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Topical Sildenafil (Viagra®) in the Treatment of Chronic Anal Fissure: A Randomized Double Blind Controlled Trial

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Abstract: The aim of the present study was to determine the efficacy of topical sildenafil in the healing of chronic anal fissure. We conducted a prospective, randomized double blind controlled trial on 61 patients with symptomatic CAF lasting more than four weeks. After simple randomization, 31 and 30 patients were assigned to receive 0.75 mL of 10% sildenafil cream (t.i.d. intra-anal) and placebo for 7 days, respectively. Patients were advised to continue the medication for the next 2 days, if their symptoms were not resolved. All patients were followed up for 2-3 months after treatment. The primary end points of the study were complete healing of the CAF at least two months after the treatment or complications of the therapy. The rate of healing was significantly higher in Sildenafil group compared with controls ($p<0.001$). Of 31 patients in sildenafil group, 19 (61.2%) were improved after 7 days of treatment. The other 12 (38.8%) were also cured during the next 2 days of therapy. We did not detect any improvement during 9 days of treatment in patients enrolled as controls. After successful follow up of 28 patients in sildenafil group, 24 (86%) did not reveal any signs or symptoms of recurrence, while 4 (14%) patients experienced them during this period. The side effects were observed in two patients of sildenafil group which happened after complete course of treatment. Topical treatment by sildenafil was accompanied by 100 and 86% effectiveness in the short term and long term management of CAF, respectively. This treatment could be useful at least to reduce the number of CAF patients who needs surgical interventions.

Key words: Chronic anal fissure, topical sildenafil, anal sphincter pressure

INTRODUCTION

Increases in resting anal pressure are documented in patients with Chronic Anal Fissures (CAF) and it has been considered as a major pathophysiologic factor (Dodi *et al*., 1986; Hancock, 1977; Lund and Scholefield, 1996). Therapies that reduce anal sphincter pressures have been used to achieve fissure healing. Lateral Internal Sphincterotomy (LIS) is the most common treatment for CAF (Jonas and Scholefield, 2001) and can be effective in more than 90 percent of cases but needs general or local anesthesia (Oh *et al*., 1995). The fundamental drawback of this surgery is its potential to cause gas, mucus or occasionally stool incontinence which is permanent in 8 to 30% of patients and may be associated with abscess and anal deformity (Abcarian *et al*., 1982; Garcia-Aguilar *et al*., 1998; Hsu and Mackeigan, 1984; Lund and Scholefield, 1996; Madoff and Fleshman, 2003; Pernikoff *et al*., 1994).

Topical therapies for anal fissure have largely focused on nitric-oxide donors (e.g., nitroglycerin), sometimes with undesirable side effects or inconsistent benefits. Torrabadella *et al*. (2004) was the first who found that topical use of Sildenafil (Viagra®), a phosphodiesterase-5 inhibitor, is a reliable and effective new option in the treatment of uncomplicated CAF in man with respect to manometric analysis. Subsequently Aygen *et al*. (2005) found that Sildenafil citrate relaxes acetylcholine stimulated contractions of isolated dog internal anal sphincter and suggest a potential role in the treatment of chronic anal fissure for this. To our knowledge there is no placebo controlled study evaluating the effects of topical Sildenafil in the treatment of chronic anal fissure. The aim of this randomized, prospective and controlled study was to compare the therapeutic efficacy of topical Sildenafil and placebo in CAF.

MATERIALS AND METHODS

Sixty one consecutive adults with symptomatic CAF between March to May 2006 were enrolled into the study. Criteria for inclusion in the study were symptoms (post-defecatory or nocturnal pain, bleeding, or both) lasting more than four weeks and appearance of chronicity of the fissure on inspection (posterior

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circumscribed ulcer, with a large sentinel tag of skin, induration at the edges and exposure of the horizontal fibers of the Internal Anal Sphincter (IAS).

Recurrent or complicated fissures, nontypical location, painless fis-sures, important secondary changes, i.e., cicatricial deformation, large sentinel pile and subfissural infiltration and patients known to have intestinal or anal Crohn's disease were excluded. None of the patients had previous anal surgery for fissure or other anorec-tal condition.

This study was approved by our local ethical committee in Taleghani Hospital of Shahid Beheshti University of Medical Sciences (Tehran/Iran) and a consent form was obtained from all participants.

According to simple randomization, patients were categorized into Sildenafil and Control groups. In Sildenafil group 0.75 mL of 10% sildenafil cream (based on Torrabadella *et al*. (2004) study), equivalent to 75 mg of sildenafil (Origyn Rx, Ocala, FL) was applied to the anal canal by the finger three times a day for 7 days. In the control group placebo was administered for the same duration.

After each application in the first day, the average time at which initial relaxation started, defined as drop in pain and time at which maximal relaxation occurred, were calculated by the patient. Then we called by phone to all the patients if their problem have resolved. If the symptoms were remained after 7 days, they were advised to continue the medication for the next 2 days.

The primary end points of the study were complete healing of the CAF and complications after treatment. The treatment was considered successful if the fissure healed with a scar at least two months after the treatment (evaluation for treatment efficacy). Unhealed fissures were considered as treatment failure. Complications were described as incontinence (soiling, flatus and feces), itching, abscess and thrombosed hemorrhoids. All the patients were followed-up for at least two and maximally 3 months.

The results are expressed as mean±SD. Statistical analysis was performed using Student's t-test or Mann-Whitney test as appropriate when comparing age, initial and maximal relaxation times and Fisher's exact test for categorical data analysis. Statistical calculations were performed utilizing SPSS version 12.0. Differences were considered significant at $p<0.05$.

RESULTS

A total of 61 patients (25 men, 36 women) with CAF were evaluated in the current study. The mean age of them was 35.14±10.77 years (range: 18-60 years). After simple randomization, 31 and 30 patients were assessed in two categories as Sildenafil and control groups, respectively. According to the Table 1, there were no statistically significant differences in age ($p = 0.85$) and gender ($p = 0.37$) between our groups.

As shown in Table 1, none of the patients in control group has felt better by using placebo, so we could not determine any initial relaxation time for our controls. In comparison, all of patients in Sildenafil group experienced relaxation for less than 3-4 min after topical use of Sildenafil. Likewise, since our controls did not report any improvement, the maximal relaxation time could not be defined for them, while the mean of maximal relaxation time in sildenafil group was 204.19±42.72 sec (Table 1).

As described in Table 2, healing rate was significantly higher in Sildenafil group compared with controls ($p<0.001$). Of 31 patients in sildenafil group, 19 were improved after 7 days of treatment. The other 12 were also cured during the next 2 days of therapy. We did not detect any improvement during 9 days of treatment in patients enrolled as controls, although seven patients explained their symptoms have got better after 15-17 days. Regarding the non response to treatment in control, three (10%) patients underwent surgery to reduce their pain or complications.

Table 1: The demographics and clinical results of the patients

Variables	Sildenafil group	Control group	P Value
Age (year)			
Mean±SD	34.90±9.46	35.40±12.14	p = 0.85
Age range (years)	19-52	18-60	
Gender			p = 0.37
Male	11 (35.5%)	14 (46.7%)	
Female	20 (64.5%)	16 (53.3%)	
Initial relaxation time (sec)	95.32±33.44	Non response	Immeasurable
Male	114.54±42.03	-	
Female	84.75±22.44	-	
Maximal relaxation time (sec)	204.19±42.72	Non response	Immeasurable
Male	223.63±38.80	-	
Female	193.50±41.83	-	

Table 2: Healing rate and follow up findings in both groups

Variables	Sildenafil group (%)	Control group (%)	p-value
Healing rate			Immeasurable
During first 7 days of trial	19 (61.2%)	0	
During next 2 days of trial	12 (38.8%)	0	
None	0	30 (100%)	
Follow up findings			Immeasurable
Successful follow up			
Relapse	4 (13%)	0	
No relapse	24 (77%)	0	
Failure to follow up	3 (10%)	30 (100%)	

All subjects in the present study were followed for 2-3 months after treatment, except three (9.7%) patients in sildenafil group. Of 28 patients undergoing sildenafil trial, after successful follow up, 24 (86%) did not reveal any signs or symptoms of recurrence, while 4 (14%) patients experienced them during this period (Table 2).

The side effects of treatment were only detected in two (6.4%) patients in sildenafil group that both experienced itching by using topical sildenafil. It is necessary to add that these complications were revealed after symptoms improvement during 7 days of therapy, so we did not detect any treatment cessation due to sildenafil side effects. There were no complications of therapy in our controls.

DISCUSSION

The results of this study have shown that topical Sildenafil (Viagra®) is accompanied by a 100% effectiveness in the short time and 86% for long term, in the treatment of chronic anal fissure.

Increase in resting anal pressure is documented in patients with chronic anal fissure, which exceeds 30 mm Hg or more when compared with healthy controls and is associated with a decrease in posterior anal blood flow (Schouten *et al*., 1994, 1996). Any prolonged increases in pressure may cause ischemic damage by decreasing blood flow to the sphincter muscle and overlying epithelium (Schouten *et al*., 1994). As a consequence, therapies that reduce IAS pressure have been used for fissure healing.

Nitric Oxide (NO) has been identified as a nonad-renergic noncholinergic inhibitory transmitter in muscle, producing relaxation of the internal anal sphincter (Stebbing, 1998; Stebbing *et al*., 1997). The action of NO on vascular smooth muscle (in-cluding the IAS) is to produce an increase of cyclic GMP (cGMP), the intracellular mediator for smooth muscle relaxation, through activation of guanylate cy-clase, the enzyme that controls the production of cGMP (O'Kelly *et al*., 1993; Palmer *et al*., 1987). NTG and isosorbide dinitrate (ISDN) are donors of NO, (Stebbing, 1998) and L-Arginine, an intrinsic NO precursor, being the substrate of NO synthase, affects on IAS via increasing the NO production and subsequently cGMP.

Phosphodiesterase (PDE), the en-zyme involved in degradation of cyclic nucleotides, contains a number of different isoenzymes. PDE-5 is primarily located in smooth muscle and is integral to the degradation of cGMP (Rattan *et al*., 1992).

Sildenafil, a PDE-5 inhibi-tor, produces inhibition of PDE-5 more selectively than other isoenzymes, resulting in increased intracel-lular concentrations of cGMP and increased smooth muscle relaxation (induced by NO) (Jones *et al*., 2002). The theoretical basis for use of sildenafil in patients with anal fissure is based on this physiologic action.

Although other PDE inhibitors have been shown to induce IAS relax-ation *in vitro* (Jones *et al*., 2002) Torrabadella *et al*. (2004) manometric study was the first use of topical sildenafil in patients with chronic anal fissure and IAS overactivity. They have shown that topical administration of 10% sildenafil in patients with CAF, significantly reduces anal sphincter pressure. Our results are consistent with these findings. The response rate was also near (94.74% vs. 100%).

Like Torrabadella *et al*. (2004) study, no permanent damage to the continence mechanism, headaches or other side effects were detected in patients treated with topical sildenafil. However they have reported mild-to-moderate anal discomfort in 26% of patients. We also found 6.4% complication (anal itching) in our series. Furthermore they have shown that the time for initial relaxation was less than three minutes with our half approximately, with maximum effect one minute later with significantly shorter initial relaxation in females accordingly. They have suggested differences from patient to patient may be related to variability in endogenous NO production as the cause of significant differences in time to initiation and maximum effect between gender groups after administration of topical sildenafil, need further investigation.

These observations suggest a possible role for increasing the effect of topical sildenafil by addition of extra NO from exogenous sources, such as L-Arginine, NTG, or ISDN. In that context, the latter donor com-pounds could theoretically be administered in tandem with sildenafil, in doses sufficiently low to avoid un-pleasant side effects. (Torrabadella *et al*., 2004)

The ideal topical treatment for anal fissure should reduce pain, promote healing and minimize recurrence without impairing continence and with the low-est possible incidence of side effects. This study has extrapolated from known sphincteric physiology to explore topical phosphodiesterase (PDE) inhibition as a means for enhancing the known effect of nitric oxide on the spastic anal sphincter, by reducing IAS pressure. Prompt reduction in IAS pressure was achieved in all but one patient using topical sildenafil, a PDE-5 inhibitor, with no significant side effects. These data suggest that indirect enhancement of the effect of NO on the spastic anal sphincter is possible without NO donors. Other PDE inhibitors, alone or in combination, also may warrant study to optimize the ratio of clinical benefit to unpleasant side effects.

Topical therapies for anal fissure have been em-braced by some surgeons and scrupulously avoided by others. Yet, increasing acceptance of the concept of topical therapy as "first aid" for fissure has been increasingly evident in recent years. Although lateral internal anal sphincterotomy remains the gold standard for definitive fissure therapy, preoperative interposition of a trial of topicals affords the potential for improvement, healing in some patients and appreciation by all patients that their surgeon has been prudent before performing an operation. Although the perfect topical dose does not yet exist, as new evidence evolves, better surgical selection and more predict-able outcomes for LIS may be indirect beneficiaries.

All the patients in sildenafil group in our series experienced a rapidly resolution of symptoms within the first two days.

The findings of our survey however should be interpreted with some limitations. The efficacy of topical sildenafil in anal sphincter pressure compared with placebo, should be determined by a precise diagnostic modality such as manometric evaluations other than subjective criteria (symptoms of CAF), so further studies should be designed in the future to assess the role of topical sildenafil on decreasing anal sphincter tonicity.

In conclusion, this study revealed that topical treatment by sildenafil in patients with CAF could be useful at least to reduce the number of patients who needs surgical interventions.

REFERENCES

Abcarian, H., S. Lakshmanan, D.R. Read and P. Roccaforte, 1982. The role of internal sphincter in chronic anal fissures. Dis. Colon Rectum, 25: 525-528.

Aygen, E., C. Camci, A.S. Durmus, O. Dogru, O. Topuz, R. Ayten and A. Ayar, 2005. Inhibitory effects of sildenafil citrate on the tonus of isolated dog internal anal sphincter. Dis. Colon Rectum, 48: 1615-1619.

Dodi, G., F. Bogom, A. Infantino, P. Pianon, L.M. Morteltaro and M. Iise, 1986. Hot or cold in anal pain? A study in internal sphincter pressure profiles. Dis. Colon Rectum, 29: 248-251.

Garcia-Aguilar, J., C. Belmonte Montes, J.J. Perez, L. Jensen, R.D. Madoff and W.D. Wong, 1998. Incontinence after lateral internal sphincterotomy: Anatomical and functional evaluation. Dis. Colon Rectum, 41: 423-427.

Hancock, B.D., 1977. The internal sphincter and anal fissure. Br. J. Surg., 64: 92-95.

Hsu, T.C. and J.M. MacKeigan, 1984. Surgical treatment of chronic anal fissure: A retrospective study of 1753 cases. Dis. Colon Rectum, 27: 475-478.

Jonas, M. and J.H. Scholefield, 2001. Anal Fissure. Gastroenterol. Clin. North Am., 30: 167-181.

Jones, O.M., A.F. Brading and C.M.N.J. Mc, 2002. Phosphodiesterase inhibitors cause relaxation of the internal anal sphincter *in vitro*. Dis. Colon. Rectum., 45: 530-536.

Lund, J.N. and J.H. Scholefield, 1996. Aetiology and treatment of anal fissure. Br. J. Surg., 83: 1335-1344.

Madoff, R.D. and J.W. Fleshman, 2003. AGA technical review on the diagnosis and care of patients with anal fissure. Gastroenterology, 124: 235-245.

O'Kelly, J., A.F. Brading and N.J. Mortensen, 1993. Nerve mediated relaxation of the human internal anal sphincter: The role of nitric oxide. Gut, 34: 689-693.

Oh, C., C.M. Divino and R.M. Steinhagen, 1995. Anal fissure: 20-year experience. Dis. Colon Rectum., 38: 378-382.

Palmer, R.M., A.G. Ferrige and S. Moncada, 1987. Nitric oxide release accounts for the biological activity of endotheliumderived relaxing factor. Nature, 327: 524-526.

Pernikoff, B.J., T.E. Eisenstat, R.J. Rubin, G.C. Oliver and E.P. Salvati, 1994. Reapprasial of partial lateral internal sphincterotomy. Dis. Colon Rectum., 37: 1291-1295.

Rattan, S., A. Sarkar and S. Chakder, 1992. Nitric oxide pathway in rectoanal inhibitory reflex of opossum internal anal sphincter. Gastroenterology, 103: 43-50.

Schouten, W.R., J.W. Briel and J.J. Auwerda, 1994. Relationship between anal pressure and anodermal blood flow. The vascular pathogenesis of anal fissures. Dis. Colon Rectum., 37: 664-669.

Schouten, W.R., J.W. Briel, J.J. Auwerda and E.J. De Graaf, 1996. Ischaemic nature of anal fissure. Br. J. Surg., 83: 63-65.

Stebbing, J.F., A.F. Bmding and N.J. Monensen, 1997. Role of nitric oxide in relaxation of the longitudinal layer of rectal smooth muscle. Dis. Colon Rectum., 40: 706-710.

Stebbing, J.F., 1998. Nitric oxide synthase neurones and neuromuscular behaviour of the anorectum. Ann. R. Coll. Surg. Engl., 80: 137-145.

Torrabadella, L., G. Salgado, R.W. Burns and I.R. Berman, 2004. Manometric study of topical sildenafil (Viagra) in patients with chronic anal fissure: Sildenafil reduces anal resting tone. Dis. Colon Rectum., 47: 733-738.