Rectogesic® (glyceryl trinitrate 0.2%) ointment relieves symptoms of haemorrhoids associated with high resting anal canal pressures

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Abstract

Objective Some haemorrhoids are associated with high resting anal canal pressures. The aim of this study was to assess if Rectogesic®, a topical glyceryl trinitrate 0.2% ointment was effective in relieving symptoms of early grade haemorrhoids associated with high resting anal canal pressures.

Method This was a prospective, two-centre, open label study of 58 patients with persistent haemorrhoidal symptoms. Patients with first or second degree haemorrhoids and a maximum resting anal canal pressure >70 mmHg were included. Rectogesic® was applied three times a day for 14 days. Anorectal manometry was performed 30 min after the first application of Rectogesic®. A 28-day diary was completed during 14 days of therapy and for 14 days after cessation of treatment. This recorded the incidence of rectal bleeding, and visual analogue scales for anal pain, throbbing, pruritis, irritation and difficulty in bowel movement.

Results Maximum resting anal canal pressures were reduced after application of Rectogesic® (115.0 ± 40.4 mmHg vs 94.7 ± 34.1 mmHg, P < 0.001). In the study period and at 14 days after cessation of Rectogesic®, there was significant reduction in rectal bleeding (P = 0.0002), and significant improvement of anal pain (P = 0.0024), throbbing (P = 0.0355), pruritis (P = 0.0043), irritation (P = 0.0000) and difficulty in bowel movement (P = 0.001). The main adverse event was headache in 43.1% of patients.

Conclusion Rectogesic® is a safe and feasible treatment for patients with early grade haemorrhoids associated with high resting anal canal pressures.

Keywords Haemorrhoids, high resting anal canal pressures, glyceryl trinitrate

Introduction

Haemorrhoids are one of the most common anorectal conditions seen. At least 50% of individuals over the age of 50 years have at some time complained of symptoms associated with haemorrhoids [1].

Haemorrhoids are graded according to the degree of haemorrhoidal prolapse [1]. For patients with first and second degree haemorrhoids, the treatment options are usually nonoperative, including dietary manipulation, oral flavinoids or topical anti-haemorrhoidal medication. Many patients do not achieve adequate symptomatic relief with these measures and may need further intervention including rubber band ligation, injection sclerotherapy and haemorrhoidectomy.

The internal anal sphincter (IAS) of some patients with haemorrhoids demonstrates an abnormal rhythm of contraction and exerts a greater force of contraction than in asymptomatic controls [2–4]. Whether this sphincter abnormality is a cause or an effect of haemorrhoids is unknown. Schouten [5] studied 119 patients with symptomatic haemorrhoids and found significantly higher maximum resting anal canal pressures in 80% of patients compared with normal controls. After performing a lateral sphincterotomy in patients with haemorrhoids, a 27% reduction in maximum resting anal canal pressure was recorded. A ‘favourable clinical outcome’ was seen in 75.3% of patients following sphincterotomy.
particularily for patients in whom pain and bleeding were the main presenting symptoms [5].

Topical glyceryl trinitrate (GTN) has been shown to significantly reduce the maximum resting anal canal pressure for patients with chronic anal fissure in several randomized clinical trials [6–8]. It is a nitric oxide donor and produces vasodilatation of blood vessels with relaxation of the IAS muscle (chemical sphincterotomy). Topical GTN has been shown to marginally reduce posthaemorrhoidectomy pain [9].

However, topical GTN has not been studied as a primary treatment modality for symptomatic first and second degree haemorrhoids. The aim of this study was to evaluate the effect of a commercially available GTN 0.2% ointment (Rectogesic®) on the relief of haemorrhoidal symptoms for patients with early grade haemorrhoids associated with high maximum resting anal canal pressure.

Method

This was a prospective, two-centre, open label study of patients with persistent symptoms associated with first or second degree haemorrhoids. At the first visit, a detailed history and physical examination, including an anorectal examination was performed.

In this study, normal resting anal canal pressure was defined as 50–70 mmHg [1]. Patients with first or second degree haemorrhoids and a maximum resting anal canal pressure >70 mmHg were included in the study. Anorectal manometry was performed using the DUET Encompass® Anorectal Physiology system (Medtronic Inc, Minneapolis, Minnesota, USA), with an eight-channel, flexible, water-perfusion system using a technique previously described [10]. Measurements were made using the standard nomenclature published by the International Working Party [11]. The functional anal canal length or length of the high pressure zone was defined as that length of the anal canal which had a pressure of at least 20 mmHg higher than the mean resting pressure on manometry.

Exclusion criteria were (1) patients who had third or fourth degree haemorrhoids; (2) maximum resting anal canal pressure <70 mmHg; (3) concurrent anorectal conditions such as anal fissure or fistula; (4) history of migraine or severe headaches; (5) pregnant patients; (6) had a known allergy to any of the components of Rectogesic ointment; (7) patients who were already on GTN or another nitric oxide donor and (8) patients with hypertension or cardiac disorders.

During the period from May 2004 to March 2005, 66 patients with symptomatic first and second degree haemorrhoids gave written consent for the study. Of these, 58 patients fulfilled the inclusion criteria.

Rectogesic® (GTN 0.2%) ointment (Cellegy Australia Pty Ltd, Sydney, Australia) is a topical anal ointment containing the active ingredient GTN in a smooth light, amber ointment formulation for topical application. The other ingredients in Rectogesic (GTN 0.2%) ointment are yellow soft paraffin, wool fat, liquid paraffin and ethanol [12].

Using a standard ruler in the Rectogesic® package, patients were instructed to measure a 1.5-cm strip of ointment (corresponding to 375 mg). This strip was then placed onto a barrier, such as a plastic wrap or latex finger cot, to prevent cutaneous absorption and applied in the anal canal and spread circumferentially over the anoderm. This procedure was performed three times a day for 14 days (days 1–14). If the patient developed severe headaches, the dose was reduced to 1.0 cm (250 mg). Concurrent usage of sitz baths, other over-the-counter or prescription medication for haemorrhoids, phosphodiesterase-5 inhibitors, chemotherapeutic agents, glucocorticoids, nonsteroidal anti-inflammatory drugs or analgesic agents was prohibited. Consumption of fibre in diet was not stratified.

Anorectal manometry was performed 30 min after application of the first dose of Rectogesic®. Patients were followed up on day 14 (the last day of treatment) and 28 respectively, and an anorectal examination and global assessment was performed by two independent investigators.

Patients were instructed to complete a daily diary for 28 days, which recorded the presence or absence of visible bleeding, and visual analogue scales (VAS, 0–100) for pain intensity, throbbing, pruritis, irritation and difficulty in having a bowel movement. A score of 0 corresponded to absence of the specific symptom, and a score of 100 represented the most severe degree of the symptom. Patients were also asked to provide a global assessment of their disease on day 14 and 28, comparing their symptoms to the period of time prior to treatment. The occurrence of any adverse event at any time was documented by the patient.

All protocols were approved by the Epworth Hospital Ethics Committee and the South Eastern Area Health Ethics Committee.

Statistical analysis was performed using SPSS® Release 6.1 statistical software (SPSS Inc., Chicago, IL, USA). Changes in variables from their baseline levels were tested using Wilcoxon matched pairs signed-rank tests.

Results

There were 58 patients recruited to the trial, 38 were male and 20 were female. The mean age was 44.9 years (range 22–76). Twenty-eight patients had first degree
haemorrhoids and 30 had second degree haemorrhoids. None of the patients had an anal fissure.

All patients satisfied the eligibility criteria. Six patients withdrew as a result of adverse events, five as a result of headache, and one patient as a result of pruritus. Of these six patients, two withdrew after 1 day of treatment, three after 2 days of treatment and one after 14 days of treatment. Two further patients withdrew without completing the diary or returning for their next visit; one because of lack of improvement before 14 days and one despite improvement after 14 days. This patient returned for the day 14 review but without the diary. He had shown some improvement, but did not attend the day 28 review nor return the diary. All the remaining patients attended both the day 14 review and the day 28 review and completed the 28-day diary Fig. 1.

Maximum resting anal canal pressure was reduced after application of Rectogesic®. The mean maximum resting anal canal pressure was 115.0 ± 40.4 mmHg at baseline, which was reduced to 94.7 ± 34.1 mmHg 30 min after application of Rectogesic® (P < 0.001), this represented a 17.7% reduction in mean maximum resting anal canal pressure.

Table 1 shows the reduction in the amount of rectal bleeding after application of Rectogesic®. There was a significant decrease in the amount of rectal bleeding 1 week after administration of Rectogesic®. This improvement was noted up to 4 weeks after commencement of the study.

<table>
<thead>
<tr>
<th>Time</th>
<th>Days of rectal bleeding (mean ± SD)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>3.8 ± 2.6</td>
<td>Not applicable</td>
</tr>
<tr>
<td>Week 1</td>
<td>2.8 ± 2.6</td>
<td>0.0063</td>
</tr>
<tr>
<td>Week 2</td>
<td>2.1 ± 2.3</td>
<td>0.0001</td>
</tr>
<tr>
<td>Week 3</td>
<td>2.1 ± 2.4</td>
<td>0.0003</td>
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<tr>
<td>Week 4</td>
<td>2.1 ± 2.5</td>
<td>0.0002</td>
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</tbody>
</table>

There was significant improvement of anal pain, throbbing, pruritis, irritation and difficulty in bowel movement over the study duration. Table 2 reflects the progressive decrease in the VAS scales of each symptom during the treatment (weeks 1 and 2) and follow-up period (weeks 3 and 4).

Adverse events were recorded in 29 patients (Table 3). None of the adverse events restricted the patients in their daily activities. The most common adverse event was headache, which was graded as mild, moderate or severe. Fifteen patients had mild headache. Three patients complained of moderate headache. Seven patients had severe headaches, and five of the seven patients involved withdrew from the study. In total, 25 patients complained of headache in the first 14 days during the period of treatment. Of these, five patients continued to have headache for the next 14 days, but none of these was severe. The severity of headache fell significantly after cessation of treatment (Fig. 2, P = 0.0003).

Six patients also noted influenza (four patients) and constipation (two patients). These were deemed to be unrelated to the use of Rectogesic® ointment.

**Discussion**

The IAS is innervated by nitric oxide releasing nerves [13–18] and stimulation of these nerves leads to a relaxation of the IAS. Topical GTN acts as a nitric oxide donor [19], and produces a similar effect in reducing the resting pressure of the anal canal [5,20]. As the resting pressure is higher in patients with haemorrhoids [2–5], a reduction in anal canal pressure could lead to an improvement in symptoms. Several studies have shown the efficacy of topical GTN on anal fissures and thrombosed external haemorrhoids [13,21]. Both calcium-channel blockers [22] and GTN have been used for pain relief after haemorrhoidectomy [9,23–25]. This is the first study to assess the effects of topical GTN on first and second degree haemorrhoids.

The treatment of early-grade haemorrhoids starts with dietary manipulation and some have advocated the use of
micronized, purified flavinoids [26]. This was shown to reduce rectal bleeding in randomized controlled trials [25–29], but as the follow-up period was short, the long-term effects were unknown. Certainly dietary management has less side effects compared with Rectogesic/C210 or any of the ambulatory techniques which are commonly used.

Many ambulatory techniques have been described for the treatment of first and second degree haemorrhoids – Lord’s anal dilatation [30], infrared coagulation [26], bipolar coagulation [26], cryotherapy [26], injection sclerotherapy [26] and rubber band ligation [31].

In 1968, Lord [30] reported a technique of anal dilatation for treatment of haemorrhoids. This procedure is simple, causing minimal postoperative pain. The efficacy of anal stretch in symptomatic haemorrhoids was thought to reflect raised resting anal canal pressures in some patients. However, modern anorectal physiology techniques were not available then to document the actual anal canal pressures. Anal dilatation fell out of favour as subsequent studies showed that 20–40% of patients who underwent Lord’s anal dilatation developed faecal incontinence because of sphincter fragmentation [32].

Infrared coagulation and bipolar coagulation have been used in the treatment of early-grade haemorrhoids, but both are associated with high rates of recurrence [26]. Cryotherapy is less frequently used as patients experience significant pain and foul-smelling discharge [26].

Injection sclerotherapy is effective and associated with minimal pain [26], but there are concerns of sepsis [33] and injury to adjacent viscera [34]. In a meta-analysis [35], sclerotherapy was not as effective as rubber band ligation for the treatment of haemorrhoids. Komborozos et al. [31] reported a success rate of 88% in 500 cases of rubber band ligation in second, third and fourth degree haemorrhoids. These measures are successful in the control of rectal bleeding [26]. For first degree and small second degree haemorrhoids, rubber band ligation is less desirable because it causes more pain; in this situation, topical therapy might be a good alternative.

The literature on topical therapy of haemorrhoids is relatively scarce. Agents, such as calcium dobesilate [36,37], steroids [37,38], herbal remedies [39], Escherichia coli suspensions [38], trypsin and heparin paste [40] and blood leech extract [41] have been used with varying degrees of success. Most such studies are single centre experiences and most were not published in English, making interpretation more difficult.

Patients in this study experienced an improvement in symptoms after application of Rectogesic/C210. There was a reduction in rectal bleeding and an improvement in anal pain, anal throbbing, perianal pruritus, irritation and 

<table>
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<th>Table 2 VAS scale of symptoms.</th>
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<tbody>
<tr>
<td>Pain</td>
</tr>
<tr>
<td>--------------------------------</td>
</tr>
<tr>
<td>Week 1</td>
</tr>
<tr>
<td>$P$-value</td>
</tr>
<tr>
<td>Week 2</td>
</tr>
<tr>
<td>$P$-value</td>
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<tr>
<td>Week 3</td>
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<tr>
<td>$P$-value</td>
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<tr>
<td>Week 4</td>
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<td>$P$-value</td>
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*Not significant.

<table>
<thead>
<tr>
<th>Table 3 Adverse events.</th>
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<tbody>
<tr>
<td>Adverse events</td>
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<tr>
<td>----------------</td>
</tr>
<tr>
<td>Headache</td>
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<tr>
<td>Dizziness</td>
</tr>
<tr>
<td>Nausea</td>
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<tr>
<td>Vomiting</td>
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<tr>
<td>Pruritus</td>
</tr>
<tr>
<td>Others</td>
</tr>
<tr>
<td>Total</td>
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Figure 2 Severity of headache.
difficulty in having a bowel movement. The maximum resting anal canal pressures were reduced after application of Rectogesic® ointment. This leads to a relief of anal sphincter spasm, and could account for the symptomatic improvement.

Patients were enrolled in this study only if resting anal canal pressures were high (>70 mmHg). Patients with normal resting anal canal pressures were excluded. Coskun et al. [23] demonstrated that the beneficial effects of GTN for posthaemorrhoidectomy pain were seen only in subjects with high resting anal pressures, and not in those with low or normal pressures. The effect of topical GTN in patients with normal or low maximum resting anal canal pressures is not clear.

The relationship between the extent of reduction in maximum resting anal canal pressure and the relief of anal discomfort is controversial [42]. Thornton et al. [42] reported that clinical reduction of symptoms was associated with a reduction of 20% in maximum resting anal canal pressure. In this study, the observations were similar.

The duration of effect of topical GTN is also controversial. Because of the pharmacokinetics of the drug, the minimum dosing interval is 8 h [42]. The effect of the drug on the relaxation of the IAS is also short-lived. Jonas et al. [43] reported that the reduction in resting anal canal pressure lasted <90 min. Guillemot et al. [44] found that even with use of 10 times the standard dose, the reduction in pressure was <48 min. Despite these findings, 64% of patients with fissures treated with GTN had complete healing [42]. Similarly, in this study, the clinical effects of Rectogesic® persist, as patients reported improvement in symptoms even at 2 weeks after cessation of treatment with topical GTN. Even though the effect of Rectogesic® ointment on the IAS is not sustained, the temporary reduction in resting anal canal pressures might be adequate to alleviated much of the haemorrhoidal symptoms.

The main side effects of GTN are because of vasodilatation [20,21]. Headache is the most common adverse reaction to GTN therapy. In most controlled clinical studies, headaches were mild and transient, and did not interfere with treatment [13,20,21]. In this study, 43.1% of patients complained of headaches, despite the use of a barrier (plastic wrap or latex finger cot). This was compared with rates of 35–36% in reported literature [13,21]. Of the patients in our study, only 6.9% had severe headache, and warranted withdrawal from the trial; the incidence of severe headache in literature has not been well documented. The high incidence of headaches in this study may be a result of heightened perception by the patient as a result of daily dairy entry. This was also noted by Loder et al. [20], where patients did not volunteer the information upfront, but admitted to having headache upon direct questioning.

Most patients in this study had mild headache, which resolved upon cessation of Rectogesic® ointment. This is consistent with the experience in other studies with topical GTN, where patients had self limiting headache, which resolved after 15 min [13].

The side effects of topical GTN are also dose related [20,21]. A preparation of 0.2% GTN is reported to effectively reduce anal tone without producing severe side effects that are associated with higher doses [20].

This is a pilot study of a novel and simple treatment for patients with early haemorrhoids associated with a high maximum resting anal canal pressure. A randomized-controlled trial comparing Rectogesic® with a placebo ointment for the treatment of first and second degree haemorrhoids is desirable to clarify this further. Given the promising data of Rectogesic® and calcium-channel blockers in relieving haemorrhoidal pain, a randomized-controlled trial comparing the two agents would be of interest. In future trials, the cost/effect ratio should be considered. An additional point to consider is assessment of quality of life, given that some treatment modalities like Rectogesic® have side effects.

**Conclusion**

Topical GTN reduced the resting anal canal pressures in patients with first and second degree haemorrhoids with a high maximum resting anal canal pressure. Patients also had a reduction in the amount of haemorrhoidal bleeding and an improvement in their symptoms. This is a safe and feasible treatment for patients with early-grade haemorrhoids associated with high maximum resting anal canal pressures.

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