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EDITORIAL

ON RANDOMIZED CLINICAL TRIALS

Randomized clinical trials have been developed in order to minimize subjective judgment as to the efficacy of drug or operative treatment. Whereas the usefulness of this approach is self-evident, it is noteworthy that Withering was able, by careful observation alone, to establish that digitalis was effective treatment for dropsy (i.e., heart failure). Similarly, aspirin, one of the most useful drugs of the last hundred years, was introduced long before randomized trials had become commonplace. In an Editorial entitled "Not So Blind, After All—Randomized Trials, the Linchpin of Medicine, May Often be Rigged," *Scientific American* (1) calls attention to the fact that randomized selection which is pivotal to the accuracy of a clinical trial is in practice often flawed. Besides the issue of "allocation concealment," there are several other concerns, including: 1) the choice of inappropriate inclusion/exclusion criteria; 2) the fetishness or overreliance on statistics; 3) financial incentives or other "conflicts of interest." Whereas the first two belong to epidemiologists and statisticians to assure non-bias, the third is insidious, coercive and potentially corrupting. As one impeachable colleague described it, "I am always willing to carry out a double-blind trial but not a treble blind one"—the third component representing his personal remuneration.

Chronic venous insufficiency (CVI) is a syndrome which interests not only the phlebologist, but also the lymphologist. CVI can be secondary, that is as a consequence of deep venous thrombosis, or primary as a result of longstanding varicose veins. "Venous edema" is classified, according to a four-tiered system of the North American Chapter of the International Cardiovascular Society, as Class 0=asymptomatic; Class 1=mild swelling; Class 2=moderate swelling with hyperpigmentation; Class 3=marked edema with skin ulceration. Edema of each Class (1-3) is, however, the cardinal sign. Lymphologists, however, have long recognized that extracellular edema accumulation ultimately requires some form of insufficiency of the lymph vascular system. In Class 1, low protein edema (<1.0 gm/dl) is typically linked to a high output failure of the lymphatic circulation (i.e., lymph flow is faster than normal but still inadequate to handle the excess net capillary filtrate produced by heightened blood capillary hydrostatic pressure). In Classes 2-3, "safety valve insufficiency" prevails (that is, intrinsic lymphatic failure supervenes) and the protein concentration of the edema fluid rises (>1.5 gm/dl).

After deep venous thrombosis, CVI is characterized by persistent ambulatory venous hypertension and is a life-long condition. Nonetheless, the patient remains in Class 0 if he/she accepts compression therapy, "the current gold standard for treatment of chronic venous insufficiency" (2). Citing reference 2, "the role of surgery in secondary venous insufficiency (i.e., postthrombotic) is ... unsettled. In most of these cases, venous damage is diffuse. Despite this, surgical approaches have been directed at discrete areas such as the femoral or

popliteal vein. Preliminary reports have been encouraging but late results have been predictably unimpressive. Surgeons remain frustrated by the inability to effectively address the widespread anatomic abnormalities which are present in most patients ...". In Class 1 of CVI, overnight elevation of the leg typically suffices to alleviate edema, and if on arising, compression stockings are worn consistently throughout the working day, CVI can be brought back to Class 0 and progression of venous disease arrested.

For the lymphologist, Class 3 of CVI is simply a combined form of venous dysfunction and lymphedema (i.e., both venous and lymphatic insufficiency). Except for poor compliance and/or lack of proper information, CVI patients in Class 3 can be successfully treated with combined physiotherapy (CPT) similarly to those with pure lymphedema. Thus, edema regresses, lipodermatosclerosis and hyperpigmentation recede, and skin ulcerations heal. The sine qua non, however, for preservation of this therapeutic effect is the life-long recognition and acceptance of "Phase 2" of CPT, namely, compression.

In the February 3, 1996, issue, *Lancet* published an article entitled "Comparison of Leg Compression Stocking and Oral Horse-chestnut Seed Extract Therapy in Patients With Chronic Venous Insufficiency" (3). It is noteworthy that one of the authors was affiliated with the pharmaceutical company which markets the seed extract under the trade name "Venostasin." In the Introduction, the authors report that "two fundamental therapeutic approaches are now used in the treatment of CVI, compression (bandages and stockings) and venoactive substances (e.g., horse-chestnut seed extract, HCSE) which exert an inhibitory action on capillary protein permeability." This statement, however, is both inaccurate and misleading. There is only one "accepted" therapeutic approach for the treatment of CVI—compression therapy. A vigorous search for a chapter on "venotropic drugs" in an up-to-date handbook of pharmacology (4) is futile. No such review exists. The authors justify their clinical study by claiming that "compression treatment is inconvenient, uncomfortable, and subject to pure compliance"; hence "the medical option is attractive." In a "novel hierarchical statistical design in 240 patients with chronic venous insufficiency," one group was treated over a period of 12 weeks with placebo, a second with HCSE, a third after a one-week-administration of 25 mg hydrochlorothiazide plus 50 mg triamterene, with Class II compression stockings. In the placebo-group the volume of the lower leg increased by 9.8 ml, decreased in the HCSE-group by 43.8 ml and in the stocking-group by 46.7 ml.

Soon after this article was published, the drug company, Klinge, circulated an advertisement which, translated from German into English, reads as follows: "Now vein-treatment takes off the stockings! ... According to *The Lancet*, compression is inconvenient, uncomfortable, and subject to poor compliance. And Venostasin offers an alternative to compression. The two therapies were shown to be equivalent."

I wrote to *The Lancet* and pointed out the article's shortcomings. First, the current basic principles of phlebology and lymphology demand that elastic stockings are not to be used to remove edema fluid but to maintain a state free of edema obtained by the "phase 1" of combined physiotherapy (CPT). Second, it is improper to calculate on the basis of the volume of fluid removed from a limb without taking into consideration the volume of edema fluid *before* treatment, that is whether the patient has Class 1, 2 or 3 edema. For example, several liters of edema fluid can be present in a leg, and it makes a considerable difference whether 50 ml are removed from a residual of 1 liter or from 100 ml. Moreover, 46.7 ml of edema fluid, the optimal amount in *The Lancet* study, can be removed from a leg with simple overnight elevation. Third, the authors do not describe how gender was "randomized." The leg

volume of a normal woman (most patients in this study were women) "spontaneously" increases in the upright position after 4 hours by 137±136 ml (5). Fourth, the fact that in the placebo subgroup edema volume increased by only 9.8 ml in the course of six weeks indicates that these patients probably belonged to Class 0 and properly did not need any treatment.

After examining 17 randomly chosen patients with CVI (post-thrombotic syndrome Class 3) from the Földiklinik undergoing an appropriate combination of various physiotherapeutic methods, we found that the most important treatment constituent proved to be circumferential bandage compression. After 65 days, 1 liter of edema fluid on the average could be removed from a swollen leg. This means that compression therapy reduces edema fluid by approximately 40 ml/day. In comparison, in *The Lancet* study, horse-chestnut seed extract or diuretic drugs reduced edema on the average of approximately 1 ml/day. In short, classic compression treatment is more than 38 times more effective than either form of alternative treatment recommended by *The Lancet* authors.

Franzeck et al (6) recently published a prospective 12-year follow-up study of the clinical and hemodynamic sequelae after deep vein thrombosis and found that "all patients who used regular compression treatment had only mild or no postthrombotic symptoms after 12 years" (6). In this study, Class 3 patients were examined. Accordingly, only a prospective study trial comparing compression treatment in Class 3 patients with HCSE showing equivalent benefit would justify a drug advertisement as promulgated by the manufacturer of Venostasin.

The major lesson derived from this analysis is that solely citing the number of published randomized trials with positive results cannot properly be used as an argument in favor of drug efficacy. Each study must be examined carefully on its own merits. Indeed, one well-done study can be definitive.

I concluded my letter to *The Lancet* as follows:

"The results of Diehm et al (3) allow only the conclusion that the inappropriate method of treating edema in CVI with inadequate elastic stockings (combined with diuretics) has brought about the same negligible effect as horse-chestnut seed extract. The only merit of the article is that it has produced an excellent example for students how statistical significance, even if it is based on a 'novel hierarchical design,' is able to disguise biological insignificance".

The Lancet opted not to publish my letter.

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