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Diltiazem Gel 2% in treatment of acute fissure in ANO

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Abstract
Background: Use of Topical diltiazem gel 2% as an agent for chemical sphincterotomy, as a pharmacological manipulation of anal sphincter tone as a modality for the treatment of acute anal fissure.
Objectives: To evaluate the influence of topical application of 2% diltiazem gel on healing of the acute fissure in ANO.
Patients and Method: This is an interventional study on 70 patients which was studied at Al- Yarmouk Teaching Hospital with acute anal fissure from the period January 2016 to September 2016. All patients were treated for a maximum period of 8 weeks with 2% diltiazem gel.
Results: Seventy patients were studied, 40 female (57.14%) and 30 male (42.86%) and female to male ratio was 1.33: 1, the age ranged from 1 to 70 years, with a mean age of 29 years $\pm$ 5 years, the majority being in the 3th decade of life constituting 20 patients (28.57%). Also our study showed that the causes of the fissure in ANO are chronic constipation and passing hard stool 45 patients (64.28%), the next was post haemorrhoidectomy 10 patients (14.28%), followed by post traumatic (post-delivery) 8 patients (11.43%), diarrhea 6 patients (8.57%) and anal sexual intercourse 1 patients (1.43%). Within 5 days, the fissure related pain was resolved in all patients. At 4 weeks the anal fissure was completely healed in 40 patients (57.14%) and at 6 weeks another 15 patients (21.43%), and at 8 weeks the anal fissure was completely healed in another 5 patients (7.14%). Six patients (8.57%) developed perianal abscess so that anal dilatation and drainage of abscess were done to them under general anaesthesia. Four patients (5.71%) not respond to treatment and lateral sphincterotomy were done to all under general anaesthesia.
Conclusion: In our study, fissure healing was found in 85.71% of the cases who received topical diltiazem. The pain relief was satisfactory in a majority of the cases. Headache and perianal itching were the two common side effects which were reported by some of our subjects. However, they were mild and tolerable. One of the drawbacks which were observed was the patient compliance, as the duration of the treatment was quite long i.e. 8 weeks. We conclude that 2% topical diltiazem is quite effective in the treatment of acute fissure in ANO. It may be considered as a first line treatment for acute fissure in ANO. When this fails or fissures recur, anal dilatation or lateral subcutaneous internal sphincterotomy under local or spinal or general anesthesia should be the preferred options for the treatment of fissure in ANO. Nevertheless, all the option should be presented to the patient with complete information about the method, cure rates, complications, and recurrence of the disease.

Keywords: Fissure in ANO, Diltiazem, Chemical sphincterotomy

1. Introduction
The anal canal is the terminal part of the large intestine and of the entire digestive tract, it extends from the superior aspect of the pelvic diaphragm to the anus, the canal (2.5–3.5 cm long) begins where the rectal ampulla narrows at the level of the U-shaped sling formed by the puborectalis muscle, the anal canal ends at the anus, the external outlet of the alimentary tract, the anal canal, surrounded by internal and external anal sphincters, descends postero-inferiorly between the anococcygeal ligament and the perineal body [1]. Developmentally the midpoint of the anal canal is represented by the dentate line (pectinate line). This is the site where the proctodeum (ectoderm) meets endoderm [2]. The nerve supply to the anal canal superior to the pectinate line is visceral innervations from the inferior *Hypogastric plexus*, involving sympathetic, parasympathetic, and visceral afferent fibers [1]. Sympathetic fibers maintain the tonus of the internal anal sphincter, Parasympathetic fibers inhibit the tonus of the internal sphincter and evoke peristaltic contraction for defecation [1]. The superior part of the anal canal, like the rectum superior to it, is inferior to the pelvic pain line, all visceral afferents travel with the parasympathetic fibers to spinal sensory ganglia S2–S4 [1]. Superior to the pectinate line, the anal canal is sensitive only to stretching, which evokes sensations at both the conscious and unconscious (reflex) levels, for example, distension of the rectal ampulla inhibits (relaxes) the tonus of the internal sphincter [1]. The nerve supply of the anal canal inferior to the pectinate line is somatic innervation derived from the inferior anal (rectal) nerves,

branches of the *pudendal nerve*, therefore this part of the anal canal is sensitive to pain, touch, and temperature, Somatic efferent fibers stimulate contraction of the voluntary external anal sphincter [1]. An anal fissure (fissure-in-ano) is a longitudinal split in the anoderm of the distal anal canal which extends from the anal verge proximally towards, but not beyond, the dentate line [3]. The site is usually posterior in the mid line in 90% of men and 70% of women and occasionally anteriorly in the mid line and rarely multiple [4]. Because of the curvature of the sacrum and rectum a hard faecal matter while passing down may cause a tear in the anal valve leading to posterior anal fissure [5]. And anterior anal fissure is common in female due to lack of support to pelvic floor [5]. And following childbirth [6]. Anal fissure is the most common cause of severe anal pain, it is equally one of the most common reasons of bleeding per anus in infants and young children, the pain of anal ulcer is intolerable and always disproportionate to the severity of the physical lesion, it may be so severe that patients may avoid defecation for days together until it becomes inevitable, this leads to hardening of the stools, which further tear the anoderm during defecation, setting a vicious cycle [7]. The fissures can be classified into Acute or superficial and Chronic fissure in ANO [7].

It has been proved that constipation is the primary and sole cause of initiation of a fissure [8]. Passage of hard stool, irregularity of diet, consumption of spicy and pungent food, faulty bowel habits, and lack of local hygiene can contribute for initiation of the pathology [7]. Acute anal fissure may heal by itself [7] or can be cured conservatively [9]. Or may progress to a chronic fissure [7]. The anoderm is more adherent to the underlying tissue in the posterior midline, the sphincter fibers form Y-shaped decussation in the posterior midline that is anchored to the mucosa, blood supply to the anoderm at the posterior midline is significantly lower. The reduced blood supply to the lesion is indicated by the absence of granulation tissue at the base of the fissure and a very slow growth of the anoderm even when the traditional conservative treatment eases the trauma due to hard faeces [7]. A well-developed idiopathic anal fissure rests directly over the internal sphincter and the circular fibers of this sphincter are visible on the floor of the fissure on naked eye inspection, the internal sphincter undergoes a perpetual state of spasm due to irritation and hypertrophies [7]. Warm water sitz bath with or without adding boric powder, povidone iodine solution, or potassium permanganate in the water, this treatment soothes the pain and relaxes the spasm of the internal sphincter for some time [10]. The addition of fibre to the diet to bulk up the stool, stool softeners and adequate water intake are simple and helpful measures, topical local anaesthetic agents relieve pain, however providing patients with anal dilators is usually associated with low compliance and consequently little effect [3]. Adequate analgesia is necessary to break the vicious cycle of pain viz. avoidance of defecation for prolonged periods leading to hard stools resulting in further tearing of the anoderm and thereby inviting increased pain, a suitable dose of analgesic consumed half an hour before going for defecation gives a good amount of post defecation pain relief [7]. The mainstay of current conservative management is the topical application of pharmacological agents (topical vasodilators) that relax the internal sphincter, most commonly nitric oxide donors, by reducing spasm, pain is relieved, and increased vascular perfusion promotes healing, such agents include glyceryl trinitrate (GTN) 0.2% applied four times per day to the anal margin (although this may cause headaches) and diltiazem 2% applied twice daily [3]. The other possible complication of this treatment includes pruritus due to allergy with the anesthetic agents and loss of anal dilator in the rectum [11]. Topical diltiazem ointment was used as an agent for chemical sphincterotomy [12]. An acute anal fissure commonly heals with 4–8 weeks of conservative therapy, if this therapy fails and the fissure becomes chronic, surgery is usually required [13-15].

2. Patients and Method

This is an interventional study on 70 patients which was studied at Al- Yarmouk Teaching Hospital with acute anal fissure from the period January 2016 to September 2016. All patients were treated for a maximum period of 8 weeks with 2% diltiazem gel. Fifty five (78.57%) fissures were located at the posterior midline, 10 (14.28%) at the anterior midline, and 5 (7.14%) both anteriorly and posteriorly. All patients were instructed to apply the gel every 12 hour around the anal verge and inside the anal canal. All patients were interviewed and examined at 2 and 4 and 6 and 8 weeks after starting treatment.

3. Results

Seventy patients were studied, 40 female (57.14%) and 30 male (42.86%) and female to male ratio was 1.33: 1, the age ranged from 1 to 70 years, with a mean age of 29 years $\pm$ 5 years, the majority being in the 3th decade of life constituting 20 patients (28.57%) as shown in table 1. Also our study showed that the causes of the fissure in ANO are chronic constipation and passing hard stool 45 patients (64.28%), the next was post haemorrhoidectomy 10 patients (14.28%), followed by post traumatic (post-delivery) 8 patients (11.43%), diarrhea 6 patients (8.57%) and anal sexual intercourse 1 patients (1.43%) as shown in table 2. Within 5 days, the fissure related pain was resolved in all patients. At 4 weeks the anal fissure was completely healed in 40 patients (57.14%) and at 6 weeks another 15 patients (21.43%), and at 8 weeks the anal fissure was completely healed in another 5 patients (7.14%) as shown in table 3. Six patients (8.57%) developed perianal abscess so that anal dilatation and drainage of abscess were done to them under general anaesthesia. Four patients (5.71%) not respond to treatment and lateral sphincterotomy were done to all under general anaesthesia.

Table 1: Age & Sex distribution of fissure in ANO in patients.

Age group (Years)	No of male	No of female	Total	%
1 – 10	3	4	7	10
11 -20	3	5	8	11.42
21 - 30	8	12	20	28.58
31 – 40	6	7	13	18.58
41- 50	4	5	9	12.85
51-60	4	3	7	10
61-70	2	4	6	8.57
Total	30	40	70	100%

Table 2: Causes of fissure in ANO.

Causes of fissure in ANO	No of patients	%
Chronic constipation and passing hard stool	45	64.28%
Post haemorrhoidectomy	10	14.28%
Post traumatic (post-delivery)	8	11.43%
diarrhea	6	8.57%
Anal sexual intercourse	1	1.43%
Total	70	100%

Table 3: No of heald fissure in ANO according to the time.

No of weeks	No of patients	%
4weeks	40	57.14
6weeks	15	21.43
8 weeks	5	7.14
Total	60	85.71

4. Discussion

Anal fissure is one of the common causes of severe anal pain and it causes considerable morbidity [16]. The posterior midline is the commonest site, followed by the anterior midline, particularly in females [17]. A number of therapies have been described, non-operative and operative, the non-operative methods include the injection of botulin toxin to the fissure, oral nifedipine, the topical application of Glyceryl Trinitrate (GTN) and topical diltiazem ointment [18]. Diltiazem are calcium channel blockers which act by blocking the slow L-type calcium channels in the smooth muscle, thus causing relaxation [12]. In Operative techniques such as Stretching of anal sphincter [Lord's anal dilatation], Anal dilation was described by Recamier in 1838, this was one of the most favored and accepted methods of treating the anal fissures [19]. Excision of the anal fissure [fissurectomy], A triangular part of the anoderm is excised along with the fissure itself, this procedure is usually preceded by anal stretch, howsoever, good and reliable this operation is, it leaves behind a large and rather uncomfortable external wound, which takes a long time to heal [20]. Division of internal anal sphincter, Division of internal sphincter fibers to relieve the sphincter spasm [21]. Our study is an interventional study on 70 patients which was studied with acute anal fissure only. All patients were treated for a maximum period of 8 weeks with 2% diltiazem gel. Fifty five (78.57%) fissures were located at the posterior midline, 10 (14.28%) at the anterior midline, and 5 (7.14%) both anteriorly and posteriorly. All patients were instructed to apply the gel every 12 hour around the anal verge and inside the anal canal. All patients were interviewed and examined at 2 and 4 and 6 and 8 weeks after starting treatment. Our study showed that the causes of the fissure in ANO are chronic constipation and passing hard stool 45 patients (64.28%), the next was post haemorrhoidectomy 10 patients (14.28%), followed by post traumatic (post-delivery) 8 patients (11.43%), diarrhea 6 patients (8.57%) and anal sexual intercourse 1 patients (1.43%) as shown in table 2. Within 5 days, the fissure related pain was resolved in all patients. At 4 weeks the anal fissure was completely healed in 40 patients (57.14%) and at 6 weeks another 15 patients (21.43%), and at 8 weeks the anal fissure was completely healed in another 5 patients (7.14%) as shown in table 3. Six patients (8.57%) developed perianal abscess so that anal dilatation and drainage of abscess were done to them under general anaesthesia. Four patients (5.71%) not respond to treatment and lateral sphincterotomy were done to all under general anaesthesia. A number of studies have reported fissure healing in 60% to 75% of the cases with topical diltiazem [22-25].

5. Conclusion

In our study, fissure healing was found in 85.71% of the cases who received topical diltiazem. The pain relief was satisfactory in a majority of the cases. Headache and perianal itching were the two common side effects which were reported by some of our subjects. However, they were mild and tolerable. One of the drawbacks which were observed was the patient compliance, as the duration of the treatment was quite long i.e. 8 weeks. We conclude that 2% topical diltiazem is quite effective in the treatment of acute fissure in ANO. It may be considered as a first line treatment for acute fissure in ANO. When this fails or fissures recur, anal dilatation or lateral subcutaneous internal sphincterotomy under local or spinal or general anesthesia should be the preferred options for the treatment of fissure in ANO. Nevertheless, all the option should be presented to the patient with complete information about the method, cure rates, complications, and recurrence of the disease.

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