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Meta-analysis: Smectite in the treatment of acute infectious diarrhoea in children

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SUMMARY

Background
Although not currently recommended, dioctahedral smectite (smectite) is commonly used to treat acute infectious diarrhoea in many countries.

Aim
To evaluate systematically the effectiveness of smectite in treating acute infectious diarrhoea in children.

Methods
Using medical subject headings and free-language terms, the following electronic databases were searched for studies relevant to acute infectious diarrhoea and smectite: MEDLINE, EMBASE, CINAHL and The Cochrane Library; additional references were obtained from reviewed articles. Only randomized-controlled trials were included.

Results
Nine randomized-controlled trials (1238 participants) met the inclusion criteria. Combined data from six randomized-controlled trials showed that smectite significantly reduced the duration of diarrhoea compared with placebo. The pooled weighted mean difference was (−22.7 h, 95% CI: −24.8 to −20.6) with a fixed model and remained significant in a random effect model (−24.4 h, 95% CI: −29.8 to −19.1). The chance of cure on intervention day 3 was significantly increased in the smectite vs. the control group (RR 1.64, 95% CI: 1.36–1.98; number needed to treat 4, 95% CI: 3–5). Adverse effects were similar in both groups.

Conclusions
Smectite may be a useful adjunct to rehydration therapy in treating acute paediatric gastroenteritis. However, the results of this meta-analysis should be interpreted with caution as most of the included studies had important limitations. Cost-effectiveness analyses should be undertaken before routine pharmacological therapy with smectite is recommended.

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INTRODUCTION

Acute gastroenteritis generally is a self-limited illness lasting 5–7 days, and thus the main aim of treatment is to prevent dehydration, metabolic acidosis and electrolyte disturbances. In the vast majority of cases of acute gastroenteritis with mild or moderate dehydration, this can be achieved with oral rehydration solutions. Despite the proven efficacy of oral rehydration, it remains underused.[1] The main reason for this is that an oral rehydration solution neither reduces the frequency of bowel movements and fluid loss nor shortens the duration of illness, which decreases its acceptance and prompts interest in adjunctive treatments.

Not only parents and caregivers but also doctors demand safe, effective and inexpensive agents as an additional treatment that will visibly reduce the frequency and fluidity of stools during gastroenteritis. There are three major classes of antidiarrhoeal agents used to possibly reduce stool frequency and/or stool volume. These consist of antimotility drugs, antisecretory drugs and adsorbents. One example of the latter is dioctahedral smectite (smectite). Smectite is a natural hydrated aluminomagnesium silicate that binds to digestive mucus[2] and has the ability to absorb endotoxins and exotoxins, bacteria and rotavirus.[3, 4] In experimental models, smectite increased water and electrolyte absorption and restored the barrier properties of human intestinal cell monolayers after exposure to tumour necrosis factor (TNF)-α.[5] It also modifies the activity of bile salts and the physical properties of gastric mucus, counteracting mucolysis induced by bacteria.[2]

Although it is currently not recommended by such medical institutions as ESPGHAN,[6] WHO[7] or AAP,[8, 9] in several countries, particularly in France and the majority of countries in central and eastern Europe, smectite is frequently used for the treatment of acute infectious diarrhoea.[10]

Objective

The purpose of this review was to systematically evaluate the efficacy and safety of smectite in treating acute infectious diarrhoea in infants and children.

METHODS

Inclusion criteria

Electronic databases (see Search strategy) were systematically searched to identify studies appropriate for inclusion in this systematic review. Inclusion criteria were as follows.

Types of studies

Randomized-controlled trials (RCTs) and 'quasi'-RCTs (i.e. allocating participants according to date of birth, the number of hospital records, etc.) that compared smectite with placebo or no additional intervention. The methodological quality of the trials was not part of the inclusion criteria, although it was later assessed.

Types of participants

Infants and children up to 18 years of age with acute gastroenteritis, who were treated in hospitals or as out-patients.

Types of interventions

Patients in the experimental groups received smectite at any dosage regimen as an adjunct to treatment of diarrhoea. Patients in the control group received placebo or no additional intervention.

Types of outcome measures

The 'primary' outcome measures were duration of diarrhoea (number of hours) and stool output.

The 'secondary' outcome measures were as follows: stool frequency, vomiting, adherence (acceptance of the treatment) and adverse effects.

Search strategy

The following electronic databases were systematically searched for relevant studies: MEDLINE (1966–July 2005), EMBASE (1980–July 2005), Cumulative Index to Nursing and Allied Health (CINAHL, 1982–July 2005), The Cochrane Database of Systematic Reviews (Issue 2, 2005) and The Cochrane Controlled Trials Register (Issue 2, 2005). The search strategy included use of a validated filter for identifying controlled trials,[11] which was combined with a topic-specific strategy. The search terms were: diarrhoea/diarrhoea, infant*, child*, toddler*, smectite*, semectite*, dioctahedral smectite*, diosmectite* and Smecta, Diosmectal. Furthermore, reference lists from the original studies and review articles identified were screened. The manufacturer of dioctahedral smectite

was contacted to help identify published and unpublished data. No limit was imposed regarding the language of publication, but certain publication types (i.e. letters to the editor, abstracts, proceedings from scientific meetings) were excluded.

Methods of review

Included and excluded studies

Two reviewers independently screened titles and abstracts identified according to the above-described search strategy. All potentially relevant articles were retained, and the full text of these studies was examined to determine which studies satisfied the inclusion criteria. The same reviewers independently carried out data extraction, using standard data extraction forms.

Studies reported in languages other than those familiar to the authors were translated. Discrepancies between the reviewers' findings were resolved by discussion.

Study quality

Two reviewers independently, but without being blinded to the authors or journal, assessed the quality of studies that met the inclusion criteria. Use of the following strategies associated with good quality studies was assessed: generation of allocation sequences and allocation concealment; blinding of the investigators, participants, outcome assessors, and data analysts (yes/no/not reported); intention-to-treat (ITT) analysis (yes/no) and comprehensive follow-up.

Generation of allocation sequences was considered adequate if the resulting sequences were unpredictable (e.g. computer-generated random numbers, table of random numbers, drawing lots or envelopes, throwing dice). Conversely, it was considered inadequate if the resulting sequences were predictable (e.g. according to case record number, date of birth, date of admission, alternation).

Allocation concealment was considered adequate when the randomization method used did not allow the investigator or the participant to identify or influence the intervention group before enrolment of eligible participants in the study. However, the quality of the allocation concealment was considered unclear when randomization was used but no or inadequate information about the method was available and when inappropriate methods of randomization (e.g. alternate medical record numbers, unsealed envelopes, open allocation schedule) were used.

With regard to the ITT analysis, an answer of 'yes' meant that the authors had specifically reported undertaking this type of analysis and/or that our own appraisal confirmed this finding. Conversely, a 'no' meant that authors did not report use of ITT analysis and/or that we could not confirm its use on study assessment. To evaluate the completeness of patient follow-up, we determined the percentage of participants excluded or lost to follow-up.

Statistical methods

The data were analysed using REVIEW MANAGER 4.2.7 (version date 27 May 2004; The Cochrane Collaboration). The weighted mean difference (WMD) between the treatment and control groups was selected to represent the difference in continuous outcomes. To perform a meta-analysis of continuous data using mean differences, one needs to extract the mean values of the outcomes, the standard deviations of the outcomes and the number of participants in whom the outcome was assessed in each of the two groups. All but one study reported these data. In the study by Madkour *et al.*,[12] missing standard deviations were obtained by multiplying standard errors of means by the square root of the sample size: s.d. $=$ S.E. $\times \sqrt{N}$.[13] The binary measure for individual studies and pooled statistics is reported as the risk ratio (RR) between the experimental and control groups with 95% confidence intervals (CI). We calculated the number needed to treat as the inverse of the pooled absolute risk differences and 95% CI. The weights given to each study are based on the inverse of the variance. We also estimated outcomes from figures in studies that gave results only in figures but not in numbers. As this was impossible in the case of one study,[14] we attempted to contact the corresponding author for clarification, but with no success.

We used the Q test (chi-square statistics) with an α of 0.1 to test heterogeneity among pooled estimates. For the primary outcomes when there was statistically significant heterogeneity in outcomes across studies, sensitivity analyses according to each of the four parameters of trial methodological quality were conducted.

To test for publication bias, we used a test for asymmetry of the funnel plot proposed by Egger *et al.*[15] This

test detects funnel plot asymmetry by determining whether the intercept deviates significantly from zero in a regression of the normalized effect estimate (estimate divided by its standard error) against precision (reciprocal of the standard error of the estimate) weighted by the reciprocal of the variance of the estimate.

RESULTS

Studies

The meta-analyses reported here are presented according to the standards set out in the 1999 Quality of Reporting of Meta-analyses (QUOROM) statement.[16]

Description of studies

The search yielded 23 citations.[12, 14, 17–37] Nine RCTs[12, 14, 17–21, 29, 31] met the inclusion criteria for this systematic review (see Table 1). The remaining 14 studies were excluded. Table 2 summarizes characteristics of the excluded trials, including the reasons for exclusion.

The nine selected studies recruited a total of 1238 participants (622 in the experimental group and 616 in the control group). Four studies were placebo controlled.[12, 17, 18, 31] In the remaining five trials, there was no additional intervention in the control group. Five studies were based in European countries with a high Human Development Index (HDI)[38] (i.e. France, Italy, Lithuania) and four, in countries with a medium HDI (i.e. Egypt, Thailand, China). The age of the participants was similar in all studies. The daily dose of the study product was similar, although there were some differences in the duration of intervention, which varied from 2 to 6 days. Three trials did not report the duration of the intervention. There was clinical heterogeneity among the trials in settings (in-patients and/or out-patients). Furthermore, there was variability in definitions of outcome measures and the termination of diarrhoea (Table 1).

The methodological quality of the trials also varied (Table 1). Allocation concealment was adequate in only one trial, unclear in three of the trials, and inadequate in the remaining five trials. Only three were double-blind studies, but often it was not stated who was blinded. The remaining trials were open trials. The completeness of follow-up was adequate in all trials. Intention-to treat analysis was performed in only five trials.

Duration of diarrhoea

Seven trials reported data on the duration of diarrhoea.[12, 14, 17–21, 31] Except for one,[17] all studies provided a measure of variance. A meta-analysis of six RCTs (1076 participants) showed a reduction in the duration of diarrhoea of −22.7 h (95% CI: −24.8 to −20.6) for those treated with smectite compared with placebo (Table 3). Changing our meta-analysis model from fixed to random effects did not change the results (−24.4, 95% CI: −29.8 to −19.1). The included studies were significantly heterogeneous ($\chi^2 = 21.4$, $P = 0.0007$). Preplanned sensitivity analyses based on the trial methodological quality were performed. Statistically significant between-study heterogeneity persisted in sensitivity analyses, suggesting that differences in outcomes between studies were caused by factors other than differences in methodological quality. A funnel plot and Egger *et al.*'s[15] regression asymmetry test ($P = 0.7$ and 95% CI included 0) did not show any publication bias or other small sample bias.

Data from one study that presented only the mean values (without the standard deviations of the outcomes)[17] were not included in the meta-analysis. These data showed a reduction in the duration of diarrhoea for those treated with smectite compared with controls.

Stool volume

Two studies provided data on the volume of diarrhoea; however, different units were used (Table 4).[12, 29] One methodologically rigorous RCT showed no effect of smectite on stool volume at various time intervals.[12] Another methodologically much weaker RCT showed a significant reduction in the stool outcome for those treated with smectite compared with placebo at various time intervals.[29]

Frequency of stools

Two studies provided a measure of variance.[12, 29] A meta-analysis of these studies did not show a reduction in the frequency of diarrhoea for those treated with smectite compared with placebo at 0–6 h (two RCTs, $n = 150$, WMD −0.07, 95% CI: −0.6 to 0.4), at 6–24 h (two RCTs, $n = 150$, WMD −0.33, 95% CI: −0.8 to 0.2), or at 24–48 h (two RCTs, $n = 147$, WMD −0.62, 95% CI: −1 to −0.2). However, it did show a reduction in the frequency of diarrhoea for those treated with smectite compared with placebo at 48–72 h (two RCTs, $n = 125$,

Table 1. Characteristics of included trials

Author (country)	Generation of allocation sequence	Allocation concealment*	Blinding	ITT†	FU‡	*N* (experimental/ control)	Inclusion criteria	Exclusion criteria	Age (months)	Dose (per day)	Duration of intervention	Definition of termination of diarrhoea
Gilbert *et al.*[17] (France)	Not described	Unclear	DB	No	+	36 (18/18)	Moderate to severe diarrhoea	Associated disorders; poor nutritional status	2–24 (hospitalized)	3–6 g/day	Not provided	Return to the average daily stool number for the patient
Guarino *et al.*[14] (Italy)	Inadequate [according to date of admission (the first two children seen each month by each paediatrician)]	Inadequate	No	No	+	804 (398/406; or 406/398 as there was inconsistency in reporting)	Acute diarrhoea (≥3 loose or liquid stools per day), age 3 months to 5 years, with acute onset diarrhoea with mild to moderate severity	Administration of antibiotics, probiotics, or other drugs considered to be active in the intestine in the prior 3 weeks; the onset of diarrhoea more than 48 h before being seen by the paediatrician; a weight–height ratio <5th percentile, and any chronic disease or immunosuppressive conditions or treatments	3–60 (out-patient)	3 or 6 g/day in subjects younger or older than 1 year, respectively	5 days	From the first to the last liquid loose stool output preceding the return of normal stools
Lachaux *et al.*[18] (France)	Adequate (by drawing lots)	Inadequate	DB	+	+	36 (17/19)	Acute diarrhoea <4 days with moderate or severe dehydration, absence of any associated disorders, good nutritional status	Not provided	2–24 (hospitalized only)	3 g/day (<1 year) or 6 g/day (>1 year)	Not provided	Time to the production of the first stool of normal appearance without a relapse
Lexomboon *et al.*[19] (Thailand)	No details on method of randomization	Inadequate	No	+	+	66 (34/32)	Acute diarrhoea (≥3 fluid stools within 24 h for <48 h), no history of previous treatment with antibiotics or antidiarrhoeal drugs	Dehydration >7%, fever >38.5%, dysentery, malnutrition >1st degree, chronic diarrhoea, parasitic diarrhoea, social or family problems incompatible with follow-up	1–24 (out-patient only)	3 g/day	Not provided	From the beginning of therapy to normalization defined as the last liquid stool followed by 2 soft or solid stools
Madkour *et al.*[12] (Egypt)	Adequate (numerically coded envelopes)	Adequate	DB	+	+	90 (45/45)	Boys; watery diarrhoea <5 days, with mild, moderate, or severe dehydration	Prolonged diarrhoea, over malnutrition, major systematic illness	3–24 (hospitalized only)	6 g/day	3 days	From 0 h to last liquid stool
Narkeviciute *et al.*[21] (Lithuania)	Inadequate (alternation)	Inadequate	No	No	+	54 (28/26)	Acute diarrhoea (≥3 stools during 24 h but not more than 72 h before admission) and mild to moderate dehydration	Age <6 or >48 months, duration of diarrhoea >72 h, severe dehydration, concomitant illness (e.g. pneumonia, urinary tract infection, meningitis, malnutrition, shock), and acute infection or other diseases requiring specific additional treatment	6–48 (hospitalized)	3 g at the beginning of rehydration and then 4.5 g/day for children up to 10 kg, and 6 g/day for children 10–20 kg	Up to 24 h after normalization of the stools	One of the following was met: (i) passage of the first formed stool; (ii) passage of the 2nd semisolid stool; (iii) passage of the last unformed (semisolid) stool if no stools were passed for 24 h

Table 1. Continued

Author (country)	Generation of allocation sequence	Allocation concealment*	Blinding	ITT†	FU‡	*N* (experimental/ control)	Inclusion criteria	Exclusion criteria	Age (months)	Dose (per day)	Duration of intervention	Definition of termination of diarrhoea
Osman *et al.*[29] (Egypt)	Inadequate (alternation)	Unclear	No	No	+	60 (30/30)	Acute watery diarrhoea <7 days duration with mild to moderate dehydration; absence of systematic illness; absence of coincident extraintestinal infection, no intake of antibiotics or antidiarrhoeal drugs, weight to height ratio >80% of then international standards	Not given	Mean age in smectite group 12.4 ± 10.3, in control group 14.5 ± 11 (out-patient and hospitalized)	4.5 g/day in children <10 kg; 6 g/day for children >10 kg	Maximum 5 days	Return of stools to the formal formed consistency; return of frequency of movements to the average daily habits
Vivatvakin *et al.*[20] (Thailand)	No details on method of randomization	Unclear	No	+	+	62 (32/30)	Acute secretory diarrhoea (3 or more liquid stools per day, <3 days prior to admission) with mild or moderate dehydration	Medical treatment during the past 2 days, <1 or >24 months, severe dehydration, serious illness or chronic disease, 3rd degree malnutrition; diarrhoea due to *Vibrio cholerae*, or dysentery	1–24 (hospitalized)	1.5 g at the beginning of rehydration and then after 3 g/day for children <3 kg; 4.5 g/day for children 4–10 kg; 6 g/day for children 11–15 kg	Minimum 48 h to maximum 120 h	From the first drug administration to the passage of the last liquid stool prior to a formed stool
Zong *et al.*[31] (China)	Adequate (computer generated)	Inadequate	No	+	+	30 (20/10)	Acute diarrhoea (not defined)	Bloody diarrhoea	<3 years	<12 months 1 g/dose 2–3 times daily; >12 months 1.5 g/dose 3 times daily	3–6 days	≤4 stools

*Allocation concealment – adequate, randomization method described that would not allow investigator/caregivers to identify or influence the intervention group before eligible participants entered the study; unclear, randomization stated but no information about method used was provided; inadequate, use of an inappropriate method of randomization (e.g. alternate medical record numbers or unsealed envelopes) and/or any information in the study indicating that investigators or participants could influence the intervention group.

† ITT analysis – yes, specifically reported by authors that ITT analysis was undertaken and this was confirmed by our study assessment; yes, not stated but confirmed by our study assessment; no, not reported and lack of ITT analysis confirmed by our study assessment (patients who were randomized were not included in the analysis because they did not receive the study intervention, they withdrew from the study, or were not included because of protocol violation); no, stated but not confirmed by our study assessment.

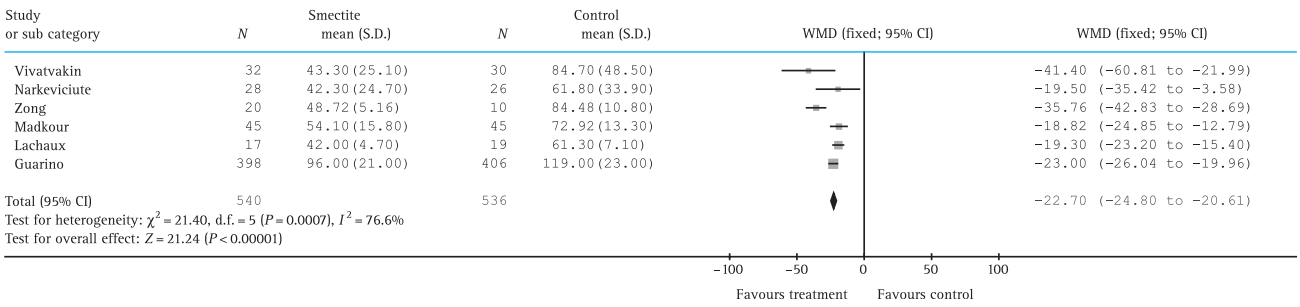
‡ Completeness of follow-up: trials with >80% follow-up of participants.

DB, double-blind; ITT, intention-to-treat.

Table 2. Characteristics of the excluded studies

Study	Reason(s) for exclusion
Anonymous[25]	Translation of reference[12]
DuPont *et al.*[26]	Non-randomized; clinical outcomes not studied
Fodor *et al.*[27]	Explored the effect of smectite compared with nifuroxazide
Kang *et al.*[33]	RCT; explored the effect of smectite given in combination with amoxicillin
Karas[24]	Non-randomized, prospective-controlled trial; compared with probiotics (*Escherichia coli*, *Streptococcus faecalis*, *Lactobacillus acidophilus*, *Lactobacillus helveticus*)
Leber[28]	Explored the effect of smectite compared with loperamide
Louchet and Chapoy[35]	Non-randomized-controlled trial in neonates
Milocco *et al.*[23]	Non-randomized-controlled clinical trial
Pociecha and Balcerska[22]	Randomized, open trial, additional treatment (probiotics) was used
Tazi-Lakhsassi and Ben Alloum[30]	Abstract (full report not published)
Wan and Zhong[34]	RCT; explored the effect of smectite given in combination with P.O. Bifidobiogen
Wu Shi *et al.*[32]	Abstract (full report not published)
Zhang[36]	Observational study in neonates
Zhou[37]	Study in neonates

Table 3. Smectite vs. control [mean duration of diarrhoea (h)]



WMD −0.58, 95% CI: −0.9 to −0.3) and at 72–96 h (one RCT, $n = 44$, WMD −1.87, 95% CI: −3 to −0.7) as well as in the total number of stools (one RCT, $n = 90$, WMD −2.5, 95% CI: −3.8 to −1.2). Data from one study that presented the results as a figure[14] only were not included in the meta-analysis. These data showed a reduction in the frequency of diarrhoea for those treated with smectite compared with controls.

Vomiting

Four RCTs provided data on vomiting.[12, 14, 21, 29] There was no difference in the number of episodes of vomiting (two RCTs,[12, 21] WMD −0.02, 95% CI: −0.5 to 0.6). Based on the results of the only one RCT to report this outcome, there was no difference in the duration of vomiting (mean difference −0.1 h, 95% CI: −0.15 to 0.3).[12] Guarino *et al.*[14] reported that administration of smectite compared with control had no effect on the incidence of vomiting on day 1 (RR 1.0, 95% CI: 0.9–1.2) and day 3 of the intervention (RR 1.2, 95% CI: 0.9–1.4). There was also a similar percentage of patients with vomiting in the study by Osman *et al.*[29] (RR 1.4, 95% CI: 0.9–2.3).

Adherence/acceptance

Adherence or acceptance was reported in only a few studies.[14, 17, 18] A meta-analysis of two RCTs[17, 18] showed no difference in the acceptance of smectite

Table 4. Results of two trials on the stool output presented as mean difference (95% CI)

Study (h)	Osman *et al.*[29] (g/day)	Madkour *et al.*[12] (g/kg/day)
0–6	−34 (−156 to 88)	1.5 (−1.7 to 4.7)
6–12	Not reported	−0.2 (−3.9 to 3.5)
6–18	−347 (−715 to 22)	Not reported
12–24	Not given	−0.3 (−3.4 to 2.8)
Total 24	−232 (−462 to −1.6)*	Not reported
24–48	−483 (−657 to −310)*	−0.9 (−4.5 to 2.7)
48–72	−486 (−672 to −300)*	−1.7 (−5.6 to 2.1)
72–96	−355 (−505 to −204)*	−3.3 (−9.1 to 2.5)
Total	Not reported	−13 (−29 to 3.0)

Negative values indicate that stool volume was reduced in the smectite group compared with the control group.
* Significant difference.

compared with control (RR 0.91, 95% CI: 0.78–1.07). Guarino *et al.*[14] reported that approximately 23% of patients refused the smectite during the study, but data for the control group were not reported.

Adverse events

Two RCTs[19, 20] indicated that there was a tendency for more patients to suffer from constipation in the smectite group, but the difference was not statistically significant (RR 5.8, 95% CI: 0.7–47.1). Three RCTs[12, 17, 18] revealed no adverse effects associated with short-term smectite therapy.

Additional outcomes

In addition to the outcome measures identified *a priori*, we also extracted data regarding the percentage of participants cured on days 3 and 5 of the intervention[12, 18–20] as well as the percentage of children with diarrhoea lasting longer than 7 days.[14]

The relative chance of cure on day 3 of the intervention (Table 5) in the smectite group compared with the control group was 1.64 (95% CI: 1.36–1.98) with a fixed effect model and 1.55 (95% CI: 1.29–1.87) with a random effect model. The number needed to treat was 4 (95% CI: 3–5). No heterogeneity in results between studies was found ($\chi^2 = 3.50$, $P = 0.32$). A funnel plot and Egger *et al.*'s[15] regression asymmetry test ($P = 0.38$ and 95% CI included 0) did not show any publication bias or other small sample bias.

The relative chance of cure on day 5 of intervention (Table 6) was significantly higher in the smectite group compared with the control group was 1.24 (95% CI: 1.08–1.42) with fixed effect model, but was not significant with random effect model (1.19; 95% CI: 0.93–1.53). Because heterogeneity was noticeable ($\chi^2 = 8.01$, $P = 0.02$), we present pooled estimates of the difference using the random effect model. A funnel plot and Egger *et al.*'s[15] regression asymmetry test ($P = 0.23$ and 95% CI included 0) did not show any publication bias or other small sample bias.

One trial[14] showed a reduction in the risk of diarrhoea lasting >7 days for those treated with smectite compared with control (RR 0.6, 95% CI: 0.42–0.85; NNT 14, 95% CI: 9–42).

DISCUSSION

A meta-analysis of data from RCTs showed that in children with acute infectious gastroenteritis, smectite compared with control is associated with a moderate reduction in the duration of diarrhoea. The chance of cure on day 3 of the intervention was significantly higher in the smectite compared with the control

Table 5. Smectite vs. control (cure rate on day 3 of intervention)

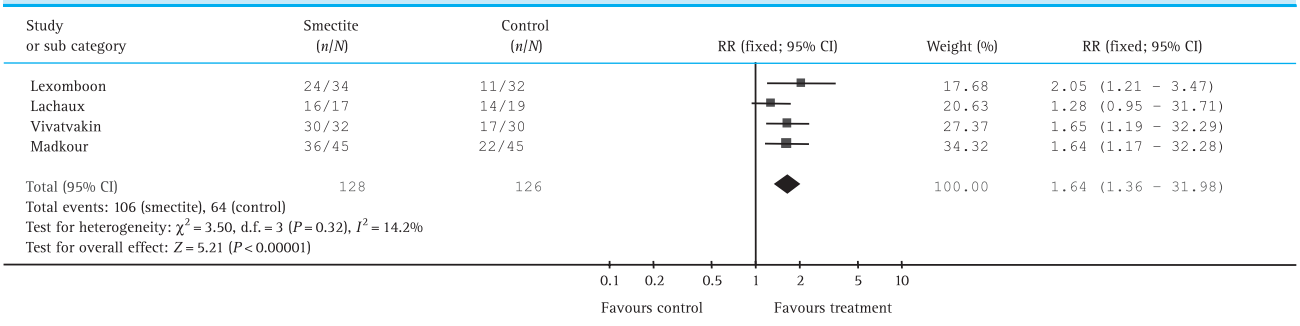
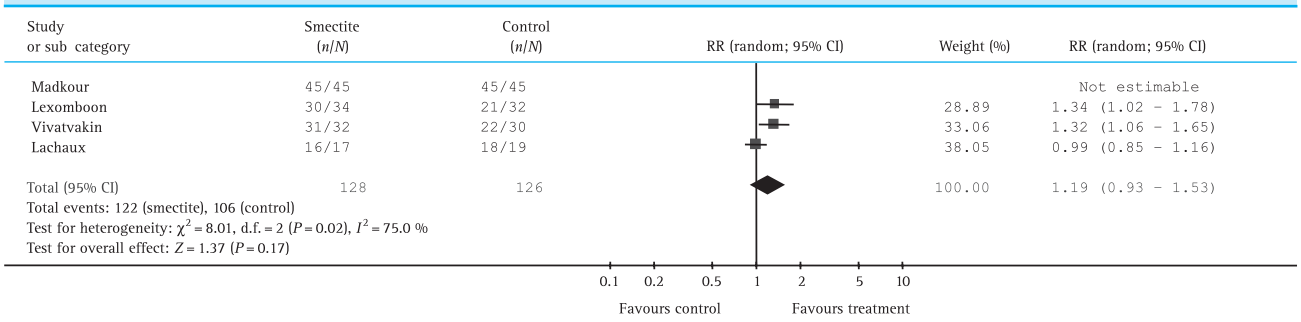


Table 6. Smectite vs. control (cure rate on day 5 of intervention)



group. The number needed to treat was 4. There was also reduced risk of diarrhoea lasting more than 7 days in the smectite group.

The duration of diarrhoea has been used as the primary measure of outcome in most, albeit not all, trials. Unfortunately, this measure alone is not considered optimal. Quantitative diarrhoea criteria are recommended by the World Health Organization for the evaluation of therapeutic agents in the management of acute diarrhoea.[39] With two exceptions, the included studies did not quantitatively evaluate stool output. The two trials that did address this issue measured stool output in various ways using different units. In such circumstances, it is possible to standardize the results of the trials to a uniform scale before they are combined.[40] However, the main disadvantage of the standardized mean difference method is that the overall treatment effect is difficult to interpret, as it is in units of standard deviations rather than in any of the units used in the individual trials. It is also unclear as to what constitutes a clinically important change.[41–43] For these reasons, we abstained from this approach and presented the results in the tabular form. However, the ultimate question is if there is any effect of smectite on stool output. The results of the two trials are mixed. But clearly when interpreting the results, more credit should be given to the trial that was methodologically strong, thus limiting bias. Given these considerations, it is likely that smectite has no effect on stool volume.

In general, smectite has been reported to have a good safety profile. This was confirmed by our review showed that adverse effects were similar in both the control and treatment groups. Previously it was reported that unpleasant taste of smectite may be of concern. However, our report provides no evidence of poor acceptance of the product.

Our analysis has some limitations. First, we cannot fully exclude publication bias. Although we did perform a statistical test for the detection of publication bias, we are aware that these tests have very low power in the meta-analysis of only few trials. However, we did not impose restrictions by language or year of publication and made attempts to identify unpublished trials. Secondly, although the included studies were not significantly heterogeneous, given the small number of studies, statistical conclusions on determinants of heterogeneity might be flawed. Thirdly, meta-analyses are only as good as the constituent studies. Only some of the trials included in our analysis seemed methodologically sound. Potential limitations included unclear or inadequate allocation concealment, no ITT analysis and no blinding. Study limitations also included a small sample size in some trials and no widely agreed-on definition of termination of diarrhoea.

In conclusion, the results emerging from our meta-analysis are promising. However, further well-conducted clinical studies using validated outcomes are recommended to: (i) address the cost-effectiveness of using smectite to treat children with acute diarrhoea, (ii) further delineate the groups (out-patient vs. in-patient, older vs. younger, viral vs. other aetiology of diarrhoea) deriving the greatest clinical benefit from smectite therapy, (iii) determine the most effective dosing schedule and (iv) address the tolerability of smectite therapy. Yet, if money is no object, there is evidence suggesting that some children with acute diarrhoea may benefit by using smectite. However, if this drug is used, it must be borne in mind, as it was recently pointed out in the guideline on management of acute gastroenteritis from the Centers for Disease Control and Prevention[9] that 'the reliance on

pharmacological agents shifts the therapeutic focus away from appropriate fluid, electrolyte and nutritional therapy'. Explanation to parents is needed when smectite is to be prescribed.

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