A randomized controlled trial of topical glyceryl trinitrate before transrectal ultrasonography-guided biopsy of the prostate

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OBJECTIVES
To evaluate the use of topical glyceryl trinitrate (GTN) ointment as an adjunct to periprostatic nerve block in reducing pain associated with transrectal ultrasonography (TRUS)-guided prostatic biopsy.

PATIENTS AND METHODS
In all, 148 consecutive patients (mean age 67.0 years) having their first TRUS-guided biopsy were randomized to receive either 0.2% GTN ointment or placebo 10 min before biopsy. All patients had a biopsy preceded by an injection with 10 mL of 1% lidocaine local anaesthesia. A 10-point visual analogue score was used to record 'Overall discomfort due to the presence of the probe', the biopsy itself and pain after the procedure.

RESULTS
There was no significant difference in age, PSA level and prostate volume between the groups. There was a significantly lower mean pain score due to probe insertion in the GTN than placebo group (1.94 vs 3.24, P < 0.01); pain perception was lower for the whole procedure in the GTN group, and was most pronounced in men aged <60 years (2.13 vs 4.61, P < 0.005).

CONCLUSIONS
Topical GTN ointment is safe and effective in reducing the discomfort associated with TRUS-guided biopsy of the prostate, in particular the insertion of the ultrasound probe. It might be of maximum benefit in the younger patient and those having a repeat biopsy who previously failed to tolerate the procedure well.

KEYWORDS
glyceryl trinitrate, prostate, biopsy, analgesia, pain

INTRODUCTION
TRUS-guided biopsy of the prostate is established as the standard test for diagnosing prostate cancer. The cancer detection rate is higher in biopsy protocols taking more needle cores [1], hence the widespread adoption of extended prostate biopsy protocols of 10–12 cores. The use of anaesthesia, analgesia or sedation for TRUS-guided biopsy has been increasingly trialled and discussed over recent years. The periprostatic nerve block (PPNB) has become the most widely adopted form of anaesthesia, and described as the current reference standard [2]. However, PPNB does not help to reduce the pain secondary to inserting the rectal ultrasound probe (before the PPNB can be applied) and in a previous randomized trial of pain perception during TRUS-guided biopsy it was the act of probe insertion that the patients described as most uncomfortable [3].

Topical glyceryl trinitrate (GTN) ointment has been shown to decrease anal sphincter tone [4] and this has been used clinically in the management of anal fissures [5]. One previous study examined GTN as the sole form of analgesia (with no PPNB) during TRUS-guided biopsy, and showed it to be effective in reducing overall pain perception compared with placebo [6], as well as being safe to administer with no serious complications reported. We assessed the effect of applying perianal GTN before a standard 12-core TRUS-guided biopsy with PPNB on the patients’ perception of pain at different stages of the procedure.

PATIENTS AND METHODS
In all, 148 patients, with a mean (SD, range) age of 67 (7.8, 41–90) years, and having their first TRUS-guided biopsy for investigation of a raised PSA level or an abnormal DRE, were recruited to participate in the study; each provided informed consent. Exclusion criteria were patients unable to provide informed consent, those on nitrate medication or recent phosphodiesterase-5 inhibitor use, a systolic blood pressure of <100 mmHg and those with severe cardiac, hepatic or renal disease.

Patients were randomized by computer to receive 1 g of topical 0.2% GTN ointment or paraffin-cream placebo 10 min before the procedure. Subjects were unaware of the preparation they would receive.

The biopsy procedure followed our standard departmental protocol; the patient was placed in the left lateral position and had TRUS using an ultrasound machine and a 7.5-MHz probe. The PPNB was administered with a 22 G spinal needle and an injection with 10 mL of 1% lidocaine under TRUS guidance. A 12-core biopsy was then taken by one of two experienced urologists, using a disposable 18 G spring-loaded core biopsy needle.

Immediately after the procedure the patients were asked to complete a questionnaire (Fig. 1) assessing their experience in terms of pain perception. They were asked to note on a 10-cm visual analogue score (VAS) the level of pain experienced due to the presence of the probe, the biopsy itself and that on leaving the department after the procedure.
The results were assessed statistically using standard statistical software, with Student's t-test used to compare variables. To detect a change in mean pain score of 1 unit with a power of 90% using a two-sided significance level of 5% it was necessary to admit at least 140 patients to the trial.

RESULTS

There were no significant differences in age or prostate volume between the groups. For the introduction of the probe the VAS pain score was significantly higher in the placebo than the GTN group, at 3.24 and 1.94, respectively (P < 0.01). The perception of pain was also significantly lower during the procedure in the GTN than the placebo group, at 2.24 vs 3.43 (P < 0.01), and by the time the patient was ready to leave the department the perception of pain was also less in the GTN than the placebo group, at 1.51 and 2.19, respectively (P < 0.01). Figure 2 shows the mean (95% CI) for these pain scores. A sub-analysis of pain scores according to patient age showed that there was a more significant and pronounced difference in pain score between the GTN and placebo groups in younger patients (Table 1).

The only reported side-effect was that of headache, reported by eight patients in the GTN group (10%). All of these patients were offered simple analgesia and all reported an improvement before leaving the department. There were no delayed discharges as a result of GTN administration.

DISCUSSION

The use of perianal GTN ointment as an adjunct to lidocaine local anaesthesia in TRUS-guided prostate biopsy significantly reduced the patients' perception of pain throughout the procedure. The benefit was most pronounced during the initial insertion of the probe, that part of the procedure before the PPNB can be applied. This is countered in that 10% of those men receiving GTN complained of a headache after the procedure.

Prostate biopsy has become more common since the increased use of PSA testing, and the evidence that taking more biopsy cores increases the cancer detection rate [7] is increasingly leading to a longer procedure for the biopsy. The false-negative rate of biopsy series also means that repeat biopsies are not uncommon. If a patient has unpleasant memories from a previous biopsy they might be naturally apprehensive about having a repeat procedure [8].

There is now strong evidence that anaesthesia and/or analgesia reduces patient discomfort during TRUS-guided biopsy [2]. The commonest agents trialled and currently used in routine practice are PPNB with a local anaesthetic agent [9–11], rectal anaesthetic gel [12] and Entonox [13] (50% nitrous oxide and oxygen) gaseous anaesthetic. Much of the anxiety a patient has when having a biopsy can be related to the anal route of penetration of the ultrasound probe. There might be much anticipation of the pain about to be experienced, and indeed if the patient finds this uncomfortable the rest of the procedure can be a difficult experience for both the patient and the urologist. Philip et al. [3] previously noted that patients had the most discomfort during TRUS-guided biopsy with PPNB when the probe was inserted. GTN causes smooth muscle relaxation and has been shown to decrease anal sphincter tone.

FIG. 1. The pain questionnaire completed by the men after the biopsy.

QUESTIONNAIRE FOR GTN STUDY

Subject number:

Thank you for taking part in the research study today. It is important you complete the following questions. The first 3 questions are a pain scale with "no pain" being 0 and "severe excruciating pain" being 10. We request that you mark with an "X" where your pain is on the scale or you can put it as a number (0–10).

Example:

Overall discomfort due to the presence of the probe

|No discomfort| Severe discomfort|

1) Overall discomfort due to the presence of the probe

|No discomfort| Severe discomfort|

2) Overall pain noticed during the biopsy

|No discomfort| Severe discomfort|

3) Overall pain felt before leaving the department

|No discomfort| Severe discomfort|

4) Briefly describe below any other symptoms / problems related to your investigation today?

FIG. 2. The mean (95% CI) pain scores for the GTN and placebo groups.

TABLE 1 The mean pain scores according to age group

<table>
<thead>
<tr>
<th>Age group, years</th>
<th>Mean VAS score, GTN/no GTN</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;60</td>
<td>2.13/4.61</td>
<td>0.005</td>
</tr>
<tr>
<td>60–70</td>
<td>1.69/3.48</td>
<td>0.005</td>
</tr>
<tr>
<td>&gt;70</td>
<td>2.24/2.57</td>
<td>0.280</td>
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and hence its therapeutic application for treating anal fissure. The evidence from the present study is that GTN offers a significant benefit in reducing the pain from probe insertion, and this then results in the patient’s perception of pain throughout the procedure being reduced. The reduction in perceived pain is countered by the risk of headache with GTN application. We report a 10% risk, and this is consistent with the experience of Rochester et al. [6]. Patients might consider this relatively high risk of an unpleasant side-effect, reducing one discomfort to endure another, and they need to be counselled appropriately. Topical diltiazem has been shown to have a similar effect in reducing anal tone but with no risk of headache [14]. However, diltiazem 2% cream is significantly more expensive than 0.2% GTN, costing £1.10 more for each 1 g application.

The present study confirms the findings of Rochester et al. [6], that perianal GTN is a useful agent for reducing probe-associated discomfort. By using it with a PPNB there was less perceived pain throughout the procedure, confirming that much of the discomfort experienced is probe-related. The PPNB is the reference standard of anaesthesia for TRUS-guided biopsy, with good efficacy, and it would seem appropriate to consider topical GTN as an adjunct to this treatment when required. The maximum benefit from GTN appears to have been in the younger patient, the most significant difference between the placebo and the GTN group being in men aged <60 years. Previous studies showed that older men have more pain during TRUS biopsy [3,15] and it might be that topical GTN has a role as an adjunct to PPNB in this group.

In conclusion, topical GTN ointment is safe and effective in reducing the discomfort associated with TRUS-guided biopsy of the prostate, in particular the insertion of the ultrasound probe. It might be of maximum benefit in the younger patient and those having a repeat biopsy who previously failed to tolerate the procedure well.

CONFLICT OF INTEREST

None declared.

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Abbreviations: GTN, glyceryl trinitrate; PPNB, periprostatic nerve block; VAS, visual analogue scale.

EDITORIAL COMMENT

Cynics might argue that PPNB has adequately eliminated pain from prostate biopsy, but the data here show that there is much work to be done before the disincentives to have a biopsy disappear. A query of my departmental database showed that depending on the probe used, its insertion is often the most painful part of the biopsy. Notably, the pain appears to be substantially less with older, lower profile probes than with newer versions that use a high-profile needle guide (VAS pain scores 24.6 vs 34.6, P < 0.001; Student’s two-sided t-test, unpublished data). The present study is significant in its focus on improving the patients’ experience beyond simply the painful part of the biopsy. Notably, the pain appears to be substantially less with older, lower profile probes than with newer versions that use a high-profile needle guide (VAS pain scores 24.6 vs 34.6, P < 0.001; Student’s two-sided t-test, unpublished data). The present study is significant in its focus on improving the patients’ experience beyond simply the painful part of the biopsy. Notably, the pain appears to be substantially less with older, lower profile probes than with newer versions that use a high-profile needle guide (VAS pain scores 24.6 vs 34.6, P < 0.001; Student’s two-sided t-test, unpublished data).
Others have shown that a diclofenac suppository has the potential to offer similar benefit during the embarrassing and painful manoeuvre of inserting the ultrasound probe and consistent with the present study it might augment the proven efficacy of PPNB on the patients’ experience. These reports and the present work by McCabe et al. should serve as the foundation for further attempts to improve the biopsy procedure, both because of the need to remove obstacles to indicated biopsies and to show the compassion our patients deserve.

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