the mesangium in these cases.^{7 8 19} Aggregated IgA can fix complement by the alternative pathway,²⁰ and it is possible that IgA immune complexes are responsible for the complement fixation in these patients, particularly as IgA is sometimes the only immunoglobulin present, as in three of our cases. Mesangial IgA deposits may recur in patients who have received renal transplants,²¹ which further suggests some humoral mechanism (we did not perform a biopsy on our single transplanted kidney).

In making comparisons with other series one must not only consider the French and American studies, in which, as in our study, patients were selected for having mesangial IgA deposits, but also the numerous reports^{6 22} over the past 50 years²³ that have discussed children and adults with the syndrome of recurrent macroscopic haematuria^{10 12 13 24-30}. These emphasize the usually associated focal nephritis and generally good prognosis, but only the more recent reports give details of immunofluorescent studies.^{10 30}

It is apparent from the literature and from our own experience that there is no consistent relation between recurrent haematuria, mesangial or focal proliferative nephritis, and mesangial IgA deposits. Recurrent haematuria is the presenting feature of other histological types of nephritis, may also occur in patients with entirely normal renal biopsy specimens, and is not always associated with mesangial IgA deposits. Moreover, in about half the cases in which mesangial IgA deposits are found they are not associated with recurrent haematuria. Finally, in our experience, mesangial IgA deposits are not the commonest finding in "idiopathic" focal or mesangial proliferative nephritis, focally distributed IgG, IgM, and C3 deposits being commoner. We and others have also found IgA deposits outside the mesangium in occasional cases of proliferative and membranous nephritis.²

Thus, though a subgroup of patients with mesangial IgA deposits are distinguished by having recurrent macroscopic haematuria, when considered as a whole patients with mesangial IgA deposits do not seem to present a completely uniform picture. Until more is known about the mechanisms resulting in IgA deposition in the glomerulus and the precise pathogenetic role of IgA in these patients it seems debatable whether the use of terms such as "mesangial IgA disease" and "IgA nephropathy" is warranted.

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Treatment of Superficial Thrombophlebitis: A Randomized, Double-blind Trial of Heparinoid Cream*

P. P. MEHTA, S. SAGAR, V. V. KAKKAR

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Summary

In a prospective, double-blind, randomized trial the efficacy of a heparinoid in ointment form was assessed in treating superficial thrombophlebitis developing after continuous intravenous infusion. One hundred surgical

patients were studied, and clinical examination and the iodine-125-labelled fibrinogen test used to assess the results. The mean time required for the relief of local symptoms and signs and the rate of local decline in radioactivity differed significantly between patients receiving the heparinoid cream and those receiving the placebo.

Introduction

Superficial thrombophlebitis remains a common complication of continuous intravenous infusion,^{1 2} despite the use of plastic infusion sets and various types of pre-sterilized plastic cannulae. Though the condition is rarely responsible for serious illness,³ it often causes considerable pain and discomfort at the site of the infusion. Commonly used treatments may limit extension of the process and relieve pain but they do not remove the thrombus; this occurs by spontaneous fibrinolysis. Heparinoid cream

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King's College Hospital Medical School, London SE5 8RX

P. P. MEHTA, M.B., M.S., Research Fellow

S. SAGAR, M.B., F.R.C.S., Research Fellow

V. V. KAKKAR, M.B., F.R.C.S., Consultant Surgeon

(mucopolysaccharide polysulphate) is absorbed into the circulation when applied topically^{4,5} and has a heparin-like action on blood clotting.⁶

We present the results of a randomized, double-blind trial designed to see whether the local application of a heparinoid cream would produce symptomatic improvement and promote early resolution of the thrombophlebitis.

Material and Methods

Patients.—One hundred patients who developed superficial thrombophlebitis after the infusion of normal saline, dextrose saline, blood, or other fluids were studied. They were admitted to four surgical wards, three male and one female, and most underwent major gastrointestinal or biliary operations. Age, sex, duration of symptoms, and fluids infused were recorded on a specially designed form. Infusions were given through a standard plastic giving set using various plastic intravenous cannulae. The technique of setting up the infusions was standardized so far as possible.

Thrombophlebitis was diagnosed when a tender palpable cord or a red flare developed over the vein after stopping the infusion. The extent of the thrombophlebitis was noted.

Design of Trial.—One hundred envelopes were prepared, sealed, and numbered in sequence, each containing one of two treatment schedules distributed in random order. As each patient was admitted to the trial his treatment was selected by opening the next envelope, which indicated whether the patient was to receive the contents of a green or a red tube. Two hundred tubes (either red or green) containing 50 g heparinoid in ointment (Hirudoid) or 50 g placebo cream were specially prepared. Cream from either the red or green tube was applied to the area of redness and tenderness, and this was followed by firm bandaging. This treatment was repeated daily for at least five days, cream from the same-coloured tube being applied in the same manner on each occasion. If at the end of five days symptoms persisted treatment was continued.

Clinical and Isotopic Assessment of Treatment.—The limbs were examined each day and changes in the local signs recorded. The radioactive fibrinogen test provides an accurate method for quantitative assessment of the fate of the thrombus.⁷ Most of the patients had already received 100 μ Ci ¹²⁵I-labelled fibrinogen for detecting the presence of early-forming thrombi in the deep veins of the lower limbs, and the opportunity was taken to record the radioactivity over the area of superficial thrombophlebitis. In patients who had not received radioactive fibrinogen before the onset of the thrombophlebitis 50 μ Ci ¹²⁵I-labelled fibrinogen was injected into the opposite arm and the radioactivity recorded 8-12 hours later. The technique followed that described for the diagnosis of thrombosis.⁸ Radioactivity was recorded daily at the site of the thrombophlebitis, at a site distal or proximal to it, and at the same positions over the opposite (unaffected) limb.

Results

After completion of the trial the red tubes were found to contain the active, heparinoid compound and the green tubes the placebo cream. Fifty patients had received the placebo cream and 50 the heparinoid cream. Subsequent comparison of the two groups showed them to be similar in many respects (table I). The extent of the thrombophlebitis is shown in table II.

CLINICAL ASSESSMENT

All patients successfully completed a full course of treatment and no local or systemic side effects were observed. The mean time required for the relief of local symptoms and signs in patients receiving the placebo was 126 hours (range 48-148 hours), while in those receiving the heparinoid cream it was 58 hours (range 36-102 hours). This difference is statistically significant ($P < 0.05$).

ISOTOPIC ASSESSMENT

¹²⁵I-labelled fibrinogen was administered before the onset of thrombophlebitis to 83 patients (44 in the placebo group and 39 in the heparinoid group) and after the onset to the other 17 (6 in the placebo group

TABLE I—Comparison of the Two Groups of 50 Patients

		Placebo Group	Heparinoid Group
Sex	Male	34	39
	Female	16	11
Age (years)	Mean	56.3	44.9
	Range	35-83	17-72
Duration of symptoms (hours)	Mean	27.3	23.8
	Range	12-48	18-36
Limbs affected	Unilateral	48	49
	Right	26	21
	Left	22	28
Duration of infusion	Bilateral	2	1
	1-2 days	14	18
	3-4 days	23	17
	5-5 days or over	13	15
Fluids infused	Primary infusion only:		
	5% Dextrose	9	7
	5% Dextrose + normal saline	6	10
	Normal saline	3	
	5% dextrose + antibiotics	5	4
	5% Dextrose, normal saline, + antibiotics	4	6
	5% Normal saline + antibiotics	2	3
	Additional infusion:		
	Blood and blood substitutes	9	7
	Other fluids	12	13

TABLE II—Extent of Thrombophlebitis in the Two Groups. Figures are Numbers of Patients

No. of Positions Affected	Placebo Group	Heparinoid Group
1	23	17
2	16	16
3	6	9
4	3	5
5	2	3
Total	50	50

and 11 in the heparinoid group). All patients showed an increased uptake of radioactive fibrinogen at the site of the thrombophlebitis. The original difference in radioactivity between this site and the corresponding area on the opposite (unaffected) limb was assumed to represent the total radioactivity contained in the thrombus and locally accumulated inflammatory exudate. The decrease in the percentage difference in radioactivity over these two sites indicated the rate of disappearance of radioactive fibrinogen/fibrin from the thrombus and inflammatory exudate.

In patients receiving the placebo the radioactivity increased during the first 48 hours, the mean being 135.4% on the second day and 116.1% on the third day (table III). In patients receiving the heparinoid cream the radioactivity decreased, the mean on the second day being 85.5% and on the third day 58.9% (table III). On the fifth day the mean levels were 76.3% in the placebo group and 23.5% in the heparinoid group. The differences between the two groups on the second, third, and fifth days were statistically significant (table III).

TABLE III—Changes in Percentage Radioactivity in the Two Groups

Day	Placebo Group		Heparinoid Group		P Value
	Mean	Range	Mean	Range	
1	100.0		100.0		
2	135.4	66-280	85.5	45-135	<0.001
3	116.1	24-224	58.9	10-120	<0.001
5	76.3	24-192	23.5	5-60	<0.301

Discussion

The overall incidence of infusion thrombophlebitis was similar to that reported.⁹ Heparinoid is a mucopolysaccharide polysulphate prepared from animal organs; experimental and clinical studies^{1,10,11} have shown that when applied topically it is absorbed into the circulation, prolongs the clotting time, and enhances the absorption of inflammatory exudate. From these findings ointment containing heparinoid has been recommended for treating patients suffering from superficial inflam-

matory conditions such as thrombophlebitis. Objective evidence of the beneficial effects of such treatment, however, has hitherto been lacking.

In our trial, the radioactivity disappeared significantly more rapidly from the site of the thrombophlebitis in the heparinoid-treated patients than in those treated with the placebo ($P < 0.001$). Furthermore, the disappearance or persistence of local symptoms and signs of thrombophlebitis closely followed the decline or increase in radioactivity.

When ^{125}I -labelled fibrinogen is injected intravenously it is incorporated into a forming thrombus. Repeated counts of radioactivity over the site of the thrombus and over areas where there are no thrombi allow a quantitative assessment of the fate of the thrombus.⁷ The decrease in the percentage difference of radioactivity over these two sites indicates the rate of thrombus dissolution; this has been confirmed by repeated phlebography. It is therefore reasonable to suggest that the rapid decline in radioactivity observed in the patients treated with the heparinoid cream probably represented lysis of thrombi and disappearance of radioactive fibrin/fibrinogen from locally accumulated inflammatory exudate.

A drawback of this trial was that it did not provide clear evidence of the true extent of thrombolysis and the nature of residual intimal damage. Phlebography before and after treatment was not performed because of the risk that injection of contrast medium might produce further damage to the already inflamed intima and thus induce extension of the thrombotic process. Another objective method would have been to remove a small segment of affected vein under local anaesthesia and study it histologically to assess residual thrombus and intimal damage; such investigations were, however, considered unethical.

In view of the clear evidence of symptomatic relief and objective evidence of rapid decline in local radioactivity it is hard to deny that the beneficial effects observed in patients receiving heparinoid ointment were due to the drug itself.

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Requests for reprints should be addressed to: Mr. V. V. Kakkar, Department of Surgery, King's College Hospital Medical School, Denmark Hill, London SE5 8RX.

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Reassessment of Failed Beta-blocker Treatment in Angina Pectoris by Peak-exercise Heart Rate Measurements

GRAHAM JACKSON, LYNNE ATKINSON, SAMUEL ORAM

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Summary

Twenty-one patients with angina pectoris were treated with adrenergic beta-receptor antagonists. Previously the resting heart rate had been used as a guide to treatment, a reduction in the rate to 55-60 beats/min without symptomatic improvement indicating failure of medical treatment. These patients were re-evaluated before coronary arteriography using the peak-exercise heart rate as an index of adrenergic beta-receptor antagonism. The dose of beta-blocking drugs was increased to produce a peak-exercise heart rate of less than 100 beats/min or a consistent rate of 100-125 beats/min which would not

lessen in spite of progressive dose increments. The resting heart rate was ignored. On these criteria 15 patients previously considered to have responded inadequately to beta-blockade responded satisfactorily and were therefore removed from the waiting list for coronary arteriography. They all remained well up to two years later. Six patients failed to respond and had coronary arteriography with a view to surgical treatment. Reliance on the resting heart rate as the index of optimum adrenergic beta-receptor antagonism is likely to lead to premature or unnecessary referral for surgery; the failure of beta-blockade in the treatment of angina pectoris can be determined simply and accurately by using peak-exercise heart rate.

Introduction

Adrenergic beta-receptor antagonists are well established in the treatment of both stable and unstable angina pectoris.^{1,2} In patients with angina pectoris the expected yearly mortality rate with medical treatment is about 4%,³ but this does not take account of long-term adrenergic beta-receptor antagonism as a

Cardiac Department, King's College Hospital, London SE5 9RS
GRAHAM JACKSON, M.B., M.R.C.P., Lecturer in Cardiology
LYNNE ATKINSON, B.Sc., Research Assistant
SAMUEL ORAM, M.D., F.R.C.P., Director