Wien Med Wochenschr (2004) 154/21–22: 498–507

WMW
Wiener Medizinische Wochenschrift
Printed in Austria

Efficacy and safety of topically applied *Symphytum* herb extract cream in the treatment of ankle distortion: Results of a randomized controlled clinical double blind study

Miroslav Kučera[1], **Miloš Barna**[1], **Ondřej Horáček**[1], **Jaroslava Kováriková**[2], and **Alexander Kučera**[3]

[1]Department for Sports Medicine and Rehabilitation, and [3] Department for Children's Surgery, 2nd Medical Faculty of the Charles University Prague, Prague, and
[2]Department for Sports Medicine, Medical Faculty of the Palacky University Hospital, Olomouc, Czech Republic

Wirksamkeit und Sicherheit von topisch angewandter Symphytumkraut-Creme in der Behandlung von Sprunggelenksdistorsionen: Ergebnisse einer randomisierten, kontrollierten klinischen Doppelblindstudie

Zusammenfassung. Im Rahmen einer kontrollierten, randomisierten, multizentrischen Doppelblindstudie an 203 Patienten mit akuter Sprunggelenksdistorsion wurde die Wirksamkeit und Verträglichkeit des topischen Beinwellproduktes Traumaplant® (10 % Wirkstoff eines wässrig-ethanolischen Presssaftes (2,5:1) aus frisch geerntetem Beinwellkraut aus Anbau (*Symphytum* × *uplandicum* NYMAN), entsprechend 25 g frischem Kraut in 100 g Creme; n = 104) gegen ein 1 %iges Referenzprodukt getestet (entsprechend zu 2,5 g frischem Beinwellkraut in 100 g Creme; n = 99). Mit der hohen Wirkstoff-Konzentration im Verum war die Abnahme der Symptomscores für Bewegungs- und Ruheschmerz sowie funktionelle Einschränkung sowohl an den Tagen T3/4 als auch T7 hoch signifikant und klinisch relevant ($p < 0{,}001$). Im Vergleich zum 1 %igen Referenzprodukt war der Rückgang von Schwellungen an T3/4 gleichfalls signifikant ($p < 0{,}01$). Die Wirksamkeit an T3/4 wurde für Verum in 85,6 % der Fälle als gut bis sehr gut bewertet, und für das Referenzprodukt in 65,7 % der Fälle. Die Verträglichkeit erwies sich als hervorragend.

Schlüsselwörter: Beinwell, Symphytum Herba-Extrakt, topische Anwendung, Doppelblindstudie, Sprunggelenksdistorsion.

Summary. In a controlled, double blind, randomized multicentre study, the efficacy and safety of the topical comfrey product Traumaplant® (10 % active ingredient of a 2.5:1 aqueous ethanolic pressed juice of freshly harvested, cultivated comfrey herb (*Symphytum* × *uplandicum* NYMAN), corresponding to 25 g of fresh herb per 100 g of cream; n = 104) was tested against a 1 % product (corresponding to 2.5 g of fresh comfrey herb in 100 g of cream; n = 99) in 203 patients with acute ankle distortion. With the high concentration, decrease of the scores for pain on active motion, pain at rest and functional impairment was highly significant and clinically relevant on days T3–4 as well as T7 ($p < 0.001$). Amelioration of swellings as compared to reference was also significant on day 3–4 ($p < 0.01$). Efficacy was judged good to excellent in 85.6 % of cases with verum and in 65.7 % of cases with reference on day 3–4. Overall tolerability was excellent.

Key words: Comfrey, Symphytum herb extract, topical application, double blind study, ankle joint distortion.

Introduction

Symphytum sp., a herb from the family of *Boraginaceae*, has long since been used in traditional medicine in the treatment of blunt traumata like distortions, contusions, or pulled muscles and tendons. Extracts from comfrey are known to possess anti-inflammatory, analgesic, anti-oedematous and wound-healing properties. The validity of the traditional use, essentially an external application in the form of ointments, is reflected in a number of clinical trials [5, 12, 15–21, 26, 29, 32], as well as in an approval by the official German commission E monograph [9], listing bruises and sprains for the external use of topical preparations with equivalents of 5–20 % of *Symphytum* herb.

As constituents contributing to efficacy, *Symphytum* contains allantoin, choline, triterpenoid saponins, derivatives of rosmarinic acid, tannins and essential oil [1–3, 6, 11, 23, 24, 27]. Especially allantoin, choline and rosmarinic acid are held responsible for the anti-inflammatory and wound-healing effects of comfrey [4, 16, 26]. Allantoin stimulates cell proliferation and improves regeneration of injured tissues, whereas choline reduces capillary permeability and thus acts anti-oedemateously. In addi-

Correspondence: Prof. MUDr. Miroslav Kučera, DrSc., Department for Sports Medicine and Rehabilitation, 2nd Medical Faculty of the Charles University Prague, V Úvalu 85, 15006 Praha 5, Czech Republic.
E-mail: miroslav.kucera@lfmotol.cuni.cz

tion, choline increases perfusion in inflamed tissues by vasodilatation, and supports the clearance of mediators of inflammation. Rosmarinic acid has antiphlogistic effects through the inhibition of the formation of proinflammatory mediators [11].

Comfrey preparations, mainly those prepared from the roots, may contain liver toxic pyrrolizidine alkaloids. Their daily intake is restricted to an equivalent of 100 µg of pyrrolizidine alkaloids with 1,2-unsaturated necine structure, including their N-oxides. In practice, this restriction is, however, irrelevant when cultivars of *Symphytum sp.* poor in pyrrolizidine alkaloids are used, and when the extract is prepared from the aerial parts of the plant instead of the roots. A suitable cultivar is *Symphytum* × *uplandicum* NYMAN (syn. *Symphytum peregrinum* AUCT. non LEDEBOUR), which in fact is a hybrid of *Symphytum officinale* [22]. The herbal raw material used for the preparation of the test product in this study and most of the previously cited studies [12, 17, 19–21, 26] was exclusively obtained from controlled cultivations of the mentioned *Symphytum* hybrid. The fact that the pressed aqueous-ethanolic juices of aerial plant parts are devoid of pyrrolizidine alkaloids allows high dosage schemes of the medication.

Hess (1991) found a distinct amelioration for pain, swellings and joint mobility in 40 patients with sports traumata of the knee [12]. Similar results were found by Koll et al. (2000) in a randomized double blind study in patients with unilateral ankle distortions [16], using a root extract in a topical preparation. The effect of a cream with an extract from the aerial parts of comfrey was shown to be superior to cryotherapy [19]. Pain reduction sets in fast, as early as 30 minutes after application of the preparations, with a maximum effect after 2 hours [21].

Another typical dermal application of comfrey products is wound-healing. Niedner (1989) demonstrated that comfrey cream (aerial parts) accelerates the reepithelization in abrasions, adding to the benefits of topically applied comfrey products in the treatment of sports traumata [26].

In a previous study, we had tested the effects of a cream with an extract from the aerial parts of comfrey in 105 patients with painful disorders of the locomotor system [17]. An application of the cream twice a day resulted in very good analgesic effects and a complete remission of muscle pain. The application was especially effective in the treatment of subacute and chronic complaints accompanied by functional symptoms like swellings (excellent results in 90–94 % of patients). Even in a subset of patients with degenerative arthrosis, the percutaneous treatment with comfrey herb cream resulted in a reduction of pain, confirming the distinct analgesic, antioedematous and anti-inflammatory effects of topically applied comfrey preparations.

Herein, we present the results of a prospective, randomized, double-blind clinical multicentre trial with this same topical comfrey preparation, aimed on the determination of efficacy and safety in patients with acute ankle distortions.

Material and methods

Study design

The clinical trial was designed as a prospective, randomized, reference controlled, double-blind clinical multicentre parallel group study in patients with acute lateral ankle distortions, testing the study preparation with 10 % extract against a low dose 1 % reference.

Study centres

The clinical trial was planned with the Department for Sports Medicine and Rehabilitation of the 2nd Medical Faculty of the Charles University Prague, Czech Republic, and in the department for Sports Medicine, Medical Faculty of the Palacky University, Olomouc, Czech Republic.

Approval of the Ethics Committee

According to the principles of the Declaration of Helsinki/Somerset West, and the ICH-GCP recommendations (CMPH/ICH/135(95)), a positive vote of the Ethics Committees responsible for the trial centres at the University Hospital of Prague and the University Hospital of Olomouc was obtained. The relevant governmental authorities were notified of the study. Written consent was obtained from the patients after thorough information. The study started on July 7, 2001 (inclusion of the first patient), and ended on October 29, 2002 (final visit of the last patient). Blinding of the study was maintained throughout the total study duration.

Study medication

Two different concentrations of active ingredients in the cream were used for the trial: 10 % active ingredient of 2,5:1 aqueous-ethanolic pressed juice of freshly harvested, cultivated comfrey herb (Symphytum × uplandicum NYMAN) corresponding to 25 g of fresh herb per 100 g of the cream, corresponding to the commercially available product Traumaplant® (Harras Pharma Curarina, Germany), and a product with 1 % of the same extract in the cream. Except for the concentration of the Symphytum juice (no detectable pyrrolizidine alcaloids), both medications were identical in composition and appearance. The creams were applied three times daily. Each time, 2–3 g of cream (corresponding to a string of 6–9 cm) had to be thoroughly massaged into the affected skin area.

Patients

The inclusion of patients had to happen within 24 hours after the trauma. The degree of pain at inclusion had to be sufficiently high to require therapy. The patients meeting the inclusion criteria had to be able to understand written and oral information on the study, the medication, the visit schedule, and the protocol requirements, and to give written consent. Concomitant therapy with anti-inflammatory or analgesic drugs, corticosteroids or antidepressants, and physiotherapy were excluded for the duration of the study. Cases of injuries requiring a different treatment, or where topical treatment was deemed inadequate, were excluded from the trial (e.g. fractures or patients with rheumatic disorders). Patients who had cryotherapy within two hours prior to the initial examination, professional sportsmen and patients with a history of bone fracture and/or tears of ligaments in the injured joint were excluded from the study. Intake of non-steroidal anti-inflammatory drugs, analgesics or glucocorticoids in the week prior to the accident was an exclusion criterion, as were patients with a known history of sensitization against comfrey extract or one

of the excipients in the cream. Patients with pre-existing inflammation, eczema or other skin disorders in the region of the ankle were not admitted. Other exclusion criteria were pregnancy, legal incapacity or the participation in a clinical trial within the last three months.

203 outpatients between the age of 18–50 years with accidental and sport injuries (acute unilateral trauma of the ankle joint: supination trauma, lateral ankle joint distortion) were included into the study (125 male, 78 female): 104 patients were randomly allocated to verum, 99 patients to reference. Data from 201 patients could be evaluated at the end of the study. There was no deviation from inclusion and exclusion criteria. Pre-existing medical conditions were assessed.

Study duration and sequence

The study was set up for a duration of 14 ± 2 days (T0-T14), with four visits on day T0 (baseline), T3/4, T7 and T14 (final visit). At all visits, the patients were examined, and the symptom scores determined as described below.

On T0, the patients selected for inclusion were properly informed and gave written consent. The patient was given a randomized number and the corresponding medication. The tube with the medication had to be shown at every visit for a check of compliance.

Primary and secondary study parameters

Primary study parameter was the reduction of pain on active motion, secondary parameters were pain at rest, improvement of functional impairment of the distorted joint, reduction of oedema, time lag until onset of efficacy, and the global assessment of efficacy and safety. All findings were documented in the clinical documentation and in the case report forms.

- *Pain on active motion, pain at rest and functional impairment* were evaluated with the aid of a non-graded 100 mm horizontal visual analogue scale (VAS-10), going from 0 (indicated as "no pain") to 10 ("intolerable pain") [13, 14]. The markings on the VAS were translated into the patients' native language. Both pain parameters were assessed on all visits, with pain at rest after 10 minutes of sitting motionless, and pain on active motion after quickly walking for a minimum distance of 10 meters. The VAS was placed in front of the patient, making sure it was not turned upside down.
- The *swelling* of the joint was measured with the "figure of eight method" [30]. The patient had to be seated in a long sitting position with both feet extended beyond the end of the plinth to the level of the midcalf. The leg with the injured ankle had to be slightly flexed over a bolster with a diameter of 15 cm. The ankle had to be maintained in a neutral dorsiflexion position. The measurement was made with tape laid out in the form of the figure "8", starting from the middle between the tendon of the musculus tibialis anterior and the malleolus lateralis, continuing medially across the instep and placed just distal to the tuberosity of the navicular. The tape was then pulled across the arch and up just proximal to the base of the 5th metatarsal bone, then pulled across the tibialis anterior tendon, continued around the ankle joint just distal to the distal tip of the medial malleolus, pulled across the Achilles tendon, placed just distal to the distal tip of the lateral malleolus, and pulled back to the starting point of the tape. The length of the tape was then documented in mm.
- *Active and passive mobility of the joint* (dorsal/plantar flexion respectively abduction/adduction) was measured goniometrically.
- *Global efficacy* was rated by the physician up to the last visit T14, using a 5-point verbal rating scale (1 = excellent effect, 2= good, 3 = moderate, 4 = minor, 5 = no effect).
- *Speed of onset* of the effects was likewise rated by the physician up to the last visit T14 on a 5-point verbal rating scale (1 = very quick onset, 2 = quick, 3 = moderately quick, 4 = slow onset, 5 = no relevant effect).
- For the assessment of *local tolerability*, the symptoms reddening, itching, urticaria, folliculitis, ulcerations and other unwanted effects (to be described) were evaluated. The assessment of the physician included the weighing of the findings in four categories: 0 = no reaction, 1 = slight, 2 = moderate, and 3 = severe reaction. Moderate and severe reactions were classified as adverse events. As the study medication is applied topically, no laboratory parameters were measured.
- *Global tolerability* was assessed by the physicians on a scale of 0 to 3 (0 = bad, 1 = good, 2 = very good, 3 = exceptional).

Biometrical evaluation

The aim of this study was to provide confirmatory and descriptive evidence of the clinical efficacy of Traumaplant® as compared to reference. In order to prove efficacy, a statistically significant difference between both treatments in favour of verum had to be shown for the primary study parameter (pain on active motion).

The main difference between Traumaplant® and reference was expected to be observed on visit T3/4, and to decrease until T7 and T14 [19]. The confirmatory analysis therefore concentrated on visit T3/4. Two primary endpoints were tested subsequently for the primary efficacy parameter "pain on active motion":

- pain reduction at T3/4
- responder rate at T3/4

The hypothesis of a superiority of verum over reference was tested by the t-test. In the case that a normal distribution was not fulfilled, an additional Mann-Whitney-U-test was performed.

Responders were defined as patients experiencing an improvement of at least 16 mm on the VAS on visit T3/4 versus baseline, in accordance to literature findings [7, 8, 28]. For the calculations of responder rates and the corresponding statistical significance tests, a two-tailed Fisher exact test was performed on the data of T3/4. Comparable analyses were made for the other visits at T7 and T14. These analyses did not contribute to the confirmatory analysis.

From the responder rates, a NNT (number needed to treat) was calculated (the number of patients to be treated in order to obtain one case of successful treatment that would not have been reached without treatment).

Secondary endpoints were analyzed descriptively as difference to baseline, respectively as inter-group differences for the global efficacy, local tolerability and speed of onset of effects. Parametric and non-parametric statistical tests were performed as appropriate, resulting p-values do not possess confirmatory value.

Finally, the data of T3/4, T7 and T14 was analyzed for the factors

- time between injury and start of treatment (in hours)

- the origin of the injury (sports, fitness workout, recreation, work, traffic, home or other)
- gender
- age (in years).

The statistical software used was SPSS v.10.0.

Protocol deviations

Based on the experience with earlier studies, a sample size of 170 patients was calculated and laid down in the protocol. During inclusion of patients it turned out that ankle distortion was much more frequent than estimated, which was expressed in a rapid recruitment of patients. Due to the administrative delay in announcing the end of recruitment to the study centres, a higher number of patients than planned was included into the study (203 in total).

Results

Demographic data

The Intention-to-treat (ITT) population was 203 patients with acute ankle joint distortion. In both study groups one dropout unrelated to the study medication was registered. The per protocol population (PPP) was thus 201 patients with 103 patients using verum, and 98 patients using reference (Table 1).

The origin of the trauma was distributed as follows (PPP, n = 201):

- home accident: 28.6 %
- sports accident: 55.2 %
- working place: 16.2 %

Primary efficacy parameter: Pain on active motion

Under application of verum, pain on active motion was decreased from initially 63.2 ± 16.4 mm on the VAS-10 on day T0 to 32.2 mm on T3/4, corresponding to an average decrease of 31.0 mm (Table 2). Application of the reference preparation only yielded a decrease of pain on active motion of 19.3 mm (baseline value at T0: 65.3 ± 15.8 mm) on the VAS-10 in the same time frame (Fig. 1). The difference between groups was highly significant ($p = 2.2 \times 10^{-7}$). The decrease of pain on active motion was also significantly higher for verum on the day of the third visit (T7) ($p = 7.6 \times 10^{-5}$), and the difference between groups was still significant on the last visit (T14) ($p = 0.03$). There was no indication for an influence of age or gender of the patients on the outcome of this evaluation.

Responder rate and number needed to treat (NNT)

The responder rate, i.e. the percentage of patients showing an improvement of ≤ 16 mm for pain on motion on the VAS-10, is shown in Table 3. The difference between the two treatment groups was statistically highly significant ($p = 1.5 \times 10^{-5}$). An NNT of 3.7 was calculated from the responder rates.

Table 1. Demographic data

	Total n = 203	Verum n = 104	Reference n = 99
Age [years; mean ± SD]		27.7 ± 8.5	28.3 ± 8.4
male	125 (61.6 %)	66	59
female	78 (38.4 %)	38	40

Table 2. Reduction of pain on active motion in mm on the VAS-10, expressed as difference to baseline (T0). Negative values stand for deterioration of pain vs. baseline. p-values relate to the difference between groups

	Visit	Average	Median	Minimum	Maximum
Cream 10 %					
($p = 2.2 \times 10^{-7}$)	T3/4	31.0 ± 17.0	27	1	78
($p = 7.6 \times 10^{-5}$)	T7	50.6 ± 18.0	49	18	91
($p = 0.03$)	T14	60.2 ± 16.9	60	24	95
Cream 1 %					
	T3/4	19.3 ± 14.0	18	-12	58
	T7	40.2 ± 18.5	38	-12	86
	T14	54.7 ± 18.6	54	19	93

Table 3. Number of responders respectively non-responders per treatment group on T3/4

	Responder	Non-Responder
Reference (1 % cream)	59 (59.6 %)	40 (40.4 %)
Verum (10 % cream)	90 (86.5 %)	14 (13.5 %)

Table 4. Reduction of pain at rest in mm on the VAS-10, expressed as difference to baseline. Negative values stand for deterioration of pain vs. baseline. p-values relate to the difference between groups

	Visit	Average	Median	Minimum	Maximum
Cream 10 %					
($p = 6 \times 10^{-10}$)	T3/4	28.7 ± 17.1	27	1	86
($p = 5.7 \times 10^{-4}$)	T7	40.1 ± 21.0	42	2	94
NS	T14	43.9 ± 22.3	46	2	95
Cream 1 %					
	T3/4	14.7 ± 13.5	14	-15	59
	T7	30.4 ± 18.5	29	-4	71
	T14	41.6 ± 21.1	43	0	86

Pain at rest

Treatment with verum led to a significantly higher reduction of pain at rest by 28.7 mm on the VAS-10 between T0 and T3/4 (baseline value 44.6 ± 22.6 mm; $p = 6 \times 10^{-10}$) as compared to the reference product, which reached 14.7 mm (baseline value 45.8 ± 21.1 mm). On T7, pain reduction with verum was still highly significantly higher ($p = 5.7 \times 10^{-4}$), whereas on T14 no more significant difference between groups was found (Table 4, Fig. 2).

Functional impairment

On visits T3/4 and T7, a reduction of functional impairment of the joint was found for both, verum and reference (Table 5; baseline values 52.7 ± 18.6 respectively 55.9 ± 18.4 mm). The difference between groups was highly significant in favour of the highly dosed study

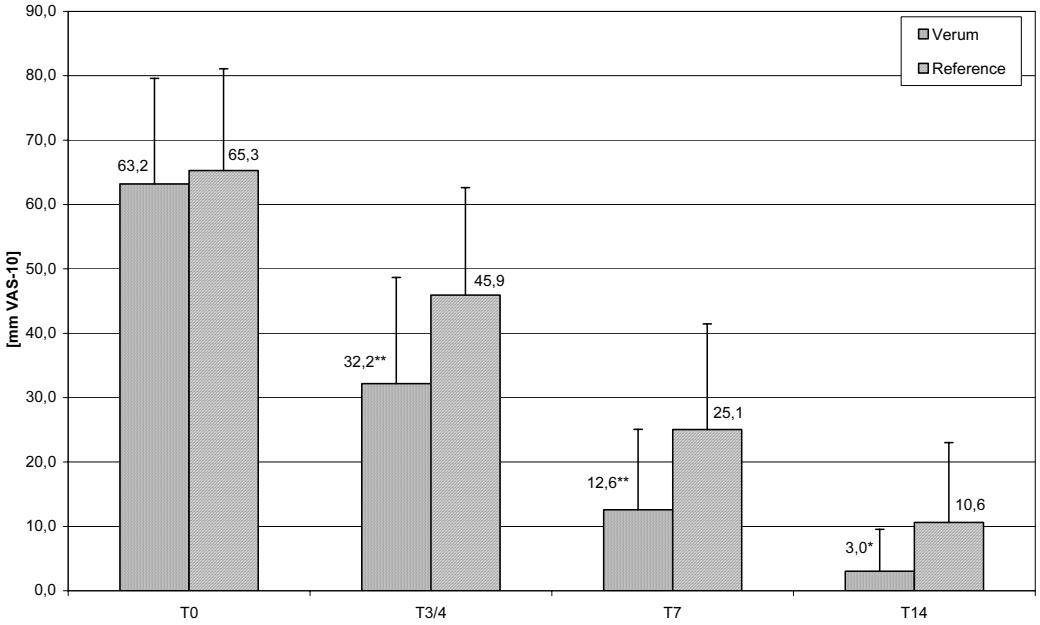

Fig. 1. Course of pain on active motion in mm on the VAS-10, expressed in absolute values

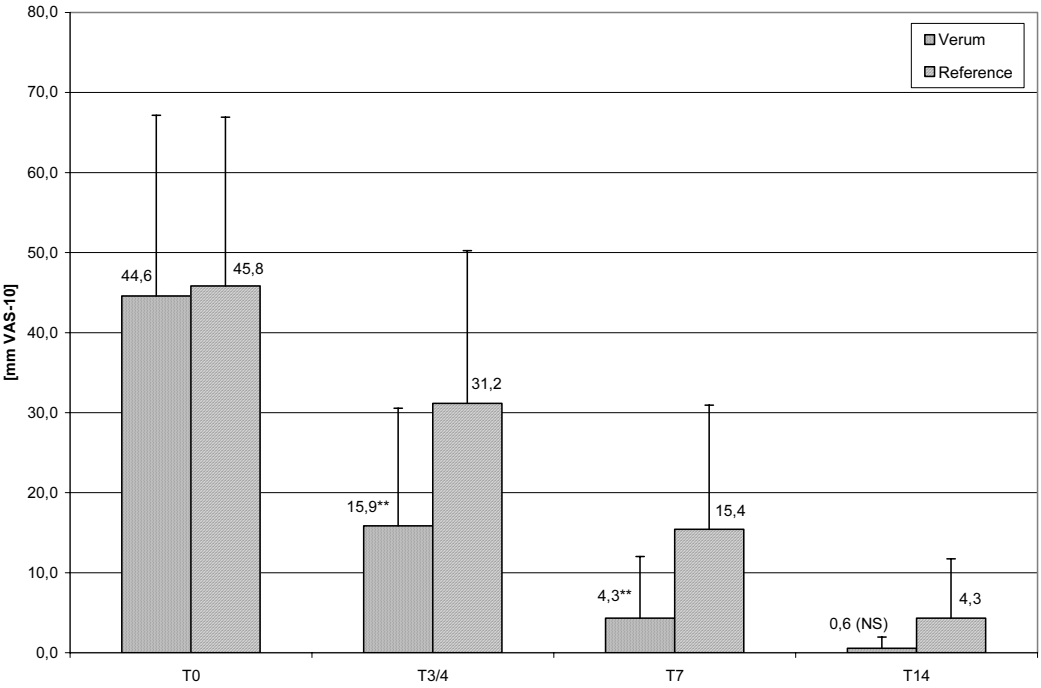

Fig. 2. Course of pain at rest in mm on the VAS-10, expressed in absolute values

medication on both days, whereas on T14 no more intergroup difference was observed (Fig. 3).

Functional impairment was also assessed goniometrically (Table 6). For active and passive range of motion as measured for pronation/supination, there was no difference between groups (data not shown). For dorsal/plantar flexion, the superiority of the high dose treatment was statistically significant on all visit days for active motion and on T3/4 for passive motion (Mann-Whitney test) (Baseline for verum respectively reference: 40.5 ± 8.6 resp. 39.7 ± 7.9 degrees for active range of motion, and 50.4 ± 10.3 resp. 48.9 ± 8.3 degrees for passive range of motion).

Swellings

On visit T3/4, the decrease of swellings was most distinct in the verum group. As compared with reference (9.8 mm; baseline at T0 566.9 ± 34.8 mm), the decrease

Table 5. Reduction of functional impairment in mm on the VAS-10, expressed as difference to baseline. Negative values stand for deterioration vs. baseline. p-values relate to the difference between groups

	Visit	Average	Median	Minimum	Maximum
Cream 10 %					
($p = 4\times10^{-6}$)	T3/4	28.7 ± 18.0	27	-11	87
($p = 2.7\times10^{-3}$)	T7	44.6 ± 18.6	45	1	96
NS	T14	50.8 ± 18.9	52	10	98
Cream 1 %					
	T3/4	18.1 ± 13.6	15	-8	59
	T7	36.5 ± 19.3	35	2	91
	T14	48.1 ± 19.8	48	10	98

Table 6. Reduction of functional impairment (in degrees on the goniometer), expressed as difference to baseline. Negative values stand for deterioration vs. baseline. p-values relate to the difference between groups

	Visit	Average	Median	Minimum	Maximum
	Active range of motion: Dorsal/plantar flexion				
Cream 10 %					
($p = 1\times10^{-3}$)	T3/4	10.9 ± 8.4	10	0	40
($p = 5\times10^{-3}$)	T7	20.7 ± 9.9	20	0	40
($p = 2\times10^{-2}$)	T14	25.7 ± 9.9	25	5	63
Cream 1 %					
	T3/4	7.1 ± 6.3	10	0	20
	T7	16.7 ± 9.7	20	0	40
	T14	22.2 ± 10.4	20	0	50
	Passive range of motion: Dorsal/plantar flexion				
Cream 10 %					
($p = 2\times10^{-3}$)	T3/4	10.2 ± 7.8	10	0	30
NS	T7	15.8 ± 9.6	10	-10	40
NS	T14	17.9 ± 10.0	20	0	61
Cream 1 %					
	T3/4	6.7 ± 7.1	10	-10	20
	T7	14.6 ± 8.5	15	-5	40
	T14	17.7 ± 8.8	20	0	50

Table 7. Reduction of swellings in mm ("figure-of-eight-method"), expressed as difference to baseline. Negative values stand for deterioration vs. baseline. p-values relate to the difference between groups

	Visit	Average	Median	Minimum	Maximum
Cream 10 %					
($p = 1\times10^{-2}$)	T3/4	13.6 ± 10.0	10	0	60
NS	T7	22.6 ± 12.0	20	0	60
NS	T14	24.6 ± 12.6	20	0	60
Cream 1 %					
	T3/4	9.8 ± 10.8	10	-30	50
	T7	22.3 ± 14.4	20	-20	70
	T14	27.9 ± 15.8	25	-10	80

Table 8. Global assessment of efficacy by the physicians

	Verum			Reference		
	T3/4 (n = 104)	T7 (n = 103)	T14 (n = 103)	T3/4 (n = 99)	T7 (n = 99)	T14 (n = 98)
no effect	0	0	0	3	1	0
minor effect	3	3	2	12	12	7
moderate	12	4	5	19	19	19
good	81	86	81	58	58	62
excellent	8	10	15	7	9	10

Table 9. Quickness of onset of the effect (physician's assessment)

	Verum			Reference		
	T3/4 (n = 104)	T7 (n = 103)	T14 (n = 103)	T3/4 (n = 99)	T7 (n = 99)	T14 (n = 98)
no relevant effect	0	0	0	1	1	0
slow onset	5	2	3	15	10	5
moderately quick	19	16	8	27	25	25
quick	78	83	88	55	62	68
very quick onset	2	2	4	1	1	0

was highly significant (p = 0.011) with 13.6 mm (baseline 561.0 ± 30.2 mm). The differences in reduction of swellings were less distinct at T7 and T14, where – as expected – no statistical significance was found (Table 7).

Global assessment of efficacy by the physicians

Global assessment of efficacy of the study medication yielded a clearly positive and statistically significant result for verum as compared with reference (Fig. 4). On T3/4, a good to excellent effect was stated for 89 out of 104 patients using verum (85.6 %) as compared to 65 out of 99 (65.7 %) patients using reference. The difference between treatment groups was statistically significant (Mann Whitney test, $p = 2.5\times10^{-3}$). On T7 and T14, the number of patients using verum with a good to excellent efficacy still increased to 93.2 % (96 patients out of 103), whereas the results for reference increased to 73.5 % (72 patients out of 98) on T14 (Table 8). The inter-group differences were statistically significant ($p = 3\times10^{-4}$ for T7 and p = 0.001 for T14).

Onset of action

The assessment of the speed of onset of the study medication by the physicians correlated with the findings for global efficacy. Again, a positive and statistically significant result in favour of verum was found (Table 9). On T3/4, the speed of onset of the effects was rated as quick to very quick in 80 out of 104 cases (76.9 %), whereas 56 out of 99 patients (56.6 %) under reference stated a comparably quick onset of effects. The difference between groups was statistically significant (Mann-Whit-

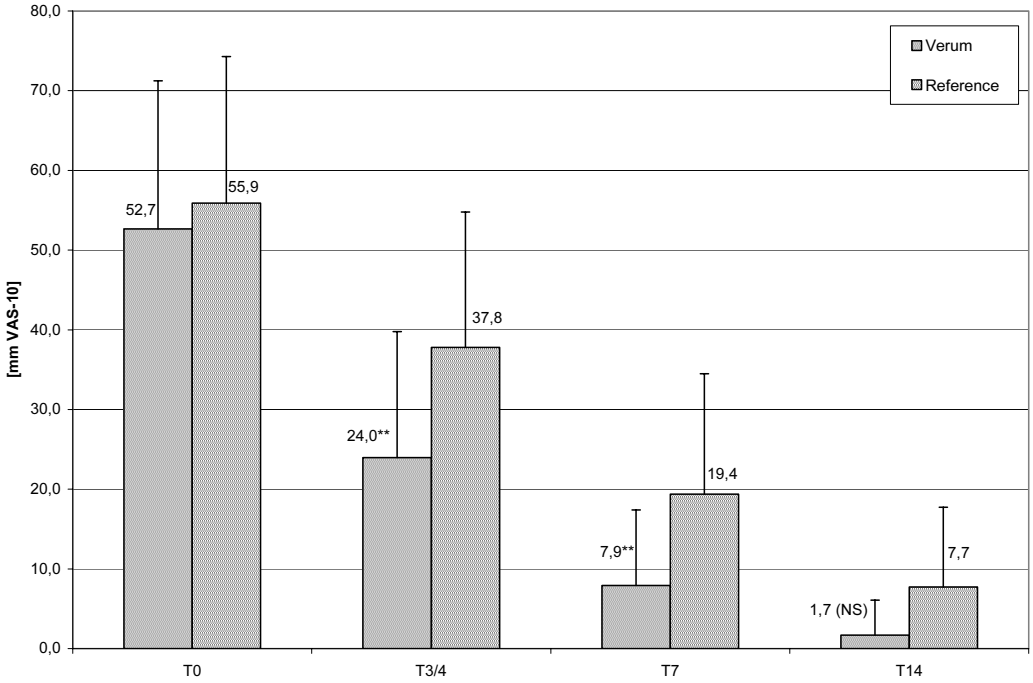

Fig. 3. Course of functional impairment in mm on the VAS-10, expressed in absolute values

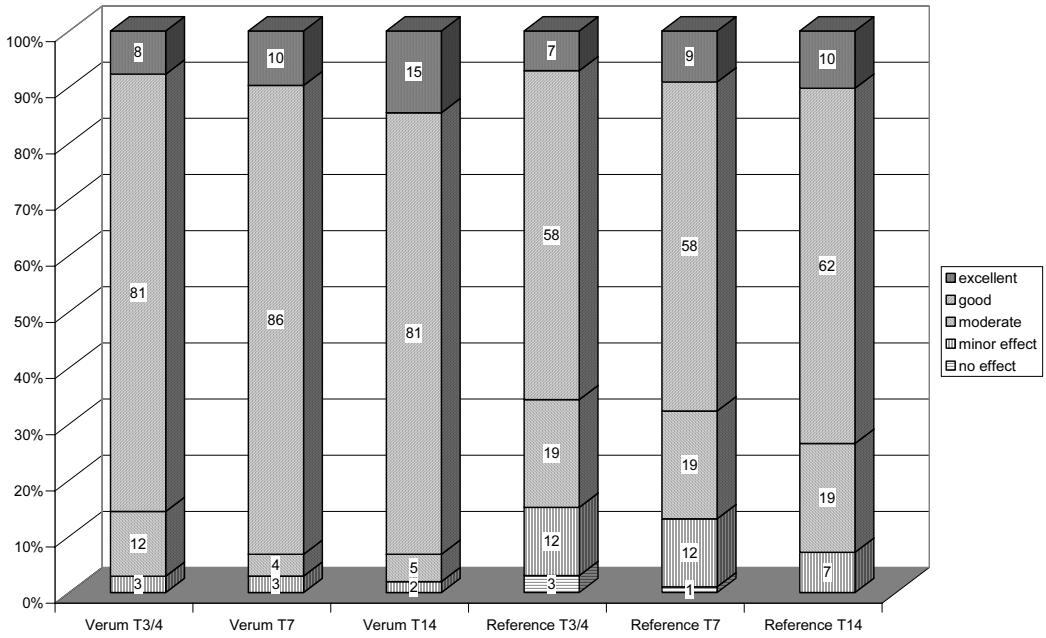

Fig. 4. Global assessment of efficacy by the physicians

ney-test, p = 0.001). On T7 and T14, the number of patients using verum, and for whom the onset of effects was judged "quick-very quick", still increased to 85 (82.5 %) respectively 92 (89.3 %) out of 103, whereas the corresponding number of patients using reference went up to 63 out of 99 (63.6 %) respectively 68 out of 98 (69.4 %) (Fig. 5). The differences between groups were statistically significant on both visits (p = 0.001 on T7 and 0.0002 on T14).

Safety and tolerability

Two cases of local skin irritation (slight reddening) were observed in the study, one in each study group. Both cases were fully reversible within 1–2 days and did not require a withdrawal of the medication. Overall tolerabil-

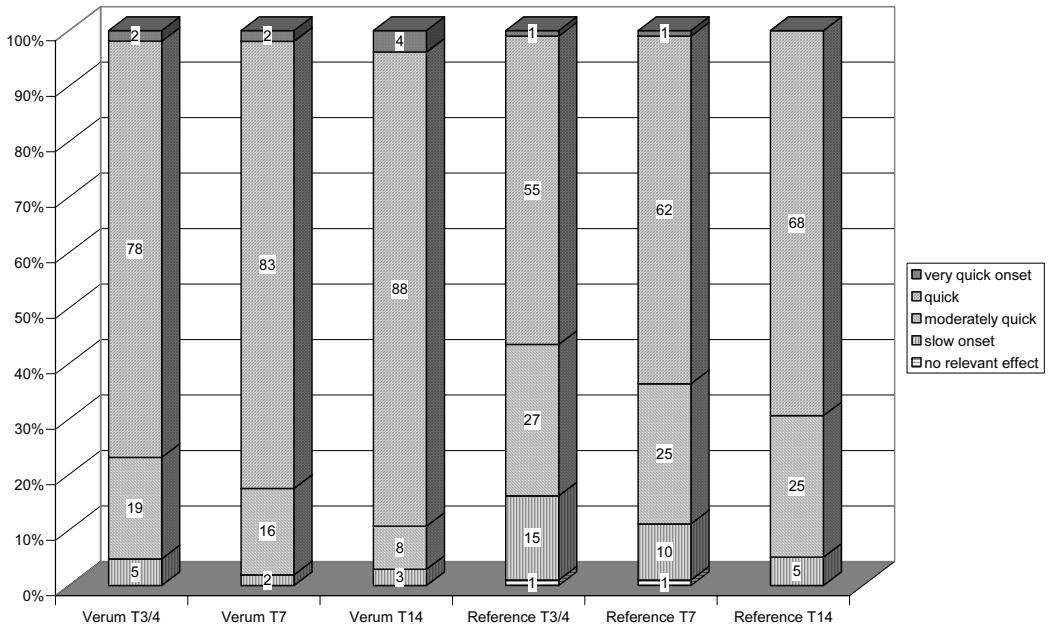

Fig. 5. Quickness of onset of the effect (physician's assessment)

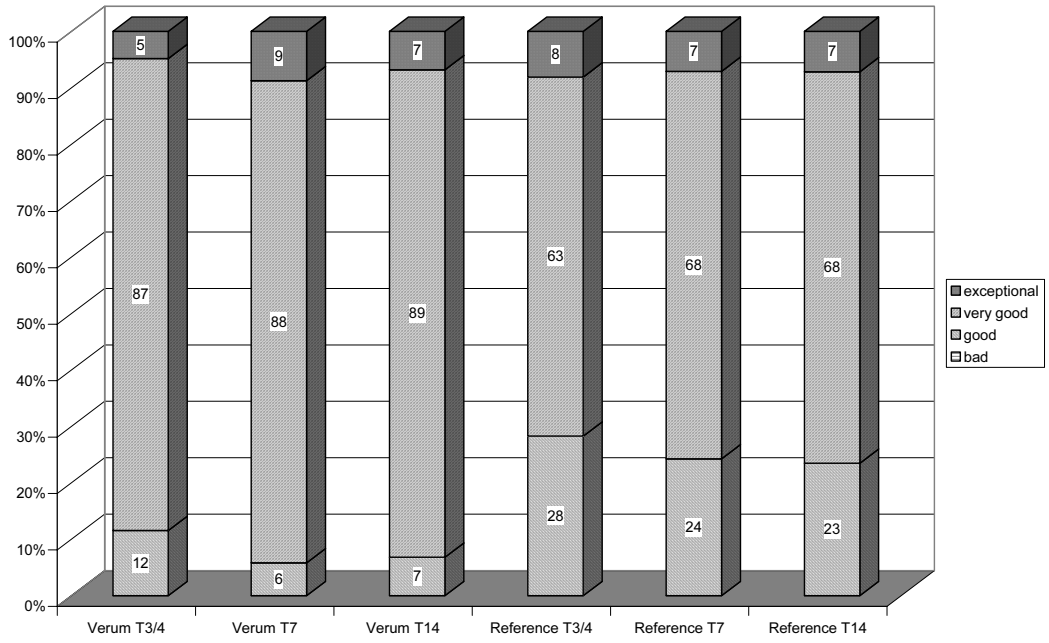

Fig. 6. Safety assessment by the physicians

ity of verum was assessed as very good or exceptional in 96 out of 103 patients on T14 (93.2 %), whereas with reference, a very good to exceptional tolerability was found in 75 out of 98 patients (76.5 %) (Fig. 6). The difference between groups was significant ($p = 0.01$) and correlates to the responder rates and calculated NTT.

Discussion

Ankle joint distortions are frequent in sports accidents. The traumata include distensions of the ligaments and joint capsules, tendons, fasciae and muscles. The main clinical symptoms are painful restrictions of active and passive motion, with local inflammation and oedema. If the severity of the injury does not require surgical treatment or plaster casts, physical methods such as cold packs are usually recommended. The medication mostly encompasses non-steroidal anti-inflammatory drugs, acting on the symptoms inflammation and pain. The systemical intake of such drugs is, however, often accompanied by problems with the tolerability including gastrointestinal disorders, changes in blood clotting, or negative influence on kidney and liver metabolism [10]. An advantage of topical treatments is that they usually do not show systemic adverse effects.

The use of *Symphytum* in topical products for the treatment of blunt traumata is covered by an official

monograph of the German commission E [9]. The positive effects were shown in a number of mostly non-blinded clinical studies. The design of the study presented here was intended to show efficacy within a GCP conform clinical trial.

Even though a trial design as a double blind study against placebo is indicated as the method of choice by the German health authorities [28], the inclusion of a placebo group is often not accepted by the ethics committees. The use of a reference product, e. g. a product with a non-steroidal anti-inflammatory drug, was not possible as this would have prevented the blinding of the trial medication for galenical reasons. In addition, there is no NSAID registered for the topical use in ankle distortion. As a compromise, the study was planned with a low dose reference product as a control group. Due to the self-healing character of ankle distortions, a cross-over design was not possible, and a parallel group design was chosen.

The trial results clearly demonstrate the efficacy of the study medication Traumaplant® containing 10 % of an aqueous-ethanolic pressed juice from freshly harvested comfrey herb (drug-extract ratio 2.5:1, corresponding to 25 g of fresh *Symphytum* herb in 100 g of cream) in the treatment of acute ankle joint distortions, and the superiority of the treatment over a 1 % reference product (corresponding to 2.5 g of fresh *Symphytum* herb in 100 g of cream). Pain on active motion was significantly reduced on T3/4 and T7, the effect still being significant on T14. The finding of significance over reference even on T14 was surprising, as it was expected that the self-healing process would level out the inter-group differences. Clearly, the higher concentration of *Symphytum* active ingredients in the study medication was responsible for a quicker healing as compared to low dose *Symphytum*.

The difference between verum and reference observed for the primary efficacy parameter "pain on active motion" was 12 mm on the VAS-10 on visit T3/4. A difference of this magnitude is clearly noticeable for the patient, and deemed clinically relevant [7, 14, 31]. The relevance is also reflected in the responder rates and the NNT of 3.7 calculated from the trial results for the primary endpoint "pain on active motion" at visit T3/4. According to Moore et al. (1998), values below 4 reflect a clinically relevant result for a topical analgesic product [25].

Statistically significant differences were also found for pain at rest on T3/4 and T7, whereas on T14 the differences were no more significant. For swellings, the group difference was only statistically significant for T3/4. Edema as a consequence of the ankle distortion are not expected to persist over longer periods, thus a group difference between the study medication group and reference was not expected. The decrease of the parameters "functional impairment" and "swellings" underlines the necessity of an early intervention with a highly dosed extract preparation. Obviously, the study medication shows the best effects in the acute phase of the injury, as seen in the visit on T3/4.

Tolerability of the study medication was excellent. Topical products with an aqueous-ethanolic juice of the aerial parts of *Symphytum sp.* have already been shown to be well tolerated. Within this study, no systemic adverse effects and interactions with other drugs were observed. Data evaluation supports a more than "acceptable" safety margin according to the European directive 1999/83/EC on "well-established medicinal use".

The findings of this trial regarding efficacy and tolerability of the study medication are consistent with previously published clinical data [12, 17, 19–21, 26] and the practical experience from daily routine. In particular, they confirm the pronounced anti-inflammatory, anti-exudative and analgesic properties of topical comfrey products. They also underline that a sufficiently high extract concentration is needed for an optimal effect. The present study was designed to prove the efficacy of the study medication. With the testing against a low dose reference it could also be regarded as a dose finding study.

In total, the study results confirm the positive benefit-risk ratio for the study medication Traumaplant® in the treatment of blunt traumata such as ankle distortion.

References

1. Aftab K, Shaheen F, Mohammad FV, Noorwala M, Ahmad VU (1996) Phyto-pharmacology of saponins from Symphytum officinale L. Adv Exp Med Biol 404: 429–442
2. Ahmad VU, Noorwala M, Mohammad FV, Sener B (1993a) A new triterpene glycoside from the roots of Symphytum officinale. J Nat Prod 56: 329–334
3. Ahmad VU, Noorwala M, Mohammad FV, Sener B, Gilani AH, Aftab K (1993b) Symphytoxide A, a triterpenoid saponin from the roots of Symphytum officinale. Phytochemistry 32: 1003–1006
4. Andres P, Brenneisen R, Clerc JT (1989) Relating antiphlogistic efficacy of dermatics containing extracts of Symphytum officinale to chemical properties. Planta Med 55: 7
5. Briel R (1953) Verwendung einer natürlichen Kombination mit Cholin und Allantoin aus Symphytum officinale in der Gynäkologie. Med Klin (München) 48: 676–678
6. Dennis R, Dezelak C, Grime J (1987) Studies on Symphytum species – HPLC determination of allantoin. Acta Pharm Hung 57: 267–274
7. Eberle E, Ottillinger B (1999) Clinically relevant change and clinically relevant difference in knee osteoarthritis. Osteoarthritis Cartilage 7: 502–503
8. Ehrich E, Davies G, Watson D (1999) Minimal perceptible clinical improvement (MPCI) in osteoarthritis: WOMAC and global assessments, influence of age, gender and geographic region. 63rd Annual Scientific Meeting of the American College of Rheumatology, Nov. 14, 1999, p438
9. German Commission E (1990) Monograph: Comfrey herb and leaf (Symphyti herba/folium). Bundesanz July 27, 1990
10. Goodman LS, Gilman A (2001) The pharmacological basis of therapeutics. Pergamon Press, New York
11. Gracza L, Koch H, Löffler E (1985) Biochemisch-pharmakologische Arzneipflanzenuntersuchungen. 1. Isolierung von Rosmarinsäure aus Symphytum officinale L. und deren anti-inflammatorische Wirkung in einem in-vitro Modell. Arch Pharm (Weinheim) 318: 1090–1095
12. Hess H (1991) Wirkung einer Symphytum-Salbe bei Sportverletzungen des Kniegelenks. Dtsch Z Sportmed 42: 156–162

13. Huskisson EC (1974) Measurement of pain. Lancet 2: 1127–1131
14. Kelly AM (1998) Does the clinically significant difference in visual analog scale pain scores vary with gender, age, or cause of pain? Acad Emerg Med 5: 1086–1090
15. Klein F (1952) Antiphlogistische Anwendung von Symphytum officinale. Hippokrates 23: 550–552
16. Koll R, Buhr M, Dieter R, Pabst H, Predel H-G, Petrowicz O, Gianetti B, Wagener S (2000) Wirksamkeit und Verträglichkeit von Beinwellwurzelextrakt (Extr. Rad. Symphyti) bei Sprunggelenksdistorsionen. Ergebnisse einer multizentrischen, randomisierten, Placebo-kontrollierten Doppelblindstudie. Z Phytother 21: 127–134
17. Kucera M, Kalal J, Polesna Z (2000) Effects of Symphytum ointment on muscular symptoms and functional locomotor disturbances. Adv Ther 17: 204–210
18. Majewska M (1955) Therapy of chronic skin ulcerations with Symphytum products. Pol Tyg Lek (Wars) 10: 333–335
19. Mayer G (1991) Die Lokalbehandlung der akuten lateralen Distorsion des oberen Sprunggelenkes mit einer Symphytum-Wirkstoffkomplexsalbe. Acta Ther 17: 89–100
20. Mayer G (1992) Die Lokalbehandlung von Kontusionen und Distorsionen des Kniegelenkes mit einer Symphytum-Wirkstoffkomplex-Salbe. Erfahrungsheilkunde 41: 888–891
21. Mayer G (1993) Die Lokalbehandlung des akuten Supraspinatussehnen-Syndroms mit einer Symphytum-Wirkstoffkomplex-Salbe. Acta Ther 44: 121–124
22. Micheler B (2001) Expert Report regarding Symphytum cultivation. University of Erlangen (Germany)
23. Mohammad FV, Noorwala M, Ahmad VU, Sener B (1995) A bidesmosidic hederagenin hexasaccharide from the roots of Symphytum officinale. Phytochemistry 40: 213–218
24. Mohammad FV, Noorwala M, Ahmad VU, Sener B (1995) Bidesmosidic triterpenoidal saponins from the roots of Symphytum officinale. Planta Med 61: 94
25. Moore RA, Tramer MR, Carroll D, Wiffen PJ, McQuay HJ (1998) Quantitative systematic review of topically applied non-steroidal anti-inflammatory drugs. Br Med J 316: 333–338
26. Niedner R (1989) Beeinflussung der Epithelialisierung durch einen Wirkstoffkomplex aus Symphytum. Acta Ther 15: 289–297
27. Noorwala M, Mohammad FV, Ahmad VU, Sener B (1994) A bidesmosidic triterpene glycoside from the roots of Symphytum officinale. Phytochemistry 36: 439–443
28. Reiter S (2000) Topische nichtsteroidale Antirheumatika: Aspekte zur Planung und Auswertung klinischer Studien und Ergebnis-Bewertung im Zulassungsverfahren. Bundesgesundheitsbl Gesundheitsforsch Gesundheitsschutz 43: 950–959
29. Schmidtke-Schrezenmeier G, Reck R, Gerster G (1992) Behandlung der nichtaktivierten Gonarthrose – Besserung durch ein Phytotherapeutikum. Therapiewoche 42: 1322–1325
30. Tatro Adams D, McGann S, Carbone W (1995) Reliability of the figure-of-eight method of ankle measurement. J Orthop Sports Phys Ther 22: 161–163
31. Wells GA, Tugwell P, Kraag GR, Baker PR, Groh J, Redelmeier DA (1993) Minimum important difference between patients with rheumatoid arthritis: the patient's perspective. J Rheumatol 20: 557–560
32. Ziolkowski Z, Orszulak J, Wojtanowska H (1957) Aqueous extract of Symphytum officinale in the treatment of some skin diseases in infants. Pediatr Pol 32: 1353–1360