

TREATMENT OF LYMPHEDEMA BY COMPLEX PHYSICAL THERAPY, WITH AND WITHOUT ORAL AND TOPICAL BENZOPYRONES: What Should Therapists and Patients Expect

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ABSTRACT

Using previously presented data, from an open multi-centered trial, the Medians and Third Quartiles were calculated for the overall edema reductions the "average" patient received from an "average" therapist using Complex Physical Therapy (CPT) on 628 lymphedematous limbs. These data provide therapists and patients a general guideline as to the minimal reductions which can be expected in three quarters of patients from average therapists, using CPT with or without the administration of benzo-pyrones. Benzo-pyrones were considered separately: oral (given for three months before and for 11 months after the course of CPT) and topical (during and after CPT). Depending on which measure of edema and its alterations were used, these reductions increased those from CPT alone from 130% to 200% and, after one year, between 150% to 300%. Whereas the effects of oral and topical benzo-pyrones were not statistically different, their combined usage was more effective than use of either alone.

Recently (1) we published a multivariate analysis of the results from the first, consecutive 618 lymphedematous limbs which had been treated using Complex Physical Therapy (CPT) (2,3) communicated to us almost entirely by therapists we have trained.

This analysis showed that some factors, which varied among the patients, had significant influence on the outcomes.

The special regimen of exercises we have developed (4) was one such factor. These had notably and significantly improved limb reductions, before CPT, during CPT, and during the Intermediate Period (some 11 months) before the next Course of CPT. They were examined separately in that study but, since they are a standard part of CPT, they are no longer considered separately here. Swelling of the arm reduced more rapidly than that of the leg, but these reductions were less well maintained during the Intermediate Period. The older the patient, the greater was the reduction during the Course, but age itself had no demonstrable effect during the Intermediate Period. Patient compliance was, however, a highly significant factor in maintaining the reduction.

Some factors which had no significant effect during the Course or the Intermediate Period were: primary *versus* secondary lymphedema, duration of lymphedema, the use of air pumps. Because we are concerned with "average" results, in what follows, none of the above factors mentioned in this and the preceding paragraph was considered separately.

The effect of benzo-pyrones combined with CPT was, however, so marked and so

significant (1) that these have been considered separately here. If oral benzo-pyrones was taken for at least three months before the Course of CPT, the outcome was notably improved. Benzo-pyrones similarly contributed to maintenance of limb reduction when taken during the Intermediate Period. These were either coumarin (5,6 benzo- α -pyrone - 400 mg/day) or hydroxy-ethyl rutosides (3,000 mg/day), which did not differ significantly from each other and accordingly the data have been combined. Similar effects were found with topical benzo-pyrone preparations: coumarin ointment (10% in polyethylene glycol), or powder (10% in sterile talc). The effects of oral and topical forms were additive.

We intend to add to the numbers of these results and to publish them in detail. However the results as presented (1), while they clearly show the significances of the additions of the various factors, are not readily applicable when therapists wish to give a patient some idea of how much benefit they are likely to receive from CPT, or from CPT and the benzo-pyrones. This limitation is because the results are presented as Means and Standard Errors. What therapists and patients need to know are Confidence Intervals for the whole population, rather than just the Means. In other words, they need to know the *probability* of a certain level of reduction for an individual patient.

The present analysis provides an indication of what the average patient can expect from CPT. Undoubtedly, some therapists perform better than this average prediction. On the other hand, a more compliant patient can expect a better outcome, especially if one is meticulous with performing remedial exercises, caring for the involved limb and applying an external garment. Elderly patients can also expect a better outcome. The following information represents the outcomes for the "average" therapist and patient, with and without the administration of benzo-pyrones.

DATA AND ITS COLLECTION

The details on the collection of the data, that of CPT and administration of benzo-pyrones, and how the various factors were quantitated and analyzed have already been provided (1). Ten more legs have been included in this analysis bringing the total number of treated limbs to 628. Whereas the exercise program was examined independently in the past, it has been included here as an integral part of CPT. Apart from the benzo-pyrones, all other factors are similarly combined (including arms and legs, which did not differ significantly with the non-parametric tests) so that we have amalgamated the average values for a relatively large group of patients.

Two sets of results are shown (*Table 1*). One is after the first Course of CPT (usually performed five or six times per week for four weeks). The second compares the pre-CPT condition and that after about 12 months, when 84 limbs received a further four-week course of CPT; 135 other limbs were simply remeasured.

Estimates of Alterations in Edema

Three estimates of the reduction of edema are shown in *Table 1*. The first (Reduction of Volume/Initial Volume of Lymphedematous Limb) is probably the best discriminator and is applicable to both bilateral and unilateral edema (5, eqn. 2). This estimate can be formulated as: $D/I = (F - I)/I$, with 'D' the difference in volume of the lymphedematous limb, 'I' its initial volume, and 'F' its final volume.

The next estimate of edema reduction (Reduction of Lymphedematous Limb/Normal Limb) is also satisfactory, but is only applicable to unilateral limb edema (5, eqn. 6): $O_d = (F - I)/N$, with 'O_d' the difference in edema and 'N' the volume of the normal limb.

The third estimate (Reduction in Edema as percentage of Initial Edema) is the most meaningful to both patient and therapist (5,

TABLE 1
Results for all Therapists and Patients; Showing Minimal Results for:
Three-quarters of the Patients (Third Quartiles) and for half of them (Medians),
for the Course of C.P.T. (usually 4 weeks), and Over the Next 11 months.

	Reduction of Volume as % Initial Vol. of Lymphedematous Limb		Reduction in Lymph- edema as % Normal		Reduction in Edema as % Initial Edema	
	{bilateral & unilateral}		{unilateral lymphedema only}			
	Course	Whole Yr	Course	Whole Yr	Course	Whole Yr
All Patients						
³ / ₄ 's better than:	-7.7%	-5.7%	-10%	-7.0%	-23%	-16%
(¹ / ₂ better than), Nos.	(-13%), 628	(-11%), 219	(-16%), 408	(-14%), 157	(-55%), 408	(-47%), 157
C.P.T. only, no benzo-pyrones						
³ / ₄ 's better than:	-6.4%	-3.1%	-8.2%	-5.0%	-19%	-13%
(¹ / ₂ better than), Nos.	(-11%), 356	(-7.6%), 90	(-14%), 216	(-9.0%), 58	(-51%), 216	(-43%), 58
C.P.T. plus oral benzo-pyrones						
³ / ₄ 's better than:	-9.4%	-8.5%	-14%	-8.7%	-26%	-16%
(¹ / ₂ better than), Nos.	(-15%), 111	(-13%), 51	(-20%), 85	(-17%), 40	(-58%), 85	(-48%), 40
<i>P-value vs. CPT only</i>	10^{-10}	10^{-4}	10^{-5}	0.0024		
C.P.T. plus topical benzo-pyrones						
³ / ₄ 's better than:	-9.7%	-5.3%	-12%	-8.9%	-23%	-17%
(¹ / ₂ better than), Nos.	(-15%), 69	(-11%), 24	(-21%), 52	(-17%), 21	(-72%), 52	(-52%), 21
<i>P-value vs. CPT only</i>	0.0004	0.016	0.0020	0.047		
<i>P-value vs. oral BPT</i>	0.49	0.22	0.39	0.49		
C.P.T. plus oral and topical benzo-pyrones						
³ / ₄ 's better than:	-12%	-12%	-14%	-9.5%	-29%	-23%
(¹ / ₂ better than), Nos.	(-18%), 92	(-18%), 54	(-27%), 55	(-26%), 38	(-67%), 55	(-64%), 38
<i>P-value vs. CPT only</i>	10^{-12}	10^{-9}	10^{-7}	$<10^{-16}$		
<i>P-value vs. oral BPT</i>	0.021	0.033	0.23	0.47		
<i>P-value vs. topical BP</i>	0.0051	0.0046	0.031	0.22		

Results are shown as negative because they were reductions.

Considering the top-left group as an example, this indicates that, at the end of the Course of C.P.T., ³/₄'s of the 628 patients had *at least* a 7.7% reduction of the volume of the lymphedematous limb compared with its initial volume, while half of them had *at least* a 13% reduction.

The oral benzo-pyrones during the Course of C.P.T. were given for at least three months before the start of the Course. These were either coumarin (400 mg/day) or hydroxyethyl rutosides (3,000 mg/day); there were no significant differences between these.

The topical benzo-pyrones were either 10% coumarin ointment in PEG or 10% coumarin powder in sterile talc; there were no significant differences between them.

P-values versus other groups are from Wilcoxon two-sample tests. They could not be given for the last two columns since these numbers are calculated from the parameters from other equations (see Text).

eqn. 7): $O_d/O_i = (F-I)/(I-N)$, with O_i the initial amount of oedema $(I-N)/N$. (This and the previous equation assume that the initial and the final N 's are the same; if not they need to be adjusted.)

However, this last equation is the least accurate and is derived from an equation in which minor errors can cause major distortions in the calculated results (5). These irregularities are not necessarily measured errors, but are caused largely by the "normal" limb being different in size from that which the lymphedematous one would be if it had all the edema removed. For example, in the present series of 408 patients with unilateral lymphedema, 57 had reductions of more than 100% and 20 had reductions of more than 150% of the edema; one even had a reduction of 900%! (This last patient had an Initial Volume of 4,047 ml, a Final Volume of 3,465 ml and a 'Normal' volume of 3,982 ml; it is an excellent demonstration of the anomaly produced when $F \ll N$ in eqn. 7 (5). Most likely all % reductions are somewhat misleading. The reasons for these "errors" have been discussed (5), with muscle wastage of the lymphedematous limb as a possible factor.

It was strongly recommended in that paper (5) that equation 7 should only be derived from $\{\text{Mean of eqn. 6}\} / \{\text{Mean of eqn. 4}\}$. That is: $(F-I)/(I-N) = \{(F-I)/N\} / \{(I-N)/N\}$, because any errors in the '{...}' terms have much less effect and tend to cancel each other out. (The Standard Errors of the Mean found in this way are obtained from those of eqns. 4 and 6, using large number theory.) If one tries to calculate these values from the individual results for each patient, the distributions are so skewed that the distortions are much greater.

Despite these limitations, the individual "Reduction in Edema as a percentage of the Initial Edema" is still what most interests the individual patient and therapist. Hence as a guide (but one prone to error), the parameters (Mean, S.E.'s, Median and Quartiles) may be calculated in this way for a group of patients (as for the final two columns in *Table 1*).

Representing the Data

What is required to describe a patient population are not Standard Errors, but Standard Deviations. While the distributions (with the exception noted above) are sufficiently normal for parametric tests to be valid using Standard Errors, they are so skewed that the Standard Deviations are overly distorted. The populations are therefore here described in non-parametric terms, using the Medians and the Third Quartiles.

Accordingly, except for the percentage reduction of the initial edema, the results of each patient have been ranked in order of size (increasingly negative). The Median and Third Quartiles are shown in *Table 1*. The Median is that derived value in which half of the patients have a greater value and the other half have a lesser value. The Third Quartile is that value for which 1/4 of the patients have less good results and 3/4's of them have better ones. Thus it gives the *minimal* reduction which was achieved by 3/4's of the patients. This is the best estimate of edema reduction until there are greater numbers for the whole population studied.

As an example of its application, consider the top left-hand values in *Table 1*. There is a Third Quartile of -7.7% for the 'Reduction of Volume as a % of the Initial Volume of the Lymphedematous Limb'. This value signifies for the average therapist, three quarters of the patients achieved *at least* an edema reduction of 7.7% during the Course of CPT. Using the Median value below this in the next row, half of the limbs had *at least* a 13% reduction. Similarly, using like figures in the bottom right-hand group, if patients received oral and topical benzo-pyrones, three quarters retained reductions of *at least* 23% of the edema after one year; half retained reductions of *at least* 64%.

Statistical Tests

The previous publication (1) has more

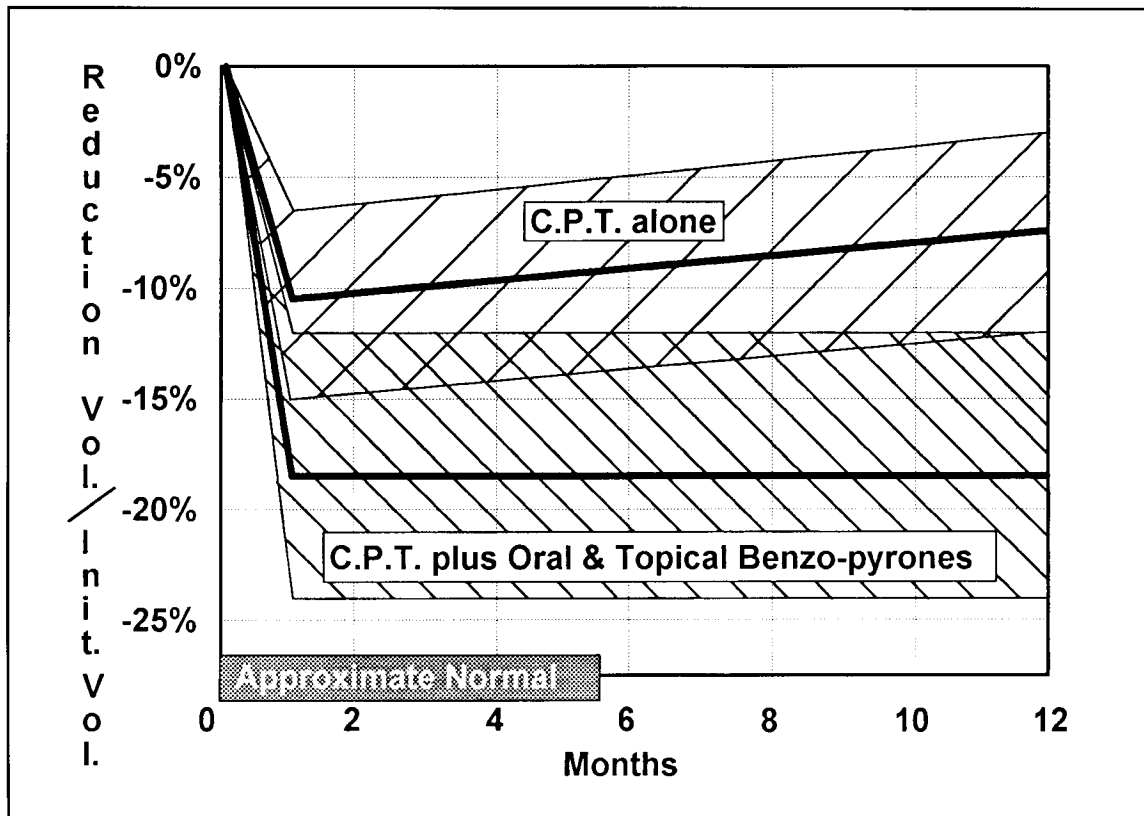


Fig. 1. Reductions of the Volume of the Lymphedematous Limblits Initial Volume, for CPT alone and CPT plus oral and topical benzo-pyrones; showing the Medians (thick lines), and the First (lower) and Third (upper) Quartiles for each group. The shaded areas between the First and Third Quartiles contain 50% of the results for each group, while 25% are above and 25% are below them.

detailed, and more revealing, multivariate analysis of the data. However, those data are obtained using parametric tests. It seemed worthwhile to perform non-parametric tests (Wilcoxon two-sample tests) on the current data to complement the previous findings. The P-values for these tests (Table 1) show that the improvements produced by oral or topical benzo-pyrones when combined with CPT are highly significant, and that this holds true both during CPT and after one year. In addition, while the effects of the oral and the topical benzo-pyrone preparations are not significantly different, their combination is more effective than either alone. (This phenomenon is shown by the, more accurate

and sensitive, first two columns but not by the less numerous middle columns.)

RESULTS AND DISCUSSION

Edema reduction for many patients is considerably better than the values in Table 1 (see Fig. 1). Third Quartiles and Medians show merely the minimal benefits which 75% and 50% of the patients can expect - given the "average" therapist. Some therapists have significantly better results than these, some worse. (Some had more than 60% Reductions in Edema in more than 75% of their patients, even without using benzo-pyrones). Inevitably therapists, situations and facilities vary. We

deliberately provide the average of all therapists so that both patients and therapists have a guide to the results they they may expect to achieve.

Patients also vary; these values thus can only be a guide. It has been shown (1) that patients have better results if they are compliant, follow advice, perform the exercises regularly, care for the limbs, and care for the garments. The reverse also applies. Grade, etiology or duration of lymphedema are not shown to have a significant effect but, the older the patient, the better the outcome. Also, a swollen arm has a better outcome during CPT than a swollen leg, but the reductions are not maintained as well.

Edema reduction is much improved by the use of oral and/or topical benzo-pyrones (1). This decrease is shown in *Table 1 (and Fig. 1)* where, depending on which measure of edema is used, these increased reduction during the Course of CPT to 130% to 200% of those with CPT alone. Over the whole year, benzo-pyrone usage improved the maintenance of these reductions even further (to 150% to 300%). Trials in many centers have shown that oral benzo-pyrones alone reduce lymphedema (6-15). On the other hand, CPT is much more effective initially, but over a whole year usage of oral benzo-pyrones alone provide about 50% reduction of CPT alone and no compression garments are needed. However these results, are less than with CPT alone, which reemphasizes the benefit of combining CPT with benzo-pyrones.

The considerably greater edema reduction after pre-treating patients with oral benzo-pyrones before CPT, and using them topically during CPT, may be due to the drug causing partial breakdown of a fibrous barrier in the lymphedematous limb, allowing more of the isolated pockets of excess protein and fluid to be emptied during CPT. Whereas the benefit from the benzo-pyrones is apparent during the course of CPT itself, improved maintenance of the edema reduction after the course has ended is perhaps even more important for the ultimate success of the

entire therapeutic endeavor (*Fig. 1*).

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