

## Intralymphatic Steroid Therapy for Lymphoedema: Preliminary Studies

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### Summary

Lymph node fibrosis is a significant feature in patients with primary lymphoedema. Its importance in causing obstruction to the flow of lymph has led to this study which is an attempt to reduce the effect of fibrosis by treatment with a corticosteroid preparation administered by direct intralymphatic infusion.

In a pilot study, twenty patients received an intralymphatic infusion of Clobetasol propionate in Ultrafluid Lipiodol (18 lower limb, 2 face).

Clinical improvement occurred in eight of the patients with leg oedema over a period of up to nine months. Both face-affected patients were helped by this form of therapy.

In patients with lymphoedema of the lower limb with lymph node abnormalities, it was advantageous if the lymph vessels leading up to the nodes were patent.

### Introduction

The majority of patients affected by lymphoedema of the lower limbs can be managed by conservative measures of treatment and only those with gross and incapacitating swelling require operative treatment. The mainstay of conservative management for mild or moderate lymphoedema is the use of suitable support stockings. With meticulous application, this method provides reasonable palliation in the majority of cases. There is, however, scope for investigation of alternative methods of conservative treatment in primary lymphoedema and a preliminary report of one prom-

ising new line of treatment, particularly for certain patients, is given in this paper.

It has become apparent that in many patients with primary lymphoedema of the lower limb, the lymph nodes, inguinal and iliac, can show a considerably greater degree of abnormality, as judged by lymphography, than the lymph vessels, and it has been suggested that many of the abnormalities seen in the peripheral lymph vessels are in fact secondary to basic changes which have occurred in the nodes (1). A histological study of regional lymph nodes in a series of patients with primary lymphoedema has recently been reported (2). Patients in whom lymphography had shown evidence of proximal obstructive hypoplasia in the lymphatic pathways of the groin and pelvis showed an excessive amount of fibrous tissue in the hilum and medulla of inguinal lymph nodes. It is likely that abnormal lymph nodal fibrosis, whatever its aetiology, exerts an obstructive effect on the passage of lymph thus engendering progressive distal lymph stasis. A study of the lymphographic consequences of the experimental induction of nodal fibrosis by silica has added support to this concept (3).

The evidence that lymph node fibrosis is an important factor in the genesis of lymph stasis, together with the existence of an apparent state of chronic inflammation in lymphoedematous tissues (4, 5) suggests that there may be a therapeutic role for corticosteroids in the treatment of this condition. This study was carried out in an attempt to assess the practicability and effectiveness of this form of treatment.

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### *Patients and Methods*

The study involved a consecutive series of 20 patients referred to our clinic with a clinical diagnosis of primary lymphoedema. Although a few patients had undergone lymphography at other centres, the majority had not been previously investigated.

Eighteen patients had oedema of the lower limb and 2 of the face. The average age of the 20 patients was 25.3 years (range 12 to 58).

The initial assessment of the patients included the following features: In the patients with oedema of the lower limb, circumferential measurements of the legs were made at points 12.5 cm above and below the upper and lower margins of the patella, 7.5 cm above the medial malleolus, and 7.5 cm above the first interdigital cleft. The measurements were carried out immediately upon admission before any subsidence of the oedema could take place. Clinical photographs were also taken at this stage.

A morning specimen of blood was obtained for plasma cortisol estimation in every case.

All patients were placed on strict bed rest with standard leg elevation for two days after which time leg dimensions were remeasured. It was found that no further reduction in size occurred after 48 hours of postural treatment. No other form of treatment was given during this period.

### *The Steroid Preparation*

The steroid used consisted of a formulation of Clobetasol propionate in Ultrafluid Lipiodol (UFL). Clobetasol propionate is a highly potent fluorinated anti-inflammatory corticosteroid, currently used in a topical preparation (Dermovate - Glaxo) in the treatment of various dermatoses. It has an anti-inflammatory potency almost six times that of Betamethasone (6). It was supplied to us as a finely divided powder and was prepared for injection the following way:

Under aseptic conditions, 20 mg of Clobetasol was weighed into a sterile 10 ml glass vial which was then immediately capped and sealed.

50  $\mu$ l of Acetone, sufficient to cause complete solution of the Clobetasol, was injected through the cap. To this solution was added 3 ml of sterile UFL. Immediately prior to administration, the solution was passed through a 0.2  $\mu$ m polytetrafluoroethylene filter (Millipore Ltd.).

### *Injection Techniques*

Pedal lymphatics were cannulated by the standard method (7), in the patients with lymphoedema of the lower limb. In the clinically affected side, or in the case of bilateral oedema, the worst affected side, 3 ml of the Clobetasol/UFL solution (containing 20 mg) was infused. This volume was found to give adequate filling of the lymph nodes whilst avoiding excessive "spill over" into the blood circulation via the thoracic duct. If in the presence of proximal obstruction the peripheral lymphatics were unduly dilated and capacious, it was sometimes found necessary to give an additional volume of plain UFL in order to achieve filling of the nodes. The progress of the injection was monitored by means of repeated x-rays. If after a careful search no vessel could be found in the foot, an injection of Clobetasol was made directly into an inguinal lymph node displayed through a small incision. This was done in five patients. An intranodal injection of steroid was also made if the patient had previously undergone satisfactory pedal lymphography (3 patients).

In the clinically normal, or less affected limb, standard lymphography was carried out using plain UFL.

Further plain x-rays were taken at 24 and 48 hours to allow assessment of the inguinal, iliac, and lumbar lymph nodes. The lymphograms were then assessed and classified according to one of four groups - distal hypoplasia, proximal hypoplasia, distal plus proximal hypoplasia and hyperplasia.

The technique was modified in the case of the patients with lymphoedema of the face. One of them had 10 mg Clobetasol in 1 ml UFL injected into a lymphatic overlying the left mastoid process and, on a separate occasion, the same amount into the contralateral upper

deep cervical lymph node. The other patient received a single intranodal injection of 15 mg of Clobetasol in 1.5 ml UFL to the right upper deep cervical node.

During the post-operative period, all patients continued on strict bed rest. Plasma cortisol levels were carried out on morning blood samples obtained daily. These estimations were carried out by a method of radioimmunoassay. The patients were discharged at 7 to 10 days and final circumferential measurements were obtained prior to discharge. No other form of treatment was given at this stage.

Patients were seen after three weeks and then at monthly intervals if a clinical improvement had occurred, and at longer intervals if not. At each attendance careful measurements and observation of the affected parts were made. Also attention was given to the patients' own subjective impression of the state of the affected part. In the case of the limb oedemas, if at the first post-operative attendance it was clear that no improvement had occurred, the patient was then fitted with an appropriate compressive stocking.

## Results

### A. Patients with Lymphoedema of the Lower Limbs

*Lymphography* showed proximal hypoplasia in four patients, distal hypoplasia in three, proximal plus distal hypoplasia in seven, and hyperplasia in four.

No complications occurred following lymphography using the UFL/steroid preparation throughout the entire study.

### Plasma Cortisols

In the leg affected patients, the mean pre-operative plasma cortisol concentration was

260 nmol/l (SEM  $\pm$  23). This value fell to a mean of 45 nmol/l (SEM  $\pm$  13) at 24 hours following the infusion and remained close to that level up to the sixth day. On the seventh day the plasma cortisol concentration returned to the pre-operative level and remained there for the duration of the remaining estimations. There was no significant difference in the cortisol suppression whether the steroid was given by intranodal or endolymphatic injection. In one patient in whom there was a total block to the flow of UFL through the pelvis with hardly any lymph nodes opacified, the cortisol suppression was as profound as in any other patient following full opacification of the iliac and lumbar nodes. This suggests that the steroid is readily absorbed through the wall of the leg lymphatics. It was of interest that even where only a few drops of the UFL/Clobetasol preparation came into contact with the wound in the course of a failed attempt at pedal lymphography, there was quite marked cortisol suppression lasting for two days. Plasma cortisol levels were measured on four patients who received UFL only and no suppression occurred.

### Follow-Up Studies

Patients have been reviewed over a period ranging from 1 to 9 months. Tab. 1 summarizes the results of treatment.

A total of eight patients (44%) showed clinical response as judged by a combination of measurements and the patients' own assessments. The patients who reported a definite improvement one month after treatment were found to have an average decrease in the aggregate of the three distal circumferential measurements of 3.68% (SEM  $\pm$  0.56) as compared with the measurements on admission. The patients who reported no improvement actually showed a mean increase of 0.49%

**Tab. 1** Response to steroid treatment in patients with lymphoedema of the lower limb, listed by lymphographic grouping

	Proximal Hypoplasia	Proximal + Distal Hypoplasia	Distal Hypoplasia	Hyperplasia	All
Improvement	1 in 4	5 in 7	0 in 3	2 in 4	8 in 18

(SEM  $\pm$  0.52). In no case did the patient's subjective impression conflict with the measurements.

The following case history which relates to our first treated patient is illustrative.

#### Case History

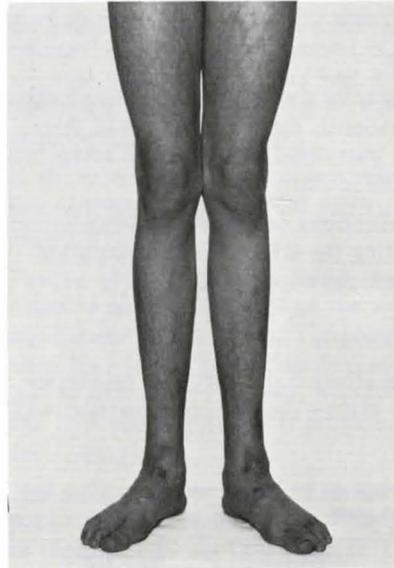
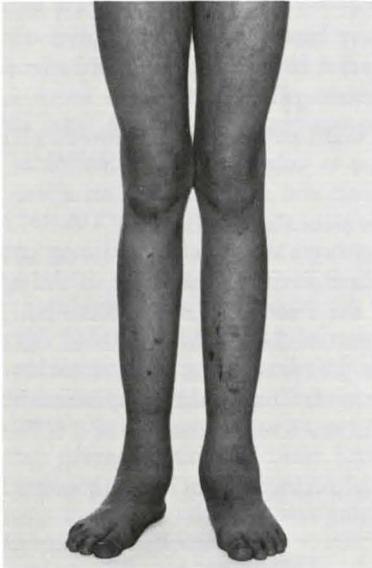
S.W., aged 15, had experienced swelling of both legs for one year. The swelling extended from foot to knee and was slightly more marked on the left. There was no family history and he had received no treatment of any kind prior to admission. Examination showed a soft oedema of the lower limbs with no other abnormality and bilaterally enlarged inguinal nodes. Bipedal lymphography showed numerical hyperplasia of the afferent lymphatics to the groins and large inguinal and iliac nodes. The lumbar nodes were fragmented and the thoracic duct abnormal. The appearances were classified as "bilateral hyperplasia". Three months later he was readmitted and a direct intranodal injection of 20 mg Clobetasol propionate was made into one of the enlarged left inguinal nodes through a

small incision. At review one month later, the patient reported that he no longer had any leg swelling on either side apart from a trace around the ankles after very prolonged standing. The improvement has persisted over a nine month period of follow-up. No other treatment has been given and he has not altered his activities in any way. Fig. 1 shows clinical photographs taken before, and eight months after treatment.

#### B. Patients with Lymphoedema of the Face

Both of these patients showed the same severe cortisol suppression for six days with sudden recovery on the seventh.

The first patient with facial lymphoedema showed response to both the intralymphatic and intranodal steroid injections within one day. There was clearly visible flattening of both cheeks. The clinical improvement has been maintained for three months on the side of the intralymphatic injection, but on the side of the intranodal injection the swelling recurred within a few days. The other face-affected patient, who had mainly infraorbital



**Fig. 1** 15 year old male. Bilateral primary lymphoedema. Appearances before (left) and eight months after (right) a left intranodal infusion of Clobetasol propionate

oedema, again showed a response within one day. The improvement was maintained for two weeks, then, quite suddenly, the infraorbital oedema recurred to its former extent.

### Discussion

Although the literature contains numerous accounts of the conservative treatment of lymphoedema by both physical and pharmacological means, most describe uncontrolled studies. The extreme variability both of the extent and severity of the oedema provides difficulties in obtaining matched controls. The problems could only be resolved by considering large groups of patients, but primary lymphoedema is an uncommon disease.

In this study, eight of the eighteen patients with lymphoedema of the lower limb who were treated with intralymphatic Clobetasol appeared to gain benefit. The untreated patients were provided with compressive stockings prior to discharge and so could not be compared. Previous experience however indicates that even after one week's bed rest, when the patient resumes normal activities, the limb very rapidly regains its former dimensions. The fact that almost half of our steroid treated patients showed a sustained *reduction* in limb dimensions for a period of at least one month strongly suggests that a genuine influence of the steroid was present.

The responding and non-responding groups have been carefully compared in terms of a variety of parameters. Table 1 shows the comparison by lymphographic grouping. None of the three patients with distal hypoplasia, alone, i.e. without lymph node disease, showed any improvement. Only one out of five patients who had nodal injections on account of "aplasia" in the foot showed any response, and this was of only one month's duration. A clinical response is therefore unlikely if there is absence of peripheral lymphatics in the limb.

Three treated patients had a total lymphatic block at inguinal level with no passage of contrast into the pelvis. None of these patients responded to treatment.

*It therefore seems that the necessary condition for the success of treatment is evidence of inguinal or iliac node disease, without total occlusion, provided that the distal limb lymphatics have remained patent.*

The age range of the two groups was broadly similar and the mean age of the responders was slightly greater (27.6 yrs and 23.2 yrs). Also the patients who responded had had a greater mean duration of symptoms (115 months and 78 months), but there was considerable overlap, and the difference is not considered significant.

Patients who showed an improvement tended to have slightly worse oedema at the outset, but again there was much overlap.

The response could not be predicted from the amount of reduction of oedema in response to leg elevation. The mean reduction in the aggregate of calf, ankle, and foot measurements in the legs of the responding and non-responding groups was 5.0% and 5.2% respectively. (S.E.M.'s  $\pm 0.6$  and  $0.7$ ).

Thus, lymphographic criteria alone determine the outcome of treatment. An example of the lymphographic appearance in an ideal case is shown in Fig. 2.

The results in the face-affected patients justify further attempts in future patients with this rare form of lymphoedema for whom there is no other effective conservative treatment. Patients with co-existent acne rosacea in whom there is probably a chronic lymphadenitis may be particularly helped.

The mechanism of action of corticosteroids in this context is uncertain. It is unlikely that they act by influencing the capillary filtration rate as the latter is known to be normal in lymphoedema (8). Whilst corticosteroids can increase the permeation of substances within the connective tissue ground substance, it appears that this is so only if they are given by prolonged administration (9).

Macrophages play a central role in the evolution of the tissue changes, including the development of fibrosis, seen in lymphoedema (10). They are known to be actively engaged in the phagocytosis of the excess tissue pro-



**Fig. 2** Suitable lymphangiographic appearances for intralymphatic Clobetasol treatment – incomplete obstruction in the left groin with fair proximal transit of contrast

teins, and the debris from disintegrating macrophages had been shown experimentally to engender collagen production by fibroblasts (11, 12). The ability to lyse protein depends on the liberation of proteases by disruption of lysosomal membranes. Since corticosteroids have known lysosomal membrane stabilising properties (13) the possibility exists that they could inhibit the deposition of collagen in this way.

Of considerable theoretical importance with respect to the lymph node fibrosis in primary lymphoedema is that corticosteroids are known to have an indirect lytic action on collagen. Houck and Sharma (14) using tissue culture techniques have shown that cortisone can promote collagenolytic activity in skin and fibroblasts by induction of collagenases.

### Conclusions

These preliminary studies have indicated the type of patient which may be expected to benefit and suggest that the method is useful and deserves further trial.

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