THE PREVENTION OF POST-OPERATIVE OEDEMA

CONTROLLED CLINICAL TRIAL OF LYOPHILIZED CHYMOTRYPSIN IN PLASTIC SURGERY

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Much of the post-operative care of wounds in plastic surgery is directed toward the prevention of oedema. It is no longer felt that post-operative swelling should be a necessary sequel to successful surgical treatment, and to both surgeon and patient such swelling is a nuisance. The suggestion that oedema could be prevented, or at least mitigated, by therapy before operation is attractive, and there can be little doubt that such would have wide and immediate application. Though oedema appears to be related to the type and severity of the operative trauma, the teleological causes and the exact mechanism of production are still largely unknown. For this reason little success has followed the use of drug therapy. Lyophilized chymotrypsin ("chymar") has been heralded as one successful agent, and after the enthusiastic report of its use in plastic surgery by Moore (1959) a critical evaluation of this preparation seemed worth while.

Material and Methods

Because of the difficulty in assessing the presence or absence of post-operative swelling in certain regions of the body, cases admitted to the trial were limited to patients who were having operations on parts of the body where swelling after operation is either common or at least easily discernible. The way in which the cases were grouped is shown in Table I.

TABLE I.—Type of Operation in 56 Patients in Trial

Type of Surgery	No. of Patients
Eyelid	4
Flaps, either tubed or direct	10
Hypospadias repair	16
Face-lift and major operations on the face	12
Nose reductions	14

The chymar was supplied lyophilized in the dry state in unlabelled ampoules of 5,000 units, in which state it will keep indefinitely. The dummy ampoules contained gelatin hydrolysed, 0.6 mg., and lactose, 5.4 mg. The diluent, normal saline, was supplied in 1-ml. phials. All the ampoules were delivered to the hospital pharmacist in bulk, the boxes containing them being clearly labelled, but all individual ampoules were unlabelled. Patients on chymar received 10,000 units in 2 ml. of fluid intramuscularly one hour before operation, and a similar dose on each of the two following days: those on the dummy ampoules received 2 ml. of the innocuous solids at similar times.

Patients were admitted in rotation from the hospital waiting-list, and, if thought medically suitable for entry into the trial, a standard prescription was sent to the

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hospital pharmacy. The trial was organized on the double-blind technique. This means that for each patient treated with the drug a control patient was given the dummy, so that surgeons and nurses were unaware which treatment was given to the patients until after the trial was completed. The treated and untreated series were matched for type of surgery (Table I). Chymar and the dummy were given to each pair, the allocation being made by the pharmacist by tossing a coin.

Though the surgical operations were performed by three surgeons, assessments were made by one of us (J.C.) and recorded on a standard form.

The trial was arranged so that it could be analysed sequentially. On this basis it is possible to assess the significance of the results as they become available, and the trial is terminated or continued according to the results already obtained. However, owing to the limited quantity of drugs available, the number of patients in the trial was inadequate to complete the original sequential analysis. Therefore the results are presented mainly in a non-sequential form.

Results

The condition at operation, in terms of the operating-time, the bleeding seen at operation, and the amount of blood loss, appeared to be the same in both series. The general anaesthetic used for all patients in the trial was supplemented by a local anaesthetic in 14 patients in the chymar group and in 11 patients in the control group.

The main results after operation are summarized in Tables II–IV. In Tables II and IV the figures enclosed within boxes indicate the number of pairs where the assessment was the same for both patients—that is, "tied pairs." The figures in the south-west corner indicate the number of instances where the result with chymar was better than the control, and those in the north-east

TABLE II.—Comparison of Immediate Post-operative Oedema (Up to 48 Hours) Between Pairs of Patients

Time Observed after Operation	Degree of Oedema in Chymar Group	Degree of Oedema in Control Group				Total No. of Pairs
		Marked	Usual	Less	None	
24 hours	Marked	1	2	1	1	5
	Usual	1	1	4	1	7
	Less	—	3	5	1	9
	None	1	1	3	2	7
	Total No. of pairs	3	7	13	5	28
48 hours	Marked	—	2	1	1	4
	Usual	1	—	5	3	9
	Less	—	1	1	3	5
	None	—	7	—	3	10
	Total No. of pairs	1	10	7	10	28

TABLE III.—Comparison of Late Post-operative Oedema (More than 48 Hours) Between Pairs of Patients

Oedema Observed in Chymar Group	Oedema Observed in Control Group			Total No. of Pairs
	Present	Not Present	Not Stated	
Present	6	7	1	14
Not present	6	4	1	11
Not stated	2	—	1	3
Total No. of pairs	14	11	3	28

TABLE IV.—*Comparison of Post-operative Bruising Between Pairs of Patients*

Time Observed after Operation	Degree of Bruising in Chymar Group	Degree of Bruising in Control Group					Total No. of Pairs
		Marked	Usual	Less	None	Indefinite or Not Stated	
48 hours	Marked ..	—	3	1	2	—	6
	Usual ..	1	—	2	4	—	7
	Less ..	—	1	2	2	—	5
	None ..	1	5	2	2	—	10
	Indefinite or not stated ..	—	—	—	—	—	—
	Total No. of pairs	2	9	7	10	—	28
7 days	Marked ..	—	—	—	2	—	2
	Usual ..	1	—	2	6	2	11
	Less ..	—	—	—	—	1	1
	None ..	—	5	2	1	1	9
	Indefinite or not stated ..	1	1	—	2	1	5
	Total No. of pairs	2	6	4	11	5	28

corner the number of instances where chymar was worse than the control. It will be seen that there were virtually no differences between the chymar group and the control group relative to post-operative oedema and bruising. The two groups were compared further for post-operative oozing, wound infection, healing-time, subjective and objective reactions, and local pain, but no differences were found that could not easily have arisen by chance (single tail test with $P=0.05$).

Further examination of the results along sequential lines confirms the conclusions. A sequential analysis chart for post-operative oedema at 24 and 48 hours is included (see Chart). In this chart a preference for chymar is indicated by extending the line one unit in a "north-easterly" direction and a preference for the blank by one unit in a "south-easterly" direction.

At the beginning of the trial the maximum number of preferences was estimated at 40–45, and a restricted sequential procedure (Armitage, 1957) was chosen accordingly. The boundary lines are drawn in such a

Sequential analysis chart comparing post-operative oedema in pairs of patients treated with chymar and dummy (see text). —: Post-operative oedema at 24 hours. - - - - -: Post-operative oedema at 48 hours.

way that if the two treatments are equivalent there is a probability of approximately 0.95 that the zigzag path will cross the inner broken boundary line and a probability of approximately 0.05 that it will reach the divergent heavy boundary line. On the other hand, if one treatment is an improvement on the other so that 85% preferences are in its favour, then in the long run the zigzag path will hit the appropriate outer boundary about 95 times out of 100. Clearly there was nothing to choose between chymar and the dummy. Most explicitly, the exact probability of reaching by chance the point observed on the inner boundary or one more extreme is, in the case of comparison, at 24 hours 0.50 and at 48 hours 0.16.

The observer was asked to state whether he thought the patient had received chymar or the blank. If there was no difference between the two treatments then one would expect that the observer would be right as often as wrong in his judgment. In fact, as Table V shows, this turned out to be the case.

TABLE V.—*Observer's Opinion on Preparation Used*

Observer's opinion	{ Chymar Dummy	Actual Preparation Given		Total
		Chymar	Dummy	
		13	15	28
		15	13	28

These results indicate that chymar, given in the stated dose, has no material effect on the degree or incidence of post-operative oedema or bruising.

Discussion

The isolation of crystalline chymotrypsin and an indication of its properties has been described by Kunitz and Northrop (1935), while Tagnon, Weinglass, and Goodpastor (1945) have studied the proteolysis of fibrinogen and prothrombin (and the associated shock) produced by its intravenous injection. Experimentally, intramuscular chymotrypsin in oil was shown to reduce quantitatively the oedema which follows induced inflammation in mice, rats, and guinea-pigs, and such anti-inflammatory activity was greater than that of trypsin (Miechowski and Ercoli, 1956). Work by Hill and Bastrian (1956) suggested that this anti-inflammatory effect was not mediated by the systemic absorption of enzyme resulting in free protease activity; indeed, the exact mechanism of action has not yet been determined.

Clinically, intramuscular chymotrypsin has been used for ocular conditions, Jenkins (1956) reporting favourably on its beneficial effect in traumatic swelling of the eyelids, inflammation of the uveal tract, hyphema, vitreous and retinal haemorrhage, and in certain secondary inflammations. As a local proteolytic agent it has been used to assist removal of the crystalline lens in cataract, though there would still seem to be some doubt about its value (Hill, 1959; Crawford, 1959; Salmony, 1959).

As a therapeutic agent of wide application chymotrypsin has been hailed by Fullgrabe (1957) as a "remarkable anti-inflammatory agent," since it hastens the absorption of oedema and of blood in the tissues. Moore (1959) was able to state, based on experience of its use in 75 patients, that "chymar will revolutionize some aspects of plastic surgery and must be compared to the introduction of antibiotics."

The dosage used in the present trial was twice that recommended by the manufacturers: it was also twice the dose used by Moore, though his patients received chymotrypsin for four days after operation, whereas in the present series treatment was restricted to two days.

In view of the previous findings, why are the results of the present series of 56 patients so disappointing? There are three possible answers.

Firstly, the assessment of the amount of swelling and bruising after operation in any individual patient is a purely subjective valuation based on experience of the type of operation performed, and for this reason a control series is essential. Because assessment is subjective (and cannot be measured objectively), clinical trials should be of the double-blind type. Only in this way is it possible to eliminate conscious or unconscious bias in the observer when a new preparation beneficial to the patient (and surgery) is being evaluated (Truelove, 1959). In none of the papers quoted was the trial "blind," nor apparently were controls included for comparison.

Secondly, bias may also be introduced through the pre-selection of the cases treated: hence the necessity for randomization at the planning stage. In the published reports selection could have contributed materially towards a favourable impression of the preparation.

Finally, a controlled clinical trial, properly conducted, tests not only the preparation under consideration but also its formulation. Hence, in spite of the favourable *experimental* results with chymotrypsin, the unfavourable *clinical* results with lyophilized chymotrypsin could be explained by the altered formulation of the preparation.

Conclusions and Summary

A double-blind controlled clinical trial was carried out on 56 patients undergoing plastic surgery.

Half the patients received chymar (10,000 units intramuscularly one hour before operation, and on each of the next two days) and half received a dummy preparation.

Chymar appeared to have no effect on the degree or incidence of post-operative oedema or bruising in such patients.

We are grateful to the Armour Pharmaceutical Company, who kindly supplied the ampoules of chymar, dummy preparation, and solvent; to the surgeons who allowed their patients to enter the trial; to Sister Sanderson and Sister Downes, who supervised the administration of the preparations; to Mr. W. Trillwood and the dispensary staff, who allocated the patients and maintained the day-to-day supplies; and to Dr. P. Armitage, of the Statistical Research Unit, for providing additional data on the sequential analysis.

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STRESS INCONTINENCE OF URINE

A SURVEY OF 34 CASES TREATED BY THE MILLIN SLING OPERATION*

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This communication is a survey of 34 cases treated by the Millin sling operation, which was first described by Millin and Read in 1948. Let me say right at the start that there is little place for this operation unless the patient has undergone a previous attempt to cure the incontinence by the vaginal route. This series of 34 cases would suggest, therefore, that my plastic repair results show a considerable number of failures, so far at least as a cure of incontinence is concerned. That, I hasten to say, is not necessarily so, for in the cases reported I have been partly or wholly responsible for the plastic repair operations on 13 cases only. The other 21 were previously treated, over the years, in all three units of the Edinburgh Royal Infirmary, in neighbouring city hospitals, and some, indeed, much further afield. So the fault, if there be one, in plastic repair operations is fairly general.

It is essential, in the first place, that there should be no confusion between the terms "stress" and "urge" incontinence. With the former there is the unconscious escape of urine on straining, laughing, coughing, sneezing, getting in or out of a car or bus, walking, running, and—because of the action peculiar to the game, bending and throwing, and because of the age-group of the women involved—curling. This leak may amount to a few drops only; on the other hand, a mere cough will project—and this can be demonstrated on the examination couch—an appreciable stream several yards across the room. I have seen this on several occasions. There is no associated history of frequency or dysuria in these cases.

With urge incontinence the picture is entirely different. Here there is a low-grade infection, there is often frequency, and there may be dysuria. The patient has the sudden desire to void urine, and if this cannot be done promptly there is a leakage, of which the woman is fully aware. And so there should be no mistake, on careful questioning, about which condition presents, and yet in the hospital out-patient departments one constantly finds a clinical confusion in the history and a faulty diagnosis as a result.

Incidence.—While Gainey (1943) has estimated that approximately 5% of all adult women suffer some degree of stress incontinence, the figure for the frequency of this symptom in association with utero-vaginal prolapse has been put by Bailey (1954) at 39% in 424 cases and at 50% by Read (1950). In a follow-up of plastic repair operations Stallworthy (cited by Read, 1950) estimated the persistence of this symptom at 16%, and both Kennedy and TeLinde (cited by Read, 1950) at 5%–10%. Millin and Read (1948) agree that this figure increases with time, and Counseller (1943) believes it to be as high at 30%. Bailey (1954) found that in a series of 84 patients who had prolapse and stress incontinence

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