Comparison of topical glyceryl trinitrate with diltiazem ointment for treatment of chronic anal fissure.
A randomized clinical trial.

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BACKGROUND: The aim of this study was to compare the effect of topical glycerol trinitrate ointment (GTN) with topical diltiazem hydrochloride ointment (DTZ) in the treatment of chronic anal fissure.

METHOD: Prospectively, 102 patients were treated randomly with either GTN ointment (0.2%) or DTZ ointment (2%) couple of times daily for 12 weeks.

RESULTS: Forty-five patients (88.2%) in group DTZ and 36 patients (70.6%) in group GTN had reduction of symptoms. The decrease in the symptoms for group DTZ were significantly more than that for group GTN (P= 0.02). Mean time of symptom reduction was 2.44±0.30 in group DTZ and 2.50±0.28 weeks in group GTN without significant differences between two groups (P>0.05). Complete relieving of symptoms was observed in 72.5%, 54.9% patients in groups DTZ and GTN, respectively. The frequency of complete relieving of symptoms between two groups was not significant (P>0.05). Complete remission of anal fissure was occurred in 66.7% patients in group DTZ and 54.9% patients in group GTN, which was no different, significantly. Mean time taken for fissure healing in GTN group was dramatically less than DTZ group (P=0.001). Finally, 33.3% of patients in DTZ group and 45.1% of patients in GTN group were operated. The need for operation was not significant between two groups (P>0.05).

CONCLUSION: Both DTZ and GTN are equally effective and can be the preferred first-line treatment of chronic anal fissure a. However, GTN is associated with a higher rate of headache, and it should be replaced by DTZ.

KEY WORDS: Anal fissure, Lateral sphincterotomy.
that reduce compliance. Topical Diltiazem 2% reduces anal pressure and is found to be equally effective as that GTN ointment with fewer side effects. In this study, a comparative evaluation of diltiazem and GTN was done to examine the efficacy in the management of chronic anal fissure.

Methods

This prospective, randomized clinical trial was conducted in the St. Zahra Hospital from June 2004 to Oct 2008. All 102 patients were informed regarding the treatment protocol and its probable complications, and informed sanction was obtained from each patient. Inclusion criteria were males and females 18 years and older with chronic anal fissure having at least two of the following three criteria: (1) pain during and after defection of more than 6 weeks duration, (2) the presence of a sentinel anal tag, and (3) visibility of the horizontal fibers of the internal anal sphincter in the base of the lesion. Patients having any of the following features were excluded from the study: 1) acute anal fissure, 2) specific local pathological conditions (Crohn's disease, anal cancer, tuberculosis), 3) presumed or confirmed pregnancy or lactation, 4) allergy to diltiazem or GTN, 5) clinically considerable cardiovascular abnormalities, 6) chronic headaches, 7) associated complications (abscess, fistula).

The 102 consecutive patients who satisfied the selection criteria were divided into 2 groups according to a computer-generated centralized randomization list, namely Group DTZ (Diltiazem), Group GTN (Glycerol trinitrate).

This was a prospective, randomized, double-blind study. The study protocol was approved by the Ethics Committee of our faculty and was carried out in accordance with the principles of the Helsinki Declaration. The methods were explained to the patients and informed consent was obtained from all patients under study. Patients in Group DTZ were treated with topical diltiazem ointment (2%), while group GTN did use GTN ointment (0.2%). Patients were advised to apply 3 gram of ointment per dose circumferentially 1 cm inside the anus, near the internal anal sphincter, every 12 hours for 12 weeks. Neither group of patients was prescribed stool softeners or bulk laxatives for the duration of treatment. The patients under study were initially followed twice a week to find the relief of pain and, thereafter, once every 2 weeks for the fissure healing. At each visit, the patients were interviewed to assess their pain relief, healing of the fissure, and side effects of treatment, if any. Patients were given daily diary cards, asked to indicate the worst pain experienced each day on linear analog charts with a scale of 0 to 10 (Visual analogue Scale), and were questioned about side effects (Headache, blood pressure changes, anal irritation, allergic reactions) of treatment. Healing was defined as complete skin closure over the fissure, confirmed by anoscopy. Patients who did not heal after 12 weeks, those intolerant to the treatment, and those who did not report any improvement of symptoms within 8 weeks were offered to undergo surgical lateral internal sphincterotomy. Data analysis was conducted with Statistical Package for Social Sciences (SPSS) V13 using Student's t, chi-squared, logistic regression, and correlation tests. A value of P < 0.05 was considered significant.

Results

There were 102 patients with mean age of 29.90 years, with a range of 17–61 years. 90.2 percent of fissures occurred in the posterior midline. All the three groups were similar in terms of age, sex distribution, signs and symptoms, and location of fissure and type of symptoms (Table I and Figure 1). Forty-five patients (88.2%) in group DTZ and 36 patients (70.6%) in group GTZ had reduction of symptoms. The decrease in the symptoms for group DTZ were significantly more than that for

Table I - Comparison of the features of patients in two groups

<table>
<thead>
<tr>
<th>Feature</th>
<th>Group DTZ (n=51)</th>
<th>Group GTN (n=51)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male: Female (M/F ratio)</td>
<td>0.88</td>
<td>0.82</td>
<td>&gt; 0.05</td>
</tr>
<tr>
<td>Age (yr), mean ± SD (range)</td>
<td>30.23 (28.29 ± 32.17)</td>
<td>29.56 (27.90 ± 31.22)</td>
<td>&gt; 0.05</td>
</tr>
<tr>
<td>Decrease in symptoms (patients)</td>
<td>45 (88.2 %)</td>
<td>36 (70.6%)</td>
<td>0.02</td>
</tr>
<tr>
<td>Complete relief of symptoms (weeks)</td>
<td>2.44 ± 0.30</td>
<td>2.50 ± 0.28</td>
<td>&gt; 0.05</td>
</tr>
<tr>
<td>Mean time taken for complete relief of symptoms (weeks)</td>
<td>37 (72.5%)</td>
<td>28 (54.9%)</td>
<td>0.06</td>
</tr>
<tr>
<td>Fissure healing (patients)</td>
<td>5.08 ± 0.64</td>
<td>4.07 ± 0.50</td>
<td>0.02</td>
</tr>
<tr>
<td>Mean time taken for fissure healing (weeks)</td>
<td>34 (66.7%)</td>
<td>28 (54.9%)</td>
<td>0.2</td>
</tr>
<tr>
<td>Surgical operation (patients)</td>
<td>7.58 ± 2.01</td>
<td>4.85 ± 1.84</td>
<td>0.001</td>
</tr>
<tr>
<td>Mean time of need for surgery (weeks)</td>
<td>17 (33.3%)</td>
<td>23 (45.1%)</td>
<td>0.2</td>
</tr>
<tr>
<td>Headache (patients)</td>
<td>9.05 ± 2.56</td>
<td>5.33 ± 1.41</td>
<td>0.001</td>
</tr>
<tr>
<td>Mean time of headache relief (weeks)</td>
<td>0</td>
<td>30 (58.8%)</td>
<td>0.001</td>
</tr>
</tbody>
</table>

group GTN (P= 0.02). Mean time of symptom reduction was 2.44 ± 0.30 in group DTZ and 2.50 ± 0.28 weeks in group GTN. There was no significant difference in time of symptom reduction between two groups (P>0.05). Complete relieving of symptoms was observed in 72.5%, 54.9% patients in groups DTZ and GTN, respectively. The frequency of complete relieving of symptoms between two groups was not significant (P>0.05). However, in the DTZ group, mean time taken for complete relieving of symptoms was 5.08 ± 0.64 weeks which was significantly different from time in the GTN group (4.07 ± 0.50) (p=0.02). Totally, complete remission of anal fissure was occurred in 66.7% patients in group DTZ and 54.9% patients in group GTN, which was no different, significantly. Mean time taken for fissure healing was 7.58 ± 2.01 weeks in DTZ group and was 4.85 ± 1.84 weeks in GTN Group. Mean time taken for fissure healing in GTN group was dramatically less than DTZ group (P=0.001). Complete relieving of symptoms was observed in 72.5%, 54.9% patients in groups DTZ and GTN, respectively.

Ultimately, 66.7% of the anal fissures healed with DTZ ointment and 54.9% of fissures healed with GTN ointment. There is no difference in the complete remission of fissure and complete pain relief between two groups.

The need for operation was not significant between two groups (P>0.05). In DTZ group, patients’ preference and no response to medical treatments were the indications of surgery in 29.4% and 70.6%, respectively. On the other side in GTN group, the indication of surgery was severe headaches (side effect of treatment) in 60.9%, patients’ preference in 34.8% and no relief following medical treatment in 4.3% of patients. Indications of surgery was significantly different in two groups (P=0.001).

Except patients’ preference, 26.1% patients in DTZ group and 34.9% patients in GTN group were operated and there was no significant difference between two groups (P>0.05). The mean time of need for surgery following medical treatment was 9.05 ± 2.56 weeks in DTZ group and 5.33 ± 1.41 weeks in GTN group (except patients who was operated due to severe headaches) and the difference was significant (P=0.001).

Resolution of symptoms of anal fissure and healing can be attained by invasive interventions or by chemical sphincterotomy. Because of the complications associated with operative lateral internal sphincterotomy and the risk of incontinence, medical alternatives for surgery have thus been tried to obtain. Chemical sphincterotomy is noninvasive, precludes the need for general anesthesia, and could be applied at home by the patient itself. GTN ointment are metabolically degraded to nitric oxide which relaxes the internal anal sphincter 12. It has been studied most widely with effective healing in most of the cases, but headache is a major side effect with its use, which may lead to a discontinuation of the treatment 11,12,19-21,23.

Diltiazem ointment is found to be effective but with no headache associated. In the present study, a comparative evaluation of DTZ and GTN has been performed to evaluate the efficacy and complications in the management of chronic anal fissure.

In our study, symptoms of 88.2 % patients reduced with DTZ ointment while symptoms of 70.6% patients reduced with GTN (P=0.001), but there is no difference in mean time taken for reduction of symptoms between two groups. Lund and Scholefield 7 found that there is marked pain relief after using GTN ointment and the effects of application are not immediate. Carapeti 10 described the early marked pain relief after using DTZ ointment. The frequency of complete relieving of symptoms between two groups was not significant. However, the time taken for complete relieving of symptoms in GTN group was about 4 weeks after treatment that was significantly less than DTZ group (P=0.02). The mean time taken for healing for the DTZ group was 7.58 ± 2.01 weeks and for the GTN group, 4.85 ± 1.84 weeks. This shows that GTN causes early healing in comparison to DTZ ointment. Complete relieving of symptoms was observed in 72.5%, 54.9% patients in groups DTZ and GTN, respectively.

Ultimately, 66.7% of the anal fissures healed with DTZ ointment and 54.9% of fissures healed with GTN ointment. There is no difference in the complete remission of fissure and complete pain relief between two groups.

Discussion

Resolution of symptoms of anal fissure and healing can be attained by invasive interventions or by chemical sphincterotomy. Because of the complications associated with operative lateral internal sphincterotomy and the risk of incontinence, medical alternatives for surgery have thus been tried to obtain. Chemical sphincterotomy is noninvasive, precludes the need for general anesthesia, and could be applied at home by the patient itself. GTN ointment are metabolically degraded to nitric oxide which relaxes the internal anal sphincter 12. It has been studied most widely with effective healing in most of the cases, but headache is a major side effect with its use, which may lead to a discontinuation of the treatment 11,12,19-21,23.

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Ultimately, 66.7% of the anal fissures healed with DTZ ointment and 54.9% of fissures healed with GTN ointment. There is no difference in the complete remission of fissure and complete pain relief between two groups.
In a study done by Lund and Scholefield 7 66% of the patients using GTN ointment regularly for 6–8 weeks showed complete healing of the fissure. Carapeti et al. 10 stated that 67% of the patients healed after 8 weeks of using GTN ointment. In our study, 30 (58.8%) of the patients using GTN ointment had headaches, while none of the patients using diltiazem ointment showed headache. Carapeti et al. 10 were reported headache in 72%, and this led to discontinuation of the treatment by many patients. In the end, lateral internal sphincterotomy was done in 33.3% of patients in DTZ group and 45.1% of patients in GTN group. The need for operation was not significant between two groups.

On the basis of above findings, we concluded that DTZ ointment (2%) and GTN ointment (0.2%) are both effective treatment modalities for chronic anal fissure. GTN caused early relief in symptoms and fissure in comparison to DTZ. From other point of view, DTZ ointment (2%) and GTN ointment (0.2%) are both equally effective and can be the preferred first-line treatment of chronic anal fissure. However, GTN is associated with a higher rate of side effects (headache), and it should be replaced by DTZ.

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