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[Intervention Review]

Pain-relieving agents for infantile colic

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ABSTRACT

Background

Infantile colic is a common disorder in the first months of life, affecting somewhere between 4% and 28% of infants worldwide, depending on geography and definitions used. Although it is self limiting and resolves by four months of age, colic is perceived by parents as a problem that requires action. Pain-relieving agents, such as drugs, sugars and herbal remedies, have been suggested as interventions to reduce crying episodes and severity of symptoms.

Objectives

To assess the effectiveness and safety of pain-relieving agents for reducing colic in infants younger than four months of age.

Search methods

We searched the following databases in March 2015 and again in May 2016: CENTRAL, Ovid MEDLINE, Embase and PsycINFO, along with 11 other databases. We also searched two trial registers, four thesis repositories and the reference lists of relevant studies to identify unpublished and ongoing studies.

Selection criteria

We included randomised controlled trials (RCTs) and quasi-RCTs evaluating the effects of pain-relieving agents given to infants with colic.

Data collection and analysis

We used the standard methodological procedures of The Cochrane Collaboration.

Main results

We included 18 RCTs involving 1014 infants. All studies were small and at high risk of bias, often presenting major shortcomings across multiple design factors (e.g. selection, performance, attrition, lack of washout period).

Three studies compared simethicone with placebo, and one with *Mentha piperita*; four studies compared herbal agents with placebo; two compared sucrose or glucose with placebo; five compared dicyclomine with placebo; and two compared cimetropium - one against placebo and the other at two different dosages. One multiple-arm study compared sucrose and herbal tea versus no treatment.

Simethicone. Comparison with placebo revealed no difference in daily hours of crying reported for simethicone at the end of treatment in one small, low-quality study involving 27 infants. A meta-analysis of data from two cross-over studies comparing simethicone with placebo

showed no difference in the number of infants who responded positively to treatment (risk ratio (RR) 0.95, 95% confidence interval (CI) 0.73 to 1.23; 110 infants, low-quality evidence).

One small study (30 participants) compared simethicone with *Mentha piperita* and found no difference in crying duration, number of crying episodes or number of responders.

Herbal agents. We found low-quality evidence suggesting that herbal agents reduce the duration of crying compared with placebo (mean difference (MD) 1.33, 95% CI 0.71 to 1.96; three studies, 279 infants), with different magnitude of benefit noted across studies ($I^2 = 96\%$). We found moderate-quality evidence indicating that herbal agents increase response over placebo (RR 2.05, 95% CI 1.56 to 2.70; three studies, 277 infants).

Sucrose. One very low-quality study involving 35 infants reported that sucrose reduced hours spent crying compared with placebo (MD 1.72, 95% CI 1.38 to 2.06).

Dicyclomine. We could consider only one of the five studies of dicyclomine (48 infants) for the primary comparison. In this study, more of the infants given dicyclomine responded than those given placebo (RR 2.50, 95% CI 1.17 to 5.34).

Cimetropium bromide. Data from one very low-quality study comparing cimetropium bromide with placebo showed reduced crying duration among infants treated with cimetropium bromide (MD -30.20 minutes per crisis, 95% CI -39.51 to -20.89; 86 infants). The same study reported that cimetropium increased the number of responders (RR 2.29, 95% CI 1.44 to 3.64).

No serious adverse events were reported for all of the agents considered, with the exception of dicyclomine, for which two of five studies reported relevant adverse effects (longer sleep 4%, wide-eyed state 4%, drowsiness 13%).

Authors' conclusions

At the present time, evidence of the effectiveness of pain-relieving agents for the treatment of infantile colic is sparse and prone to bias. The few available studies included small sample sizes, and most had serious limitations. Benefits, when reported, were inconsistent.

We found no evidence to support the use of simethicone as a pain-relieving agent for infantile colic.

Available evidence shows that herbal agents, sugar, dicyclomine and cimetropium bromide cannot be recommended for infants with colic.

Investigators must conduct RCTs using standardised measures that allow comparisons among pain-relieving agents and pooling of results across studies. Parents, who most often provide the intervention and assess the outcome, should always be blinded.

PLAIN LANGUAGE SUMMARY

Pain-relieving agents for infantile colic

Review question

Do infants who have colic during the first four months of life benefit from pain-relieving agents (substances to alleviate/prevent pain) when compared with infants who are given no substance or a placebo (a substance that is identical to the drug but has no active ingredient)?

Background

Infantile colic, which is a common problem in infancy, occurs in the first four months of life in otherwise healthy infants. It is characterised by episodes of excessive crying and often leads to anxiety in parents and in doctors who work with infants.

Pain-relieving agents, such as drugs (e.g. simethicone, dicyclomine, cimetropium), herbal remedies (e.g. *Matricaria recutita*, *Foeniculum vulgare*, *Melissa officinalis*) and sugar, have been proposed to reduce the symptoms associated with infantile colic, particularly the amount of time spent crying.

Study characteristics

We found 18 randomised controlled trials (studies in which participants were randomly assigned to one of two or more treatment groups) involving 1014 infants with infantile colic. The evidence is current to May 2016.

Infants were eight to 16 weeks old, and males and females were equally represented. All infants had colic, defined in one of two ways. Some studies defined it as inconsolable crying in otherwise healthy infants, lasting longer than three hours per day for more than three days a week for longer than three weeks. Other studies defined colic as attacks of screaming and crying (usually in the afternoon, or in the early evening) during which the infant failed to respond to any amount of comforting by adults.

Four studies explored the effects of simethicone (a drug used to reduce excess gas in the intestinal tract); four studies looked at herbal agents (plant-derived remedies that might have relaxing properties that reduce cramps and pains in the bowel); two studies looked at

sugar; and five studies explored the effects of dicyclomine and two the effects of cimetropium bromide (drugs that relieve bowel muscle spasms). One study compared sucrose and herbal tea in a group of infants who received no treatment for colic.

Sixteen of 18 studies compared the intervention with a placebo. Among the other two studies, one compared simethicone with *Mentha piperita*, and the other compared two different dosages of cimetropium.

Included studies received funding from different sources: a public institution (two studies), academic funds (one study) and private companies (three studies). Three studies received no funding. Nine studies did not report whether the study received funding. In four studies that reported no funds and no details about funds, private companies supplied the products (pain-relieving agents).

Key results

Available data provide no evidence that sugar, dicyclomine and cimetropium are effective interventions in the treatment of colic. Some evidence suggests that, compared with placebo or no treatment, herbal agents may reduce crying time. However, because the quality of these studies was very poor and the extent of the benefit observed was variable, these results should be interpreted with caution. The same is true for sugar, dicyclomine and cimetropium, for which we judged the quality of evidence as low or very low.

Studies that tested simethicone reported no benefit from administration of this drug over placebo.

Two studies reported side effects for dicyclomine, for example, difficulty awakening, wide-eyed state and drowsiness. Studies of other pain-relieving agents reported no side effects as a result of treatment.

Quality of the evidence

Low-quality evidence indicates that infants with colic may benefit from treatment with sugar and cimetropium, and that herbal agents may reduce crying time. Moderate-quality evidence suggests that these agents increase the number of children experiencing improvement in symptoms. Overall, evidence is insufficient to allow firm conclusions about the benefits and side effects of the pain-relieving agents examined for treatment of crying due to infantile colic.