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Original Article

Effects of Spascupreel versus hyoscine butylbromide for gastrointestinal cramps in children

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Abstract

Background: Gastrointestinal spasms and cramps are common in children as well as in adults. Alternative medical practices such as chiropractice and homeopathy are becoming increasingly popular in Europe and the USA. The effectiveness and tolerability of the homeopathic preparation Spascupreel was compared with that of hyoscine butylbromide treatment in children <12 years of age.

Methods: An observational cohort study in 204 children <12 years was conducted over a 1 week treatment period. The efficacy of the respective therapies were evaluated on the effect on severity of spasms and clinical symptoms (pain/cramps, sleep disturbances, distress, eating or drinking difficulties and frequent crying). Compliance was evaluated on a four-point scale from 'very good' to 'low'. Evaluation was done by the practitioner based on information given by the patient or minder.

Results: The analysis showed comparative improvements with the homeopathic preparation and hyoscine butylbromide therapy on severity of spasms, pain/cramps, sleep disturbances, eating or drinking difficulties, and frequent crying, all as evaluated by the practitioner. Both treatments were very well tolerated.

Conclusions: For patients opting for a homeopathic therapy, Spascupreel seems to be an effective and well tolerated alternative to conventional therapies in children suffering from gastrointestinal spasms.

Key words gastrointestinal spasms, homeopathic preparation, non-inferiority analysis, observational cohort study, scopolamine.

Gastrointestinal and urogenital cramps are common in children as well as in adults. Overall, gastrointestinal and urogenital cramps lead to around 10 million prescriptions and an undocumented number of over-the-counter (OTC) acquired self-medications yearly in Germany[1] with similar situations in other countries. In the USA, $1.2 billion worth of antacids, antidiarrhetics and anti-gas products were sold OTC in 2002.[2] Colic and gastrointestinal spasms are well definable conditions, and treatment is almost exclusively with symptomatic therapies. Since colic and spasm are rarely isolated and definable separately from each other, preferred therapies have both analgesic and spasmolytic properties.

The increasing popularity of alternative medications in the developed world[3,4] is also reflected in the use of medications for colic and gastrointestinal ailments. Hyoscine butylbromide (Buscopan, Boehringer Ingelheim, Germany) is an alkaloid with spasmolytic and parasympatholytic properties such as effecting a reduction in basal pressure and the magnitude of the superimposed phasic contractions of the sphincter of Oddi.[5] Hyoscine butylbromide has long been used widely for the treatment of acute colic pain.[6–8] The effects of orally administered hyoscine butylbromide on gastric motility were documented as early as in 1968.[9] However, hyoscine (scopolamine)-containing treatments are associated, although infrequently, with dry mouth, urinary retention and increases in ocular pressure.[10,11]

Spascupreel (Heel GmbH, Baden-Baden, Germany) is a homeopathic preparation consisting of plant and mineral extracts at a high dilution (10^{-2}–10^{-6}). The constituents of Spascupreel (listed in Table 1) are officially listed in the Homeopathic Pharmacopoeia of the United States.[12] Spascupreel has a long record of successful use in Germany and Austria for the treatment primarily of spasms of smooth muscles of the stomach, intestines, bladder or uterus.[1]

The aim of the present study was to compare the effects of oral administration of the Spascupreel with those of common hyoscine butylbromide therapy, similarly administered, in children <12 years with gastrointestinal or urethral spasms.

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Table 1 Constituents of Spascupreel

Extracts
Citrullus colocynthis (bitter-apple) D4, 30 mg
Veratrum album (white hellebore) D6, 30 mg
Gelsemium sempervirens (wild jasmine) D6, 30 mg
Passiflora incarnata (passion flower) D2, 15 mg
Amanita muscaria D4, 15 mg
Camomilla recutita (chamomile) D3, 15 mg
Aconitum napellus (monkshood) D6, 60 mg
Other substances
Atropine sulphate D6, 30 mg
Copper sulphate D6, 30 mg
Magnesium phosphate D6, 30 mg
Ammonium bromide D6, 30 mg

The approach was to use a non-randomized, observational study. As Black has pointed out,[13] randomized and observational studies are complementary approaches and there are several instances where randomized trials are inappropriate. Many of these relate to trials with complementary practices. For example, the effectiveness of the intervention in alternative medicine is often influenced by the subjects' beliefs and preferences, from which follows that the act of random allocation may reduce the effectiveness of the intervention. The artificiality of the randomized trial also risks influencing patients. Further, randomized trials frequently exclude patients not meeting certain predefined criteria and homeopathic remedies are prescribed to a very wide range of patients. So, a non-randomized observational study may better reflect the broad spectrum of individuals treated in clinical practice.

Methods

This was a prospective, observational, non-interventional cohort study. Included were 204 children in 57 centers in Germany. Each center could enroll up to five patients, with the choice of treatment left to the practitioner's discretion. Each patient was treated with either Spascupreel (tablets) or hyoscine butylbromide (10 mg tablets) administered orally. The treatment doses were decided according to patient age and to the recommendations in the respective product information sheets. For very young subjects, it was admissible to subdivide or crush the tablets to ease the way of administration.

Included were children <12 years of age, with newly diagnosed or recurring gastrointestinal or urethral spasms. Excluded were children of 12 years or older, as well as patients already undergoing treatment for gastrointestinal spasms, or children contraindicated for one of the study treatments.

All patients and their minders were informed about the background and purpose of the study, which was conducted in full compliance with the principles of the Declaration of Helsinki and with the German regulations for the conductance of observational studies (Bundesanzeiger Federal Gazette No 299, December 1998).

At the first visit, patients were examined and demographic data were collected as well as data on the localization, intensity and duration of spasms, on etiology, auscultation findings, ultrasound, possible adjunctive diseases, possible earlier therapies and the presence of risk factors (adiposity, asthma, diabetes mellitus, eczema, bronchitis, decreased renal function). Treatment was evaluated continually by the practitioner in contact with child minders, with a planned maximal study duration of 1 week. Discontinuation of therapy was possible on grounds of adverse events, unsatisfactory treatment effects or the disappearance of further symptoms.

The efficacy of the respective therapies were evaluated on the effect on severity of spasms and clinical symptoms (pain/cramps, sleep disturbances, distress, eating or drinking difficulties and frequent crying). The effects on these variables were graded from 0 to 3 when 0 indicated asymptomatic, 1 mild, 2 moderate and 3 severe symptoms. Further, time to first improvement of symptoms was recorded (after the first administration, after 12–24 h of treatment, after 1–3 days, after >3 days, and no improvement) and the physician gave an estimate of the total effect of treatment (not as a summary of individual scores) graded from 1 to 5 where 1 indicated asymptomatic, 2 clear improvements, 3 moderate improvements, 4 no improvement and 5 indicated a worsening of symptoms. It was further recorded whether patients stayed on treatment after the 1 week study period.

Compliance was evaluated on a four-point scale from 'very good' to 'low'. These values were given by the practitioner based on information given by the patient or minder, but there was no strict monitoring of compliance by pill counting or by other quantifying means. Tolerability was evaluated by the practitioner on a four-point scale ('very good', 'good', 'moderate' and 'low') where 'very good' indicated no tolerability complaints whereas patients with the score 'low' showed reactions after each administration. Patients were monitored for adverse events which were documented descriptively with the possible relation to treatment evaluated. Potentially serious adverse events were to be reported within 24 h of appearance.

Statistical evaluation

For the comparison of the two treatment groups, the efficacy analysis was carried out on the variation in symptom and global scores from enrollment to the final evaluation in an ANCOVA adjusted for baseline and propensity score (PS) score. For children who discontinued for disappearance of symptoms or unsatisfactory treatment effects, the last observation was used in the analysis.

As this was an exploratory observational study, attempting to compare the use of two different treatment options in clinical practice, the aim was not to confirm or reject a pre-defined hypothesis. For the non-inferiority analysis, the criterion used to determine non-inferiority of Spascupreel over standard therapy was that the lower limit of the one-sided 95% confidence interval for the differences in changes from baseline between treatment did not cross the value of 10% of the evaluation scale with an error probability of 0.05. This corresponded to a value of −0.3 for the separate variables analyses, and −1.8 for the total score in the study. The choice of 10% was to a certain extent arbitrary, as there are no comparative analyses available in the conditions and populations studied to guide the investigator. The null hypothesis was that there would be a greater than 10% difference between the Spascupreel and control groups in reduction of symptom scores adjusted for baseline values and PS score.

As this was a non-randomized study, there was a risk that the population receiving the homeopathic medication would show differences from the population receiving conventional treatments.[14] To compensate for such differences, the established methodology of PS analysis was applied to construct matched strata that balance observed co-variates. It is possible to express the probability of belonging to a treatment group as a function of baseline criteria. The term PS refers to the probability that an individual will belong to one of the treatment groups, given a certain set of baseline criteria. Two patients with similar PS values can be shown to have highly similar criteria, whichever treatment group they belong to and, therefore, patients in similar PS strata will show comparable baseline criteria. So, applying PS to observational studies reduces bias and allows for the application of standard statistical methods.[15]

A PS was estimated for each patient using logistic regression and patients were divided into four strata according to quartiles of PS scores. The following variables were used as underlying co-variates: age, presence of risk factors, localization of spasms in the urinary tract, sleep disturbances and presence of psychological basis of symptoms. Treatment groups were compared after adjustment for PS using a two-way ANOVA model for co-variates based on interval data and Cochran–Mantel–Haenszel test for co-variates with dichotomous values. Differences between groups in symptoms and endpoints were likewise calculated after PS adjustment and mean differences were estimated within each PS stratum. Overall estimates were calculated through weighted means taking into account the variance of the mean differences within each stratum.

Since this was an exploratory analysis, a univariate analysis of all criteria were conducted. However, a summary score of clinical symptoms was calculated; a calculation which corresponds to a multivariate summary of the results. Data were analyzed with SAS version 8.1 (SAS Institute Inc., Cary, NC, USA).

Results

Patients

A total of 204 patients were included in the study, 99 in the Spascupreel arm and 105 in the control arm. Baseline criteria are given in Table 2. All centers enrolled more than one patient. Each center treated all patients with either Spascupreel (29 centers) or hyoscine butylbromide (28 centers). There were no statistically significant differences in gender between the groups, but patients in the Spascupreel group tended to be younger (mean age, 7.6 ± 2.7 years vs 9.2 ± 2.2 years) and consequently shorter and lighter than patients receiving hyoscine butylbromide. The age range in the Spascupreel group was 1.3–11.7 years; in the control group 0.2–12.0 years. Furthermore, before a PS adjustment, there were differences between patient groups in terms of the presence of risk factors, localization of spasms in the urinary tract, sleep disturbances and psychological basis of symptoms. However, these differences were no longer statistically significant ($P > 0.05$) after the PS adjustment.

Patients were treated for a mean 6.1 days in both groups, 3–9 days in the Spascupreel group and 2–9 days in the control group. A total of 15 patients (20%) discontinued Spascupreel treatment before 1 week compared with 31 patients (30%) in the control group. In the large majority of cases (88%), discontinuations were because of the disappearance of symptoms during therapy.

Treatment efficacy

In both groups, the scores for all variables improved during the treatment period. The time to first improvement of symptoms was less than 1 day in 12% of patients receiving Spascupreel and 13% of patients on hyoscine butylbromide. The majority of patients experienced an improvement in symptoms within 2 days of treatment (80% in the Spascupreel group and 89% in the control group, respectively) with no significant differences between the treatment groups. Only for 4% of the patients in the Spascupreel group and 2% in the control group was no improvement reported during the course of the study.

Similarly, the physicians' evaluation of the therapies as a whole showed great satisfaction overall, with treatment success in 75% of Spascupreel-treated cases judged to be 'very good' compared with 79% of treatments in the control group. Only 1% of Spascupreel treatments and no case of control therapy were evaluated by the practitioners as having 'bad' overall outcomes. Both treatment groups had similar levels of overall satisfaction with treatment ($P = 0.44$ for the comparison).

For all studied variables the patient population shifted from a predominance of severe or medium degree of symptoms, to a majority of asymptomatic patients at the end of the study.

Table 2 Baseline characteristics

Variable	Spascupreel ($n=99$)	Control ($n=105$)	P-value for comparison (before correction for propensity score)
Age, years (mean ±SD)	7.6 (±2.7)	9.2 (±2.2)	<0.001
Height, cm (mean ±SD)	126.9 (±18.3)	136.3 (±13.6)	<0.001
Weight, kg (mean ±SD)	28.6 (±11.0)	33.2 (±9.8)	<0.002
Infectious etiology (n, %)	21 (21%)	36 (34%)	0.043
Localization of spasms (multiple entries possible)			
Urinary tract	20 (20%)	5 (5%)	0.001
Intestines	20 (20%)	31 (30%)	0.146
Stomach	7 (7%)	7 (7%)	1.000
Gastrointestinal	54 (55%)	62 (59%)	0.572
Other	2 (2%)	1 (1%)	
Palpation findings			$P=0.485$
Normal	43 (43%)	51 (49%)	
Abnormal	56 (57%)	54 (51%)	
Pain	5 (5%)	5 (5%)	
Increased pressure	46 (47%)	46 (44%)	
Severity of spasms			0.079
Mild	10 (10%)	10 (10%)	
Moderate	51 (52%)	76 (72%)	
Severe	35 (35%)	17 (16%)	
Not classified	3 (3%)	2 (2%)	
Duration of spasms at presentation			0.122
<1 day	32 (32%)	22 (21%)	
1–3 days	51 (52%)	64 (61%)	
4–7 days	10 (10%)	8 (8%)	
>1 week	5 (5%)	10 (10%)	
No data available	1 (1%)	1 (1%)	
Sleep disturbances			0.003
Mild	41 (41%)	38 (36%)	
Moderate	27 (27%)	14 (13%)	
Severe	7 (7%)	6 (6%)	
Asymptomatic	24 (24%)	47 (45)	
Psychological basis of symptoms	9 (9%)	3 (3%)	0.076
Crying			0.011
Mild	33 (33%)	23 (22%)	
Moderate	21 (21%)	13 (12%)	
Severe	2 (2%)	2 (2%)	
Asymptomatic	43 (43%)	67 (64%)	

This trend was evident for all variables, with the strongest effect observed for the variables pain/cramps and severity of symptoms. The shift in scores was less strong for the variables sleep disturbances and crying; probably because of the milder baseline scores on those variables.

The mean changes from baseline to study end in the quantified evaluations of all variables are shown in Figure 1. This evaluation confirmed the beneficial effects of treatment on all variables. The mean change from baseline in total score was −7.9 ± 3.8 in the Spascupreel group versus −6.6 ± 3.2 for patients receiving hyoscine butylbromide. Negative values indicate an improvement in symptoms.

For the non-inferiority analysis, the data were adjusted for PS and differences between treatments analyzed. The difference between Spascupreel and hyoscine butylbromide on all variables are shown graphically in Figure 2. The null hypothesis of inferiority of Spascupreel was disproved on all variables included in the analysis, with the exception for distress, where the boundary of the one-sided confidence interval crossed the limit of −0.3 which was set as criterion for non-inferiority. The confidence intervals for all other scores were well within the stipulated boundary, including the confidence interval for the total score, where the non-inferiority boundary was set at −1.8 (Fig. 2).

Tolerability and compliance

Tolerability and compliance were very good with both treatment regimens. A large majority of patients reported ‘very

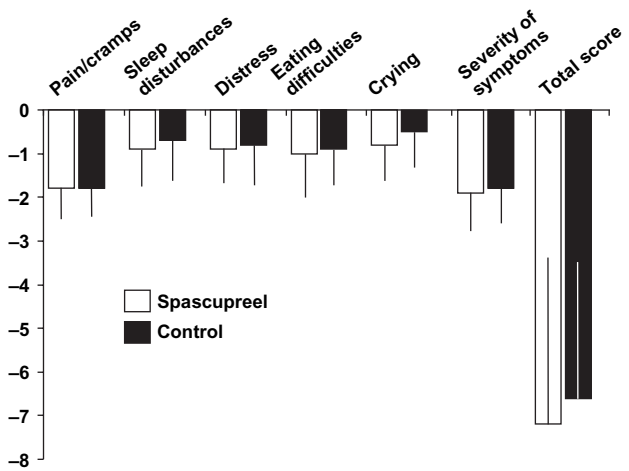

Fig. 1 Mean changes from baseline to study end in the quantified evaluations of all variables. Lines represent standard deviations. Negative values indicate improvement in symptoms.

good' tolerability with both therapies, 91% with Spascupreel and 93% with hyoscine butylbromide ($P = 0.83$ for comparison between groups). Only 2% of patients in the Spascupreel group and <1% in the control group reported moderate or low tolerability. No adverse events were reported with any of the treatments. More than two-thirds of patients (72%) reported 'very good' compliance with Spascupreel and a similar number (68%) was seen for patients receiving hyoscine butylbromide. Only 1% of patients receiving Spascupreel and 3% of patients receiving hyoscine butylbromide reported compliance scores of 'moderate' or lower. There were no statistically significant differences between the groups in compliance scores ($P = 0.44$ for the comparison).

Discussion

This observational study indicates that the effects of the homeopathic preparation Spascupreel, consisting of highly diluted plant and mineral extracts, are comparable to those of commonly used oral hyoscine butylbromide therapy (Buscopan) for gastrointestinal spasms in children aged up to 12 years.

Colics and spasms are common and there is a variety of treatment choices.[16] As many treatments are given without consulting a physician, it is difficult to evaluate effects and tolerability in everyday use. Common medications are drugs such as dicyclomine that reduce painful gut contractions, or simethicone that reduce the formation of intraluminal gas.

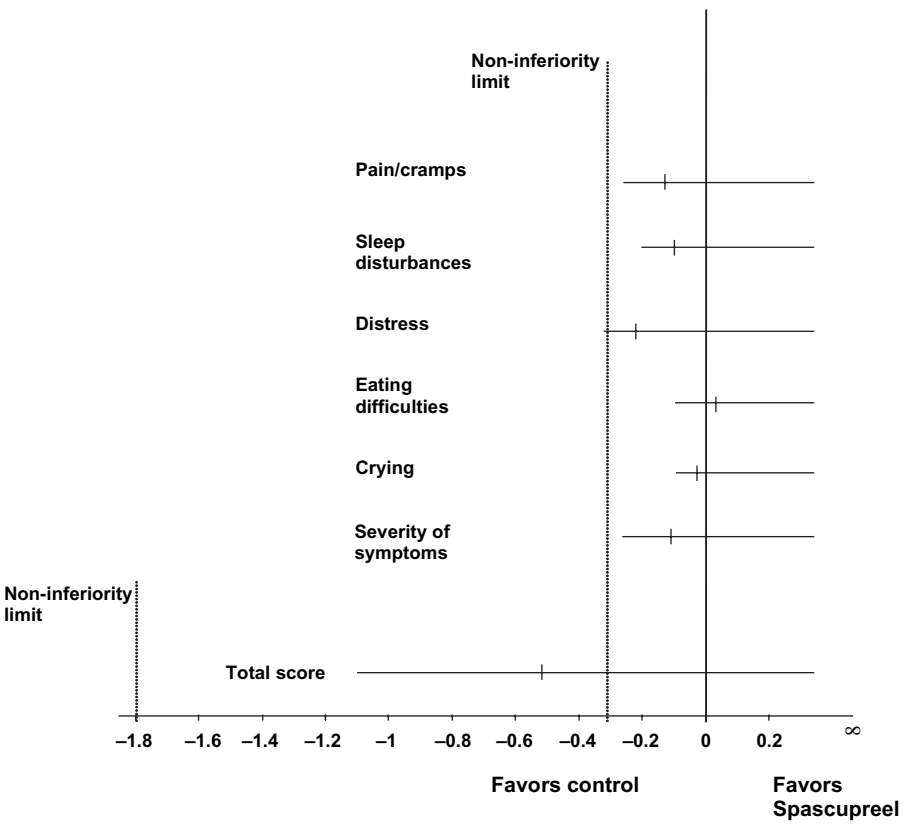

Fig. 2 Non-inferiority analysis showing one-sided 95% confidence intervals of the difference between Spascupreel and hyoscine butylbromide on all variables. Negative values favor control. Note that the non-inferiority limit for all individual variables is −0.3 whereas the limit for the total score is −1.8.

Hyoscine butylbromide, the medication used in the present comparison, is a well-established parasympatholytic and antispastic agent with a wide use in children. Our data indicate that the homeopathic preparation Spascupreel represents an additional choice of therapy and an alternative to conventional treatments.

The use of alternative medications is growing in the industrialized world. A recent survey of treatment patterns in Germany showed alternative treatments to be widely prescribed for musculoskeletal conditions, vertigo and respiratory and gastrointestinal disorders.[17] Among the reasons for the popularity of alternative medical practices is the generally lower rate of adverse events with treatment and a closer interaction between patient and practitioner.[17] Therefore, the option of a homeopathic remedy would expand the range of choice available to practitioners and patients.

In the current comparison, all variables were evaluated by the practitioner. A weakness of the study is the vagueness of the variables chosen which may be subjective to the interpretations and evaluations of each individual practitioner and patient. However, variables such as crying are widely used in evaluating infant colics[16] with apparent good reproducibility. Moreover, individual patient behavior in cases of colic and gastrointestinal spasms is reported to be very similar between cases.[18] So, although there would be a need for validation of the scores used in this exploratory analysis, we expect the evaluations not to vary to any appreciable degree between centers and between practitioners, who have a long experience with the investigated symptoms. This is particularly important with a study in children, who are not always reliable in their assessments if prodded by a parent or physician. A further risk of bias may be seen in the fact that all centers treated all patients with either Spascupreel or hyoscine butylbromide which may indicate a bias in favor of homeopathy or conventional medicine. However, as a similar number of centers gave one or the other treatment, such bias would be expected to be canceled out in the overall analysis.

This was an observational cohort study and patients were not randomized. This design was chosen to capture the broad range of patients who opt for homeopathic therapies and the highly individualized treatments typical of the practice. Further, patients opting for alternative medical treatment tend to have a stronger involvement in their treatment decisions than patients in conventional medicine.[17] In such a situation when the effectiveness of the intervention depends on the subjects' beliefs and preferences, random allocation may reduce the effectiveness of the intervention.[13] The risk with the non-randomized observational approach is that the patients receiving homeopathic therapy may differ from the control population so as to introduce selection bias and reduce the validity of the conclusions.[14] To minimize these effects, we applied the established methodology of PS analysis to construct matched strata that balance observed co-variates. This score is a measure of the probability of receiving one treatment or the other and correcting for PS score reduces differences between the groups, as strata in the Spascupreel group are matched against similar strata in the control group. Differences were seen between the two treatment groups before adjusting for PS, but after the adjustment, there were no significant differences between the two treatment groups.

This was an exploratory observational study and the choice of a non-inferiority margin of 10% of the evaluation scale could not be based on previous data. Therefore, the results should be taken as an indication of comparative effects rather than as a proof of non-inferiority and there is a clear need for greater understanding of the relevance of differences in treatment effects in the populations and indication studied here.

Both treatments were very well tolerated. No adverse events were reported with either therapy. On a four-graded scale ('very good', 'good', 'moderate' and 'low'), 2% of patients in the Spascupreel group and <1% in the control group reported less than 'good' tolerability. There are reports that scopolamine-containing treatments may cause dry mouth, urinary retention and increases in ocular pressure.[10,11] These reports could not be substantiated in the current study. One reason may be the short duration of the respective therapies. Most studies on colic in children are of approximately 1 week duration[16] and this appears to be a sufficient time period for effects of therapies to become manifest. Homeopathic remedies have a general record of excellent tolerability[17] which is corroborated by the current findings for Spascupreel.

In summary, the homeopathic preparation Spascupreel seems to be an effective and well tolerated alternative to conventional therapies in children suffering from gastrointestinal spasms.

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