemical sphincterotomy in comparison with topical nitroglycerine(NTG), as PAP is hypothesized to be more effective, cheaper with fewer side effects.*
Methods: *A prospective assessment of 65consecutive patients with chronic anal fissure (CAF) randomized to receive topical therapy with either 3% PAPcream or 0.2% NTG from July. 2002 to August. 2003.*
Results: *In PAPgroup, in 26/30(86.7%) treatment was labeled "successful" with 19 (63.3%) showing actual fissure healing and 7(23.3%) showing only symptomatic improvement. None experienced headache but one reported face flushing &one reported tachycardia and 2reported perianal allergic dermatitis. In NTG group in 20/29(68.9%)treatment labeled" successful" with15(51.7%) showing actual healing and 5(17.2%)showing only symptomatic improvement. 19/29(65%)reported headache&10 reported face flushing&6 reported tachycardia and2 reported perianal dermatitis. Recurrence was not a problem as nearly all patients responded to repeat topical therapy.*
Conclusion: *Topical PAP as a novel agent for chemical sphincterotomy seems to be superior to NTG, it offers comparable healing rates, faster onset of action and doesn't have significant side effects, suggesting that it may become the first line treatment of choice for CAF and open the door for further research on the use of other PDE inhibitors or even other altremative smooth muscle relaxants for chemical sphincterotomy.*

Keywords: *Anal fissure, phosphodiestrase, sphincterotomy*

INTRODUCTION

Anal fissure is a painful tear or split in the distal anal canal.(1)

Most acute fissures heal spontaneously, but a proportion become chronic, chronicity is defined both chronologically and morphologically, the chronological definition is rather loose , but most surgeons regard persistence beyond 6 weeks as reasonable point when an acute fissure, now unlikely to heal conservatively, may be considered chronic. Morphologically; the presence of visible transverse internal sphincter fibres at the base of the fissure typifies chronicity and provides a more clear cut definition. associated features include; indurated edges, sentinel pile and hypertrophied anal papilla. A reasonable definition might be the presence of visible transverse internal anal sphincter (IAS) fibres at the base of anal fissure of a duration not less than 6 weeks.(2)

A recent theory states that anal fissure is caused by ischemia of the anal canal posterior comissure excerbated by internal anal sphincter (IAS) hypertonicity.(3,4)

The common goal for all therapies for anal fissure is to improve blood supply to the ischemic area to facilitate healing by reducing resting anal pressure, a function of IAS.

Chronic anal fissure (CAF) has traditionally been treated surgically by either anal dilatation or partial division of IAS.(5) Both techniques carry the risk of irreversible impairment of anal continence.(6.7)

That is whay an enthusiasm towards chemical sphincterotomy using a variety of novel agents including nitroglycrine (NTG),[8,9] calcium channel blockers , such as nifedipine and dilitiazem[10,11] and botulinum toxins[12] has evolved. NTG has recently been described as having disappointing results with significant side effects especially headache[13,14] that might affect compliance to treatment.[12,15]

Papaverine (PAP) is a phosphodiestrese (PDE) inhibitor, and PDE inhibitors were found to relax IAS invitro.[16] This is a theoretical merit for its use in treatment of CAF. To our knowledge there have been no trials on the use of papaverine in the treatment of CAF, and the aim of this study is to investigate topical papaverine as an alternative novel agent for chemical sphincterotomy in comparison with NTG in treatment of CAF.

PATIENTS AND METHODS

65 consecuetive adult patients with symptomatic CAF attending to El-Salam general hospital, El-Salam city, ciaro and the private practice presented from January 2002 to February 2003 were enrolled in the study.

An informed consent was taken from each patient. CAF was defined in chronological and morphological terms , by the persistence of symptoms (post defecation pain with or without bleeding, pruritis and / or discharge) beyond 6 weeks and the presence of visible transverse IAS fibres at the base of the fissure on inspection with or with out the presence of the associated secondary features that include indurated edges, sentinel pile and hypertrophied anal papilla. Exclusion criteria were; acute fissures, atypical locations and associating inflamatory bowel disease. Eligible patients were randomly assigned to receive topical therapy with either 3% PAP cream or 0.3 NTG ointment. This randomization led to the formation of two comparable groups (PAP Group n = 33, NTG group n = 32) in regard to number of patients , age and sex, symptom profile and fissure characteristics Table 1. 3% PAP cream was prepared by a pharmacist by levigating commercial PAP Hcl in an oil in water cream (vanishing cream) as a base to prepare 3% weight by weight cream. Different types of neutral or inert creams from the local market were tested and we selected only that one which give the smoother, more uniform and stable product. 0.3% NTG ointment was prepared by diluting commercial 2% nitroglycrine with petrolatum (vasline®). Patients were instructed to apply the topical agent externally to the anal verge with their finger tips three times daily and post defecation for a minimum of 4 weeks, if there was no improvement after this period, treatment was discontinued, if there was symptomatic improvement or fissure was healed treatment was continued for another 4 weeks. Treatment was stopped after a total of 8 weeks, but patients were instructed to restart another 4 weeks course if symptoms recur. Patients were not prescribed stool softeners, bulk formers, local anesthetics or sitz baths.

Patients were followed up by a neutral examiner who is unaware of the assignment of the patients, by weekly office visits for 8 weeks then monthly thereafter for at least 6 weeks to asses durability of treatment response, median duration of follow up was 37 weeks (Range=25–50 weeks). Those who did not attend were contacted by phone. on follow up visits patients were assessed by specific inquiry about headache and any other side effects , and about the amelioration of their post defecation pain and the onset of symptom improvement. Anal examination was also performed at each visit. Treatment was considered "successful" if either fissure healed or patient reported adequate relief of symptoms sufficient to obviate surgery despite a persistent fissure.

Statistical methodology: Analysis of data was done by IBM computer using SPSS (statistical program for social science) as follows:

- Description of quantitative variables in the form of mean, SD and range
- Description of qualitative variables in the form of frequency and percentages.
- Unpaired t-student test used to compare each two independent groups as regard quantitative variables.
- Chi-square test used to compare qualitative variables.
- Significance level (p) value:
  - P> 0.05 ---- insignificant test
  - P< 0.05 ---- significant test
  - P< 0.01 ---- highly significant test

RESULTS

Patient's demographics and fissure pattern: 65 consecutive patients with chronic anal fissure were enrolled in the study. 6 patients withdrew, some after the first visit and thereafter subsequent visits and did not attend the follow up program (3 in PAP Group & 3 in NTG group). So there were no data from them and were excluded from the trial. A total of 59 patients become the study population with a mean age of 33years (Range=17:63y). Table 1. shows that our 2 groups of the study were comparable in regard to number , age , gender , & fissure pattern (symptoms, mean duration, physical signs and fissure position) and duration of follow up .

Treatment outcome: Treatment outcomes are summarized in (Fig. 1). In PAP group, treatment was labeled

"successful" in 24/30 (80%) after an 8 weeks course , with a mean duration of symptom disappearance of 4±0.8 days and a mean of 4.1±1.2 (range of 6-8 weeks) for fissure healing . Of the remaining 6 patients 2 have improved on further 8 weeks treatment course and 4 did not improve and undergone lateral internal sphincterotomy (LIS). So in a total of 26 /30 (86.7%), treatment was labeled "successful" where 19 (63.3%) showed actual fissure healing and 7 (23.3%) showed only symptomatic improvement sufficient to obviate the need for surgery in spite of persistence of the fissure. As regards the side effects profile one patient reported some flushing of the face which resolved on continuing treatment & one patient reported tachycardia & 2 patients reported perianal allergic dermatitis and none experienced headaches Table 2. With in the period of follow up of 44+6.7 weeks (25–50 weeks) recurrence occurred in 6 patients (20%), of them 4 experienced only symptomatic recurrence which resolved with further course of topical 3% papoverine cream for few days and 2 showed actual fissure recurrence which healed on further 8 weeks course of topical PAP.

In the NTG group, 19/29 (65.5%), treatment was labeled "successful" after an 8 weeks course with a mean duration if symptom disappearance of 4.9+0.8 (significant difference in favour of PAP group, t= 4.5 & P<0.01 Table 2.) days and a mean of 5.2+0.9 weeks (range of 5–7 weeks) for fissure healing. only one of the remaining 10 has healed on further 8 weeks treatment course. So in a total of 20/29 (68.9%), treatment was labeled "successful" with 15 cases (51.7%) with actual fissure healing and 5 patients (17.2%) with only symptomatic improvement. Table 3. Shows that there's no significant difference between both groups of the study in regard to actual fissure healing and symptomatic improvement (x2=0.02, P>0.05). 19/29 (65%) reported headaches & 6(20.6) reported tachycardia, 10 (34.3%) reported face flushing and 2 (6.8) reported allergic perianal dermatitis. with in the period of follow up. Table 4. shows that there's significant difference between both groups of the study in regard to side effects namely headic, face flushing, tachycardia in favour of PAP (P<0.05 & P<0.01) recurrence occurred in 8 patients (40%), 5 showed only symptomatic recurrence which resolved with further topical NTG for few days, and 3 showed actual fissure recurrence of them two have healed on further 8 weeks treatment course and the remaining one preferred to undergo LIS.

Table 1. Patients' demographics and fissure pattern and duration of follow up.

	PAP group n=30	**NTG group n=29**
Mean age (years)	33,2 ± 11.5(17-63)	34.1±8.9(17-51)
M:F ratio	20: 10	18 : 11
Mean duration of symp.	45 ± 8.5 wk	40 ± 7.3 wk
Pain	30 (100%)	29 (100%)
Bleeding	22 (73.3%)	19 (68.9%)
Anal pruritis	20 (66.6%)	19 (65.6%)
Discharge	10 (33.3%)	9 (31 %)
Fissuret + sentinel pile + papilla	16 (53.3%)	15 (51.7%)
Fissure + sentinel pile	14 (46.6%)	13 (44.8%)
Fissure + indurated edges only	7 (23.3%)	8 (27.5%)
Fissure position		
Anterior	5 (16.6%)	4 (13.7%)
Posterion	23 (76.6%)	25 (86.2%)
Ant t post	2 (6.6%)	1 (3.4%)
Duration of follow up	44 ± 6.7wks	43 ± 7.3 wks

*P>0.05

Table 2. Comparison between both groups of the study as regard duration of symptom improvement (in days).

	PAP group n=30	NTG group n=29
Mean	4	4.9
±SD	0.8	0.8
Significance test	t= 4.5 P<0.01**	

** Highly significant test p<0.01
Duration of symptom disappearance was significantly shorter in PAP group compared to NTG group.

Table 3. Comparison between both groups of the study as regards treatment outcome.

	PAP group n=30	NTG group n=29
Actual healing	19(63.3%)	15(51.7%)
Symptomatic improvement	7(23.3%)	5(17.2%)
Total	26(86.7%)	20(68.9%)
Mean duration of fissure healing(Wks)	5.2+ 0.9 (6-8)	4.1 + 1.2 (5-7)
Significance test	X2=0.02 P>0.05	t=1.3 P>0.05

There is no statistically significant difference between both groups of the study regarding the final outcome by using chi-square test. for qualitative variables and t – student test for qualitative variables.

Table 4. Side effects profile.

	PAP. Group N = 30	NTG group N = 29
Headache*	0 (0.0%)	19 (65.5%)
Flushing*	1 (3.3%)	10 (34.3%)
Tachycardia**	0 (0.0%)	6 (20.6%)
Perianal dermatitis	2 (6.6%)	2 (6.8) %

Chi square test was used for comparison of qualitative variables
Fisher exact test instate of Chi square , when one expected cell ≤ 5
* <0.01 _____ highly significant
** <0.05 _____ significant

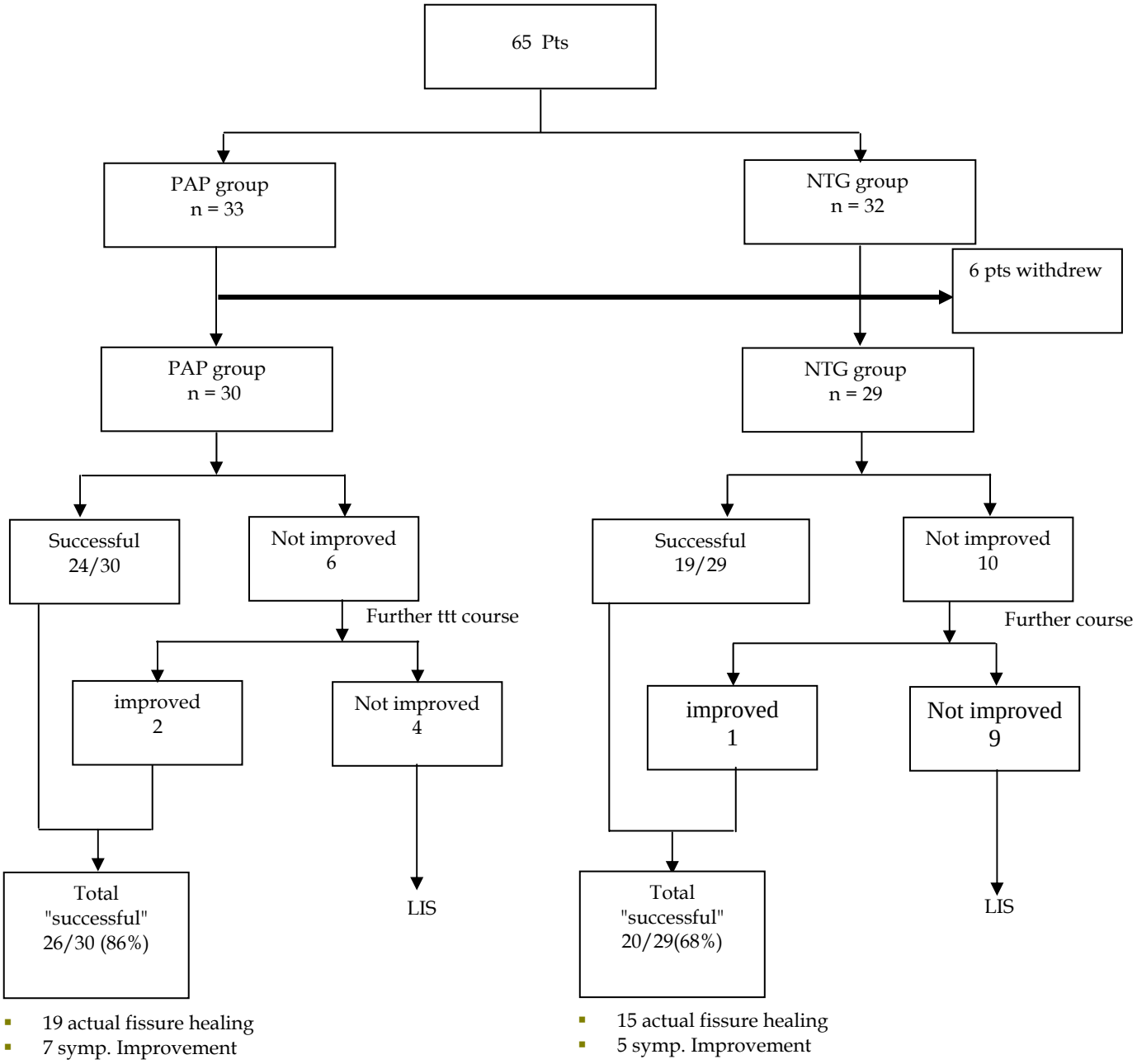

Fig 1. diagram of treatment outcome.

DISCUSSION

CAF has been described as an ischemic ulcer, the ischemicnature of CAF is due elevated resting anal pressure,[4-17] which is a function of IAS. IAS spasm appears to predate the fissure and it has been demonstrated that anodermal blood flow is closely inversely correlated with anal pressure,increasing as pressure falls, Supporting the ischemic basis for CAF.[4]

CAF may be treated by either chemical or surgical sphincterotomy at present, either techniques, share the common goal of reducing the raised resting anal pressure by relieving IAS spasm with the resulting reversal of anodermal ischemia. LIS results in a healing rate of95%, but besides the anesthetic risk and costs, it is not without complications, which include anal incontinence, primarily to flatus in up to one third of patients, bleeding, abcess and fistula.[18,19]As such, treatment that allows for reversible diminution in the sphincter tone to permit healing of the fissure but avoids permanent sphinctric disruption has merit. There have been two forces behind the development of pharmacological treatment for CAF, not only the concern over rates of postsurgical incontinence, but also a deeper understanding of IAS pharmaco-physiology has allowed a reasoned approach to manipulation of sphincter tone.[20-22]

IAS tonicity is modulated via three main influences, the first is the intrinsic myogenic tone which depends on the extracellular calcium entering via L. type calcium channels[22] The second influence is the enteric nervous system, referred to as Auerbach's and Meissner'ss plexi in the gut wall.[23] these nerves are non-adrenergic non-cholinergic and their main neurotransmitter is nitric oxide (NO).[20,21] NO relaxes IAS, its action is to increase intracellular (cGMP) the intracellular mediator of smooth muscle relaxation through activation of gynylate cyclase, the enzyme controlling the production of cGMP[20,24] . The third influence is the autonomic nervous system which affects contraction and relaxation of IAS via sympathetic and parasympathetic postganglionic fibres respectively it may act directly on the smooth muscles or indirectly in the enteric nervous system or both. The concept of nonoperative trial of topicals before performing LIS has definitely gained favour in recent years.[25-28] Avoiding sphincteric division in patients with low resting anal pressure and its attendant hazard of diminished postsurgical anal continence is one factor. Separate from this many clinician are motivated to give patients a trial of topical therapy to avoid costly surgery and some patients want to avoid surgery altogether and prefere to stay on a chronic conservative therapy. Such topical agents comprise several classes of compounds that are capable of temporarily reducing IAS tone and increasing anodermal blood flow[4] NTG is a NO donor [20],on topical application, it produces prompt but transient drop in resting anal pressure in patients with IAS hypertonicty associating anal fissure,[29] however despite encouraging clinical trials,[8,9]it has not been universally accepted as a topical treatment for anal fissure.[30,31] The principle side effect was headache,which causes up to 20% of patients to discontinue therapy.[12,32] So, alternative topical drugs have been investigated recently on an attempt to achieve IAS relaxation without significant sideffects.[10-12,26,27] Calcium channel blockers have comparable healing rates as NTG and significantly lower side effects,[10,11] but still the principle side effect is headache together with flushing and symptomatic hypotension.[22] The theoretical basis behind investigating PAP as an alternative topical agent in treatment of CAF was that, PDE inhibitors have been demonstrated to induce relaxation of IAS in vitro,[16] PDE is an enzyme responsible for degradation of cGMP, there by, PDE inhibitors increase the intracellular cGMP, the mediator of smooth muscle relaxation, cGMP production is promoted by NO via the activation of the enzyme guanylate cyclase.[20,21] Being a PDE inhibitor, PAP is suggested to increase intracellular, GMP, thus enhancing the known effect of NO on spastic IAS. In the laboratory PAP as a smooth muscle relaxant has been proven to work via a variety of mechanisms[32.33.34]:-

- PDE inhibtion/NO mechamisms
- Ca channel blocking
- Mitochondrial respiration inhibition (main mechanism)

Also, PAP cream has been shown to permeate through skin and maintain high concentration and continuous effect on local tissues,[35] NTG is the standard for chemical sphincterotomy against which other newer agents have to be compared. This randomized prospective study was conducted to investigate topical PAP. in comparison with topical NTG as PAP is hypothesized to be more effective, cheaper, with fewer side effects. The results in this study show that topical PAP seems to be superior to NTG in treating CAF, it has no significant difference in comparison with NTG in regard to actual fissure healing and symptomatic improvement ($p>0.05$). Also it was found that the duration of symptom disappearance was significantly shorter in case of PAP group ($p<0.01$) which can be explained by the high penetrance capacity of topical PAP cream through skin and attaining high concentration and continuous effect on local tissues.[35] but regarding the side effects profile, the difference in the number of headaches reported was highly significant ($P<0.01$), also there was a significant difference in the incidence of face flushing and tachycardia ($P<0.05$), in favor of PAP.

In this preliminary study, resting anal pressure was not measured, however a study is now in progress to asses the effect of topical PAP. on resting anal pressure of healthy volunteers and patients with CAF.

Until the finishing of this study and its presentation at the 5th annual scientific conference of the Egyptian group of colon and rectum surgeons in Sharm–El shekh, Egypt, April, 9to12 2003 there have been no trials on using topical PDE inhibitors for the treatment of CAF. However in 2004 a study on the topical use of sildenfail (viagra®), a PDE inhibitor, in CAF has appeared in the journal of Dis Colon Rectum.[36] This study has demonstrated that, topical phosphodiastrase–5-inhibitor (sildinafil) significantly reduces the anal sphincter pressure in patients with CAF with no significant side effects, suggesting that indirect enhancement of the effect of NO on the spastic sphincter is possible without NO donners and other PDE inhibitors,also may warrant study to optimize the ratio of clinical benefit to unpleasant side effects.

In conclusion, topical PAP. cream used as a novel agent for chemical sphincterotomy for CAF seems to be superior to topical NTG,it offers comparable healing rates, faster onset of action and dose not has significant side effects, suggesting that it may become the preferred first line treatment of choice for CAF and open the door for further researches to investigate other PDE inhibitors or even other different types of smooth muscle relaxants, individually or in combination in an attempt to maximize efficacy and minimize side effects of topical therapies of chemical sphincterotomy.

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