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Original article

Tolerability and effectiveness of an antitrauma cream with comfrey herb extract in pediatric use with application on intact and on broken skin

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ABSTRACT

Objective: The safety of comfrey herbal cream application to broken skin is still a matter of regulatory debate. It was therefore examined in children with intact and with broken skin treated for blunt traumas and sports injuries, with the aim of collecting data for pharmacovigilance and clinical safety assessments.
Methods: A total of 712 children (386 children with intact skin and 326 children with abrasions and superficial wounds) were openly treated for up to 2 weeks with 1–5 applications daily of comfrey herb cream after presenting for blunt traumas and sports accidents. The incidence rate of adverse events was calculated, next to a global assessment of treatment effects.
Results: No adverse events occurred in the group of children with intact skin, and one intolerability reaction (burning and reddening) was observed after application to broken skin. The overall incidence rate of intolerability reactions per patient was calculated as 0.14% (95% CI 0.00–0.78%) and that of systemic adverse effects as 0.00% (95% CI 0.00–0.42%). Accordingly, the probability of the occurrence of local reactions and systemic adverse events is well below, which is one in 100 treated patients. The global assessment of effects corresponded to previously published experience.
Conclusion: These studies confirm an excellent benefit-to-risk ratio for the application of comfrey herb cream in the treatment of blunt traumas and sports injuries in children with intact and with broken skin.

1. Introduction

Comfrey, generally described as *Symphytum officinale* senso latu, has a long history of use in the treatment of injuries. The botanical taxonomical description is rather wide and includes a broad variety of hybrids with similar phytochemical constituents but with distinct differences with regard to potentially toxic pyrrolizidine alkaloids. A medicinal comfrey variety was specifically selected and cultivated for exclusive use in the topical preparation examined in this study. The exact botanical description of this comfrey variety is *Symphytum* × *uplandicum* Nyman 'Harras' [1–3] – a specific taxon within the general group of *S. officinale,* which is devoid of detectable pyrrolizidine alkaloids in the aerial parts. It has been used as a consistent and reproducible starting material in the manufacture of the study medication for several decades. The topical preparation containing an extract from the freshly harvested flowering plant parts of *S.* x *uplandicum* has proven its usefulness in the treatment of blunt traumas such as sprains, contusions, and strains [4–9] and also against muscle pain [10–12]. In the past years, an acceleration of wound healing was

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demonstrated as an additional benefit [13,14], based on earlier observations [4,15].

The benefits of the comfrey cream in pediatric use were examined in observational studies including 361 children with blunt traumas [16,17] and in a clinical double-blind trial with 108 children treated for fresh abrasions [14]. The currently available data support an excellent tolerability and efficacy of the comfrey cream formulation used in these trials, including the application in children and adolescents.

For the age group of children between 4 and 12 years, the documented exposure in interventional and noninterventional clinical trials accumulates to approximately 520 patients treated for blunt traumas and abrasions [13,14,16]. The number of children treated to date would statistically translate into the conclusion of any given adverse effect being unlikely to be observed in approximately 1.5 out of 100 children with intact skin and, due to the smaller documented case numbers, in approximately 2 out of 100 cases with broken skin.

The aim of this study was securing an upper limit of the theoretical incidence rate of approximately one case of any given adverse reaction in 100 patients in those with injured and uninjured skin. Statistically, this requires the treatment of approximately 300 patients, which defined the number of children to be included in this study.

2. Material and methods

2.1. Ethical issues

In planning the study, the principles of the Declaration of Helsinki/Somerset West and the International Conference on Harmonization (ICH)—Good Clinical Practice recommendations (Center for Medicine and Public Health [CMPH]/ICH/135[95]) were adhered to. As this study was an open, uncontrolled observational trial, vote from an ethics committee did not have to be obtained. Relevant governmental authorities were notified about the study. In all cases, the parents or legal guardians of the children signed a written informed consent form.

2.2. Study design

The study was designed as an open, noninterventional prospective trial with an observation of the application of the topical medication for 7 days and, if medically justified, a follow-up for a maximum of 14 days. Three ambulatory study centers specialized on orthopedic diseases in Prague and one general physician with specific expertise in skin disorders in Brno (Czech Republic) were involved in recruiting patients and assessing case data.

The design of the study specifically considered the German recommendations on the conduct of observational studies published by the German regulatory authorities on 7 July 2010 [18], already circulated before the official publication and therefore applied for this study. In addition, the European recommendations on postapproval safety studies written down in “Volume 9A of the Rules Governing Medicinal Products in the European Union – Guidelines on Pharmacovigilance for Medicinal Products for Human Use” (Final version of 2008) and the 2008 Guidelines for Good Pharmacoepidemiology Practices issued by the International Society for Pharmacoepidemiology [19] were used for the definition of the study parameters.

The study was performed in two parts between January 2010 and May 2011 by recruiting and treating children with blunt traumas and/or sports injuries. The first substudy involved children suffering from blunt traumas with intact skin, whereas for the second substudy, children suffering from blunt traumas with concomitant superficial wounds or abrasions were recruited.

2.3. Study duration and visits

The duration of the study was up to 14 days. Safety of application and therapeutic effects were assessed after 1 week and, if the patient came back for a second consultation, again after 2 weeks.

2.4. Study preparation and dosing

The testing of the study medication was carried out with a comfrey herb cream preparation authorized as a medicinal product in Germany, the Czech Republic, and other countries for the treatment of blunt traumas such as contusions and sprains (Traumaplant®, Harras Pharma Curarina, München, Germany). The study was conducted in the Czech Republic, where, as in most countries where the study preparation is authorized as a medicinal product, the application on nonintact skin (e.g., on abrasions and superficial wounds) is part of the authorized indication. Per 10 g of cream, the study preparation contains 1 g of a preparation of freshly harvested aerial parts of medicinal comfrey from controlled cultivation (*S.* x *uplandicum* Nyman) consisting of a blend of 0.4 g of pressed plant juice (drug-to-extract ratio of 3–8:1) and 0.6 g of an extract from the press residue with 30% ethanol v/v (drug-to-extract ratio 3–10:1). The combined herbal active substance is characterized by a ratio of fresh plant to extract of 2–3:1, which corresponds to an average quantity of 25 g of fresh comfrey herb in 100 g of cream preparation, with a defined and reproducible composition and quality. Potentially toxic pyrrolizidine alkaloids were not present in either the active substance concentrate or the cream preparation (detection limit <0.01 μg/g). Further constituents (excipients) are macrogol-20-glycerol monostearate, glycerol mono/di (palmitate and stearate), octyldodecanol, isopropyl myristate, propylene glycol, dimeticone 100, rosemary oil, all-rac-α-tocopherol acetate, citric acid, purified water, sorbic acid, and hydroxyethyl salicylate.

The official recommendation for application is “several times daily,” which was not more closely defined by the investigators. The typical frequency of application is 2–4 times daily. The individual dose cannot be predefined, as it depends on the size of the injury. Frequency of administration was recorded from patient/caretaker indications at each visit, as was the area of the lesion. The latter parameter was, however, not statistically examined.

2.5. Assessment parameters

Local tolerability of the cream was assessed by the physician using a four-step verbal rating scale (0 = normal, 1 = slight reaction, 2 = moderately strong reaction, 3 = severe reaction), specifically judging visible occurrences of scratching and inflammation, and asking the patient or their caretaker at each visit for the following symptoms: burning sensation, scaling of skin, reddening, itching, urticaria, and folliculitis. Other symptoms could be freely defined and assessed in the same manner. Eventually observed adverse reactions were to be described as precisely as possible. Patients/caretakers were instructed to report adverse events at any time.

Effectiveness of treatment was assessed at each visit by the physician and the patients or their caretakers for comparison with previous experience and observations in double-blind trials using a five-step verbal rating scale (1 = very good effect, 2 = good effect, 3 = moderate effect, 4 = minor effect, and 5 = no effect). In the case of children with intact skin, the assessment of effects was focused on the healing process of the blunt traumas, i.e., the overall impression of pain reduction, reduction in swelling, and improvement in joint mobility. The assessment in the case of children with

broken skin also included the impression of the healing process of the wound.

2.6. Inclusion and exclusion criteria

Children in the age range of 4–12 years suffering from blunt traumas or sports accidents were included, with a separate assessment of children with intact skin and children with concomitant superficial wounds or abrasions. Eligible patients were enrolled only after the physicians had decided to recommend treatment with the study preparation.

Patients showing skin disorders in the treatment area (e.g., burning, scaling, reddening, itching, urticaria, folliculitis, and superinfection) or having an allergy to comfrey or one of the excipients of the cream (sorbic acid, rosemary oil, isopropyl myristate, propylene glycol, and salicylates) were not included. Concomitant treatment with other preparations in the treatment area was not permitted.

2.7. Case number calculation

The number of patients to be included was calculated to possess a power of 95% to detect adverse events with an incidence rate of ≥1%. This condition requires the treatment of 300 patients per subgroup: if any given adverse event is not detected in this sample, its incidence is below one in 100 treated patients.

2.8. Statistical analysis

Data obtained in this observational study were evaluated descriptively. Statistical tests were not applied. Missing values were not replaced. SPSS was used for the calculation of 95% confidence intervals for the incidence of adverse events.

3. Results

3.1. Study populations

A total of 712 children were recruited: 386 children with intact skin and 326 children with broken skin (ITT-populations for the subgroup analyses). The flowchart of patient group allocation is presented in Fig. 1. There were three protocol deviations in the subgroup of children with intact skin, as three of the recruited children were aged 3 years and therefore younger than the age defined in the protocol (4–12 years). The per-protocol population (PP population) of the subgroup with intact skin therefore consisted of 383 patients. Similarly, there were three children younger than 4 years (3 years) and one child older than 12 years (15 years) in the substudy with children with broken skin. In addition, there was one drop-out because of an intolerability reaction with the first application (see Safety results). The PP population of the substudy with children with broken skin was therefore n = 321.

The results were in both substudies practically identical for the ITT and the PP population. The presentation of results is therefore made with the ITT populations (n = 386 and n = 326).

In the subgroup of children with intact skin, 198 of 386 (51%) came back for this additional visit after 2 weeks, whereas almost all of the patients with broken skin (n = 324, 99%) returned for a second consultation after 2 weeks.

3.2. Demographic data

Twenty-six percent of the children with intact skin and 41% of the children with broken skin were female (n = 99 and 135). The median time between occurrence of the trauma and the first application of the study medication was 12 h for children with intact skin and 6 h for children with broken skin.

The mean age was 8.6 (2.6) and 7.6 (2.6) years, respectively. The age distribution is displayed in Fig. 2.

The major indications for the application of the study

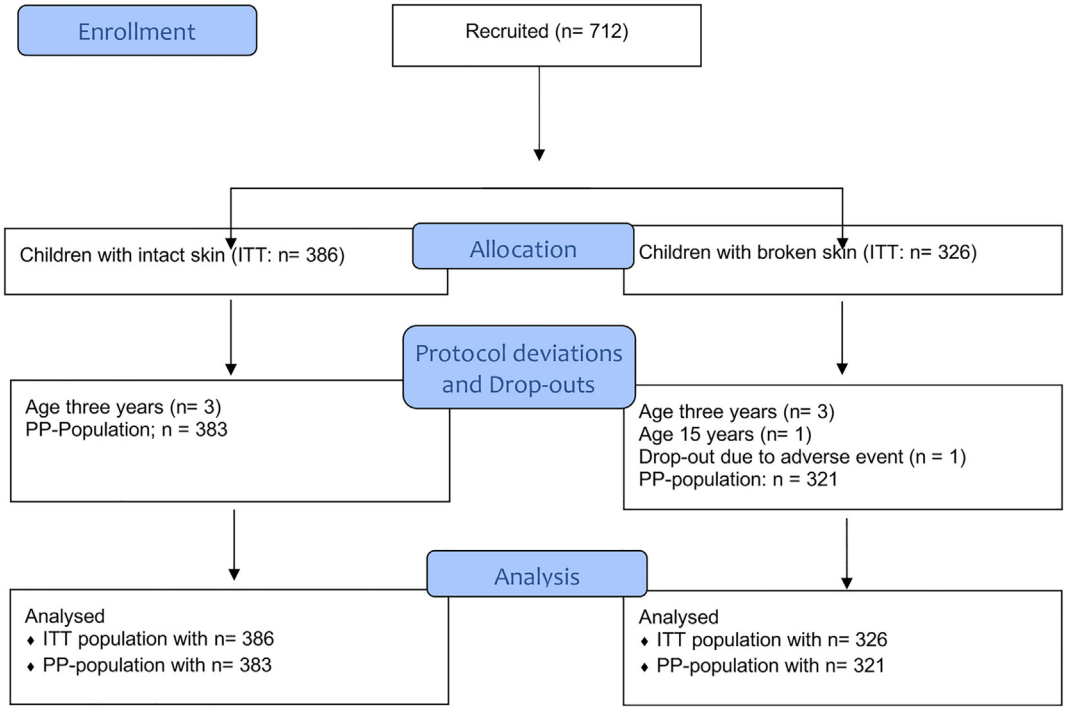

Fig. 1. Flowchart of patient allocation to treatment groups.

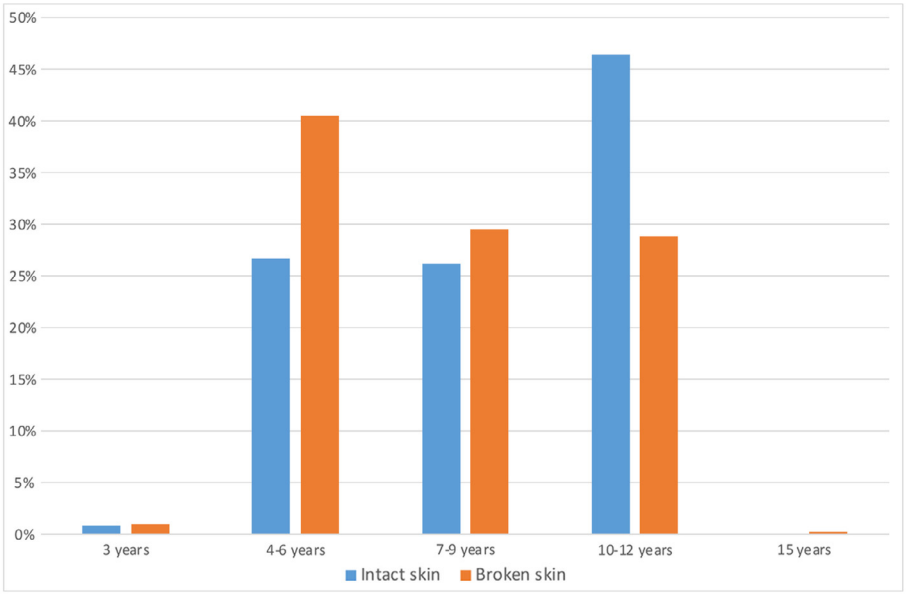

Fig. 2. Distribution of patient age in the two study groups.

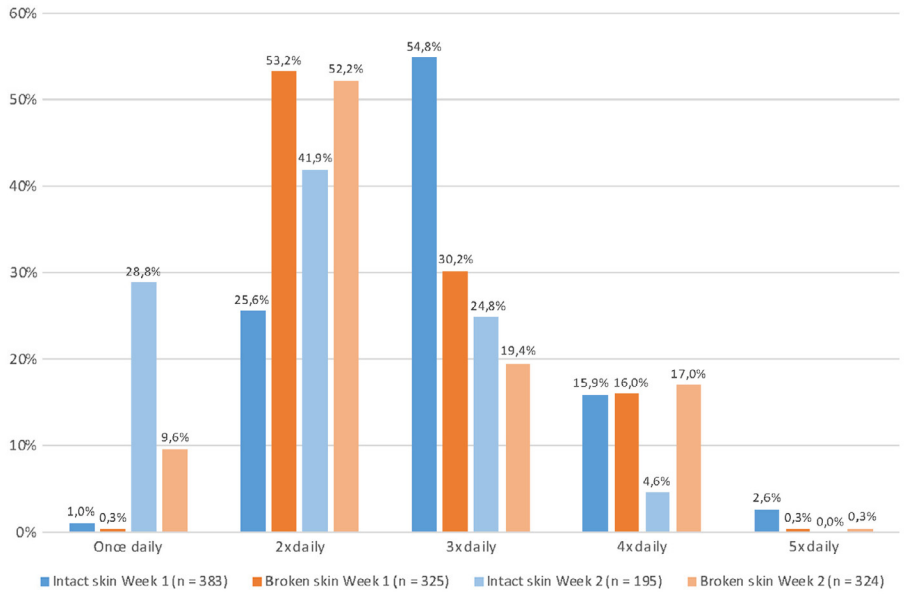

Fig. 3. Frequency of application of the study preparation.

medication in patients with intact skin were in 90.4% of cases contusions, distortions, muscle pain, strains, and joint pain. The major indications for the application of the study medication in patients with broken skin were superficial wounds and abrasions with and without blunt traumas.

3.3. Frequency of application

The majority of patients had applied the cream two to three times daily (Fig. 3). The patients returning for the second visit had mostly reduced the frequency of application. The theoretical maximum number of exposures (number of applications per day times number of patients with this exposure times 7 days) amounted to 10,507 exposures for patients with intact skin and 11,459 exposures for patients with injured skin.

3.4. Safety results

None of the patients with intact skin showed a local reaction or any other adverse event. One of the patients with broken skin developed severe local burning and reddening at the application site within 15 min after the first application of the study medication. The patient terminated study participation. There were otherwise no systemic or other adverse reactions.

The 95% confidence intervals for the incidence of local intolerability reactions and of adverse events in general after application

Table 1
Assessment of effectiveness by physicians and patients/caretakers.

Physicians	Intact skin		Injured skin	
	Week 1 n = 386 (%)	Week 2 n = 198 (%)	Week 1 n = 325 (%)	Week 2 n = 325 (%)
Very good	173 (44.8)	151 (76.6)	146 (44.9)	196 (60.5)
Good	173 (44.8)	35 (17.7)	118 (36.3)	99 (30.6)
Moderate	35 (9.1)	10 (5.1)	36 (11.1)	25 (7.7)
Minor	5 (1.3)	2 (1.0)	25 (7.7)	4 (1.2)
No effect	0 (0)	0 (0)	0 (0)	0 (0)
Patients/caretakers	Intact skin		Injured skin	
	Week 1 n = 386 (%)	Week 2 n = 198 (%)	Week 1 n = 324 (%)	Week 2 n = 324 (%)
Very good	206 (53.4)	198 (75.3)	166 (51.1)	230 (71.0)
Good	155 (40.2)	38 (19.2)	104 (32.0)	86 (26.5)
Moderate	20 (5.2)	5 (2.5)	54 (16.6)	7 (2.2)
Minor	5 (1.3)	6 (3.0)	1 (0.3)	1 (0.3)
No effect	0 (0)	0 (0)	0 (0)	0 (0)

of the study medication to intact skin were calculated as 0.0–0.77%, thus indicating that the true incidence of adverse reactions is below 0.8% with 95% certainty.

Similarly, the 95% confidence interval for the incidence of local intolerability reactions after application to broken skin, specifically for burning and reddening, was calculated for both the ITT and the PP group as 0.31% (95% CI 0.01–1.7%). The theoretical 95% confidence intervals for the incidence of systemic adverse events and local intolerability reactions (which were not observed, i.e., scaling of skin, itching, urticaria, and folliculitis) with the application of the study medication to nonintact skin was calculated as 0.00–0.92%, again with no difference between the ITT and PP groups.

Combining the patient populations of the two substudies accumulates to 712 children exposed to the study medication. The overall point estimate and 95% CI for the overall incidence of local intolerability reactions were calculated as 0.14% (0.00–0.78%). The 95% CI interval for the overall incidence of systemic adverse events was calculated as 0.00–0.42%.

3.5. Effectiveness results

The global assessment of treatment effectiveness by the physicians and the patients or their caretakers is given in Table 1. Both physicians and caretakers came to highly comparable assessment. In both cases, there was still improvement during the second week (Figs. 4 and 5).

4. Discussion and conclusions

The study presented herein was not a controlled clinical trial and hence not intended to present a formal proof of efficacy. The focus of this study was on safety, with the aim to produce an impression of hazards and their statistical importance under real-life conditions. These real-life conditions also included the recording of adverse events during the next visit (although patients and their caretakers were encouraged to call in with any observation of adverse events) and thus potentially several days after the occurrence of the event. Particularly, very mild events not re-occurring with continued application might therefore not be remembered. This procedure was still deemed sufficient for addressing safety because (a) it reflects clinical realities applicable to all kinds of medication and (b) it was assumed that a true adverse event such as a skin reaction would aggravate with continued application and would therefore be noted and reported. There would even be visible signs upon examination by the physician.

The open study design also implies that the frequency of identified adverse events cannot be compared with a placebo group. This potential weakness of the study is, however, irrelevant in this case, as there was no adverse event in the group of children with intact skin and only one event of irritation in the group with broken skin. This adverse event was assumed to be causally related to the study medication, but technically, it cannot be attributed to comfrey as the active ingredient, as it also has been caused by one of the cream excipients.

Patients applied the study preparation 1–5 times daily for up to 2 weeks, which accumulates to a theoretical maximum exposure to 22,148 applications in the study period, 11,459 of which occurred on the injured skin. The calculations are made for orientation only, as

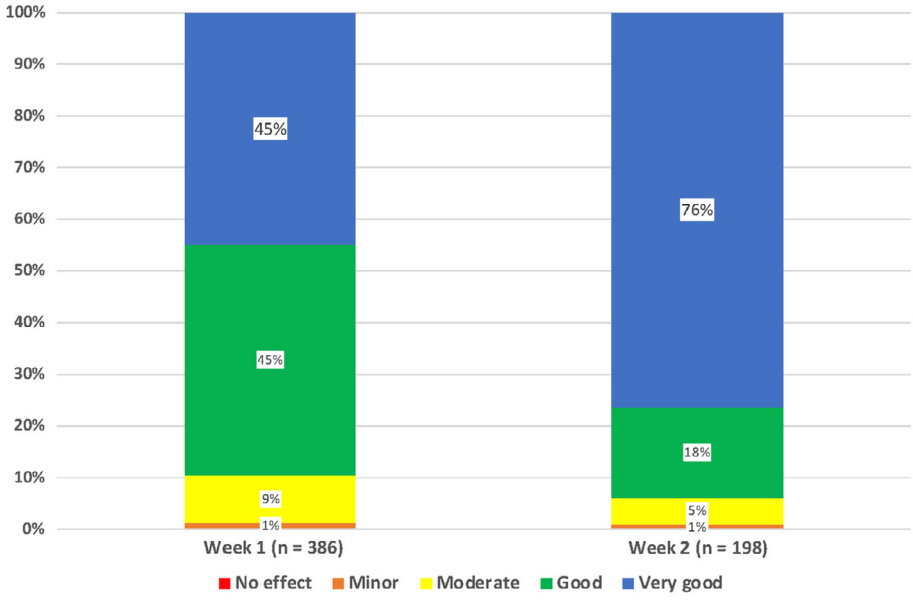

Fig. 4. Global assessment of effectiveness of treatment in children with intact skin by the physician.

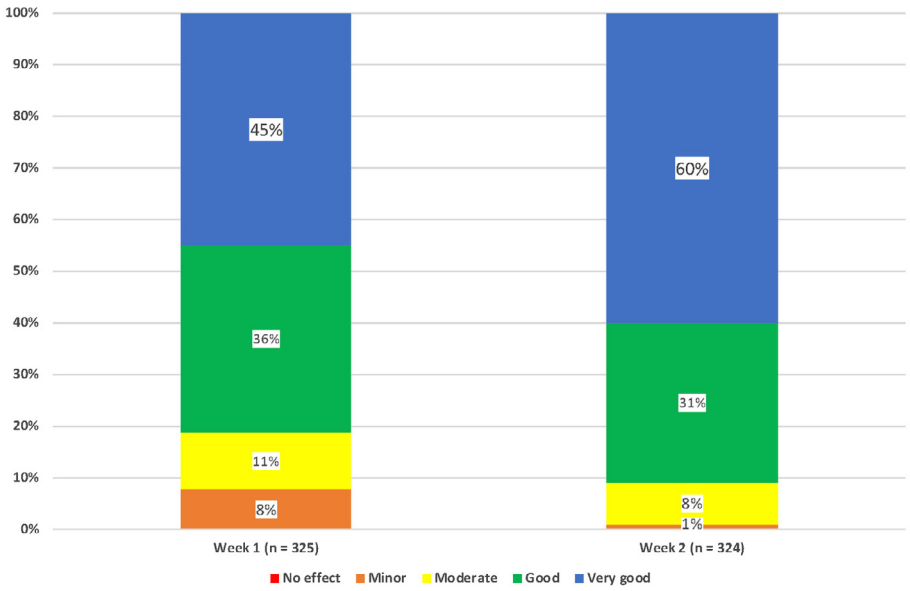

Fig. 5. Global assessment of effectiveness of treatment in children with broken skin by the physician.

they assume that the frequency of application indicated by an individual patient after the first and the second week of treatment would not change for the entire week. The calculated exposures are therefore probably very high, but still they provide a background for comparing the single observed adverse event with exposure estimates.

The practical applicability of the same preparation as used in the two observational studies presented herein was already demonstrated in children in observational studies with blunt traumas [16] and in randomized clinical double-blind trials [13,14]. The number of children exposed to the study preparation described in the literature adds up to 529 patients. The safety and effectiveness/efficacy profile reported in these previously published studies was fully confirmed herein. The results are also in accordance with those reported in recent studies performed in adults [8–13]. The available data show that experience with efficacy and safety in adults is apparently transferable to the situation in pediatric patients.

Comfrey herb extract cream is a popular medication for the treatment of blunt traumas, both in adults and in children. Traditional uses of comfrey also include the treatment of injuries with broken skin; however, such uses are usually discommended because comfrey may contain toxic pyrrolizidine alkaloids [20]. In the case of the study medication, this specific problem was avoided by the selection and cultivation of a comfrey variety devoid of measurable quantities of pyrrolizidine alkaloids in the aerial plant parts [1,3], a variety exclusively used for the manufacture of the study preparation. Because of the selection of this specific comfrey variety, safety concerns with regard to pyrrolizidine alkaloids do not apply and the corresponding medicinal preparation can be used in medical conditions in adults and children where the skin is injured. This may be considered as an advantage in comparison to other local treatments of blunt traumas, e.g., diclofenac is typically contraindicated on broken skin.

The spontaneous reporting systems for adverse drug reactions never showed signals for any untoward reaction. The data presented in this study indicate that this lack of signals from spontaneous reporting is clearly not due to underreporting. The results reported herein increase the number of children exposed to the study medication to 1,241, which allows concluding on the statistical absence of any adverse event in far less than one child in 100 treated patients.

The global assessment of effects corresponds to the findings in previous controlled studies with regard to the clinical improvement of symptoms of blunt traumas and wound healing. It therefore underlines the transferability of the observations to daily routine practice.

5. Summary declaration of interest statement

The study was sponsored by Harras Pharma Curarina Arzneimittel GmbH (München, Germany). The sponsor contributed to the definition of the general study parameters in the study plan and provided the medication but was otherwise not involved in the execution, evaluation, and publication of the clinical trial. These tasks were carried out under the responsibility of the principal investigator.

Ethical statement

The following details on the ethical conduct of the study are also part of the manuscript:

In planning the study, the principles of the Declaration of Helsinki/Somerset West and the International Conference on Harmonization (ICH)—Good Clinical Practice recommendations (Center for Medicine and Public Health [CMPH]/ICH/135[95]) were adhered to. As this study was an open, uncontrolled observational trial, vote from an ethics committee did not have to be obtained. Relevant governmental authorities were notified about the study. In all cases, the parents or legal guardians of the children signed a written informed consent form.

The design of the study specifically considered the German recommendations on the conduct of observational studies published by the German regulatory authorities on 7 July 2010 [18], already circulated before the official publication and therefore applied for this study. In addition, the European recommendations on postapproval safety studies written down in “Volume 9A of the Rules Governing Medicinal Products in the European Union — Guidelines on Pharmacovigilance for Medicinal Products for Human Use” (Final version of 2008) and the 2008 Guidelines for Good

Pharmacoepidemiology Practices issued by the International Society for Pharmacoepidemiology [19] were used for the definition of the study parameters.

Declaration of interests

We wish to draw the attention of the Editor to the following facts that may be considered as potential conflicts of interest and to significant financial contributions to this work.

This study did not receive any specific grant from funding agencies in the public or not-for-profit sectors. It was sponsored by Harras Pharma Curarina Arzneimittel GmbH (München, Germany). The sponsor contributed to the definition of the general study parameters in the study plan and provided the medication but was otherwise not involved in the execution, evaluation, and publication of the clinical trial. These tasks were carried out under the responsibility of the principal investigator.

Acknowledgements

A.K. was the principal investigator of the study. M.B., S.H. and O.H. were treating physicians. M.H. was responsible for statistical evaluations. O.B. created the study plan and the study report.

This study did not receive any specific grant from funding agencies in the public or not-for-profit sectors.

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