BRIEF COMMUNICATION

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EFFICACY OF DILTIAZEM IN THE TREATMENT OF CHRONIC ANAL FISSURE: AN OVERVIEW

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Abstract: *Anal fissure is a common medical problem which effect both sexes equally. Until recently the gold standard treatment for chronic anal fissure was surgical lateral internal spincterotomy but recently chemical spinteractomy has become popular in the surgical practice. In the treatment of chronic anal fissure Ca^{2+} channel blockers play an important role which was proved to be efficacious in various clinical trials. Mechanism involved in these drugs supposed to be due to vasodilatation at the fissure site and hence it increases local blood circulation leads to enhance healing. Studies showed that healing occurs with infrequent headache and hypotension, with diltiazem treatment compared to glyceryl trinitrate therapy.*

INTRODUCTION

Anal fissure (AF) is traumatically induced longitudinal tear in the squamous epithelium of anal canal. It was originally described by Recamier in 1829. Studies suggested that one in five person developed anal fissure during there lifetime and occurred in all most all age group. Most commonly identified AF in clinical setup is posterior about 90% where as anterior it is 10% and less than 1% in both position[1]. Anal fissure is mainly characterized by the severe pain during and after defecation and bright red rectal bleeding which may last for an hour. Acute anal fissure (AAF) resolves spontaneously or with conservative treatment in 10 to 14 days but complete tear to may takes 6 – 8 weeks. The chronic and to assure (CAF) of more than 6 weeks. Needs surgical intervention. When fissure becomes large, deep and chronic they are called anal ulcers.[3] When a fissure is located in atypical locations or multiple and fail to heal following treatment, other conditions such as inflammatory bowel disease, neoplasm, leukemia, syphilis, tuberculosis, HIV has to be ruled out.[2,3,4]

TREATMENT STRATEGIES

In the treatment of AF, aim of treatment is to ***avoid constipation***, soften stool and reduce anal sphincter spasm. Bulk is added to diet and stool softener is prescribed. Increased fiber in the diet softens and bulks the stool. Regarding ***pharmacotherapy*** different Ca^{2+} channel blockers, vasodilators and cholinomimetics were tried.

ROLE OF DILTIAZEM

A calcium dependent mechanism is required to maintain internal sphincter muscle tone. ***Calcium channel blocker*** [CCB's]causes relaxation of gastrointestinal smooth muscle[1,2] ***oral diltiazem*** has been shown to reduce the resting anal pressure.[3] Carapeti EA et al, explored the possible use of calcium channel blockers and cholinomimetic to lower anal sphincter pressure. Both oral diltiazem and topical gel containing varying concentration was tested on healthy adult volunteers in order to determine dose response characteristics of these agents. They found that single dose of 60mg diltiazem lowered maximum resting pressure [MRP] by a mean of 21%. Once daily diltiazem produced clinically insignificant effect but twice daily regimen reduced anal pressure by mean of 17%. Study used 2% diltiazem gel produced a maximal 28% reduction, the effect lasting 3-5 hrs, this study also reported potential low side effect alternative to topical nitrates for the treatment of anal fissure.[14] Carapeti EA et al, conducted study on patients with chronic anal fissure. Patients were treated with 2% diltiazem gel 3 times daily for 8 weeks. Fissure healed in 67% of patients. There was no significant difference in maximum resting sphincter pressure between responders and non-responders. There was significant decrease in pain score after treatment with diltiazem (p=0.002). MRP was significantly lowered [p=0.001]. No headache or side effects were reported.[5] Jonas M et al, assessed the effectiveness of oral and topical diltiazem in healing chronic anal fissure. MRP fell by 15% and 23% in oral and topical group. Fissure healing was 38% in oral and 65% in topical treated group by 8 weeks. Oral diltiazem caused side effects such as rash, headache, nausea, vomiting, decreased smell and taste, while topically treated groups showed no side effects.[6] Knight JS et al, studied 2% topical diltiazem in 71 patients. 75% experienced healing in 2-3 months and in further 2 months 88% experienced healing. Minor side effects were perianal dermatitis, 1 patient had headache, and 6 of 7 patients with recurrent fissure were treated successfully by repeat chemical sphincterotomy.[7] Jonas M et al, did a study the efficacy of diltiazem for fissures that failed to heal with glyceryl trinitrate [GTN]. There were 39 patients with chronic anal fissure received GTN therapy of which 27 patients completed course and 12 patients discontinued. Out of 27 patients who completed GTN course and presented with resistant chronic anal fissure, 44% were healed with topical diltiazem while 56% of the patients the fissure persisted and had to undergo surgical sphincterotomy. In his trial 12 patients discontinued GTN therapy and 58% were healed with topical diltiazem.[8] Dasgupta D et al, also evaluated the treatment of patients with chronic anal fissure with diltiazem gel. Investigators found that fissure healed in 48% including 75% of the patients who previously failed to heal with GTN therapy. There were no recurrence and no adverse effects[9]. Griffin et al, also studied the role of topical diltiazem in the treatment of chronic anal fissure that have failed with GTN therapy. He concluded that topical 2% diltiazem is an effective and safe treatment for patients who have failed topical 0.2% GTN therapy. Sphincterotomy can be avoided in 70% of patients with chronic anal

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Table: *Reported efficacy of Diltiazem in chronic anal tissue in different series*

Author (Year)	Patients (Duration)	% healing	Remarks
Carapeti EA et al[14] (1999)	30	Oral -21% Topical-28% Placebo Bethanicol	Effective
Carapeti EA et al[5] (2000)	30	67%	Comparable .
Jonas M et al[6] (2001)	50	52% (topical diltiazem)	Effectious than control
Knight JS et al[7] (2001)	71	83%	Effective
Jonas M et al[8] (2002)	39	48%	Effective in GTN failure patients
Dasgupta et al[9] (2001)	23	48%	Effective
Griffin et al[10] (2002)	47	48%	Effective
Kocher HM et al[11] (2002)	60	41%	Comparable
Bleleki et al[12] (2002)	43	86%	Comparable
Nash GF et al[13] (2006)	112	41%	Safe for long term use

fissure.[10]

Kocher HM et al, conducted a randomized control trial assessing adverse effects of GTN and diltiazem in treatment of chronic anal fissure. More headache occurred with GTN therapy than diltiazem [p=0.01]. There was no significant difference in healing and symptomatic improvement rates between the two groups.[11] Other study also showed similar result like Bleleki et al, conducted prospective randomized trial of diltiazem and GTN therapy in treatment of chronic anal fissure and this study concluded that diltiazem and GTN therapy are equally effective in healing anal fissure. But diltiazem reported in few adverse effects.[12] Study evaluated long-term outcome of diltiazem in chronic anal fissure. Total one hundred and twelve patients were treated for 6-week with 2% diltiazem cream for twice-daily topical application. The success rate and satisfaction of topical diltiazem were each over two thirds. Nearly 80% of patients reported no adverse effects, and it seems that those complaints attributed to diltiazem rarely led to reduced compliance. After completion of diltiazem therapy for fissure, 59% of patients required further treatment (medical and/or surgical) over the average 2-year period of follow-up[13].

In conclusion several trials have already conducted to proved safety and efficacy of topical diltiazem in chronic anal fissure. So diltiazem may emerged as main therapeutic agent in the management of chronic anal fissure in near future but surgery should be preferred to the patients with relapse or in patients not responding to diltiazem therapy.

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LITERATURE REVIEW

Intensive Blood Glucose Control and Vascular Outcomes in Patients with Type 2 Diabetes

The ADVANCE Collaborative Group

Background *In patients with type 2 diabetes, the effects of intensive glucose control on vascular outcomes remain uncertain.*

Methods *We randomly assigned 11,140 patients with type 2 diabetes to undergo either standard glucose control or intensive glucose control, defined as the use of gliclazide (modified release) plus other drugs as required to achieve a glycated hemoglobin value of 6.5% or less. Primary end points were composites of major macrovascular events (death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke) and major microvascular events (new or worsening nephropathy or retinopathy), assessed both jointly and separately.* Results *After a median of 5 years of follow-up, the mean glycated hemoglobin level was lower in the intensive-control group (6.5%) than in the standard-control group (7.3%). Intensive control reduced the incidence of combined major macrovascular and microvascular events (18.1%, vs. 20.0% with standard control; hazard ratio, 0.90; 95% confidence interval [CI], 0.82 to 0.98; P=0.01), as well as that of major microvascular events (9.4% vs. 10.9%; hazard ratio, 0.86; 95% CI, 0.77 to 0.97; P=0.01), primarily because of a reduction in the incidence of nephropathy (4.1% vs. 5.2%; hazard ratio, 0.79; 95% CI, 0.66 to 0.93; P=0.006), with no significant effect on retinopathy (P=0.50). There were no significant effects of the type of glucose control on major macrovascular events (hazard ratio with intensive control, 0.94; 95% CI, 0.84 to 1.06; P=0.32), death from cardiovascular causes (hazard ratio with intensive control, 0.88; 95% CI, 0.74 to 1.04; P=0.12), or death from any cause (hazard ratio with intensive control, 0.93; 95% CI, 0.83 to 1.06; P=0.28). Severe hypoglycemia, although uncommon, was more common in the intensive-control group (2.7%, vs. 1.5% in the standard-control group; hazard ratio, 1.86; 95% CI, 1.42 to 2.40; P<0.001).* Conclusions *A strategy of intensive glucose control, involving gliclazide (modified release) and other drugs as required, that lowered the glycated hemoglobin value to 6.5% yielded a 10% relative reduction in the combined outcome of major macrovascular and microvascular events, primarily as a consequence of a 21% relative reduction in nephropathy. (ClinicalTrials.gov number, NCT00145925 [ClinicalTrials.gov] .)*