The Canadian Medical Association Journal

JUNE 1954 • VOL. 70, NO. 6

HEPARIN IN THE TREATMENT OF ANGINA PECTORIS*

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RECENTLY, while investigating the effect of heparin administration on blood fats, Lyon *et al.*[1] incidentally observed dramatic and uniform relief of pain in 93% of 59 cases of severe angina pectoris. Because of the obvious clinical importance of this observation a study was undertaken to assess this form of treatment using the rigidly controlled technique of the "double blind" test.[2] To comply with this method, the effects of intramuscular injection of heparin and a placebo were compared in each of 20 patients with angina, the identity of the solutions not being disclosed to the patients or to those conducting the investigation. At the completion of the study of intramuscular injections, a few patients were given heparin intravenously.

METHOD

The frequency of anginal pain was used to evaluate treatment. At each visit patients were given a card on which to note each anginal attack and each nitroglycerin tablet used. The cards were carried by the patients at all times, and the importance of recording pain at the time of its occurrence was emphasized. To establish a baseline, no injections were given during the first three weeks of observation, after which "treatment" was administered for a period of six months. "Treatment" consisted of administration of one preparation (heparin or the placebo) for three months followed without interruption by injections of the other solution for three months, reversing the order in alternate cases. The preparations were injected intramuscularly twice weekly in doses of 0.75 or 1.0 ml. so that in the case of heparin each injection contained 75 or 100 mgm., as recommended by Lyon *et al.*[1] The heparin used was concentrated aqueous heparin, 10,000 units per ml.

The placebo and heparin solutions were identical in colour, viscosity, odour and packaging and their identity was withheld from the authors until completion of the study and analysis of the data. None of the patients became aware of the existence of two solutions.

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SELECTION OF CASES

The patients in this study were in attendance at Sunnybrook Hospital and the Toronto General Hospital and the investigation was conducted at these two institutions. From approximately 200 case records of patients with angina pectoris, 30 patients were chosen who fulfilled the following criteria: (1) unequivocal history of angina pectoris; (2) absence of other types of thoracic discomfort, or ability of the patient to distinguish clearly between these and cardiac ischæmic pain; (3) absence of factors which are believed to affect coronary insufficiency, such as aortic valvular disease, paroxysmal arrhythmias, anæmia and diabetes mellitus (patients with congestive failure or recent hæmorrhagic episodes were excluded); (4) willingness to co-operate in regular attendance at the clinic and in faithful tabulation of all anginal attacks. Twenty of the 30 patients selected completed the study; the important findings in these 20 are summarized in Table I.

TABLE I.

THE FINDINGS IN 20 CASES OF ANGINA PECTORIS COMPLETING THE STUDY PERIOD

1. Age	42-73 years, average 57 years	
2. Sex	17 males, 3 females	
3. Duration of angina	4 months to 7 years; average 3 years	
4. Previous myocardial infarction	documentary proof in 13 (65%); suspected but unproven in 2 (10%); apparently absent in 5 (25%).	
5. E.C.G. findings	evidence of coronary artery disease in 12; left ventricular hypertrophy—2; normal in 6 (2 of these had significant changes on 2 step test).	
6. Miscellaneous	Hypertension (180 100 or higher)	6 patients
	Peripheral atherosclerosis	6 patients
	Cardiac enlargement	5 patients
	Chronic auricular fibrillation	1 case

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Ten patients dropped out of the series for various reasons including moving from the vicinity, interference with their work and development of other disorders, such as diabetes mellitus, acute anxiety state, congestive heart failure, cerebral embolism, rectal carcinoma and myocardial infarction. The myocardial infarction occurred in a patient who had been receiving heparin injections for six weeks. These 10 cases are not included in the consideration of the results

RESULTS

All 20 patients said that they had improved at one time or another. Most often they stated they had experienced a reduction in the intensity and duration of the anginal pains and usually it was noticed after the first few injections, regardless of which solution was being administered. Analysis of the recorded pains revealed that 18 patients (90%) had fewer attacks per week during "treatment" than during the initial baseline period. The comparative effectiveness of heparin and the placebo with the control period

TABLE II.

FREQUENCY OF ANGINAL PAIN IN 20 PATIENTS DURING "TREATMENT" PERIODS AS COMPARED WITH CONTROL PERIOD

Number of attacks of anginal pain	*While on heparin*	*While on placebo*
	No. of patients	*No. of patients*
Fewer than during control period	15 (75%)	16 (80%)
Unchanged	3	4
More than during control period	2	0

is shown in Table II: the number of patients benefited by placebo therapy was similar to the number showing improvement on heparin administration.

When the effects of heparin and placebo were compared with each other, there was no appreciable superiority of either in reducing the frequency of attacks of anginal pain per week (see Table III, A). Engelberg[3] noted that the improvement from heparin therapy in patients with angina pectoris may occur gradually over a period of several months and that a time lag of one to eight weeks often elapsed between cessation of treatment and the recurrence of symptoms. To avoid missing such a delayed response, the data were recalculated considering only the last month on each solution. The number of patients who experienced greater improvement from heparin in the third month was not significantly different from those who found more benefit from the placebo (Table III, B).

To determine whether there might be a short period of relief from a possible immediate vasodilator effect of heparin, the frequency of attacks in the 24 hour period after each dose was determined for the last month on each solution (Table III, C). No such effect was apparent.

TABLE III.

COMPARISON OF THE EFFECTS OF HEPARIN AND PLACEBO IN REDUCING THE FREQUENCY OF ANGINAL PAIN IN EACH OF 20 PATIENTS

	A considering the 3-month period on each	*B considering only 3rd month on each*	*C considering only 24 hr. after injection*
	No. of patients	*No. of patients*	*No. of patients*
Heparin superior	7	6	3
Placebo superior	8	7	3
Heparin and placebo equal	5	7	14

UNTOWARD REACTIONS

Reactions to the placebo were few. One patient complained of nervousness, trembling and dizziness after the initial injection of placebo and refused further treatment. Another patient had slight bruising and induration at the site of placebo injections. In the case of heparin, five patients suffered hæmatomas at the injection site. Giant urticaria developed in one patient six weeks after beginning heparin therapy. Sensitivity to heparin was demonstrated by skin testing in this patient; it was overcome by temporarily reducing the size of the injections and administering an antihistamine for two weeks.

DISCUSSION

After the study had been in progress for about three months the identity of the heparin solution was strongly suggested by the occurrence of hæmatomas at the sites of injection of one of the solutions. It could not be ascertained by any difference in relief of anginal pain. The frequency of anginal pain was used to assess the value of treatment since this was considered a

more physiological criterion than electrocardiographic changes or results of exercise tolerance tests. It was also considered that the actual recording of pains was more accurate than the patient's impression expressed as "good" or "bad days".[2] This was borne out by the fact that patients often reported having improved during a particular week, whereas in fact the recorded number of attacks was unchanged.

The familiar but nevertheless remarkable beneficial response to placebos emphasizes the influence of the mental attitude of the patient on the symptoms of severe coronary artery disease. Angina pectoris induces fear in those afflicted which is seldom equalled by any other disease except cancer. In the majority of patients this anxiety is increased still further by personal recollection of one or more episodes of acute coronary occlusion. In a study such as this, repeated examinations by one particularly interested in the patient's disease cannot help but inspire confidence which is augmented by hope for the success of the "new" drug. It is not difficult to understand how the unintentional suggestion accompanying a series of injections can lessen the patient's anxiety and result in symptomatic improvement. It is just as readily apparent how this psychological effect can be a pitfall in uncontrolled studies.

A finding of interest in this study was the fact that 15 of the 20 patients obtained a greater measure of relief during the second injection period, regardless of the order in which the solutions were given. A similar number of patients were started on "treatment" during warm weather and during cold weather, so this response cannot be attributed to climatic changes. Ten of the patients received heparin initially and 10 were given the placebo first. This progressive improvement was also observed by Binder[4] and, while a final explanation cannot be offered, it seems likely that it is an expression of longer exposure to the incidental psychological aspect of the treatment.

Although the alternate use of placebos in testing the effectiveness of heparin in angina pectoris has been criticized,[3] this observation strongly supports this method. Had placebos been used originally in all cases (even for as long as three months), 75% of the patients would have been considered to have greater relief from the subsequent heparin injections and false conclusions might have been drawn.

Apart from the temporary discomfort of hæmatomas there were no serious untoward effects from intramuscular heparin.

INTRAVENOUS HEPARIN

Engelberg[3] found that the best clinical results in angina pectoris were obtained when heparin was given intravenously in doses of 100 mgm. twice weekly. Following the appearance of this report, it was decided to give patients a trial of heparin administered intravenously after they had completed the course of intramuscular injections. No intravenous placebo was used. Seven patients were treated in this manner for periods of from three weeks to three months. Three of these seven patients showed a further slight decrease in frequency of pain, but in no instance was this as great a degree of improvement as that induced initially by the intramuscular injections in these same patients. Three patients showed no change, and one patient had slightly more frequent anginal attacks as compared with the period of intramuscular therapy.

Three of the seven patients had untoward reactions while receiving intravenous heparin. In two, this appeared to be an anaphylactic reaction occurring one or two minutes after the injection during the third week of intravenous therapy. Both patients showed marked flushing of the face, injection of the scleræ and lacrimation. One experienced constricting chest pain which made breathing and speaking difficult for about five minutes. The other patient noticed severe lumbar pain and a pounding occipital headache.

Skin tests, which had been negative a few months before, now revealed sensitivity to heparin in both these patients. The frequency of allergic reactions to heparin in this series is possibly due to sensitivity induced by the long period of intramuscular administration of heparin that preceded the intravenous injections.

The third patient had a sudden hæmorrhage into the right ear drum 20 minutes after an intravenous injection of 100 mgm. of heparin. The resulting deafness improved gradually over the next few weeks. It has been stated that this dose of heparin is quite safe.[3] While this is generally true, it is well known that for an hour or so after such a dose the whole blood clotting time is usually prolonged from the normal of 10-12 minutes (Lee White) to one or several hours. The risk of bleeding during this period should not be overlooked.

TABLE IV.

SUMMARY OF REPORTS ON HEPARIN IN ANGINA PECTORIS

Author	*No. of cases*	*Dose of heparin*	*Duration*	*Comments*	*Results*
1. Lyon *et al.*[1]	59	50 to 100 mgm. i.m. or i.v. once or twice weekly.	1- 8 months	Placebos afterwards in 7 cases.	55 improved on heparin; none improved on placebo.
2. Engelberg[3]	29	25 to 100 mgm. i.m. or i.v. twice weekly.	6-12 months	Placebo controls first in 11 cases.	55% improved on heparin.
3. Zinn *et al*[5]	14	100 mgm. i.m. three times weekly.	6 weeks	Double blind control	Placebo just as effective as heparin.
4. Binder *et al*[4]	34	100 mgm. i.v. twice weekly.	1 month	Double blind control	Placebo just as effective as heparin.
5. Rinzler *et al*[6]	18	100 mgm. i.v. twice weekly.	8-9 weeks	Double blind control	Placebo just as effective as heparin.
6. Gruner *et al*[7]	27	100 mgm. i.v. twice weekly.	7-11 weeks	Placebos, then heparin, then placebos.	9 improved on placebo; 6 improved on heparin.
7. Port *et al*[8]	13	75 mgm. i.v. twice weekly.	10 weeks	Four alternating 10-week courses of heparin and placebo.	Placebo just as effective.
8. Russek *et al*[9]	14	50-100 mgm. i.v.	1 to 7 injections, 1 to 3 days apart.	No placebos	Subjective benefit in 3; no significant changes in 2-step test.
9. Present series.	20	75 to 100 mgm. i.m. twice weekly.	3 months	Double blind control	Placebo just as effective as heparin.

Since this study was undertaken, additional reports on the use of heparin in angina pectoris have appeared. These are summarized in Table IV. The majority of these show results similar to those in the present series.

SUMMARY

1. Under controlled conditions, the effectiveness of heparin administered intramuscularly in reducing the frequency of pain in 20 cases of angina pectoris was no greater than that of the placebo.

2. In this study, as in others, the psychological benefit from a new form of treatment of angina pectoris was striking.

3. Intravenous heparin was administered to seven patients with angina pectoris following the course of intramuscular injections. No appreciable improvement was noted.

4. Side effects of intramuscular and intravenous heparin were observed occasionally and are described.

The heparin and placebo used in this study was prepared and supplied by The Connaught Medical Research Laboratories, University of Toronto. Dr. R. Ian Macdonald made available to us facilities of Sunnybrook (D.V.A.) Hospital, Toronto, where part of this study was carried out.

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RÉSUMÉ

Les auteurs de cette communication ont cherché à reproduire les résultats obtenus par Lyon et Yankley, dans le traitement de l'angine de poitrine par les injections d'héparine. Les vingt malades traités accusèrent une amélioration à une phase ou à une autre du traitement; 90% eurent moins d'attaques par semaine pendant la durée du "traitement" qu'au début, sans égard au fait qu'ils aient reçu de l'héparine ou une substance inerte ayant l'apparence de l'héparine.

Comme on avait déjà rapporté, dans le passé, que l'amélioration produite par l'héparine peut être tardive et ne se manifester qu'après une période de plusieurs mois, l'expérience fut répétée en tenant compte seulement des données obtenues pendant le dernier mois de traitement avec chaque produit. Le nombre de malades améliorés par l'héparine était sensiblement le même que celui des cas soulagés par la substance contrôle. Celle-çi ne produisit que de rares effets fâcheux. Par contre, cinq malades traités à l'héparine firent des hématomes dans la région des injections. Un patient sensible à l'héparine présenta un urticaire géant six mois après le début du traitement.

L'amélioration apportée par une substance quelconque sert à démontrer, une fois de plus, l'importance de l'attitude mentale des angineux vis-à-vis de leurs symptômes. L'amélioration progressive notée au cours de la deuxième série d'injections montre l'effet d'une diminution de l'angoisse du malade et d'une augmentation de confiance en son médecin.

L'administration intra-veineuse d'héparine telle que recommandée par Engelberg donna des résultats encore moins satisfaisants que par voie intra-musculaire. Le risque d'hémorragie dans l'heure qui suit l'injection de 100 mgm. d'héparine dans la veine ne doit pas être perdu de vue.