



ORIGINAL ARTICLE

Infantile colic: A systematic review of medical and conventional therapies

Belinda Hall, Janice Chesters and Anske Robinson

Department of Rural and Indigenous Health, Faculty of Medicine, Nursing and Health Sciences, Monash University, Moe, Victoria, Australia

Aim: Infantile colic is a prevalent and distressing condition for which there is no proven standard therapy. The aim of this paper is to review medical and conventional treatments for infantile colic.

Methods: A systematic literature review was undertaken of studies on medical and conventional interventions for infantile colic from 1980 to March 2009. The results and methodological rigour of included studies were analysed using the CONSORT (Consolidated Standards Of Reporting Trials) 2001 statement checklist and Centre for Evidence Based Medicine critical appraisal tools.

Results: Nineteen studies and two literature reviews were included for review. Pharmacological studies on Simethicone gave conflicting results and with Dicyclomine hydrochloride and Cimetropium bromide results were favourable but side effects were noted along with issues in study methodology. Some nutritional studies reported favourable results for the use of hydrolysed formulas in bottle-fed infants or low-allergen maternal diets in breastfed infants but not for the use of additional fibre or lactase. There were several issues in regards to methodological rigour. Behavioural studies on the use of increased stimulation gave unfavourable results, whereas results from the use of decreased stimulation and contingent music were favourable. These studies demonstrated poor methodological rigour.

Conclusion: There is some scientific evidence to support the use of a casein hydrolysate formula in formula-fed infants or a low-allergen maternal diet in breastfed infants with infantile colic. However, there is little scientific evidence to support the use of Simethicone, Dicyclomine hydrochloride, Cimetropium bromide, lactase, additional fibre or behavioural interventions. Further research of good methodological quality on low-allergenic formulas and maternal diets is indicated.

Key words: infantile colic; medical and conventional therapies; systematic review.

What is already known on this topic

- 1 There are a wide range of pharmacological, nutritional and behavioural interventions used for infantile colic but there is no standard care.
- 2 Infantile colic is estimated to affect up to 40% of infants aged from 2 weeks to 3 months.
- 3 Infantile colic is associated with higher levels of maternal stress and anxiety.

What this paper adds

- 1 Pharmacological interventions for infantile colic are not effective or appropriate.
- 2 There is some scientific evidence to support the use of some nutritional interventions for infantile colic.
- 3 Studies on behavioural interventions for infantile colic are limited and do not provide adequate evidence for the use of these treatments.

Infantile colic is estimated to affect between 3 and 40% of infants aged from two weeks to three months.¹ Although benign and self-limiting, it is associated with higher levels of maternal stress and anxiety,^{2,3} and increased infant crying has even been suggested as a factor in shaken baby syndrome.⁴ Suggested possible implications later in life include difficulties in family communication, dissatisfaction, sleeping disorders and psy-

chological and gastrointestinal disorders.⁵⁻⁷ Other researchers however, have concluded that there are no long-term consequences.⁸

The most widely used definition for infantile colic is based on Wessel's 1954 description of an infant who, otherwise healthy and well-fed, had paroxysms of irritability, fussing or crying lasting for a total of more than three h a day and occurring on more than three days in any one week.⁹ Additional features may include drawing up of the knees, excessive flatus, no relief upon feeding and a mainly late afternoon/early evening timing of episodes.^{9,10}

Proposed causes for this condition have included alterations in gut hormones, microflora, molecular absorption and gas

Correspondence: Dr Anske Robinson, Department of Rural and Indigenous Health, School of Rural Health, Faculty of Medicine, Nursing and Health Sciences, Monash University, PO Box 973, Moe, Vic. 3825, Australia. Fax: +61 3 51281080; email: anske.robinson@monash.edu

Accepted for publication 19 December 2010.

production^{11–16} along with allergy to cows milk proteins or other substances in the maternal diet.^{17–21} Lactose intolerance has been suggested as a cause of infantile colic by some²² but not others.²³ Behavioural issues such as family tension, parental anxiety or inadequate parent-infant interaction have also been explored.^{9,24,25} Earlier papers suggest a possible imbalance of the central nervous system^{9,26} although later studies do not agree.²⁷ Others have claimed that infantile colic is a manifestation of normal emotional development.¹⁰ Possible risk factors include maternal smoking, increased maternal age and firstborn status.^{28–32} There appears to be no association between method of feeding and infantile colic.^{33,34}

The above possible causes of infantile colic have led to a variety of available treatments. These range from drug therapies, various nutritional changes and behavioural strategies through to the use of several complementary and alternative therapies, such as chiropractic or herbal remedies. Drug therapies have included Simethicone or Dicyclomine hydrochloride.^{35–37} Nutritional interventions range from different types of hydrolysed formula to hypoallergenic maternal diets.^{35–37} Behavioural interventions include parental counselling and advice on methods that either increase or decrease stimulation.^{35–37} However, despite the plethora of information on this prevalent condition, there is as yet no standard care.

The primary focus of this paper is to review the effectiveness of pharmacological, nutritional and behavioural interventions for infantile colic. A secondary aim is to explore issues relevant to future investigations into management of this condition.

Methodology

A systematic review of literature³⁸ was undertaken between January and June 2009 drawing on studies of interventions for infantile colic published between 1980 and March 2009. Electronic databases searched included Ovid Medline, Embase, the Cochrane Library, CINAHL, Meditext and Proquest. Key search terms utilised, both as MeSH and key words are provided in Table 1. English language studies were included.

Results were screened according to the process given in Figure 1.

Studies used in the review included randomised controlled trials, cohort studies, pilot studies and quasi-experimental studies assessing a treatment for infantile colic. Literature reviews of treatments for infantile colic were also included.

Papers Included in the study were read and assessed for methodological quality and results according to the CONSORT 2001 checklist³⁹ plus Centre for Evidence Based Medicine critical appraisal tools.⁴⁰ Results from this analysis were summarised within a matrix.⁴¹ Comments on each intervention type and relevant studies were drawn from these.⁴²

Hall, the first author, carried out the search for relevant literature for this review. Hall also created the matrix and the tables, which are included methodology and key results of each included study. Chesters and Robinson reviewed the articles against the extracted data in the matrix. Regular discussions were held among all authors throughout the search for relevant articles, analysis of papers, construction of the tables and development of the manuscript. All the authors contributed to the final manuscript.

Table 1 Key terms

Infant*colic AND (each of separately)

- Drug*/medication
- Simethicone
- Dicyclomine
- Relaxation therapy
- Family therapy
- Music therapy
- Behavioural therapy
- Parent-child /parent*
- Education
- Lactose
- Milk/milk protein/whey/casein
- Formula
- Diet*
- Soy*/soy milk
- Allergy/hypersensitivity

*Includes any extension to the listed word.

Results

There were 19 studies and two literature reviews retrieved on medical and conventional therapies of which five were on pharmacological treatments, 10 on nutritional interventions and four on behavioural therapies. Study details are given in Table 2.

Pharmacological studies

Studies on three different drugs were found.

Simethicone

Danielsson and Hwang found a comparable decrease in crying duration from 6.27 ± 2.40 h to 4.24 ± 2.18 h per day in infants given Simethicone to that of placebo results of 4.37 ± 2.55 h per day.⁴³ Metcalf *et al.* also found no significant difference between Simethicone and placebo for infantile colic.⁴⁴

Dicyclomine hydrochloride

Hwang and Danielsson found a decrease in crying time from 4.9 ± 3.7 h to 3.3 ± 3 h per day in infants given Dicyclomine hydrochloride compared to 4.3 ± 3.9 h per day with a placebo.⁴⁵ Weissbluth *et al.* found mean hours of colic while using this drug to be 1 ± 0.8 h per day compared to 3.9 ± 1.4 h per day with a placebo.⁴⁶ Side effects of drowsiness were reported in both these studies.^{45,46}

Cimetoprium bromide

Savino *et al.* found a significant decrease in the duration of each colic episode to 17.3 ± 12.6 min with Cimetoprium bromide compared to 47.5 ± 28.5 min with a placebo.⁴⁷ There were reported side effects of increased sleepiness.⁴⁷

Validity of pharmacological study results

All pharmacological studies used a randomised controlled trial design. However, the authors of the majority of these studies did

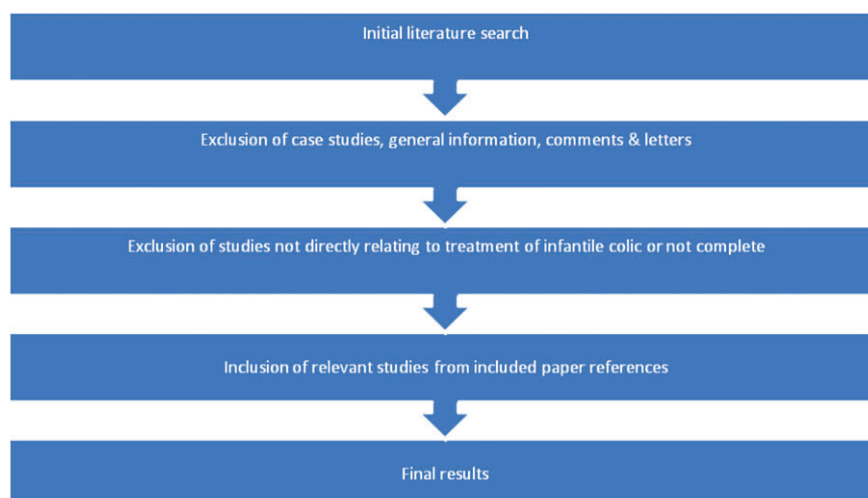


Fig. 1 Literature search process.

not provide clear information for the method of generating the random allocation sequence,^{43,45–47} and the method for implementing randomisation was also unclear in two studies.^{45,47} There was no definition given for infantile colic in one study on Simethicone⁴³ and no presentation of baseline demographics in the study on Cimetropium.⁴⁷ Although statistical tests were quoted by some authors, results of these tests were not always clearly presented.^{43–45} Appropriate further statistical tests including analysis accounting for loss of subjects were used by Weissbluth.⁴⁶ There were no calculations presented or reasoning given to estimate sample sizes in any of the studies or analysis of the number of patients needed to treat (NNT) in order to obtain a significant result.^{43–47}

Nutritional studies

Studies on several different nutritional interventions were included for review.

High-fibre formula

Treem found no significant change in crying in formula-fed infants with the use of a high-fibre soy formula with an average duration of crying and fussing by the end of this study of 3.8 h (1.5–10.8) for the fibre group and 4.4 h (1.4–10.2) for the placebo.⁴⁸

Low-allergenic formulas

Jakobsson *et al.* found a significant reduction in crying duration in formula or breastfed infants with the use of two different casein hydrolysate formulas from 7.36 ± 1.32 h per day to 2.21 ± 0.40 and 2.93 ± 0.70 h per day.⁵⁰ Forsyth found no significant difference in the duration of crying in formula-fed infants by the end of their study utilising a similar low-allergenic formula.⁴⁹

Lucassen *et al.* found a reduction in the average duration of crying per day in formula-fed infants within one week with the use of a Whey hydrolysate formula.⁵¹ Savino *et al.* demonstrated a significant decrease in the number of colic episodes in

formula-fed infants after one week with the use of a formula containing partially hydrolysed whey, oligosaccharides, B-palmitic acid and low lactose.⁵² By day 14 of this study, hours crying per day in the formula group decreased to 1.76 ± 1.60 and in the placebo group to 3.32 ± 2.06 .⁵²

Low-allergenic maternal diet or formula

Hill *et al.* demonstrated a significant reduction in infant distress levels with the use of a low-allergen diet for a week either as a casein hydrolysate formula in formula-fed infants or low-allergen maternal diet in breastfed infants compared to a control diet.⁵⁴ Oggero *et al.* found a low-allergen maternal diet resulted in a 62.5% improvement in the duration of crying in breastfed infants with infantile colic compared to a 66.6% improvement with the drug Dicyclomine hydrochloride.⁵³ In formula-fed infants, soy formula resulted in a 65.9% improvement compared to 53.3% with this drug and soy followed by hydrolysed milk a significant improvement of 95.4%.⁵³ A low-allergen maternal diet for one week demonstrated a decrease in cry/fuss duration in breastfed infants by 74% compared to 37% for a control diet in a study by Hill *et al.*⁵⁵

Lactase

The use of this enzyme resulted in a non-significant decrease in crying time of 22.4% in a study by Kanabar.²² By only including compliant subjects, this figure was increased to 40.4%.²² Miller found a reduction in crying/fussing duration with lactase to 225 ± 22 min compared to 185 ± 25 min for the placebo.⁵⁶

Of note is that there were no side effects reported in any of the above nutritional studies.

Validity of results of nutritional studies

Despite the use of a controlled trial design, the method for generating the random allocation sequence was not clearly stated in the majority of papers on nutritional interventions,^{22,48,50,52–54,56} and the method for implementing

Table 2 Analysis of studies – medical and conventional treatments for infantile colic

Studies			Results		
Intervention/study design	Author/year/country	Sample/outcome/definition	Effectiveness	Validity	Other
Pharmacological Simethicone vs. Placebo X-over RCT	Danielsson & Hwang 1985 ⁴³ Sweden	27/32 infants 2–8 weeks Crying duration, frequency, intensity No definition for colic	Significant decreased crying in both groups Overall 67% improvement	Randomisation unclear Blinding unclear Statistics unclear No dates	
	Metcalfe <i>et al.</i> 1994 ⁴⁴ US	83/92 infants 2–8 weeks Crying duration Symptoms Wessel criteria	No statistical difference between each group Improvement 28% with simethicone 37% with placebo	Some randomisation unclear Blinding unclear No other statistics given	Cash incentives for participants
Dicyclomine hydrochloride vs. Placebo X-over RCT	Hwang & Danielsson 1985 ⁴⁵ Sweden	30 infants av. 4.5 weeks Crying duration Wessel criteria	Significant improvement with Dicyclomine but not symptom-free Reduced crying to 3.3 h with drug, 4.3 h with placebo	Randomisation unclear Blinding unclear No other statistics No dates	3.3 h/day crying still colic according to Wessel Side effect of drowsiness Very brief article
	Weissbluth <i>et al.</i> 1984 ⁴⁶ US	42/48 infants age unspecified Colic duration/elimination Wessel criteria	Dicyclomine significantly more effective than placebo P = 0.02 (Students t test) Dicyclomine eliminated colic in 65% of infants, placebo 32%†	Some randomisation unclear Blinding flawed (placebo = cherry syrup) No baseline outcome measurements Minimal statistics No CI	Varying doses of drug used Side effect of drowsiness
Cimetropium bromide vs. Placebo RCT	Savino <i>et al.</i> 2002 ⁴⁷ Italy	86/90 infants aged 15–60 days Duration of crying episodes Side effects Wessel criteria	Reduced crying with drug compared with placebo P < 0.005† (t test) Response to drug 74%, placebo 33%	Randomisation unclear No baseline characteristics Double blinding Minimal statistics No CI	No mention of total crying duration per day Side effect of sleepiness
	Nutritional Fibre-enriched formula vs. Placebo X-over RCT	27/33 infants 2–8 weeks, breastfed Duration of crying & crying/fussing† Breath hydrogen levels Wessel-like criteria	No significant difference in crying between formulas Significantly higher hydrogen levels with fibre formula P = 0.01	Randomisation unclear Single blinding? Small sample size No dates	Soy often allergenic
Caesin hydrolysate formula vs. Cows milk formula X-over RCT	Forsyth 1989 ⁴⁹ US	17/32 infants < 8 weeks, formula-fed Crying duration Wessel-like criteria	On initial change more crying and colic on cows milk formula than hydrolysate P < 0.01 (Sign test) No significant difference on final change	Some randomisation unclear Some blinding unclear Small sample size No dates	Found great day to day variability in colic and crying independent of formula used

Casein hydrolysate 1 vs. Casein hydrolysate 2 vs. Challenge with Cows milk X-over RCT	Jakobsson <i>et al.</i> 2000 ⁵⁰ Sweden	15/22 infants 2–8 weeks, formula or breastfed Duration of crying† Modified Wessel criteria	Significant reduction in crying with both casein formulae $P < 0.01$ (Wilcoxon signed-rank test) Significant difference on challenge	Randomisation unclear Blinding unclear Statistics but no CI Small sample size No dates	Trial terminated due to time factors Natural resolution of colic around 3 months
Whey hydrolysate formula vs. Cows milk formula RCT	Lucassen <i>et al.</i> 2000 ⁵¹ Netherlands	38/98 infants < 6 months, formula-fed Duration of crying/behaviour† Wessel-like criteria	Significant decrease in crying duration with whey formula compared to cows milk formula $P = 0.04$ adjusted for confounders (95% CI 1 to 127 min)	Randomisation clear Double blinding Intention to treat large number of drop-outs Problems with sampling size	
Modified formula vs. Standard formula & Simethicone RCT	Savino <i>et al.</i> 2006 ⁵² Italy	199/267§ infants < 4 months, formula-fed Duration of crying/colic episodes Wessel criteria	Greater number of colic episodes with standard formula than new formula at end of trial $P < 0.0001$ (95% CI –1.0 to 2.1, Student t test)	Randomisation unclear Single blinding only 95% CI	Multiple variables in formula (partially hydrolysed whey, oligosaccharides, B-palmitic acid and low lactose)
Low-allergen maternal diet or formula (soy or hydrolysate) vs. Regular diet or formula & Dicyclomine Controlled trial	Oggero <i>et al.</i> 1994 ⁵³ Italy	120 infants 3–12 weeks Breast or formula-fed Duration of crying Wessel-like criteria	No significant difference between breastfed low-allergen diet and Dicyclomine or soy formula and drug Significant positive difference between hydrolysed formula and drug $P < 0.01$	No randomisation? Blinding unclear Baseline characteristics unclear Drop-outs unclear No CI	Conclude dietary modifications give better results than drugs but only hydrolysed formula better than drug, low-allergen maternal diet and soy formula no different to drug
Low-allergen maternal diet or formula (casein hydrolysate) vs. Regular diet or formula RCT	Hill <i>et al.</i> 1995 ⁵⁴ Australia	115/158§ infants 4–16 weeks, breast or formula-fed Infant distress levels Wessel criteria	Significant decrease in distress levels in low-allergen diet by 61% compared to 43% on regular diet, $P = 0.047$ (OR 2.12, 95% CI 1.00–4.46) Crying reduced more in low-allergen group $P < 0.001$ (95% CI 18.5–6%, two sample t test) Absolute risk reduction of 37%, adjusted = 21%	Randomisation stratified but unclear Double blinding Many drop-outs Results adjusted No dates Randomisation unclear No blinding intention to treat	
Low-allergen maternal diet vs. Normal diet RCT	Hill <i>et al.</i> 2005 ⁵⁵ Australia	90/107‡, § infants av. 5.7 weeks, breastfed Duration of crying/fussing† Wessel criteria			

Table 2 Continued

Studies			Results		
Intervention/study design	Author/year/country	Sample/outcome/definition	Effectiveness	Validity	Other
Lactase vs. Placebo X-over RCT	Miller <i>et al.</i> 1990 ⁵⁶ Australia	12/15 infants av. 6.4 weeks, breastfed Breath hydrogen level Duration of crying	No significant difference between lactase & placebo in crying time or hydrogen levels	Randomisation unclear Drop-outs not accounted for Blinding unclear	Lactase not incubated Lactose intolerance is different clinical condition to infantile colic?
Lactase vs. Placebo X-over RCT	Kanabar <i>et al.</i> 2001 ²² UK	46/53 infants‡ 3–13 weeks, breast or formula-fed Breath hydrogen levels Duration of crying Wessel-like criteria	Significantly lower hydrogen levels with lactase compared to placebo with & without non-compliers $P = 0.0007$ & $P < 0.0001$ Significant lower crying time without non-compliers $P = 0.052$ but not with non-compliers $P = 0.09$ (95% CI 12.9% to 44.4%)	Some randomisation unclear Some blinding unclear High number of drop-outs No baseline characteristics No dates	Lactose intolerance is different clinical condition to infantile colic?
Behavioural Decreased stimulation vs. Modified interaction vs. Control Controlled trial	Taubman 1984 ⁵⁷ US	60 infants <6 months Decreased stimulation Duration of crying Wessel criteria	No significant change with decreased stimulation Significant decrease with modified interaction $P < 0.001$ (Students t test)	No randomisation No blinding Minimal statistics No CI	Natural regression by 3–4 months of age Not all Wessel criteria Control = no colic rather than just no treatment
Supplemental carrying vs. Standard advice RCT	Barr <i>et al.</i> 1991 ⁵⁸ US	66/78‡ infant < 5 weeks Duration & frequency of crying, fussing or crying & fussing Non-Wessel criteria	No difference between groups $P > 0.05$ (95% CI –3.7 to 3.2, Student one way t test) Supplemental carrying of no benefit	Randomisation unclear No blinding No baseline measurement	Minimal detail of intervention
Counselling vs. Car ride simulation vs. Support alone RCT	Parkin <i>et al.</i> 1993 ⁵⁹ Canada	38/45§ infants av. 6.8 weeks Duration of crying Maternal anxiety Modified Wessel criteria	No significant difference between groups under 6 weeks age $P = 0.28$ Over 6 weeks $P = 0.002$ Combining groups 24% decrease in crying and 18% decrease in maternal anxiety	Randomisation No blinding No CI No dates	
Non-contingent music vs. Contingent music X-over trial	Larson 1990 ⁶⁰ US	8 infants 3–7 weeks Duration & frequency of crying Non-Wessel criteria	No change with non-contingent music Decreased crying by 80–90% with contingent music	No randomisation No blinding No baseline characteristics Limited statistics Small sample size	

‡Baseline data. §Dropouts in analysis, §Calculated. av., average; CI, confidence interval; N/N, final participants/initial participants; OR, odds ratio; RCT, randomised controlled trial; vs., versus; X-over, crossover.

Table 3 Systematic reviews including medical and conventional treatments for infantile colic

Author/year	Interventions included (N)	Inclusion criteria	Analysis	Conclusions
Lucassen <i>et al.</i> 1998 ⁶¹	Drugs (10) – dicyclomine, simethicone Diet (10) – soy, hypoallergenic formula, low lactose, fibre, herbal tea Behavioural (4)- increased carrying, decreased stimulation, car ride simulation, specific management techniques other (3)	RCT Some studies more on aetiology rather than treatment eg. Evans <i>et al.</i>	Jadad scale Pooled effect sizes Conclusions from studies with good methodology	Elimination of cows milk protein, certain behavioural interventions and Dicyclomine effective treatments for infantile colic Inconclusive for low lactase and herbal tea
Garrison & Christakis 2000 ⁶²	Pharmacological (7)- Simethicone, Dicyclomine, Scopolamine Dietary (8) – soy, fibre, hypoallergenic formula, lactase Behavioural (4) Naturopathic(3)- sucrose, herbal tea	RCT, no comparison studies Wessel definition English	Based on case definition, randomisation and double-blinding Meta-analysis inappropriate given variability in studies	No conclusive benefit with Simethicone, scopolamine, fibre, removal of cows milk from diet, increased carrying or decreased stimulation. Benefit with Dicyclomine (but side effects), herbal tea, sucrose and hypoallergenic formula

(N), number of studies.

randomisation was also unclear in several studies.^{22,50,53} One study did not use any randomisation.⁵³ A clear description of double blinding was only given by two authors.^{51,54} No baseline demographic characteristics for subjects were presented in two studies,^{22,53} and no definition for infantile colic was provided in one study on lactase.⁵⁶ Only two studies did not give a clear description of statistical test used by the authors.^{48,56} No authors calculated the NNT for the intervention they had studied.

Behavioural studies

Studies on several behavioural interventions for infantile colic were found. Barr found no difference over 12 weeks between a control group and subjects undergoing supplemental (additional) carrying in the duration or frequency of crying/fussing.⁵⁸ Parkin found no significant difference in the duration of crying between subjects who underwent two weeks of counselling on specific management techniques, car ride simulation or in a control group in infants under six weeks of age but a significant difference in infants over six weeks of age.⁵⁹ Taubman found a significant decrease in crying with the use of modified parent-child interaction, involving decreased stimulation, with a mean crying time of 0.8 ± 0.3 reduced from 2.6 ± 1.2 h with the treatment and 0.9 ± 0.5 from 1.0 ± 0.5 h for the control group of non-colicky infants.⁵⁷ The use of contingent music was found to decrease crying in one study by Larson.⁶⁰ There were no reported side effects in any of these studies.

Validity of studies on behavioural interventions

None of the studies on behavioural interventions for infantile colic were of a good quality randomised, controlled trial design.

There was a lack of blinding reported in all these studies.^{57–60} Randomisation was absent in two studies,^{57,60} and the method for generating randomisation was not clearly described in another study.⁵⁸ Taubman used a group of infants without infantile colic as the control.⁵⁷ Two authors used inclusion criteria that were non- or only partially Wessel-like.^{57,58} Results for the amount of improvement in one study were presented as all three interventions combined with no clear individual results.⁵⁹ There was a very small sample size in the study on contingent music along with minimal use of statistics.⁶⁰

Results of previous systematic reviews

There were two systematic reviews that considered a variety of treatments for infantile colic including medical and conventional therapies. A summary of these is given in Table 3.

Lucassen *et al.*

Lucassen *et al.* conducted a systematic review into the effectiveness of treatments for infantile colic that included pharmacological, nutritional and behavioural interventions.⁶¹ Results from their meta-analysis demonstrated elimination of cows milk protein/hypoallergenic formula, Dicyclomine hydrochloride and advice to decrease stimulation to be beneficial for infantile colic.⁶¹ The effect size for these was 0.22, 0.46 and 0.48, respectively.⁶¹ (The side effects of Dicyclomine were considered) Using trials of good quality, the effect size for soy formula was 0.32 with the authors concluding these results were unclear.⁶¹ No significant difference between the use of breastmilk and standard cows milk was found with an effect size of -0.40 .⁶¹ No

benefit was found with the use of Simethicone and increased carrying and holding.⁶¹ There was uncertainty in regards to the use of low-lactose formulas.⁶¹ Conclusions of this study were that treatment for infantile colic should include a trial of hypoallergenic formula along with advice to decrease infant stimulation.⁶¹

Garrison & Christakis

Garrison and Christakis undertook a systematic review of treatments for infantile colic inclusive of pharmacological, nutritional and behavioural treatments.⁶² Results from this review included the use of NNT with hypoallergenic diet giving NNT = 6, soy formula NNT = 2 and reduced stimulation NNT = 2.⁶² The authors concluded that significant benefits for infantile colic were obtained with Dicyclomine (side effects noted) and with hypoallergenic formulas.⁶² No conclusive benefits were found with Simethicone, Scoplamine, fibre, removal of cows milk from diet, increased carrying or decreased stimulation.⁶²

Discussion

Results from literature on pharmacological interventions for infantile colic do not suggest this to be an either effective or appropriate treatment option. The two papers on Simethicone demonstrated this drug to be ineffective for the treatment of infantile colic.^{43,44} Although results from studies on Dicyclomine hydrochloride found this drug to be effective for infantile colic, there were a limited number of studies.^{43,46} Plus in Danielson and Hwang crying time was reduced to 3.3 h but clinically, this still fits the Wessel definition of infantile colic.⁴⁵ There were also reported side effects in both studies on this drug.^{45,46} These side effects are consistent with reported cases of infants where symptoms including apnoea resulted after the ingestion of Dicyclomine.⁶³ The use of this drug is now contraindicated in infants under six months of age.⁶⁴ A Study on Cimetropium bromide found this also to be an effective treatment for infantile colic. However, only one study was retrieved for review and there were reported side effects.⁴⁷ There were methodological issues in most of these drug studies.

These findings on pharmacological treatments for infantile colic are consistent with prior reviews by Lucassen *et al.* and Garrison and Christakis.^{61,62} Of note is that no additional studies to those in aforementioned reviews on pharmacological treatments for infantile colic were found in this systematic review.

Results from several studies on nutritional interventions for infantile colic suggest that the use of casein hydrolysate is beneficial in formula-fed infants.^{50,53,54} Only one study provided results favouring the use of a whey hydrolysate formula.⁵¹ Another study used a modified whey hydrolysate formula with several other modified ingredients which makes it difficult to ascertain the effects of whey hydrolysate alone.⁵² Two out of three studies supported the use of a low-allergen maternal diet for infantile colic in breastfed infants.^{53–55} Results from the only study on the use of a fibre-enriched formula do not suggest this to be an effective treatment for infantile colic.⁵² The use of lactase for infantile colic is also not supported by the literature with two studies giving conflicting results.^{22,56} There were

several problems with methodological rigour in many of these nutritional intervention studies that may have altered the validity of the above findings.

These results on nutritional interventions are consistent with those of prior systematic reviews on treatments for infantile colic by Lucassen *et al.*⁶¹ and Garrison and Christakis.⁶² Of note is that similar overall results were found even with the inclusion of additional more recent studies in this review.

A limited number of studies were found on behavioural interventions for infantile colic. These all lacked methodological rigour and so do not provide adequate evidence for the use of these treatments. This is consistent with the findings of Garrison and Christakis⁶² but not with Lucassen who conclude that advice to decrease stimulation may be beneficial for infantile colic.⁶¹ These findings however do not necessarily mean that psychosocial factors do not play a role in this condition and that empathetic reassurance of parents is important.

The most common problems with methodological rigour in the literature on medical and conventional therapies for infantile colic appeared to be a lack of detail on how randomisation sequences were generated and procedures implemented plus no calculations or reasoning behind sample sizes used. Most studies however used some form of randomisation. In some studies, there was also a lack of a clear or standard definition for infantile colic or an outcome measure other than that of duration of crying.

In conclusion, there is some scientific evidence to support the use of a casein hydrolysate formula in formula-fed infants with infantile colic. There is weaker evidence to support the use of a whey hydrolysate formula in formula-fed infants and a low-allergen maternal diet in breastfed infants. There is no valid evidence to support the use of Simethicone, lactase, additional fibre or behavioural interventions. The use of Dicyclomine hydrochloride and Cimetropium bromide are not indicated for infantile colic.

Additional well-designed studies on low-allergenic formulas and maternal diets for infantile colic may be useful to increase the evidence supporting their use. Recommendations for further research include a clear description of randomisation procedures, adequate double blinding and use of statistics plus the use of a standard definition and outcome measure for infantile colic.

Acknowledgement

This project has been supported with funding from the Australian Government Department of Health and Ageing under the Primary Health Care Research Evaluation and Development (PHCRED) Initiative.

References

- 1 Lucassen PLBJ, Assendelft WJ, van Eijk JThM, Gubbels JW, Douwes AC, van Geldrop WJ. Systematic review of the occurrence of infantile colic in the community. *Arch. Dis. Child.* 2001; **84**: 398–403.
- 2 Stifter CA, Bono MA. The effect of infant colic on maternal self-perceptions; perceptions and mother – infant attachment. *Child Care Health Dev.* 1998; **24**: 339–51.
- 3 Humphry RA, Hock E. Infants with colic: a study of maternal stress and anxiety. *Infant. Ment. Health J.* 1989; **10**: 263–72.

- 4 Talvik I, Alexander RC, Talvik T. Shaken baby syndrome and a baby's cry. *Acta Paediatr.* 2008; **97**: 782–5.
- 5 Rautava P, Lehtonen L, Henius H, Sillanpaa M. Infantile colic: child and family three years later. *Pediatrics* 1995; **96**: 43.
- 6 Raiha H, Lehtonen L, Korhonen T et al. Family life 1 year after infantile colic. *Arch. Pediatr. Adolesc. Med.* 1996; **150**: 1032–6.
- 7 Savino F, Castagno E, Bretto R et al. A prospective 10-year study on children who had severe infantile colic. *Acta Paediatr.* 2005; **94**: 129–32.
- 8 Clifford TJ, Campbell MK, Speechley KN, Gorodinsky F. Sequelae of infant colic: evidence of transient infant distress and absence of lasting effects on maternal mental health. *Arch. Pediatr. Adolesc. Med.* 2002; **156**: 1183–8.
- 9 Wessel MA, Cobb JC, Jackson EB et al. Paroxysmal fussing in infancy, sometimes called colic. *Pediatrics* 1954; **14**: 421–35.
- 10 Brazelton TB. Crying in infancy. *Pediatrics* 1962; **29**: 579–88.
- 11 Lothe L, Ivarsson S, Ekman R, Lindberg T. Motilin and infantile colic. *Acta Paediatr. Scand.* 1990; **79**: 410–16.
- 12 Lothe L, Ivarsson S, Lindberg T. Motilin, vasoactive intestinal peptide and gastrin in infantile colic. *Acta Paediatr. Scand.* 1987; **76**: 316–20.
- 13 Huhtala V, Lehtonen L, Uvhas-Moberg K, Korvenranta H. Low plasma cholecystokinin levels in colicky infants. *J. Pediatr. Gastroenterol. Nutr.* 2003; **37**: 42–6.
- 14 Savino F, Cresi F, Palumeri E et al. Intestinal microflora in breastfed colicky and non-colicky infants. *Acta Paediatr.* 2004; **93**: 825–9.
- 15 Lothe L, Lindberg T, Jakobsson I. Macromolecular absorption in infants with infantile colic. *Acta Paediatr. Scand.* 1990; **79**: 417–21.
- 16 Belson A, Shetty AK, Yorgin P et al. Colonic hydrogen elimination and methane production in infants with and without infantile colic syndrome. *Dig. Dis. Sci.* 2003; **48**: 1762–6.
- 17 Jakobsson I, Lindberg T. Cow's milk as a cause of infantile colic in breast-fed infants. *Lancet* 1978; **2**: 437–9.
- 18 Lothe L, Lindberg T, Jakobsson I. Cow's milk formula as a cause of infantile colic: a double-blind study. *Pediatrics* 1982; **70**: 7–10.
- 19 Jakobsson I, Lindberg T. Cow's milk proteins cause infantile colic in breast-fed infants: a double-blind crossover study. *Pediatrics* 1983; **71**: 268–71.
- 20 Lothe L, Lindberg T. Cow's milk whey protein elicits symptoms of infantile colic in colicky formula-fed infants: a double-blind crossover study. *Pediatrics* 1989; **83**: 262–6.
- 21 Lust KD, Brown JE, Thomas W. Maternal intake of cruciferous vegetables and other foods and colic symptoms in exclusively breast-fed infants. *J. Am. Diet. Assoc.* 1996; **96**: 46–8.
- 22 Kanabar D, Randhawa M, Clayton P. Improvement of symptoms in infant colic following reduction of lactose load with lactase. *J. Hum. Nutr. Diet.* 2001; **14**: 359–63.
- 23 Liebman WM. Infantile colic. Association with lactose and milk intolerance. *JAMA* 1981; **245**: 732–3.
- 24 Canivet CA, Ostergren PO, Rosen AS, Jakobsson I, Hagander BM. Infantile colic and the role of trait anxiety during pregnancy in relation to psychosocial and socioeconomic factors. *Scand. J. Public. Health* 2005; **33**: 26–34.
- 25 Raiha H, Lehtonen L, Huhtala V, Saleva K, Korvenranta H. Excessively crying infant in the family: mother-infant, father-infant and mother-father interaction. *Child Care Health Dev.* 2002; **28**: 419–29.
- 26 Barr RG. Colic and crying syndromes in infants. *Pediatrics* 1998; **102**: e1282–86. Available from: <http://www.pediatrics.org/cgi/content/full/102/SE1/1282> [accessed 4 May 2009].
- 27 Kirjavainen J, Jahnukainen T, Huhtala V et al. The balance of the autonomic nervous system is normal in colicky infants. *Acta Paediatr.* 2001; **90**: 250–4.
- 28 Canivet CA, Ostergren PO, Jakobsson I, Dejin-Karlsson E, Hagander BM. Infantile colic, maternal smoking and infant feeding at 5 weeks of age. *Scand. J. Public. Health* 2008; **36**: 284.
- 29 Said G, Patois E, Lellouch J. Infantile colic and parental smoking. *BMJ* 1984; **289**: (Clin Res Ed):660.
- 30 Ståhlberg MR, Savilahti E. Infantile colic and feeding. *Arch. Dis. Child* 1986; **61**: 1232–3.
- 31 Crowcroft NS, Strachan DP. The social origins of infantile colic: questionnaire study covering 76,747 infants. *BMJ* 1997; **314**: 1325–8.
- 32 Paradise JL. Maternal and other factors in the etiology of infantile colic. Report of a prospective study of 146 infants. *JAMA* 1966; **197**: 191–9.
- 33 Evans K, Evans R, Simmer K. Effect of the method of breast feeding on breast engorgement, mastitis and infantile colic. *Acta Paediatr.* 1995; **84**: 849–52.
- 34 Lucas A, St James-Roberts I. Crying, fussing and colic behaviour in breast- and bottle-fed infants. *Early Hum. Dev.* 1998; **53**: 9–18.
- 35 Savino F. Focus on infantile colic. *Acta Paediatr.* 2007; **96**: 1259–64.
- 36 Lehtonen LA, Rautava PT. Infantile colic: natural history and treatment. *Curr. Probl. Pediatr.* 1996; **26**: 79–85.
- 37 Cohen-Silver J, Ratnapalan S, Cohen-Silver J, Ratnapalan S. Management of infantile colic: a review. *Clin. Pediatr.* 2009; **48**: 14–17.
- 38 Aveyard H. *Doing a Literature Review in Health and Social Care. A Practical Guide.* Maidenhead: McGraw-Hill, 2007.
- 39 Moher D, Schulz KF, Altman D. The CONSORT statement: revised recommendations for improving the quality of reports of parallel-group randomized trials. *JAMA* 2001; **285**: 1987–91.
- 40 Centre for Evidence Based Medicine, University of Oxford. *Critical Appraisal Sheets.* Oxford: Centre for Evidence Based Medicine. University of Oxford, 2005; Available from: <http://www.cebm.net/index.aspx?0=1157> [accessed 6 August 2009].
- 41 Garrard J. *Health Sciences Literature Review Made Easy. The Matrix Method*, 2nd edn. Sudbury, MA: Jones and Bartlett, 2007.
- 42 Hulley SB, Cummings SR, Browner WS, Grady D, Newman TB. *Designing Clinical Research*, 2nd edn. Philadelphia, PA: Lippincott Williams & Wilkins, 2001.
- 43 Danielsson B, Hwang CP. Treatment of infantile colic with surface active substance (simethicone). *Acta Paediatr. Scand.* 1985; **74**: 446–50.
- 44 Metcalf TJ, Irons TG, Sher LD, Young PC. Simethicone in the treatment of infant colic: a randomized, placebo-controlled, multicenter trial. *Pediatrics* 1994; **94**: 29–34.
- 45 Hwang CP, Danielsson B. Dicyclomine hydrochloride in infantile colic. *BMJ* 1985; (Clin Res Ed); **291**: 1014.
- 46 Weissbluth M, Christoffel KK, Davis AT. Treatment of infantile colic with dicyclomine hydrochloride. *J. Pediatr.* 1984; **104**: 951–5.
- 47 Savino F, Brondello C, Cresi F, Oggero R, Silvestro L. Cimetropium bromide in the treatment of crisis in infantile colic. *J. Pediatr. Gastroenterol. Nutr.* 2002; **34**: 417–19.
- 48 Treem WR, Hyams JS, Blankschen E et al. Evaluation of the effect of a fiber-enriched formula on infant colic. *J. Pediatr.* 1991; **119**: 695–701.
- 49 Forsyth BWC. Colic and the effect of changing formulas: a double-blind, multiple-crossover study. *J. Pediatr.* 1989; **115**: 521–6.
- 50 Jakobsson I, Lothe L, Ley D, Borschel MW. Effectiveness of casein hydrolysate feedings in infants with colic. *Acta Paediatr.* 2000; **89**: 18–21.
- 51 Lucassen PL, Assendelft WJ, Gubbels JW, van Eijk JT, Douwes AC. Infantile colic: crying time reduction with a whey hydrolysate: a double-blind, randomized, placebo-controlled trial. *Pediatrics* 2000; **106**: 1349–54.
- 52 Savino F, Palumeri E, Castagno E et al. Reduction of crying episodes owing to infantile colic: a randomized controlled study on the efficacy of a new infant formula. *Eur. J. Clin. Nutr.* 2006; **60**: 1304.
- 53 Oggero R, Garbo G, Savino F, Mostert M. Dietary modifications versus dicyclomine hydrochloride in the treatment of severe infantile colic. *Acta Paediatr.* 1994; **83**: 222–5.

- 54 Hill DJ, Hudson IL, Sheffield LJ *et al.* A low allergen diet is a significant intervention in infantile colic: results of a community-based study. *J. Allergy Clin. Immunol.* 1995; **96**: 886–92.
- 55 Hill DJ, Roy N, Heine RG *et al.* Effect of a low-allergen maternal diet on colic among breastfed infants: a randomized, controlled trial. *Pediatrics* 2005; **116**: 1211.
- 56 Miller JJ, McVeagh P, Fleet GH, Petocz P, Brand JC. Effect of yeast lactase enzyme on “colic” in infants fed human milk. *J. Pediatr.* 1990; **117**: 261–3.
- 57 Taubman B. Clinical trial of the treatment of colic by modification of parent-infant interaction. *Pediatrics* 1984; **74**: 998–1003.
- 58 Barr RG, McMullan SJ, Spiess H *et al.* Carrying as colic “therapy”: a randomized controlled trial. *Pediatrics* 1991; **87**: 623–30.
- 59 Parkin PC, Schwartz CJ, Manuel BA. Randomized controlled trial of three interventions in the management of persistent crying of infancy. *Pediatrics* 1993; **92**: 197–201.
- 60 Larson K, Ayllon T. The effects of contingent music and differential reinforcement on infantile colic. *Behav. Res. Ther.* 1990; **28**: 119–25.
- 61 Lucassen PLBJ, Assendelft WJJ, Gubbels JW *et al.* Effectiveness of treatments for infantile colic: systematic review. *BMJ* 1998; **316**: 1563.
- 62 Garrison MM, Christakis DA. A systematic review of treatments for infant colic. *Pediatrics* 2000; **106**: 184–90.
- 63 Williams J, Watkins-Jones R. Dicyclomine: worrying symptoms associated with its use in some small babies. *BMJ* 1984; **288**: (Clin Res Ed):901.
- 64 Rx Drugs Info. *Dicyclomine Hydrochloride (dicyclomine hydrochloride)*. Available from: <http://rxdrugsinfo.com/drug-info-label/dicyclomine-hydrochloride> [accessed March 2011].