Crossover study of glyceryl trinitrate patches for controlling pain in women with severe dysmenorrhoea

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Primary dysmenorrhoea affects up to half of post-pubescent women and is one of the commonest gynaecological complaints. Combined oral contraceptives and non-steroidal anti-inflammatory drugs are often used to treat dysmenorrhoea but are not effective in 10-20% of patients¹ and are contraindicated or unsuitable for many others. There is a need for a simple and safe new treatment for this condition.

The pain of dysmenorrhoea is associated with increased intrauterine resting pressures and peak pressures,² and effective treatment is associated with uterine relaxation.³ Glyceryl trinitrate seems to relax uterine contractions in preterm labour,⁴ and we investigated whether it could be used to treat dysmenorrhoea.

Patients, methods, and results

We enrolled 14 women in a randomised, double blind, placebo controlled, two period crossover trial for two successive menstrual cycles. All had persistent and regular severe dysmenorrhoea which seriously interfered with their social and professional lives. Their mean age was 27 years (range 17-36), and in all cases gynaecological investigations—including a transvaginal ultrasound scan—revealed no important pathology. The women were given adhesive matrix patches (Schwarz Pharma AG, Monheim, Germany) that were placebo or released 10 mg glyceryl trinitrate transdermally over 24 hours. The patches were cut into quarters at the start of each menstrual cycle, and the women applied one quarter (releasing about 2.5 mg glyceryl trinitrate from active patches) to their abdomen when menstrual pain began. The quarter patches were replaced every 24 hours while pain persisted, up to a maximum of four consecutive days per cycle. Women who received active patches in the first menstrual cycle were given placebo patches in the next cycle and vice versa. The participants recorded their menstrual symptoms and possible side effects of treatment with a visual analogue self assessment form and recorded their usual use of analgesic drugs.

Eleven participants completed the study; one was lost to follow up, one withdrew because of presumed side effects (headache), and one did not complete her self assessment forms. Table 1 gives results for six outcome measures. The total score was the sum of the daily scores during each treatment cycle. Pain was of primary interest, and the total pain score was lower with active treatment than with placebo (Wilcoxon matched pairs $P=0.059$). The reduction represented on average 10.5% of the maximum possible pain score

and 19.5% of the pain score recorded with placebo. The pain recorded on the worst day of the treatment cycle was also lower with active treatment (Wilcoxon matched pairs $P=0.048$). The reduction represented on average 10.2% of the maximum possible score and 11.6% of the score recorded on the worst day with placebo. The effects of treatment on the other measures were small and not significant. Headache showed no significant worsening ($P=0.4$ for total and worst day scores), and the only adverse reaction recorded was mild skin irritation.

Comment

Transdermal glyceryl trinitrate might have several important advantages over conventional treatment for dysmenorrhoea: none of the contraindications to non-steroidal anti-inflammatory drugs or combined oral contraceptives apply to it. Combined oral contraceptives have to be used throughout the menstrual cycle, and non-steroidal anti-inflammatory drugs are most effective when started before the onset of menstrual symptoms. Glyceryl trinitrate has a short half life and disappears rapidly from the circulation,⁵ and patches are convenient and have an established record of safety at higher doses for treating angina. The patches can be applied and removed as required and so give patients control in treating symptoms. The power of this study to detect the level of pain reduction shown in Table 1 was small; 40% for total pain score and 35% for the worst pain score recorded for a two tailed t-test with $P=0.05$. Nonetheless the observed reductions are of a clinically useful size and suggest that transdermal glyceryl trinitrate may be an effective treatment for dysmenorrhoea.

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Table 1—Mean (SD) scores for outcome measures recorded by 11 women given active treatment (glyceryl trinitrate) or placebo during menstrual period. Scores are given as percentage of maximum possible score unless stated otherwise

	Total score			Score on worst day		
	Active treatment	Placebo	Difference (95% confidence interval)	Active treatment	Placebo	Difference (95% confidence interval)
Period pain	45.7 (23.6)	56.2 (16.8)	10.5 (-2.2 to 23.2)	64.5 (20.8)	74.4 (18.6)	10.2 (-3.4 to 23.8)
Headache	17.1 (22.6)	25.2 (30.4)	8.0 (-10.6 to 26.6)	41.8 (35.0)	30.3 (29.9)	-11.6 (-37.5 to 14.4)
Loss of period	56.3 (23.3)	57.9 (20.8)	1.6 (-10.0 to 13.1)	79.0 (22.0)	77.5 (49.0)	-1.5 (-8.6 to 5.6)
Poor concentration	35.9 (18.3)	34.7 (25.2)	-1.2 (-13.7 to 11.4)	53.3 (30.6)	57.3 (29.4)	3.9 (-8.5 to 16.4)
Interference with daily activities	32.7 (27.7)	46.1 (24.8)	14.4 (-4.4 to 33.2)	55.9 (29.8)	67.3 (26.2)	11.4 (-4.5 to 27.3)
Need for analgesics (No of tablets a day)	2.62 (1.60)	2.93 (1.61)	0.31 (-0.39 to 1.00)	4.36 (2.20)	4.90 (2.38)	0.55 (-1.50 to 2.59)