Alternative & Integrative Medicine

Jong, et al., Altern Integ Med 2015, 4:1
http://dx.doi.org/10.4172/2327-5162.1000178

Research Article Open Access

A Randomized Open Comparative Clinical Trial on the Effectiveness, Safety and Tolerability of a Homeopathic Medicinal Product for the Treatment of Painful Teething in Children

Miek C Jong[1,2,3,*], **Cynthia Verwer**[1], **Lucy van de Vijver**[1], **Petra Klement**[4], **Julia Burkart**[4] **and Erik Baars**[1,5]

[1]*Department Nutrition & Health, Louis Bolk Institute, Driebergen, The Netherlands*

[2]*Department of Health Sciences, Mid Sweden University, Sundsvall, Sweden*

[3]*National Information and Knowledge Center on Integrative Medicine (NIKIM), Amsterdam, The Netherlands*

[4]*Deutsche Homöopathie-Union, DHU-Arzneimittel GmbH & Co. KG, Karlsruhe, Germany*

[5]*Department of Care, Professorship Anthroposophic Healthcare, University of Applied Sciences, Leiden, The Netherlands*

[*]**Corresponding author**: Miek C Jong, Louis Bolk Institute, Department Nutrition & Health, Hoofdstraat 24 and 3972 LA Driebergen, The Netherlands, Tel : +31 343 523 860; Fax: +31 343 515 611; E-mail: m.jong@louisbolk.nl

Rec date: Nov 14, 2014; **Acc date**: Nov 20, 2014; **Pub date**: Nov 22, 2014

Abstract

Background: Homeopathic products are sold over the counter and are often used for treatment of self-limiting complaints in children such as painful teething.

Objective: To investigate the effectiveness, safety and tolerability of the homeopathic product ChamBell-5-02, in the treatment of children with painful teething in comparison to another homeopathic product.

Design: A multicenter, randomized, open, comparative clinical trial with two parallel treatment groups at three outpatient pediatric clinics in Russia.

Methods: Children aged ≤ six years with painful teething were enrolled from March-July 2009 in the study and randomized to receive either ChamBell-5-02 tablets (Dentokind®; intervention group) or homeopathic suppositories (Viburcol®; control group). Exclusion criteria were: fever of ≥38°C and severe comorbidity. Primary effectiveness endpoints were change of total severity scores of subjective complaints (TSSC) and clinical signs (TSCS) rated by investigators after seven days of treatment. Treatment satisfaction and safety (via number of adverse events (AEs)) were assessed.

Results: A total of 200 children (100 per group) were included and analyzed. TSSC/ TSCS decreased after the 7-day treatment period from median 7.0 to 1.0/6.0 to 1.0 points in the intervention group and from median 5.0 to 1.0/5.5 to 1.0 points in the control group. Compared to the control group children receiving ChamBell-5-02 had about five/2.5 time higher odds of showing improvement (TSSC/TSCS: odds ratio resulting from proportional odds model was 5.1 (95%-CI: 2.7-9.4, p<0.0001) / 2.5 (95%-CI: 1.5-4.4, p=0.0011). Furthermore the intervention group showed a more favorable outcome regarding treatment satisfaction (ratings very satisfied: intervention group: n=94; control group: n=58). No AEs were recorded in the intervention group. In the control group three mild to moderate, non-serious AEs occurred.

Conclusions: Overall it can be concluded that in this study ChamBell-5-02 tablets showed to be effective, safe and well tolerated.

Keywords: Homeopathy; Randomized clinical trial; Children; Dentition; Teething; Dentokind; Viburcol

Introduction

Teething is known as a natural process by which the first teeth appear in children. The first period of teething takes about two and a half years, with the first tooth erupting between four and ten months and all other teeth before the age of three years. Around the age of six, children begin to lose their primary teeth and the first permanent teeth erupt [1]. A variety of symptoms has been shown to accompany teething [2]. This includes irritated and painful gums, crying, irritability, drooling, sleep disturbances and loss of appetite. Teething symptoms in children can create much distress in parents [3,4]. Often, parents consult family or friends for advice on effective treatments as to alleviate their child's discomfort and pain [5]. It has been reported that the majority of parents (63-88%) manage teething symptoms using some form of over-the-counter (OTC) medication [3,6,7]. The most commonly used medications for painful teething in children are paracetamol and analgesic and anesthetic gels, containing choline salicylate, lidocaine hydrochloride or benzocaine [3,6,7]. However, use of these OTC medications might be associated with unwanted side-effects and for some topical teething gels cases of potential life-threatening risks have been reported [8-10]. There is growing interest

among parents for safe and effective medicinal products. Some Complementary and Alternative Medicine (CAM) may offer these medicinal products.

As defined by the National Center for Complementary and Alternative Medicine (NCCAM), CAM covers a broad variety of therapy approaches that are not generally considered part of conventional medicine. A recently published review reported that prevalence rates for overall CAM use in children ranged from 10.9–87.6% for lifetime use and from 8–48.5% for current use [11]. Homeopathy is listed in many studies among the most popular CAM modalities for children [12-16]. A population-based cohort study in the South-West of England showed that 11.8% of children up to 8.5 years of age had used a homeopathic product, most common for self-limiting infantile conditions such as colic, cuts and bruises, and teething [17]. The predominant reason why parents choose homeopathy is that they want safe treatment options for their children. Parents have reported to fear side effects associated with conventional medication and to seek effective and safe alternatives [18,19].

The investigational homeopathic preparation (Dentokind®, ChamBell-5-02) is sold over the counter since 1984 in the Netherlands and up to now also in 18 other countries for self-care of painful teething in children. ChamBell-5-02 is a complex homeopathic product containing five individual homeopathic substances. It was developed by homeopathic physicians through careful selection of individual remedies based on their clinical experience and with the goal of addressing the most common acute symptoms associated with teething. The present study was proposed as a randomized controlled study to obtain data on the clinical use, safety and effectiveness of ChamBell-5-02 for regulatory purposes as required for marketing authorization in Russian Federation. A comparative design with another homeopathic product (Viburcol®, VIB), which was already on the market in the Russian Federation for treatment of painful teething, was requested by the Russian regulatory authorities.

Material and Methods

Study design and approval

A prospective, multicenter, randomized, open-label, comparative, controlled clinical trial with two parallel groups was conducted in Moscow, Russia. The study was approved by the Independent Ethics Committee of the Russian Federation (Protocol No. 23, December 10, 2008) and by the Ethics Committee of the Russian State Medical University of the Federal Agency for Healthcare and Social Developments (Protocol No. 86, January 19, 2009). The study was conducted in accordance with the Russian Federation National Standards of Good Clinical Practice.

Study population

Children were recruited at three outpatient pediatric clinics in Moscow, Russia (The State Educational Institution for Higher Professional Education "Russian State Medical University" and the State Healthcare Institution of Moscow City “Children City Clinical Hospital No. 13” and “Children City Policlinic No. 55”). Eligible children were those of either gender, aged up to six years, with one or several symptoms accompanying teething. Exclusion criteria were hyperthermia of over 38.0°C, severe concomitant diseases (renal failure, heart anomalies, circulatory failure, cardiomyopathy, decompensated kidney and liver, immunosuppressive conditions, oncological diseases), known or suspected hypersensitivity to any component of the study medication, participation in clinical studies within the past six months before the start of the study or use of any other medicinal products used for the treatment of symptoms accompanying teething within the last seven days. Informed consent was obtained from the parents for participation of their child in the study. The first child was included in March 2009 and the last child completed the study in July 2009.

Intervention

Children who fulfilled all eligibility criteria were randomly allocated either to the intervention group (n=100) or to the control group (n=100). ChamBell-5-02 tablets; the treatment of the intervention group, is a complex homeopathic product containing five homeopathic substances: Belladonna D6, Chamomilla D6, Ferrum phosphoricum D6, Hepar sulfuris D12 and Pulsatilla D6 and was administered orally for seven days. Children aged up to one year received ChamBell-5-02 tablets with a dosage regime of one tablet every hour up to six tablets per day (acute symptoms). After symptoms reduced one tablet three times a day was administered. Children aged 1-6 years received two tablets every hour up to a maximum of twelve tablets per day (acute symptoms). After symptoms reduction the dosage was two tablets three times per day.

The control group received VIB suppository, which is a complex homeopathic medicinal product with six homeopathic ingredients: Chamomilla recutita D1, Atropa bella-donna D2, Solanum dulcamara D4, Plantago major D3, Pulsatilla pratensis D2, Calcium carbonicum Hahnemanni D8. It was administered rectally for a period of seven days. For children aged up to six months the maximum daily dose was two suppositories a day. Children older than six months of age received a maximum of four suppositories (at a body temperature of ≥ 37.5°C) a day. When body temperature normalized one suppository was used for further 3-4 days 1-2 times per day (with preventive purpose).

Study procedure

The study involved three clinic visits. At baseline visit (Day 0), children were randomly allocated to the intervention or control group, baseline values of subjective complaints and clinical signs were assessed, study medication was handed out and treatment started. Randomization lists were generated by the Laboratory of Biostatistics State Research Center for Preventative Medicine (Moscow, Russia) with a random block size of four in order to guarantee a balanced allocation. According to the randomization list, 50% of the children were allocated to the intervention group and 50% to the control group. At each center, children were assigned a study number in ascending order based on entry in the trial. For each study number, the investigator received a sealed envelope containing the name of the study medication to be given to the child according to the randomization list. The envelope was opened after the children’s parents had provided signed informed consent. The second visit (Day 3-5) was a follow up visit at which subjective complaints, clinical signs and possible adverse events (AEs) were evaluated. The third visit (Day 7) was the termination visit and end of the study with final assessment of subjective complaints and clinical signs, evaluation of study medication’s effectiveness and tolerability, as well as evaluation of overall satisfaction with the treatment. Duration of individual observation was eight days. There was no run-in or post-treatment period.

Objectives

The purpose of this study was to assess the effectiveness, safety and tolerability of ChamBell-5-02 compared with another homeopathic medicinal product in the treatment of children with painful symptoms of teething. Primary endpoints were changes in total severity scores of subjective complaints (TSSC; unmotivated anxiety, gingival tenderness and appetite disorder – each of the above with maximum two points, otalgy, stool softening, sleep-onset insomnia and frequent awakenings – each of the above with maximum one point; maximum total score: ten points) and changes in total severity scores of clinical signs (TSCS; skin pallor, gingiva condition: hyperemia, gingiva condition: swelling, gingiva condition: hematoma and hyperemia around the mouth – each of the above with maximum one point, drooling and hyperthermia – each of the above with maximum two points, maximum total score: nine points) after treatment with study medication for 3-5 and seven days. Complaints and clinical signs were evaluated and scored by the investigator at the respective center. Secondary endpoints regarding effectiveness were changes in the severities of individual complaints, changes in the severities of individual signs, effectiveness assessments by investigators and children/parents using the 4-point rating Integrative Medicine Outcome Scale (IMOS [20]), treatment satisfaction assessment by children/parents using the 4-point rating Integrative Medicine Patient Satisfaction Scale (IMPSS [20]) and time taken for all subjective complaints and for all clinical signs to disappear. Secondary endpoints regarding safety were tolerability of study medication assessed by investigators and children/parents and incidence of AEs and adverse drug reactions (ADRs).

Sample size

Calculation of sample size was carried out based on power estimation assuming a scenario if 100 children per group are recruited. The primary outcome refers to the difference on a 10-point and 9-point scale respectively. As a measurement of the minimal relevant effect in case of questionnaires the minimal important clinically relevant difference can be regarded. It is usually set as 10% of the range (here: about one point). The standard deviation of the scale is about two. At a level of significance of α=0.05 and n=100 per group power of β=0.94 would be achieved to potentially distinguish a difference of greater than one point between the effectiveness of the study medications.

Statistical analyses

The statistical analysis was based on the full analysis data set (FAS), including all children who were randomized and who received the study medication at least once and had at least one measured post baseline effectiveness response. In case of premature withdrawal of children, the LOCF (last observation carried forward) method was used to replace missing observations regarding primary effectiveness variables. In order to assess the impact of drop-outs on effectiveness results, a subset of observed cases (OC) was evaluated. Safety analysis included all randomized children who received at least one dose of study medication. The homogeneity of the two treatment groups was assessed by comparison of demographic data and data obtained at the baseline visit (Day 0). Baseline values of primary variables were included as covariates in the respective models. Continuously or quasi-continuously scaled variables were investigated whether prerequisites for parametric approach were fulfilled. In case of categorically scaled variables, counts and percentages were reported, and ordinal logistic regression (proportional odds model (POM)), χ^2-Test as well as Armitage Trend Test were applied for comparisons. A rejection-criterion of 0.05 was set for all statistical tests. If tests allowed, the statistics were two-tailed.

Results

Baseline characteristics

A flow diagram of children included and excluded in the study is shown in Figure 1. A total of 200 children were randomized, 100 in each group. Recruitment took place from March-June 2009. Study follow-up was performed from March-July 2009. The trial ended because the planned number of participants was reached. The FAS population consisted of 200 children (100 in each group) and 198 children were included in the OC analysis. In Table 1, demographic and clinical characteristics are shown.

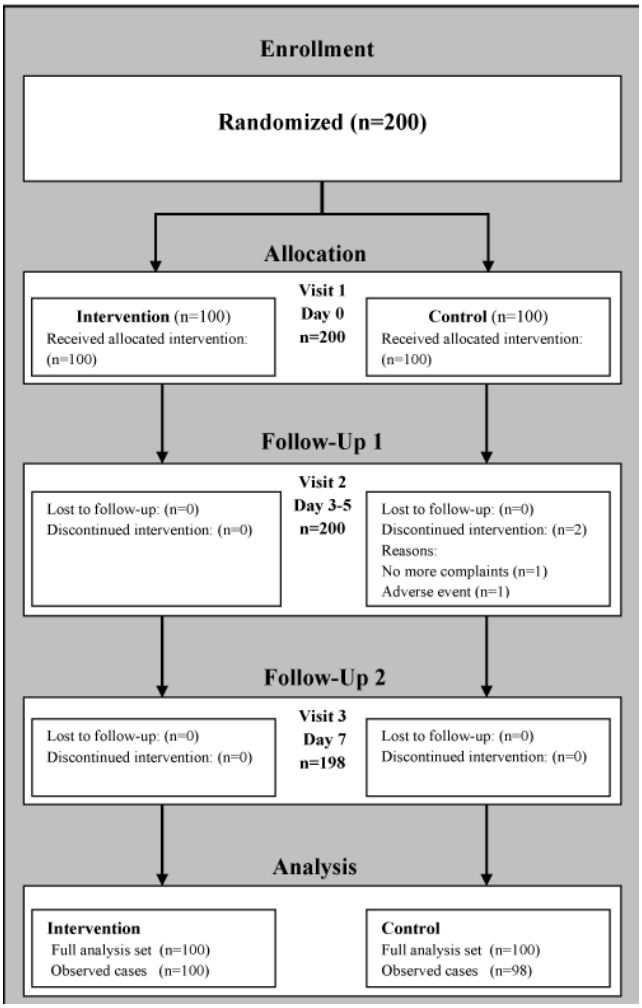

Figure 1: Flow diagram of participants.

Characteristics	Intervention group (n=100)	Control group (n=100)
Age [months] (median [P25, P75]		
Infants <12 months Toddlers/ children ≥ 12 months	7.5 [6.5, 9.0] 19.5 [14.0, 33.5]	6.0 [4.0, 8.0] 18.0 [14.0, 26.0]
Sex (n boys/n girls)	47/53	48/52
Duration of painful teething prior to study start (n)		
1 day 2 days 3-4 days More than 4 days	16 34 23 26*	25 44 18 13
Concomitant diseases (n)	32	29
Concomitant medication (n)	6	6
n- refers to number of children * - for one child duration of painful symptoms prior to study start was unknown		

Table 1: Demographic and clinical characteristics, FAS analysis.

Primary and secondary effectiveness endpoints

Primary effectiveness endpoints: In the intervention group the TSSC reduced from baseline median value 7.0 points over 3.0 points (Day 3-5) to 1.0 point after seven days of treatment. The TSSC assessed in the control group decreased from median 5.0 points (baseline) to 3.0 points (Day 3-5) to 1.0 point after seven days (Figure 2).

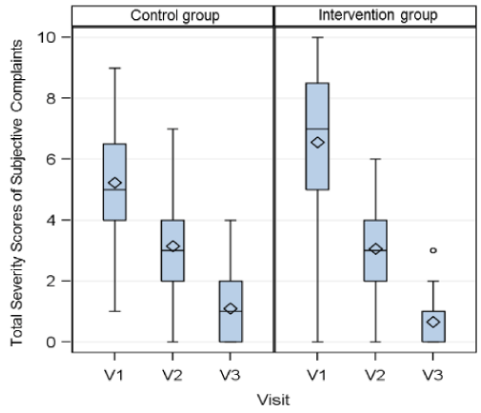

Figure 2: Total Severity Scores of Subjective Complaints (TSSC) at baseline visit (V1, Day 0), follow-up visit (V2, Day 3-5) and termination visit (V3, Day 7), FAS analysis. Note: Boxwhiskerplot showing mean, SD, median, minimum, P25%, P75% and maximum.

In a baseline adjusted POM those children receiving ChamBell-5-02 had five times higher odds of showing improvement after seven days of treatment than children in the control group (odds ratio resulting from baseline adjusted POM: 5.1 (95%-CI: 2.7-9.4, p<0.0001; FAS). After 3-5 days of treatment odds ratio resulting from baseline adjusted POM was 4.5 (95%-CI: 2.4-8.2, p<0.0001; FAS).

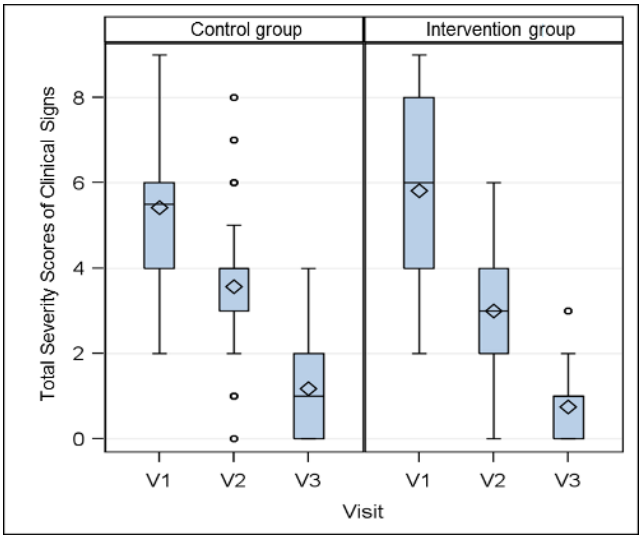

Figure 3: Total Severity Scores of Clinical Signs (TSCS) at baseline visit (V1, Day 0), follow-up visit (V2, Day 3-5) and termination visit (V3, Day 7), FAS analysis. Note: Boxwhiskerplot showing mean, SD, median, minimum, P25%, P75% and maximum.

TSCS assessed in the intervention group at each visit day (Day 0, Day 3-5, Day 7) decreased from median 6.0 points over 3.0 points to 1.0 point. In the control group a reduction from baseline median value 5.5 points to 4.0 points to 1.0 point was recorded (Figure 3). An odds ratio of 2.5 (95%-CI: 1.5-4.4) was found, indicating that children of the intervention group had 2.5 times higher odds of showing improvement after seven days of treatment compared to the children

of the control group (baseline adjusted POM: p=0.0011; FAS). The odds ratio resulting from baseline adjusted POM at Day 3-5 was 4.8 (95%-CI: 2.7-8.5, p<0.0001; FAS). The OC analysis confirmed the findings for the primary effectiveness criteria of the FAS analysis (data not shown).

Secondary effectiveness endpoints: Improvement of individual complaints after seven days of treatment was seen in the following number of children of the intervention/control group (out of 100 children each): unmotivated anxiety– 88%/79%, gingival tenderness – 73%/55%, appetite disorder– 83%/66%, otalgy– 56%/18%, stool softening- 75%/36%, sleep-onset insomnia- 57%/54% and frequent awakenings- 74%/59%. With the exception of the complaint sleep-onset insomnia with a recorded deterioration in 3%/2% of children in the intervention and control group respectively, no change in the severity of respective complaint was recorded for the remaining number of children after seven days of treatment (most of these children didn't show the complaint at baseline at all).

Compared to the control group improvement of two out of seven individual complaints (gingival tenderness: Armitage Trend Test: p=0.0130, appetite disorder: Armitage Trend Test: p=0.0107; FAS) was observed in significantly more children of the intervention group.

Individual signs improved after seven days of treatment in following numbers of children of the intervention/control group (out of 100 children each): skin pallor 33%/30%, gingival hyperemia 91%/75%, gingival swelling 59%/41%, drooling 86%/83%, hyperemia around the mouth 51%/37%, hyperthermia 82%/86%. For the remaining number of children no change in the severity of respective sign was recorded after seven days of treatment (many of the children didn't show the sign at baseline at all). Comparing the two groups the signs gingival hyperemia (Armitage Trend Test: p=0.0057; FAS) and gingival swelling (Armitage Trend Test: p=0.0157; FAS) improved in significantly more children of the intervention group than in children of the control group. For all other categories no significant differences were observed. For the sign gingival hematoma no valid results were obtained for the comparison between the groups as strong baseline differences existed (only eight children of the control group and 24 children of the intervention group showed the sign at baseline at all).

After seven days of treatment with ChamBell-5-02 almost all children/parents and investigator (n=99 out of 100 each) of the intervention group rated "no complaints" or "major improvement" (final effectiveness assessments by investigators and children/parents by means of IMOS). In comparison to the other homeopathic preparation the overall outcome in the intervention group was significantly better (Armitage Trend Test: p<0.0001; FAS) (Table 2). Furthermore almost all children/parents (n=99 out of 100) in the intervention group were 'very satisfied' or 'satisfied' with the ChamBell-5-02 treatment (assessment by means of IMPSS). Compared to the assessment of children/parents in the control group the outcome in the intervention group was more favorable (Armitage Trend Test: p<0.0001; FAS) (Table 3).

Assessment	**Investigator**		**Children/Parents**	
	Control group (n=100)	Intervention group (n=100)	Control group (n=100)	Intervention group (n=100)
No complaints	28	47	36	62
Major Improvement	52	52	54	37
Improvement	20	1	9	1
No change	0	0	1	0
Deterioration	0	0	0	0
Result (Armitage Trend Test)	p<0.0001		p<0.0001	

Table 2: IMOS: Final effectiveness assessments by investigators and children/parents at termination visit (Day 7), FAS analysis. Note: Analyzed by means of descriptive statistics (counts) for the different categories of the IMOS.

Regarding the time taken for all subjective complaints and clinical signs to disappear (TSSC/TSCS = 0) in few children of the intervention group (complaints: n=8 children, signs: n=1 child) and the control group (complaints: n=7 children, signs: n=2 children) first clinical effects were seen after three to five days. At the end of treatment duration, subjective complaints and clinical signs disappeared completely in 47%/45% out of 100 children of the intervention group and in 33%/39% out of 100 children of the control group. Between the treatment groups no significant differences were noted with respect to time for complete disappearance of signs (Armitage trend test: p=0.5008; FAS). With respect to the time for disappearance of complaints a tendency for shorter durations was seen for the intervention group (Armitage trend test: p=0.0829; FAS).

Assessment	**Control group (n=100)**	**Intervention group (n=99*)**
Very satisfied	58	94
Satisfied	38	5
Neutral	3	0

Dissatisfied	1	0
Very dissatisfied	0	0
Result (Armitage Trend Test)	p<0.0001	
* For one patient assessment was unknown.		

Table 3: IMPSS: Treatment satisfaction evaluation by children/parents at termination visit (Day 7), FAS analysis. Note: Analyzed by descriptive statistics (counts) for the different categories of the IMPSS.

Safety and tolerability

During the 7-day treatment period children of the intervention group took on average 78 ChamBell-5-02 tablets (median: 78, P25%: 51, P75%: 88). Children of the control group received on average 23 suppositories (median: 24, P25%: 23, P75%: 24).

During the whole treatment period three out of 200 (1.5%) children experienced AEs. Serious AEs were not reported. The recorded AEs (allergic dermatitis (probably related), erythema (likely related) and anorectal discomfort (unlikely related) occurred in three children of the control group (3.0% out of 100 children) and were all of mild to moderate intensity. One of these children discontinued treatment and withdrew from the study due to the AE. In the intervention group no AEs were reported. Results of final treatment tolerability evaluated by investigators and children/parents are shown in Table 4.

Assessment	**Investigator**		**Children / Parents**	
	Control group (n=100)	Intervention group (n=99)*	Control group (n=100)	Intervention group (n=99)*
Very good	57	95	56	97
Good	41	4	43	2
Satisfactory	1	0	1	0
Poor	1	0	0	0
Result (Armitage Trend Test)	p<0.0001		p<0.0001	
*For one patient assessment was unknown				

Table 4: Final tolerability evaluation by investigators and children/parents at termination visit (Day 7), FAS analysis. Note: Analyzed by descriptive statistics (counts) for the different categories.

Almost all children/parents and investigators rated the tolerability of ChamBell-5-02 as 'very good' or 'good'. In comparison to the homeopathic suppositories the outcome in the intervention group was significantly better (Armitage Trend Test: p<0.0001; FAS).

Discussion

The present study demonstrated that both homeopathic study medications reduced total severity scores of subjective complaints, including individual symptoms such as unmotivated anxiety, gingival tenderness, appetite disorders and otalgy in teething children after seven days of treatment. Total severity scores of clinical signs, as associated with individual signs such as drooling, hyperemia and hyperthermia, also lowered after seven days of treatment in the homeopathic treatment groups. ChamBell-5-02 tablets appeared to be slightly more effective than the homeopathic suppositories in reducing teething complaints and clinical signs. The observed reductions in total severity scores of subjective complaints and clinical signs were also reflected by the effectiveness assessments of investigators and children/parents, as either a major improvement or total recovery from painful teething was observed for almost all children (99%) in the intervention group and 80-90% of the children in the control group.

To our best knowledge, this study is the first randomized controlled trial on effectiveness of homeopathic medications for painful teething. A number of studies have demonstrated the effectiveness of homeopathy for other (self-limiting) conditions in children. A study by Haidvogl et al. [21] in children with acute respiratory tract infections and ear complaints, showed significant rapid improvements upon homeopathic medications compared to conventional treatment. The rate of symptom improvement in children with acute otitis media was also faster upon treatment with homeopathic ear drops compared to standard therapy only [22]. Another randomized-controlled study on acute otitis media reported that children who received homeopathic treatment improved faster than those conventionally treated [23]. Furthermore, children treated with homeopathy did not require any additional antibiotic treatment [23].

Despite these positive finding, the effectiveness of homeopathy is still heavily debated [24]. Based on the perceived implausibility of any conceivable mechanism of action for homeopathy, specifically the highly diluted medications, all (placebo)-controlled studies and other

available evidence on homeopathy is rejected [25] or regarded as placebo effects [26]. Regrettably, the rejection of homeopathy within conventional medicine is in sharp contrast to the beliefs and behaviors of patients and parents. Many patients and parents accept and use homeopathic medicines for themselves or their children, either prescribed by (homeopathic) physicians or through self-care [12,27,28]. The observation that personal use of CAM (including homeopathy) is relatively high among conventional healthcare professions [29,30], could indicate that attitudes shift when conventional healthcare professions become patients or parents themselves. Although the scientific critique on homeopathy is expected to continue, recent studies on cost-effectiveness of homeopathy may bring another viewpoint into the debate. Studies by Kooreman and Baars [31,32] reported that patients whose general practitioner has additional CAM training (including homeopathy) had lower health costs. Furthermore, homeopathic treatment of children with rhinopharyngitis was associated with lower direct medical costs and less sick leave time for their parents compared to standard antibiotic treatment [33]. Because of the rapidly growing health care cost in Western societies, cost-effective treatment options such as homeopathy may gain new (politic) interest.

Another important advantage of the use of homeopathy in children is its apparent excellent safety profile. In the present study, both homeopathic medications were very well tolerated in children. Only three mild, non-serious adverse reactions (1.5% of total study population) were reported in the control group. Conventional OTC medications for painful teething, such as teething gels, have failed to demonstrate any specific benefits and have the potential to be harmful in overdose [34]. Unintentional parent-caused overdose in the form of frequent use of teething gels over several months has led to potential lethal risks as children were hospitalized due to salicylate intoxication [9] or methemoglobinemia [10]. Common side effects such as reduced gag reflex and irritated oral sensation have also been reported for teething gels [35]. Altogether, these findings suggest that the presently investigated homeopathic product ChamBell-5-02 may be a better alternative for children with painful symptoms of teething, with lower risks than conventional OTC treatment options like teething gels.

The present study was specifically designed for regulatory purposes. It also had its limitations. First of all, the study had an open label design. Both investigators and children/parents knew that the study was undertaken to investigate whether ChamBell-5-02 was comparable with the other homeopathic product in symptom relief of teething. Even though the primary effectiveness endpoints were partly based on objective clinical signs such as skin pallor, gingiva condition, drooling, hyperemia and hyperthermia, it cannot be excluded with certainty that in particular the subjective complaints measured in the intervention group may have been overestimated relative to the control group. Secondly, ChamBell-5-02 was administered orally and compared to a homeopathic medicinal product as control that was administered rectally. To specifically investigate comparable effectiveness, it would have been better if the homeopathic medicinal products under investigation were administered in a similar manner. Another limitation was that the current study design did not control for the natural course of the disease and regression to the mean. Teething symptoms such as drooling, ear rubbing, irritability, hyperthermia and loss of appetite have been reported specifically within an eight-day time frame of teething [36]. This covers a four day period before the tooth emerges, the day itself, and up to three days after tooth eruption. As children in the present study already exhibited teething symptoms for some days prior to start of the study, the observed reduction in total severity scores of subjective complaints and clinical signs may have reflected the natural decline of teething symptoms, rather than a direct effect of the homeopathic study medication itself. Teeth often emerge in clusters, meaning that successive non-first teeth emerge on the same day as another tooth, or teeth emerge within five days of another tooth [36]. Thus teething symptoms can be exhibited over a longer period of time, dependent on the number of teeth erupting. The number of erupting teeth however, was not recorded in the present study. Other studies in children have shown that homeopathic medications achieve symptom relieve specifically within the first week after treatment, more so than standard, conventional therapy [21-23]. Based on these findings, it can be hypothesized that ChamBell-5-02 may have reduced symptoms more rapidly than the natural course of teething. Further research is warranted to confirm this hypothesis. As recommended in the roadmap for future CAM research [37], further research on ChamBell-5-02 may include comparative effectiveness research in a real world setting comparing ChamBell-5-02 to conventional treatment strategies. Despite these limitations, the present study served its purpose as a large randomized controlled study demonstrating the clinical use of ChamBell-5-02 in children, its excellent safety profile and treatment satisfaction of parents/children with ChamBell-5-02.

As nowadays healthcare costs are escalating, the attention for managing one's own health and self-care is growing [38]. It is expected that the use of OTC medications for symptom management in children will further increase [39]. Since in the present study, ChamBell-5-02 was shown to be safe, excellently tolerated and to reduce symptoms of teething, ChamBell-5-02 could be advised in the support of self-management of teething in children. It is known that the use of OTC medications may increase the risk that self-treatment is undertaken when medical care should have been sought [40]. Therefore, it remains important that parents are always alert that some symptoms in their children could not be attributed to teething and may have a more serious underlying cause. This would require the physicians' attention and conventional treatment if necessary.

In conclusion, the findings in the present study suggest that the OTC homeopathic medicine ChamBell-5-02 may offer a pragmatic treatment alternative to conventional OTC teething gels for symptom relieve of painful teething in children.

Acknowledgement

The study was sponsored by the Deutsche Homöopathie-Union, DHU-Arzneimittel GmbH & Co. KG, Karlsruhe, Germany.

We thank all investigators and children with their parents who participated in this study and T Keller (Leipzig) for his assistance in the statistical analysis and the preparation of the publication manuscript.

Additonal Declaration of Former Publication

Information about the study has been published on the website of Federal Service for Surveillance in the Sphere of Healthcare and Social Development of Ministry of Health of Russian Federation at:

http://www.roszdravnadzor.ru/medicines/control_for_doklin_i_klin_issl/info?year=2009

Study registration number: 567

Parts of the results of this study have been published earlier by Ilyenko LI, Kholodova IN, Syrieva TN, Il'ina ID, and Kholodov DI, in the Russian language in the Journal Pediatriya, 2010. 89 (4): 106-110©. For the present study all data were newly entered, validated and analysed according to ICH-GCP guidelines. Permission to publish the newly analyzed data was obtained from the Pediatriya Journal on November 9, 2013 by the Deputy editor-in-chief of the Journal Pediatriya" (n.a. G.N. Speransky), Prof. T.V. Kazyukova, PhD, MD.

Conflict of Interest

M. Jong was an employee of VSM Geneesmiddelen bv (sister-company of Deutsche Homöopathie Union) from 2001 till 2008.

P. Klement and J. Burkart are employees of Deutsche Homöopathie-Union, DHU-Arzneimittel GmbH & Co. KG, Karlsruhe, Germany.

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