

Efficacy and tolerance of systemic enzyme therapy in the treatment of acute thrombophlebitis—a randomised double-blind controlled trial

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Objective: Investigation of efficacy and safety of systemic enzyme treatment (SET)-the oral administration of proteolytic enzymes (trypsin, bromelain) plus antioxidants (rutin)-in acute thrombophlebitis.

Subjects and Methods: In this double-blind study, 100 patients with acute thrombophlebitis were randomised 1:1, and treated with either SET or placebo for 14 days. Analgesic drugs were allowed; compression treatment was not allowed. Primary endpoint was reduction in resting pain within 7 days. Further endpoints were reduction in pain and thrombophlebitis symptoms on days 4, 7 and 14 as well as safety.

Results: Within 7 days of treatment, resting pain was reduced significantly better with SET than placebo (64% vs. 29%, $p < 0.0001$), meeting the primary

endpoint. In the course of treatment, most symptoms improved in both the SET and the placebo group. However, reduction in resting pain and pain under pressure occurred faster and was significantly greater in the SET group compared to placebo on days 4, 7 and 14. The leading symptoms of acute thrombophlebitis (redness of the skin, hyperthermia, phlebitis cords, feeling of heaviness and tenseness) were all relieved significantly better with SET. The risk profile of SET was favourable, with only mild to moderate adverse events (AEs) and fewer AEs detected in the SET than the placebo group, where the majority of AEs were attributed to analgesic drugs. Use of SET may thus avoid analgesic-associated AEs.

Conclusion: SET is shown to be a safe and effective option to treat acute thrombophlebitis in the absence of compression treatment.

KeyWords: Systemic enzyme therapy, Oral enzyme combination, Thrombophlebitis, Pain.

Acute thrombophlebitis or superficial thrombophlebitis is the inflammation of superficial veins caused by a thrombus, most frequently in the legs. While acute thrombophlebitis is often considered to be relatively benign, it may be associated with more severe conditions such as deep vein thrombosis and life-threatening pulmonary embolism. The main symptoms of acute thrombophlebitis include pain at rest and upon pressure, local hyperthermia and redness of the skin as well as formation of tender and hard veins (phlebitic cords).

The precise aetiology of acute thrombophlebitis remains unknown. Thrombophlebitis often occurs under conditions of reduced blood flow. Relevant risk factors are immobility, varicosis and conditions of increased coagulation, as well as trauma of the affected vein, for instance due to catheters or surgery. Acute thrombophlebitis may also be associated with bacterial infection. The incidence of acute thrombophlebitis is estimated to be about one per 1,000 [1].

There are various therapeutic options to treat acute thrombophlebitis [1,2]. Many of these options primarily aim at reducing the burden of pain and symptoms of inflammation, for example by local cooling and the use of analgesic non-steroidal anti-inflammatory drugs (NSAID), typically in an over-the-counter (OTC) setting. Compression stockings are often employed since they help improve venous blood flow. Dissolution of the thrombus and thus relief of acute thrombophlebitis can be achieved by anticoagulant therapy with heparin or fondaparinux.

Systemic enzyme therapy (SET) may serve as another treatment option for acute thrombophlebitis. SET is the oral application of proteolytic enzymes such as trypsin and bromelain in combination with antioxidants like rutin. Enzymes are absorbed in the small intestine and taken up into the bloodstream, at least to some extent [3]. There, they act in an anti-inflammatory manner, as was first described for the serine protease trypsin [4]. Similarly, the cysteine protease bromelain, extracted from the stems of pineapples, is an effective phytotherapeutic drug with anti-inflammatory properties [5]. The immunomodulatory function of proteolytic enzymes is thought to be mediated by direct proteolytic and thrombolytic activity as well as a variety of immunomodulatory mechanisms. These mechanisms include

interaction with protease-activated receptors (PAR, for trypsin: PAR2) on certain immune cells, e.g. macrophages [6,7], and binding to alpha-2-macroglobulin followed by clearance of associated cytokines [8-10]. Proteases have also been indicated to show a certain improvement of the fluidity of the blood [11]. An additional component of SET can be rutin, or rutin, a flavonoid known to have cytoprotective and anti-inflammatory properties [12].

SET has become increasingly popular with patients as an OTC option to treat pain and inflammation. Still, there is only limited evidence for efficacy and safety of SET from randomized clinical trials and previous evidence hints at additional effects to compression stockings, but do not show singular effects of enzyme combinations. Here we report the results of a randomized, double-blind, placebo-controlled clinical trial in 100 patients with acute thrombophlebitis in the leg, comparing treatment with the SET trypsin:bromelain:rutin trihydrate (Wobenzym[®], Mucos Pharma, Berlin, Germany) to placebo without compression stockings.

MATERIALS AND METHODS

Patients, inclusion and exclusion criteria, randomisation

One hundred adult patients (age ≥ 18 years) of either gender were recruited. To be included in the study, patients had to suffer from acute thrombophlebitis in the lower leg, with moderate to severe pain as monitored on a visual analog scale (VAS, value ≥ 3 cm), pain under pressure, and presence of at least three of the following symptoms: skin redness, hyperthermia, phlebitic cords, feeling of heaviness and tenseness. Exclusion criteria included known deep phlebothrombosis, flourishing ulcer cruris, arterial occlusive disease, peripheral neuropathy, malignant disease, concomitant anticoagulant treatment, pregnancy, lactation, known alcohol or drug abuse and participation in another clinical study. The study was approved by an independent ethics committee (Freiburg Ethics Commission International, Freiburg, Germany) in accordance with the declaration of Helsinki. Informed written consent was obtained from each patient.

Randomization

Patients were randomly allocated to one of the study groups, either treatment

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with SET or placebo, in a 1:1 ratio, based on a randomisation list generated using Rancode (IDV, Gauting, Germany). Only managers for study material, production and quality assurance had access to the randomisation list. Both investigators and patients were blinded to the treatment.

Intervention and investigation

The study was conducted in one centre in Italy. Study medication was either SET or placebo. SET tablets (Wobenzym®, Mucos Pharma, Berlin, Germany) contained bromelain standardised to 450 Fédération Internationale de Pharmacie [FIP] units, trypsin standardised to 24 µkat, and 100 mg rutoside trihydrate per tablet. Placebo tablets were of identical appearance but lacked any active substance. The patients received 2 tablets t.i.d. (i.e., 6 tablets per day) for a planned treatment duration of 14 days. Self-medication with analgesics was allowed and was monitored. Compression treatment was not allowed.

At baseline (day 0), patient characteristics, history as well as concomitant diseases and medications were recorded. Patients were investigated on day 0 (baseline) as well as on days 4, 7 and 14 in order to closely monitor symptoms and development of thrombophlebitis. Patients were asked to evaluate pain at rest on a 10 cm VAS, with the left end (0 cm) indicating “no pain” and the right end (10 cm) “unbearable pain” [13]. The distance from the left end was recorded. Patients with a value ≤ 1 were defined as “responders”. Pain under pressure was assessed using Meyer’s pressure points at the lateral side of the tibia and Krieger’s pressure point in the popliteal space (see also schematic depiction in Figure 1). For each of these pressure points, pain was judged by the physician on a scale ranging from 0 (no pain) to 3 (severe pain). Assessment of symptom severity was done by the physician (skin redness, hyperthermia, palpable/visible phlebotic cords) or the patient (heaviness, tenseness), respectively, by assigning a score of 0 (not present), 1 (mild), 2 (moderate) or 3 (severe). A sum score was calculated by summarising the respective values for the five symptoms. Efficacy of the therapy was independently assessed by the physician and the patient (1=very good, 5=poor) on day 14. Primary efficacy endpoints were the mean difference of rest pain between day 0 and 7 and the number of responders on day 7.

Any adverse event (AE) had to be documented with symptoms, day of onset, duration, frequency and severity (mild, moderate or severe). The causality of AE with the study medication, measures taken and patient’s outcome (sequelae) were documented. Tolerance of the therapy was determined independently by the physician and the patient on day 14, using a scale from 1 (very good) to 5 (poor).

Patients were instructed to return their drug medication after completion of the study in order to measure compliance via drug accountability.

Concomitant use of analgesics was allowed if needed, and documented with name, dose, number of intakes.

STATISTICAL METHODS

The following statistical evaluations were performed as pre-defined in the study protocol: Two-tailed Wilcoxon-Mann-Whitney U test to test comparability of groups at baseline and to assess differences between groups, and two-tailed Fisher’s exact test to evaluate AE frequency and the number of responders. The level of significance was set to 5% (l-error=0.05). Fifty patients were required per group, taking into consideration a statistical power of 80% (l-error=0.20) and a dropout rate of 10%. Missing data were substituted by carrying forward the last value. Data are reported as mean ± standard deviation (SD).

RESULTS

Patient characteristics

One hundred patients were randomized in a 1:1 ratio to either SET or placebo group. All patients except for 1 patient in the SET and 3 in the placebo group finished the therapy according to protocol (Figure 1). Patients had a mean age of 60 years and were predominantly female. Patient characteristics are given in Table 1. There were no statistically significant differences between groups regarding age, sex, body height, body weight and duration of thrombophlebitis before start of therapy. Baseline values for pain and symptoms were comparable between groups, with the exception of the resting pain value, which was significantly higher in the SET group (Figure 2, p=0.0027). All subjects who completed the therapy were deemed compliant based on returned tablet count.

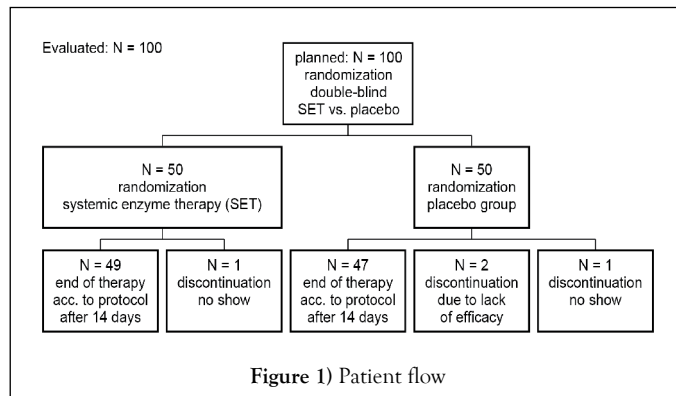


Figure 1) Patient flow

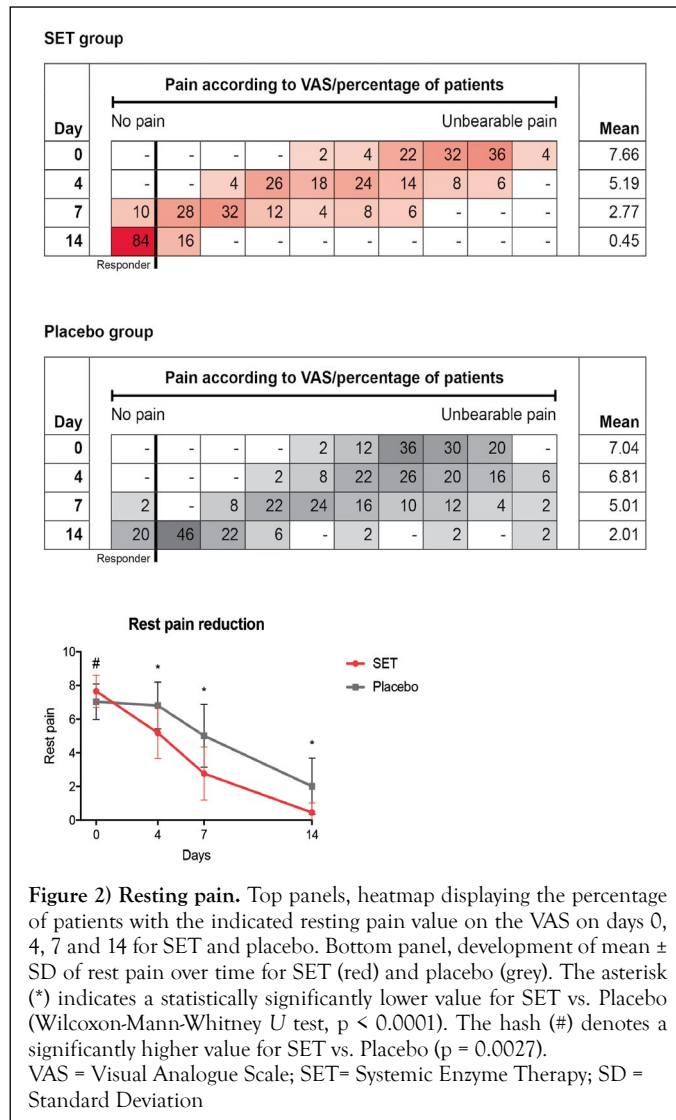


Figure 2) Resting pain. Top panels, heatmap displaying the percentage of patients with the indicated resting pain value on the VAS on days 0, 4, 7 and 14 for SET and placebo. Bottom panel, development of mean ± SD of rest pain over time for SET (red) and placebo (grey). The asterisk (*) indicates a statistically significantly lower value for SET vs. Placebo (Wilcoxon-Mann-Whitney U test, p < 0.0001). The hash (#) denotes a significantly higher value for SET vs. Placebo (p = 0.0027). VAS = Visual Analogue Scale; SET= Systemic Enzyme Therapy; SD = Standard Deviation

Pain at rest

Pain at rest was moderate to severe at baseline in both groups, with a mean VAS value of 7.66 cm (SET) and 7.04 cm (placebo), respectively. Pain at rest was reduced in both SET and placebo group in the course of treatment (Figure 2). This pain reduction was significantly better (p<0.0001) in the SET group at all-time points investigated: On day 4, pain reduction was 32% in SET, as opposed to 3% in the placebo group. On day 7, average pain was 64% less than at baseline, as compared to a reduction by 29% in the placebo group. Thus, the primary endpoint of the study was met, showing significantly better rest pain reduction by SET compared to placebo within 7 days of treatment.

At the end of the study (day 14), average rest pain was reduced by 94% from baseline in the SET group and by 71% in the placebo group. No patients in the SET group still had pain exceeding 2 cm on the VAS on day 14, compared

Table 1
Patient characteristics

	SET	Placebo
Mean age (range; SD)	60.3 years (24.0–85.0; 14.49)	59.3 years (28.0–84.0; 15.20)
Female gender	70 %	76 %
Mean body height (range; SD)	165.6 cm (150.0–198.0; 9.51)	164.2 cm (154.0–180.0; 6.90)
Mean body weight (range; SD)	72.75 kg (49.0–113.0; 13.658)	70.12 kg (50.0–95.0; 11.299)
Mean duration of thrombophlebitis before treatment (range; SD)	7.4 days (0–56; 9.44)	4.5 days (2–7; 1.99)
Pre-treatment of thrombophlebitis	24 %	16 %
- Analgesics	10 %	6 %
- Preparations for varicose veins	12 %	4 %
- Topical preparations	4 %	2 %
- Other/unknown	-	4 %
Concomitant disease with medication	36 %	30 %
- Diabetes mellitus	8 %	4 %
- Hypertension	18 %	12 %
- Other	10 %	14 %

SET= Systemic Enzyme Therapy; SD = Standard Deviation

Table 2
Safety

	SET	Placebo
Adverse events, total	6 (12 % of patients)	13 (26 % of patients)
- Mild	5	11
- Moderate	1	2
- Severe	0	0
Treatment change due to AE	0	0
Type of AE:		
- Pain in the stomach	-	7
- Vertigo	-	1
- Loose stool	2	-
- Diarrhoea	3	-
- Sensation of repletion	-	1
- Pressure over the stomach	-	4
- Bursitis	1	-
Frequency of AE		
- Single episode	4	2
- Intermittent	1	10
- Continuous	1	1
Sequelae	0	0

SET= Systemic Enzyme Therapy; AE = Adverse Event

to one-third of patients in the placebo group. Most (84%) of the patients in the SET group but just 20% in the placebo group were “responders” to treatment, with pain of no more than 1 cm on the VAS. By day 7, 10% in the SET group were already responders, as opposed to a single patient in the placebo group.

Pain upon pressure

Pain upon pressure was equivalent at baseline and was reduced in both groups in the course of treatment (Figure 3). Pain reduction with respect to baseline was significantly more pronounced in the SET group than the placebo group for each of the four pressure points and at all-time points investigated. Within the first 4 days, pain under pressure was considerably reduced in the SET group (by between 19 and 36%, depending on the pressure point) but not in the placebo group (slight increase). By day 14, pain was almost completely relieved in the SET group (up to 96% reduction from baseline) but significantly less so in the placebo group.

Symptoms

Five key symptoms were further analyzed in the course of treatment (Figure 4). Redness of the skin, hyperthermia, feeling of heaviness and tenseness were all reduced within 14 days in both the SET and the placebo groups, with scores that were significantly lower in the SET group at most time points. The reduction in intensity of these symptoms within 14 days was between 81 and 100% compared to baseline in the SET group, indicating that these symptoms were almost completely alleviated in the SET group. Symptoms of redness and hyperthermia were also almost completely resolved in the placebo group by 14 days. Phlebotic cords did not resolve in either group

within the 14 days of the study. In the placebo group, the mean scores for phlebitis cord severity exceeded baseline values at all times investigated, while these scores were reduced by 38.5% in comparison to baseline in the SET group by day 14. In the patients receiving SET, each of the symptoms was less severe on day 4 compared to baseline, while all symptoms intensified in the placebo group within the first 4 days. At no time after the start of treatment were any of the symptoms more severe in the SET group than the placebo group. Overall, symptom relief was significantly effective in the SET group compared to placebo in the course of treatment, as is also demonstrated in the “sum score” of all five symptoms under study (Figure 4, bottom right).

Evaluation of efficacy

Efficacy of the study drug was independently assessed by the physician and the patient. Efficacy was assessed as “very good” by 78% of physicians and 76% of patients in the SET group, as opposed to 0% and 2%, respectively, in the placebo group. On a scale from 1 to 5, SET was assessed with a mean value of 1.3 (very good) by both patients and physicians, while the mean value was 2.7 and 3.3 in the placebo group. There were no major deviations between judgements made by physicians and patients.

Safety and rescue medication

Adverse events (AE) are listed in Table 2. AEs occurred in 12% of the patients in the SET group and in 26% of the placebo group (Table 2). All AEs were mild to moderate; no severe AE was detected in any group. In the SET group, AEs were mostly diarrhea and loose stool, while the most frequent AE in the placebo group was stomach pain. In 69% of the cases, AE occurrence in the placebo group was attributed to concomitant medication. While 80% of the

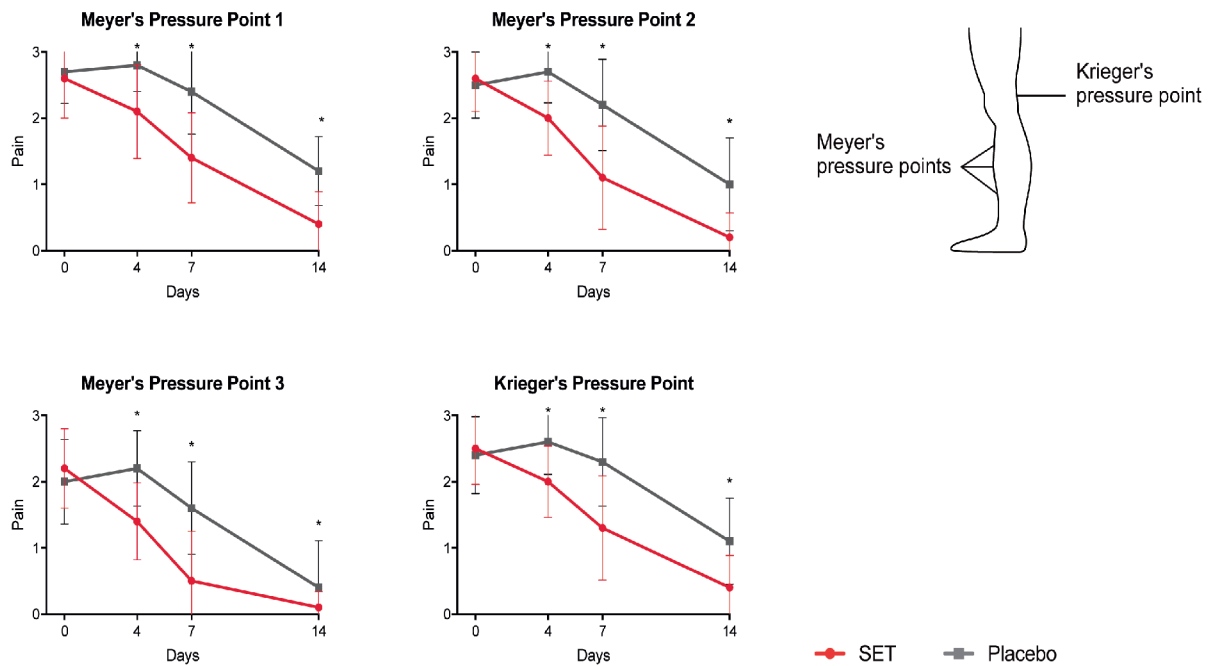


Figure 3) Pain under pressure. Means ± SD of the scores for pain under pressure for SET (red) and placebo (grey), utilising the respective pressure point as displayed in the sketch on the right-hand side. The asterisk (*) indicates a statistically significantly lower value for SET vs. placebo (Wilcoxon-Mann-Whitney *U* test, $p < 0.0001$ except for Meyer's pressure point 3 on day 14 [$p = 0.0002$]).
SD = Standard Deviation; SET= Systemic Enzyme Therapy

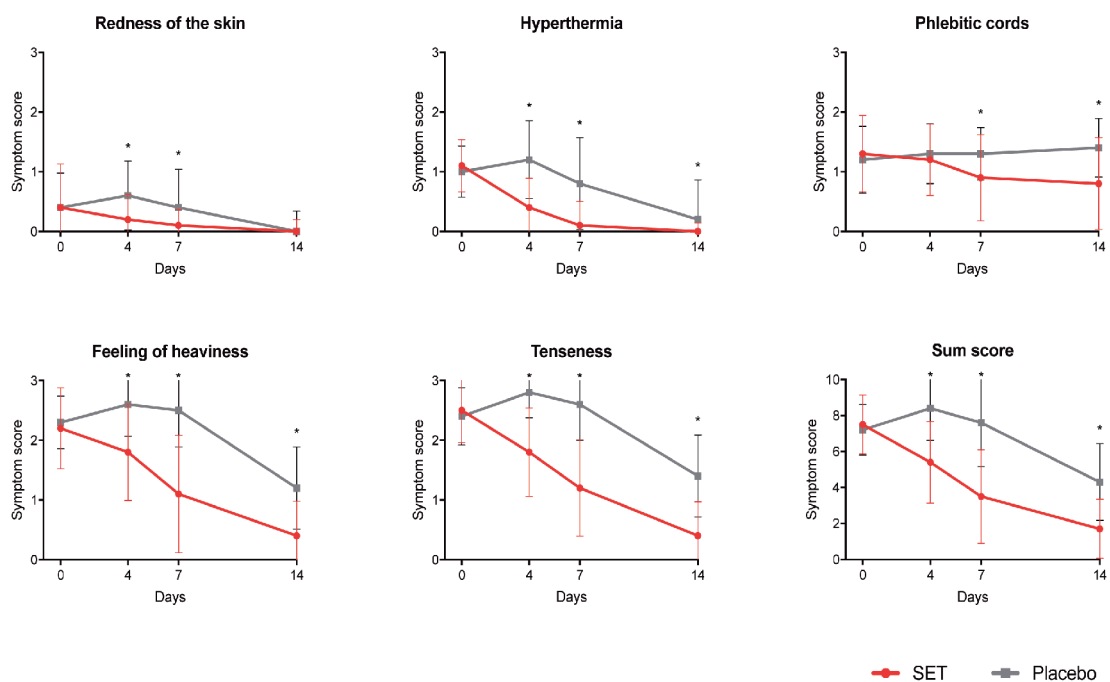


Figure 4) Symptoms. Means ± SD of the scores for severity of the indicated symptoms for SET (red) and placebo (grey). The sum score describes the sum of all five symptoms. The asterisk (*) indicates a statistically significantly lower value for SET vs. placebo (Wilcoxon-Mann-Whitney *U* test, $p < 0.0001$ for all values except redness of the skin on day 7 [$p = 0.0013$], hyperthermia on day 14 [$p = 0.0246$] and phlebitic cords on day 7 [$p = 0.0038$]).
SD = Standard Deviation; SET= Systemic Enzyme Therapy

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patients in the placebo group elected to use analgesics during the course of study (diclofenac in all patients but one), significantly fewer patients (8%) in the SET group did so.

Tolerance of SET was assessed significantly better than that of placebo by both physicians and patients: On a scale from 1 to 5, tolerance of SET was on average rated with 1.1, while the mean tolerance value of placebo was 2.1 (physician's judgement) and 2.2 (patient's judgement), respectively. The value "very good" was given in 4% of cases in the placebo group but a respective 84 and 82% of cases with SET.

DISCUSSION

The results of this randomized, double-blind, placebo-controlled clinical trial in 100 patients demonstrates the efficacy and safety of SET in comparison to placebo in the treatment of acute thrombophlebitis. Reduction of pain and symptoms was observed in both groups over the course of the two-week treatment period, but was significantly better with SET than placebo, with a favourable risk profile and fewer AEs in the SET group.

The results of this study largely confirm earlier investigations on SET in acute thrombophlebitis, where superiority of SET was demonstrated [14,15], also with compression stockings. Of note, this study is the first where compression was not employed in the management of acute uncomplicated thrombophlebitis. Hence, the results of this study indicate that SET is also efficacious without compression. Thus, in order to achieve pain and symptom relief, patients do not require supportive compression when taking SET. This makes SET an attractive OTC treatment option for patients who cannot or do not want to wear compression stockings, difficulties that may occur in hotter climates for example in Italy, where this study was undertaken.

Strikingly, amelioration of pain and symptoms like feeling of heaviness was already evident in the SET group on day 4, the first time point of investigation. In the placebo group, most symptom scores were even slightly increased compared to baseline on day 4, while improvement of the condition did not start before day 7 and only for some of the factors under study. Thus, in general, recovery from acute thrombophlebitis was much quicker and more pronounced with SET than placebo. It can be expected that this is perceived as a benefit in terms of quality of life by the patients.

Gradual pain and symptom relief, albeit less pronounced, was also observed in the placebo group. One likely reason for this is the use of concomitant analgesic medication, in most cases diclofenac, which was employed by most patients in the placebo group (80%) but only very few in the SET group (8%). This suggests that SET can reduce reliance on other analgesic drugs to alleviate the pain that is associated with acute thrombophlebitis. In consequence, the patients employing SET also avoid the toxicity that is linked to other analgesics like NSAID. In accordance with this, more AEs were observed in the placebo group than the SET group. More than two thirds of the AEs in the placebo group were attributed to the use of analgesics/diclofenac, in the majority gastrointestinal AEs, a well-known risk of NSAID administration [16]. In the SET group, the only AEs that were observed were mild to moderate diarrhoea and loose stool, in line with expectations [17]. This confirms the beneficial safety profile of SET.

There are limitations in this study. One limitation is that imaging of thrombus expansion e.g. by ultrasound was not performed. This study focused on the assessment of symptoms and pain, features that are of direct relevance for patients in the self-medication setting, where imaging techniques would typically not be available. Patients with deep vein thrombosis or arterial occlusive diseases were excluded from participation beforehand and inclusion criteria defined patients with acute superficial thrombophlebitis in the lower extremities, therefore concentrating on uncomplicated cases.

Another limitation of this study is that no extended follow-up was performed beyond the 14 days of the study, and it was not systematically assessed in this study whether SET reduces the risk of severe long-term complications. However, pain and symptoms were essentially relieved within 14 days of SET and also reduced in the placebo group. A large-scale non-interventional study may provide insights into long-term effects of SET. Another limitation is that this study does not comprise a head-to-head comparison with another treatment option for acute thrombophlebitis. Such analyses should be performed in larger-scale follow-up studies.

In conclusion, this randomized, double-blind, placebo-controlled study shows efficacy and tolerance of SET in the treatment of acute thrombophlebitis. SET has also been shown to be similarly effective in the treatment of pain and inflammation associated with injury [18], urinary tract infection [19] or osteoarthritis [20-22]. Thus, SET is a good and safe treatment option to

alleviate pain and symptoms in a wide range of conditions including acute thrombophlebitis.

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CONFLICT OF INTERESTS

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