

## PAPERS AND SHORT REPORTS

## Comparative trial of rectal indomethacin and cryoanalgesia for control of early postthoracotomy pain

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### Abstract

A randomised double blind trial was carried out over the first two days after thoracotomy to compare the analgesic effects of rectal indomethacin 100 mg administered eight hourly, cryoanalgesia, and a combination of both of these with the effects of conventional intramuscular opiate analgesia. Pain scores were significantly reduced with both rectal indomethacin alone and cryoanalgesia alone; these treatments had an additive effect when used in combination. Pain on movement was significantly increased, and indomethacin was more effective in reducing this than cryoanalgesia. Groups receiving either indomethacin alone or the combination treatment required significantly less opiate on the first day and exhibited improved peak flow values over the first two days.

It is concluded that rectal indomethacin, in this dosage, can provide good, safe analgesia after thoracotomy with minimum administrative difficulty. When used as an adjunct to cryoanalgesia it has an additive effect. There are many potential uses for this drug in other branches of surgery.

### Introduction

Thoracotomy causes severe postoperative pain,<sup>1</sup> and of the many measures that have been advocated to mitigate this, few are free from untoward side effects<sup>2</sup> and many require specialist staff and equipment. These include continuous intravenous opiate infusion,<sup>2-4</sup> epidural administration of local anaesthetics,<sup>5,6</sup>

and cryoanalgesia.<sup>2,7-9</sup> Most workers however, agree that conventional intermittent intramuscular injections of opiates provide inadequate analgesia.<sup>10</sup>

We noted that patients undergoing thoracic surgery who were receiving non-steroidal anti-inflammatory agents administered rectally for other indications appeared to experience less post-operative pain. We devised the present study to compare the analgesic effects of indomethacin, cryoanalgesia, and a combination of the two with those of conventional periodic intramuscular injections of opiate in controlling pain immediately after thoracotomy.

### Patients and methods

Sixty patients, after giving informed consent, were allocated randomly to one of four groups of 15 to receive rectal indomethacin, cryoanalgesia, or a combination of rectal indomethacin and cryoanalgesia or to serve as controls. All patients in the trial had access, on request, to analgesia in the form of intramuscular papaveratum 10-15 mg according to body weight. All received suppositories, placebos being used for those not receiving indomethacin. Indomethacin 100 mg eight hourly was started immediately after thoracotomy and continued for three days. Cryoanalgesia was carried out in the standard way.<sup>2</sup> Before closure of the wound the two intercostal nerves above, the two intercostal nerves below, the nerve of the interspace, and the nerve of the drainage site, if not already included, were dissected out and frozen for 45 seconds with a cryoprobe (Spemby).

*Technique*—Any patient undergoing a full thoracotomy was admitted to the trial, exclusions being those undergoing combined procedures necessitating an additional incision—for example, mediastinotomy. Pulmonary resections were performed via a posteriolateral thoracotomy, generally through the fifth intercostal space, while oesophageal surgery was performed through the seventh or eighth interspace. Anaesthesia was induced with thiopentone and maintained with oxygen, nitrous oxide, muscle relaxants, and either fentanyl or papaveratum.

*Measurement*—Each patient graded the severity of his pain on a 100 mm visual analogue scale,<sup>11</sup> one end of which, represented no pain at all and the other the most severe pain imaginable; the distance in mm was taken as the pain score. Measurements were made while the patients were at rest and after physiotherapy and were supervised by our senior physiotherapist. Additionally, she graded the overall degree of comfort of each patient as being good, moderate, or poor during the same period. The total dose of papaveratum administered during the first day and the number of doses given were recorded.

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Peak flow was measured with a Wright peak flow meter preoperatively and on the first and second postoperative days. On each occasion the value noted was the average of three attempts.

**Statistical methods**—The pain scores were treated by an arc sine transformation<sup>12</sup> as a visual analogue scale may not permit a normal distribution because of its constraint by finite ends. Results were then analysed using a factorial model by means of an analysis of variance on the computer program Genstat. The results for analgesic dosage and peak flow values were analysed using the same computer program.

## Results

The 60 patients (36 men, 24 women) had a mean age of 61 years and underwent 40 pulmonary resections, 18 oesophageal procedures, and two thoracotomies for inoperable tumours (table I). There was no significant difference between the four groups with respect to age, sex, weight, operation, or surgeon.

Table II shows that only indomethacin ( $F_{2,1} = 4$ ;  $p < 0.05$ ) and the combination of indomethacin and cryoanalgesia significantly reduced the opiate requirement. When the two treatments were used together their effects were additive, but the reduction in pain scores achieved by one treatment was not affected by the other treatment ( $F_{1,56} = 0.98$ ;  $p < 0.05$ ). The mean numbers of requests for analgesia during the first day were analysed with the Mann-Whitney U test, which showed that only the combination treatment produced a significant reduction ( $p < 0.01$ ).

The decreases in peak flow values from the preoperative baseline values were significantly smaller, on both days, with indomethacin than with cryoanalgesia ( $F_{1,56} = 12.66$ ;  $p < 0.001$ ). The combination of indomethacin and cryoanalgesia did not confer any additional benefit. Observer grading of pain (table IV) showed a similar trend, results being analysed with the  $\chi^2$  test.

The 30 patients receiving rectal indomethacin did not suffer any complication related to the drug. One patient in the trial, who had undergone cryoanalgesia, required bronchoscopy for retained secre-

TABLE I—Characteristics of the four groups of patients

	Controls	Indomethacin	Cryoanalgesia	Indomethacin and cryoanalgesia
Mean (SD) age (years)	65 (7.6)	62 (10.2)	54 (15.3)	62 (10.0)
Mean (SD) weight (kg)	64.1 (11.5)	74.8 (13.5)	63.6 (10.1)	64.3 (9.7)
Sex (M:F)	10:5	8:7	8:7	10:5
Procedure:				
Pulmonary resection	13 (1 inoperable)	9	10 (1 inoperable)	10
Oesophageal surgery	2	6	5	5

TABLE II—Pain, analgesic requirements, and peak flow in each group

	Controls	Indomethacin	Cryoanalgesia	Indomethacin and cryoanalgesia
Mean pain score*	46.9	29.3	35.0	21.6
Papaveratum administered during first 24 h:				
Total dose (mg)	49.7	45	47.3	33.5
Mean No of injections	4.1	4.1	3.5	2.6
Peak flow (%)†	46	53	46	63

\*Pain scores (with an arc sine transformation) at rest and on movement for both days combined.  
†Values obtained on the first day expressed as a percentage of the preoperative value.

The figure shows the untransformed means of the pain scores at rest and on movement. Statistical analysis of the transformed scores showed a significant reduction in pain with both cryoanalgesia ( $F_{1,56} = 14.4$ ;  $p < 0.01$ ) and rectal indomethacin ( $F_{1,56} = 36.1$ ;  $p < 0.001$ ). Combining the treatments appeared to have an additive effect (table II). There was no significant reduction in pain on the second postoperative day, although pain on movement was significantly increased, as expected ( $F_{1,55} = 15.6$ ;  $p < 0.001$ ). Rectal indomethacin was significantly effective in reducing the pain provoked by movement ( $p$  (one sided)  $< 0.05$ ) whereas cryoanalgesia was not ( $p$  (one sided)  $> 0.1$ ) (table III).

TABLE III—Mean pain scores showing interaction of movement with the two treatments

	At rest	On movement
Indomethacin	23.9	27
No indomethacin	34.4	47.5
Cryoanalgesia	24.4	32.1
No cryoanalgesia	33.9	42.3

TABLE IV—Observer's grading of overall pain relief in each patient over both days ( $\chi^2 = 14.6$ ,  $p < 0.05$ )

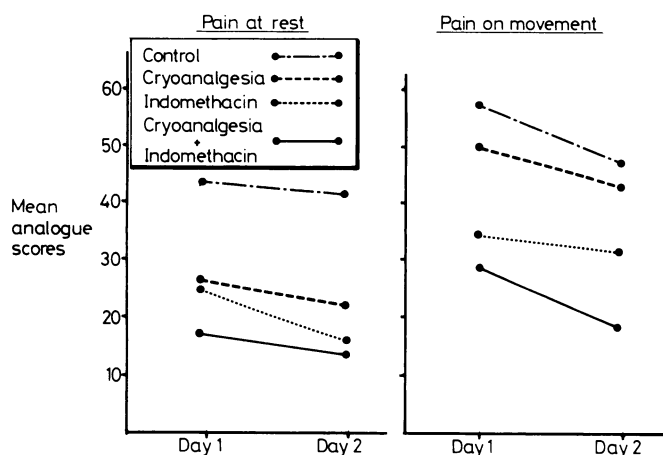
	Control (n=30)	Indomethacin (n=30)	Cryoanalgesia* (n=30)	Indomethacin and cryoanalgesia (n=30)
Good	14	24	11	19
Moderate	10	6	12	6
Poor	6		5	5

\*Two observations missing.

tions. One further patient, who had received the combination treatment, required reoperation to arrest a haemorrhage due to a clearly definable surgical cause.

## Discussion

This study confirms that cryoanalgesia after thoracotomy is an effective form of pain relief, but not all pain after thoracotomy is directly related to the wound and thus the pain is not totally



Changes in mean pain scores during study.

amenable to blocking of the local nerves.<sup>7</sup> Rectal indomethacin with its systemic effect was shown to be a more efficient analgesic agent, providing a broader degree of pain control. On all the variables we measured rectal indomethacin had a stronger analgesic effect than cryoanalgesia. The combination of rectal indomethacin and cryoanalgesia produced an additive effect. The ease of administration of rectal indomethacin, with its simplicity in use, its absence of noted side effects, and its low cost, has much to commend it in thoracic surgery. Its potential benefit in other branches of surgery is apparent. We should like to add a cautionary note, however, concerning the concurrent administration of subcutaneous heparin: before conducting this trial we saw several cases of persistent bleeding after surgery, but no such cases occurred after we stopped the routine use of subcutaneous heparin.

Of the available methods for effectively controlling pain after thoracotomy, the epidural route, although effective, has much against it in terms of possible complications and the need for specialised staff, while a cryoprobe is simple to use provided that the equipment is available. Similarly, continuous intravenous infusions of opiate are effective<sup>2-3</sup> but require an infusion pump and trained medical staff to start and supervise treatment, while intramuscular injection of opiate, in sufficient dosage to produce satisfactory analgesia, may produce appreciable respiratory depression. Indomethacin administered rectally has none of these drawbacks. We recommend its use after thoracotomy, both alone and as an adjuvant to other analgesic regimens. We found it singularly efficacious in reducing pain on movement, and it could thus make a considerable contribution to effective physiotherapy and earlier mobilisation.

It is difficult to produce useful objective data on the influence of analgesics on changes in respiratory function after thoracotomy. We were impressed with the way in which peak flow values mirrored the other variables and provided useful information.

We conclude that rectal indomethacin provides good, safe, simply administered analgesia after thoracotomy and has an additive effect when used as an adjuvant to conventional analgesia such as cryoanalgesia.

We thank Mr I K R McMillan for allowing us access to his patients and Dr M Campbell for performing the statistical analysis of our results.

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(Accepted 18 August 1983)

# Sex hormones and skin collagen content in postmenopausal women

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## Abstract

Skin biopsy specimens were taken from 29 postmenopausal women who had not been given hormone replacement therapy and from 26 women who had been treated with oestrogen and testosterone implants for two to 10 years. The mean hydroxyproline content and therefore the mean collagen content in the skin was found to be 48% greater in the treated than the untreated women,

who were matched for age. This difference was significant ( $p < 0.01$ ).

The implication of this finding is that oestrogen or testosterone, or both, prevents the decrease in skin collagen content that occurs with aging and protects skin in the same way as it protects bone in postmenopausal women.

## Introduction

Oestrogen treatment is gaining widespread use as its ability to relieve symptoms of the climacteric and prevent osteoporosis become better appreciated.<sup>1-2</sup> Studies on oestrogens and bone have not been matched with work on the skin,<sup>3</sup> although the biochemistry of the collagen matrix of bone is basically similar to that of the collagen in skin. There is only indirect evidence of the effects of oestrogens and testosterone on the skin. Shuster *et al* showed a linear decrease in skin collagen content of about 1% per year through adult life, with the skin collagen being less in women than in men.<sup>4-6</sup> This difference between the sexes was attributed to testosterone. They also showed that

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