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Gluckman S, Karpelowsky J, Webster AC, McGee RG

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[Intervention Review]

Management for intussusception in children

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ABSTRACT

Background

Intussusception is a common abdominal emergency in children with significant morbidity. Prompt diagnosis and management reduces associated risks and the need for surgical intervention. Despite widespread agreement on the use of contrast enema as opposed to surgery for initial management in most cases, debate persists on the appropriate contrast medium, imaging modality, pharmacological adjuvant, and protocol for delayed repeat enema, and on the best approach for surgical management for intussusception in children.

Objectives

To assess the safety and effectiveness of non-surgical and surgical approaches in the management of intussusception in children.

Search methods

We searched the following electronic databases: Cochrane Central Register of Controlled Trials (CENTRAL; 2016, Issue 8) in the Cochrane Library; Ovid MEDLINE (1950 to September 2016); Ovid Embase (1974 to September 2016); Science Citation Index Expanded (via Web of Science) (1900 to September 2016); and BIOSIS Previews (1969 to September 2016).

We examined the reference lists of all eligible trials to identify additional studies. To locate unpublished studies, we contacted content experts, searched the World Health Organization International Clinical Trials Registry Platform (ICTRP) and ClinicalTrials.gov (September 2016), and explored proceedings from meetings of the British Association of Paedatric Surgeons (BAPS), the American Soceity of Pediatric Surgery, and the World Congress of Pediatric Surgery.

Selection criteria

We included all randomised controlled trials comparing contrast media, imaging modalities, pharmacological adjuvants, protocols for delayed repeat enema, and/or surgical approaches for the management of intussusception in children. We applied no language, publication date, or publication status restrictions.

Data collection and analysis

Two review authors independently conducted study selection and data extraction and assessed risk of bias using a standardised form. We resolved disagreements by consensus with a third review author when necessary. We reported dichotomous outcomes as risk ratios (RRs) with 95% confidence intervals (CIs). We analysed data on an intention-to-treat basis and evaluated the overall quality of evidence supporting the outcomes by using GRADE criteria.

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Main results

We included six randomised controlled trials (RCTs) with a total of 822 participants. Two trials compared liquid enema reduction plus glucagon versus liquid enema alone. One trial compared liquid enema plus dexamethasone versus liquid enema alone. Another trial compared air enema plus dexamethasone versus air enema alone, and two trials compared use of liquid enema versus air enema.

We identified three ongoing trials.

We judged all included trials to be at risk of bias owing to omissions in reported methods. We judged five of six trials as having high risk of bias in at least one domain. Therefore, the quality of the evidence (GRADE) for outcomes was low. Interventions and data presentation varied greatly across trials; therefore meta-analysis was not possible for most review outcomes.

Enema plus glucagon versus enema alone

It is uncertain whether use of glucagon improves the rate of successful reduction of intussusception when compared with enema alone (reported in two trials, 218 participants; RR 1.09, 95% CI 0.94 to 1.26;*low quality of evidence*). No trials in this comparison reported on the number of children with bowel perforation(s) nor on the number of children with recurrent intussusception.

Enema plus dexamethasone versus enema alone

Use of the adjunct, dexamethasone, may be beneficial in reducing intussusception recurrence with liquid or air enema (two trials, 299 participants; RR 0.14, 95% CI 0.03 to 0.60; *low quality of evidence*). This equates to a number needed to treat for an additional beneficial outcome of 13 (95% CI 8 to 37). It is uncertain whether use of the adjunct, dexamethasone, improves the rate of successful reduction of intussusception when compared with enema alone (reported in two trials, 356 participants; RR 1.01, 95% CI 0.92 to 1.10;*low quality of evidence*).

Air enema versus liquid enema

Air enema may be more successful than liquid enema for reducing intussusception (two trials, 199 participants; RR 1.28, 95% CI 1.10 to 1.49; *low quality of evidence*). This equates to a number needed to treat for an additional beneficial outcome of 6 (95% CI 4 to 19). No trials in this comparison reported on the number of children with bowel perforation(s) or on the number of children with recurrent intussusception nor any intraoperative complications, such as bowel perforation, or other adverse effects. Only one trial reported postoperative complications, but owing to the method of reporting used, a quantitative analysis was not possible. We identified no studies that exclusively evaluated surgical interventions for management of intussusception.

Authors' conclusions

This review identified a small number of trials that assessed a variety of interventions. All included trials provided evidence of low quality and were subject to serious concerns about imprecision, high risk of bias, or both. Air enema may be superior to liquid enema for successfully reducing intussusception in children; however, this finding is based on a few studies including small numbers of participants. Dexamethasone as an adjuvant may be more effective in reducing intussusception recurrence rates following air enema or liquid enema, but these results are also based on a few studies of small numbers of participants. This review highlights several points that need to be addressed in future studies, including reducing the risk of bias and including relevant outcomes. Specifically, surgical trials are lacking, and future research is needed to address this evidence gap.

PLAIN LANGUAGE SUMMARY

Management of intussusception in children

Review question

How is intussusception best managed in children?

Background

Intussusception is a medical emergency that occurs in children when a part of the bowel 'telescopes' (folds) into another part of the bowel. This causes pain, vomiting, and obstruction, preventing passage. If left untreated, the bowel can perforate, resulting in passage of its contents into the abdominal cavity, causing further complications. In rare cases, these events can cause death. Prompt diagnosis and management reduces associated risks and the need for surgery.

Once intussusception is diagnosed, most doctors agree on the use of enema as initial treatment. This procedure involves introducing a substance (air or liquid) into the bowel, via the rectum, with a particular pressure that reduces the 'telescoped' bowel into its normal position.

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Debate persists on specifics regarding what type of substance should be used for the enema, how the substance is visualised during the process, whether extra medications should be given to enhance treatment, and how one should deal with treatment failure, as well as the best approach to surgical management of intussusception in children.

Study characteristics

Evidence is current to September 2016. We identified six randomised studies, with a total of 822 participants, that explored the management of intussusception in children and assessed different types of interventions. We also identified three ongoing trials.

Main results

The main outcome was the number of children with a successfully reduced intussusception. Furthermore, outcomes included the number of children returning with a recurrent intussusception and evaluation of harms (adverse events) resulting from the interventions.

Evidence from two studies suggests that using air for the enema to reduce intussusception is superior to using liquid for the enema. Evidence from two studies also suggests that giving the child with intussusception a steroid medication, such as dexamethasone, may reduce the recurrence of intussusception, irrespective of whether liquid or air is used for the enema.

We identified only sparse information on intraoperative and postoperative complications and on other adverse events.

Quality of the evidence

Of the six trials identified, we considered all to be potentially biased owing to lack of detail in reporting of how each study was undertaken. We found lack of consistency in how outcomes were defined and measured. All included studies were subject to serious concerns of imprecision based on few events, wide confidence intervals,or high risk of bias, Overall, we concluded that the quality of evidence provided by these studies was low, and that the real effects may differ significantly from those noted in these studies.

Further research is needed to help doctors better understand the most effective way to manage intussusception in children.

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SUMMARY OF FINDINGS

Summary of findings for the main comparison. Enema plus glucagon versus enema alone

Enema plus glucagon versus enema alone summary of findings table

Patient or population: children with intussusception
Setting: single centre, in-patient setting
Intervention: liquid enema plus glucagon
Comparison: liquid enema alone

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	Number of participants (studies)	Quality of the evidence (GRADE)
	Risk with liquid enema alone	Risk with liquid enema plus glucagon			
Successfully reduced intussusception	Study population		RR 1.09 (0.94 to 1.26)	218 (2 studies)	Low[a]
	739 per 1000	805 per 1000 (694 to 931)			
	Moderate				
	649 per 1000	707 per 1000 (610 to 818)			
Bowel perforation(s)	Outcome not reported in any studies				
Recurrent intussusception (follow-up: 6 months)	Outcome not reported in any studies				
Bowel resection	Outcome not reported in any studies				
Postoperative complication(s)	Outcome not reported in any studies				

*__The risk in the intervention group__ (and its 95% confidence interval) is based on assumed risk in the comparison group and __relative effect__ of the intervention (and its 95% CI)
CI: confidence interval; RR: risk ratio

GRADE Working Group grades of evidence
High quality: We are very confident that the true effect lies close to the estimate of effect
Moderate quality: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of effect but may be substantially different
Low quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of effect

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Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

[a]Downgraded two levels for serious concerns for high risk of selection, attrition, and performance bias

Summary of findings 2. Enema plus dexamethasone versus enema alone

Enema plus dexamethasone versus enema alone summary of findings table

Patient or population: children with intussusception
Setting: single centre, in-patient setting
Intervention: enema plus dexamethasone
Comparison: enema alone

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	Number of participants (studies)	Quality of the evidence (GRADE)
	Risk with enema alone	Risk with enema plus dexamethasone			
Successfully reduced intussusception	Study population		RR 1.01 (0.92 to 1.10)	356 (2 studies)	Low[a]
	157 per 1000	159 per 1000 (144 to 173)			
	Moderate				
	771 per 1000	779 per 1000 (710 to 849)			
Bowel perforation(s)	Study population		RR 2.63 (0.11 to 62.66)	75 (1 study)	Low[b,c]
	125 per 1000	329 per 1000 (14 to 1000)			
	Moderate				
	125 per 1000	48 per 1000 (3 to 995)			
Recurrent intussusception (follow-up: 6 months)	Study population		RR 0.14 (0.03 to 0.60)	299 (2 studies)	Low[a]
	69 per 1000	10 per 1000 (2 to 42)			

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	Moderate				
	370 per 1000	52 per 1000 (11 to 222)			
Bowel resection	Study population		RR 0.88 (0.19 to 4.06)	75 (1 study)	Low[b,c]
	86 per 1000	75 per 1000 (16 to 348)			
	Moderate				
	375 per 1000	330 per 1000 (71 to 1000)			
Postoperative complication(s)	Outcome not reported in any studies				

*__The risk in the intervention group__ (and its 95% confidence interval) is based on assumed risk in the comparison group and __relative effect__ of the intervention (and its 95% CI)
CI: confidence interval; RR: risk ratio

GRADE Working Group grades of evidence
High quality: We are very confident that the true effect lies close to the estimate of effect
Moderate quality: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of effect but may be substantially different
Low quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of effect
Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

[a]Downgraded two levels for serious concerns for high risk of attrition and performance bias
[b]Downgraded one level for serious imprecision (95% CI is wide and includes null effect)
[c]Downgraded one level for concerns for high risk of performance bias

Summary of findings 3. Air enema versus liquid enema

Air enema versus liquid enema summary of findings table

Patient or population: children with intussusception
Setting: single centre, in-hospital setting
Intervention: air enema
Comparison: liquid contrast enema

Outcomes	Anticipated absolute effects* (95% CI)	Relative effect (95% CI)	Number of participants	Quality of the evidence

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	Risk with liquid contrast enema	Risk with air enema		(studies)	(GRADE)
Successfully reduced intussusception	Study population		RR 1.28 (1.10 to 1.49)	199 (2 studies)	Low[a]
	677 per 1000	867 per 1000 (745 to 1000)			
	Moderate				
	712 per 1000	911 per 1000 (783 to 1000)			
Bowel perforation(s)	Outcome not reported in any studies				
Recurrence of intussusception (follow-up: 6 months)	Outcome not reported in any studies				
Bowel resection	Outcome not reported in any studies				
Postoperative complication(s)	Outcome not reported in any studies				

*__The risk in the intervention group__ (and its 95% confidence interval) is based on assumed risk in the comparison group and __relative effect__ of the intervention (and its 95% CI)
CI: confidence interval; RR: risk ratio

GRADE Working Group grades of evidence
High quality: We are very confident that the true effect lies close to the estimate of effect
Moderate quality: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of effect but may be substantially different
Low quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of effect
Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

[a]Downgraded two levels for serious concerns for high risk of selection, performance, and detection bias

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BACKGROUND

Description of the condition

Intussusception in children is a medical emergency that requires prompt diagnosis and management. It occurs when a segment of bowel (the *intussusceptum*) invaginates or telescopes into the lumen of another segment of bowel (the *intussuscipiens*). Both small and large bowel can be involved, but the most common kind of intussusception arises at the junction between the ileum and the caecum and is called *ileocaecal intussusception* (Loukas 2011). When untreated, intussusception may cause bowel perforation, peritonitis, and shock (Ko 2007). Mortality is rare, with the USA reporting a stable mortality rate of 2.1 per 1 million live births between 1997 and 2007 (Buttery 2011; Davis 2003; Desai 2012; Parashar 2000). Case fatality rates are higher in developing countries, particularly in Africa (9.4%), than in other regions (< 1%). This may be due to delays in treatment, a higher incidence of non-viable bowel, and lack of adequate medical care (Iwase 2010; Jiang 2013; Meier 1996).

Intussusception is one of the most common abdominal emergencies for children younger than age three (Applegate 2009). Its incidence varies from 0.24 to 2.4 per 1000 live births (Bines 2002; Eng 2012; Fischer 2004; Huppertz 2006; Samad 2014), although evidence suggests that this rate is higher in developing countries (Ugwu 2000). Boys are affected two to eight times more often than girls (Bines 2002), and peak incidence occurs between five and nine months of age (Daneman 2003; Samad 2012). Vaccination against rotavirus has been shown to increase the risk of intussusception. Currently, the monovalent rotavirus vaccine (Rotarix, GlaxoSmithKline, Abbott Park, North Carolina, USA) accounts for an increase of 5.3 cases of intussusception per 100,000 infants receiving the two doses of vaccine (Weintraub 2014). However, each year, rotavirus infection causes gastroenteritis, resulting in 592,000 deaths among children younger than five years of age, with 82% of deaths reported in developing countries (Parashar 2000). Hence, rotavirus vaccination is considered beneficial. A much stronger link between intussusception and an older rotavirus vaccine (RotaShield, Wyeth Laboratories, Marietta, Pennsylvania, USA) (Kramarz 2001; Murphy 2001; Peter 2002; Soares-Weiser 2004) led to its worldwide withdrawal in 1999.

The cause of intussusception is often idiopathic (Staatz 1998), although any condition that produces pathological lead points (lesions in the bowel) can cause intussusception (Loukas 2011). Of these conditions, lymphoid hypertrophy seems to be the most common (Applegate 2009; Staatz 1998), implicating a viral or bacterial origin for most cases (Nylund 2010; Okimoto 2011; Parashar 2000; Staatz 1998). Other potential causes of pathological lead points include Meckel's diverticulum, duplication cyst, polyp, and lymphoma (Daneman 2003; Daneman 2004). Compared with idiopathic intussusception, intussusception caused by lead points is associated with poorer outcomes and may not be amenable to standard treatment owing to different intussusception locations (Applegate 2009; Loukas 2011).

Diagnosis is challenging because the symptoms of intussusception are wide-ranging and non-specific (Beasley 1988); the classic triad of symptoms associated with intussusception comprises vomiting, colicky abdominal pain, and bloody stool, but this triad is noted in less than half of cases (Blanch 2007; Lehnert 2009; Samad 2012). Three studies found that physicians correctly diagnosed intussusception in less than half of initial clinical encounters (Beasley 1988; Blanch 2007; Budwig 1994). Following successful reduction of the intussusception, early recurrence is rare, with rates ranging from 2.7% to 5.4% (Beres 2014; Gray 2014). Diagnostic delay increases the risk of surgical intervention (Lehnert 2009), thus emphasising the importance of prompt and effective management.

Description of the intervention

Non-surgical management of intussusception in children consists of contrast enema (Applegate 2009; Daneman 2004; Ito 2012; Ko 2007), which involves instilling contrast medium (i.e. air, saline, or barium) into the rectum via a rectal tube to reduce the intussusceptum by increasing intraluminal pressure (Davis 2003). Fluoroscopy or, in the case of liquid contrast media, ultrasonography can guide the procedure and monitor the reduction. Ultrasonography avoids the radiation exposure associated with fluoroscopy and is an effective diagnostic tool (del-Pozo 1999).

Pharmacological adjuvants can facilitate non-surgical management, but their efficacy remains controversial. For example, glucagon is an antispasmodic adjuvant used by 10% to 21% of surveyed practitioners (Cachat 2012; Katz 1992; Meyer 1992; Rosenfeld 1999). It provides analgesia (Lappas 1995) and reduces colonic muscle tone (Skucas 1994). However, a recent narrative review suggests that glucagon does not improve the rate of reduction in the non-surgical management of intussusception (Cachat 2012). Other adjuvants include antibiotics (Ein 2006; Moss 2000; Pepper 2012). One prospective study concluded that the actual risk of bacteraemia following fluoroscopically guided air reduction is low (Somekh 1996), although two other studies reported an elevated risk for intussusception following antibiotic administration (Hviid 2009; Spiro 2003).

Surgical management entails open laparotomy with manual reduction of the intussusception, although case series and retrospective studies show that laparoscopy may be safer and just as effective and may result in shorter hospitalisation (Bailey 2007; Bonnard 2008; Kia 2005; Sklar 2014). Surgical management is generally indicated only if peritonitis, bowel perforation, or shock occurs; when appropriate radiological facilities are unavailable; or when contrast enema fails (American College of Radiology 2007; Daneman 2004). However, because non-surgical management may be associated with lower morbidity and shorter hospitalisation (Bruce 1987), delayed repeat attempts at contrast enema may be preferred to surgical management (Gonzalez-Spinola 1999; Navarro 2004; Sandler 1999).

Why it is important to do this review

Intussusception is a common abdominal emergency in children with significant morbidity. Despite widespread agreement on the use of contrast enema for initial management, debate persists on the appropriate contrast medium, imaging modality, pharmacological adjuvant, and protocol to be used for delayed repeat enema (i.e. duration of delay and number of repeated attempts) (Beasley 1998; Daneman 2004; Davis 2003; del-Pozo 1999; Littlewood 1998; Liu 1986; Schmit 1999). Debate also surrounds the best approach for its surgical management (i.e. open laparotomy vs laparoscopy). Prior reviews of non-surgical management (Applegate 2009; Cachat 2012; Daneman 2003; Gray 2014; Ko 2007) are narrative in nature. In contrast to narrative reviews, systematic

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reviews use transparent, objective, and reproducible methods to locate and assess studies (Borenstein 2009).

To the best of our knowledge, this is the first systematic review of non-surgical and surgical approaches in the management of intussusception in children.

OBJECTIVES

To assess the safety and effectiveness of non-surgical and surgical approaches in the management of intussusception in children.

METHODS

Criteria for considering studies for this review

Types of studies

We considered for inclusion all randomised controlled trials (RCTs) comparing contrast media, imaging modalities, pharmacological adjuvants, protocols for delayed repeat enema, surgical approaches, or other curative techniques for the management of intussusception in children. Both quasi-RCTs and cluster-RCTs were eligible for inclusion.

Types of participants

Any child, younger than age 18, with a clinical diagnosis of intussusception as determined by study authors. For this review, we considered intussusception at any point in the gastrointestinal tract distal to the pylorus. Although the Brighton Collaboration established a validated and standardised case definition (Bines 2004a; Bines 2004b; Kohl 2008; Tapiainen 2006), this definition has been used only in the context of rotavirus vaccine post licensure monitoring. We have not used the Brighton Collaboration case definition in assessing eligibility of participants for inclusion in this review.

Types of interventions

We included all trials that compared different contrast media, imaging modalities, pharmacological adjuvants, protocols for delayed repeat enemas, and/or surgical approaches.

Types of outcome measures

When possible, we extracted the following primary and secondary outcome measures. We assessed outcomes at the time points reported by study authors unless otherwise noted. As recurring intussusception is associated with various outcomes (Applegate 2009), we conducted our assessment by using the participant as the unit of analysis. If we identified cluster trials, we planned to involve a statistician to ensure that we did not create unit of analysis errors.

Primary outcomes

- Number of children with successfully reduced intussusception, characterised by radiologically confirmed passage of contrast media into the ileum
- Number of children with radiologically confirmed or clinically suspected (intraoperative or endoscopic) bowel perforation(s)
- Number of children with recurrent intussusception (recurrence is defined as occurring after a minimum of 12 hours following a successful reduction)

Secondary outcomes

- Number of children who underwent a bowel resection (defined by any transection of the lumen, with removal of a segment of bowel)
- Number of children with a diagnosis of sepsis (defined as life-threatening organ dysfunction caused by a dysregulated host response to infection (Singer 2016))
- Radiation exposure (measured in milli-Sieverts (mSv)) resulting from intervention
- Length of hospitalisation (measured in days) associated with intervention
- Intraluminal pressure (measured in mm Hg) used to achieve reduction
- Number of attempts required to achieve successful reduction
- Length of operation (measured in minutes) in the case of surgical intervention
- Number of intraoperative complications (as defined by study authors) in the case of surgical intervention
- Number of postoperative complications (as defined by study authors) in the case of surgical intervention
- Number of intraoperative conversions (i.e. open laparotomy required) in the case of laparoscopic intervention
- Time to resumption of full diet (measured in hours), as defined by study authors

Search methods for identification of studies

Electronic searches

We conducted a comprehensive literature search to identify all published and unpublished randomised controlled trials with no language or date of publication restrictions. We searched the following electronic databases for relevant studies.

- Cochrane Central Register of Controlled Trials (CENTRAL; 2016, Issue 8) in the Cochrane Library (Appendix 1).
- MEDLINE Ovid (1950 to 16 September 2016) (Appendix 2).
- Embase Ovid (1974 to 16 September 2016) (Appendix 3).
- Science Citation Index (via Web of Science) (1900 to 16 September 2016) (Appendix 4).
- BIOSIS Previews (1969 to 16 September 2016) (Appendix 5).

Our subject search in MEDLINE followed the sensitivity-maximising version of the Cochrane Highly Sensitive Search Strategy (CHSSS) for identifying randomised trials in MEDLINE (Lefebvre 2011). Similarly, our subject search in Embase followed sensitivity-maximising strategy as recommended by Cochrane (Wong 2006).

Searching other resources

Two review authors (SG and RGM) searched the reference lists of all eligible trials and contemporary reviews to identify further trials. To identify unpublished studies, we contacted content experts and searched the World Health Organization International Clinical Trials Registry Platform (ICTRP) (http://www.who.int/ictrp/en) and the US National Institutes of Health Ongoing Trials Register ClinicalTrials.gov (http://www.clinicaltrials.gov) up to 16 September 2016. We also examined proceedings from meetings of the British Association of Paediatric Surgeons (BAPS), the American Society of Pediatric Surgery, and the World Congress of Pediatric Surgery (2009-2015).

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Data collection and analysis

Selection of studies

Two review authors (SG and RGM) screened titles and abstracts for study eligibility using the inclusion criteria of this review. When necessary, we read the full text of the paper or requested additional data from study authors. A third review author (ACW) adjudicated disagreements about study eligibility. We were not blinded to study details during this process.

Data extraction and management

Two review authors (SG and RGM) independently extracted data and assessed risk of bias using a standardised data extraction form. We resolved disagreements by consensus, involving a third review author (ACW) when required. Review authors were not blinded to study details during this process.

We extracted the following data.

- General information: study author(s), title, source, contact address, country of study, language of publication, year of publication, any author conflicts of interest, study setting (e.g. hospital emergency department, specialised paediatric hospital).
- Study characteristics and eligibility for review: study design, randomisation method, allocation concealment, recruitment method, duration of trial, study location, length of follow-up, operator allocation, any obvious concerns of bias.
- Participants: inclusion and exclusion criteria, age, gender, presence of pathological lead points, anatomical location of intussusception, criteria used to diagnose intussusception, total number of participants, country of origin, number of dropouts or withdrawals and reasons if recorded.
- Interventions: number of participants for each intervention, a detailed description of interventions and comparison interventions including, when relevant, type, dose, concentration, and duration of application.
- Outcomes: specific outcomes reported and rates of recurrence, perforation, resection, sepsis, and, when applicable, operative complications and intraoperative conversions.

We entered relevant data into Review Manager software (RevMan version 5.3) (RevMan 2014).

We contacted study authors via email when data were unclear or missing. Study authors provided no new information.

Assessment of risk of bias in included studies

We assessed risk of bias using the 'Risk of bias' tool of the Cochrane Collaboration, as detailed in Section 8.5 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011) (see Appendix 6). We assessed the following domains: selection bias (due to inadequate random sequence generation or allocation concealment); performance bias (due to inadequate blinding of participants or personnel); detection bias (due to inadequate blinding of outcome assessment and data analysis); attrition bias (due to incomplete outcome data); reporting bias (due to selective reporting); and other potential biases. We planned to assess publication bias by visually inspecting funnel plots and using Egger's linear regression (minimum 10 studies required). When we assessed studies as having 'unclear risk' in any domain, we attempted to contact study authors for clarification.

We planned to perform sensitivity analyses using risk of bias as one of the sensitivity factors (see Subgroup analysis and investigation of heterogeneity).

Summary of findings

Two review authors (SG and RGM) assessed the overall quality of the evidence using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach (Schünemann 2008) and presented these results in 'Summary of findings' tables. We resolved disagreements by consensus, involving a third review author (ACW) when required. In the 'Summary of findings' tables, we included all primary outcomes, as well as secondary outcomes, reported by included studies for the following comparisons: enema plus glucagon versus enema alone; enema plus dexamethasone versus enema alone; and air enema versus liquid enema. We calculated baseline risk using the event rate in the control group.

The GRADE system classifies the quality of evidence as one of four grades.

Grade	Definition
High	Further research is very unlikely to change our confidence in the estimate of effect
Moderate	Further research is likely to have an impact on our confidence in the estimate of effect and may change the estimate
Low	Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate
Very low	Any estimate of effect is very uncertain

We judged the quality of evidence according to the following factors.

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Downgrades the evidence
Risk of bias
Inconsistency of results
Indirectness of evidence
Imprecision
Publication bias

We described results while taking into account the quality of evidence and the importance (size) of the effect as follows.

	Important benefit or harm	Less important benefit or harm	No important benefit/harm or null effect
High-quality evidence	Improves/decreases/prevents/leads to [outcome]	Improves slightly/decreases slightly/leads to slightly fewer (more) [outcome]	Results in little or no difference in [outcome]
Moderate-quality evidence	Probably improves/decreases/prevents/leads to [outcome]	Probably improves slightly/decreases slightly/leads to slightly fewer (more) [outcome]	Probably leads to little or no difference in [outcome]
Low-quality evidence	May improve/decrease/prevent/lead to [outcome]	May slightly improve/slightly decrease/lead to slightly fewer (more) [outcome]	May lead to little or no difference in [outcome]
Very low-quality evidence	It is uncertain whether [intervention] improves, decreases, prevents, leads to [outcome] because the quality of the evidence is very low		
No data or no studies	[Outcome] was not measured or was not reported, or no studies were found that evaluated the impact of [intervention] on [outcome]		

Measures of treatment effect

We conducted our analysis according to the guidelines set out in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011).

We presented results for dichotomous data as summary risk ratios (RRs) with 95% confidence intervals (CIs) and as number needed to treat for an additional beneficial outcome (NNTB) or number needed to treat for an additional harmful outcome (NNTH) as appropriate. NNTB and NNTH reflect the numbers of participants who need to be treated for an additional beneficial and harmful outcome, respectively. For continuous data, we planned to present results as mean differences (MDs), if outcomes were measured in the same way between trials. We planned to use standardised mean differences (SMDs) to combine studies that measured the same outcome but used different methods. For rate data, we planned to present results as rate ratios with 95% CIs, and for survival data, we planned to present results as hazard ratios (HRs) with 95% CIs.

Unit of analysis issues

As recurring intussusception is associated with differing outcomes (Applegate 2009), when possible we conducted our assessment with the participant as the unit of analysis. If we had identified cluster-randomised trials, we had planned to involve a statistician, to ensure that we did not create unit of analysis errors. However, we did not identify any cluster-randomised trials for this systematic review.

Dealing with missing data

We analysed data for all participants in the group to which they were allocated, regardless of whether they received the allocated intervention. If in the original reports, participants were not analysed in the group to which they were randomised, and if information in the trial report was sufficient, we attempted to restore these participants to the correct group, that is, we conducted intention-to-treat analysis when it was possible to do so. When data were missing, we sought clarification from the authors

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of the trial. When intention-to-treat analysis was not possible, we conducted available-case analysis or per-protocol analysis.

Assessment of heterogeneity

To deal with clinical heterogeneity, we analysed studies of each intervention and presented them separately. We conducted subgroup analyses when required to deal with variations in the study population age (Subgroup analysis and investigation of heterogeneity).

To deal with statistical heterogeneity, we used the I^2 statistic and Chi^2 statistics to measure the proportion of total variation in estimates of treatment effect that was due to heterogeneity beyond chance (Borenstein 2009; Higgins 2003). We judged statistical heterogeneity to be substantial for I^2 values greater than 50% or Chi^2 P values less than 0.10. In the case of substantial statistical heterogeneity, we planned to perform prespecified subgroup and sensitivity analyses (see Subgroup analysis and investigation of heterogeneity).

Assessment of reporting biases

We planned to investigate publication bias by visually assessing funnel plots for the primary outcome if the number of identified and included trials exceeded 10. However, this review included only six trials.

Data synthesis

We analysed data using Review Manager software (RevMan Version 5.3) (RevMan 2014). For trials judged to have similar interventions, populations, and outcomes, we used fixed-effect model meta-analysis, as random-effects models produce poor estimates with small numbers of studies (Higgins 2011), and we considered a P value of 0.05 or less to be statistically significant.

Subgroup analysis and investigation of heterogeneity

We expected the following areas to contribute to study heterogeneity, and we planned to conduct subgroup analyses of relevant models when necessary.

- *Care setting.* Different care settings, such as tertiary care centres, are associated with differing outcomes (Bratton 2001; Calder 2001; Rosenfeld 1999).
- *Participants with confirmed presence of pathological lead point.* The presence of lead points is associated with differing outcomes (Loukas 2011).
- *Participants with previous intussusceptions.* Recurrence is associated with different patient characteristics and outcomes (Applegate 2009).
- *Bowel structures involved in the intussusception.* Intussusception involving different bowel structures (e.g. ileocaecal vs ileoileal) are associated with different outcomes (Loukas 2011).
- *Studies with high risk of bias.* We identified these studies as having one or more domains judged 'high risk' by the risk of bias tool, as suggested in Chapter 8 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011).
- *Quasi-randomised trials.* These studies by their design fail to implement optimal sequence generation and so are prone to bias (Higgins 2011).
- *Age.* Children younger than one year of age or older than three years of age are more likely to possess pathological lead points (Applegate 2009).
- *Geographical region.* Regional differences in epidemiology, equipment availability, and operator experience are known (Beasley 1998; Liu 1986; Schmit 1999; Ugwu 2000).

We planned to assess differences among subgroups using analysis of variance (Altman 1996).

However, we could not perform any of the planned subgroup analyses owing to the limited number of included studies.

Sensitivity analysis

We planned to conduct sensitivity analysis when unforeseen or arbitrary decisions were made, as per the guidance provided in Section 9.7 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011).
However, we were unable to perform the planned sensitivity analysis owing to the limited number of included studies.

RESULTS

Description of studies

We included six RCTs with a total of 822 participants (Essa 2011; Franken 1983; Hadidi 1999; Lin 2000; Meyer 1993; Mortensson 1984), and we identified three ongoing trials (El Fiky 2016; Mehraeen 2011; Zhang 2015).

Please see Characteristics of included studies; Characteristics of excluded studies; and Characteristics of ongoing studies.

Results of the search

We outlined in Figure 1 (study flow diagram) the process of identifying RCTs for inclusion in the review.

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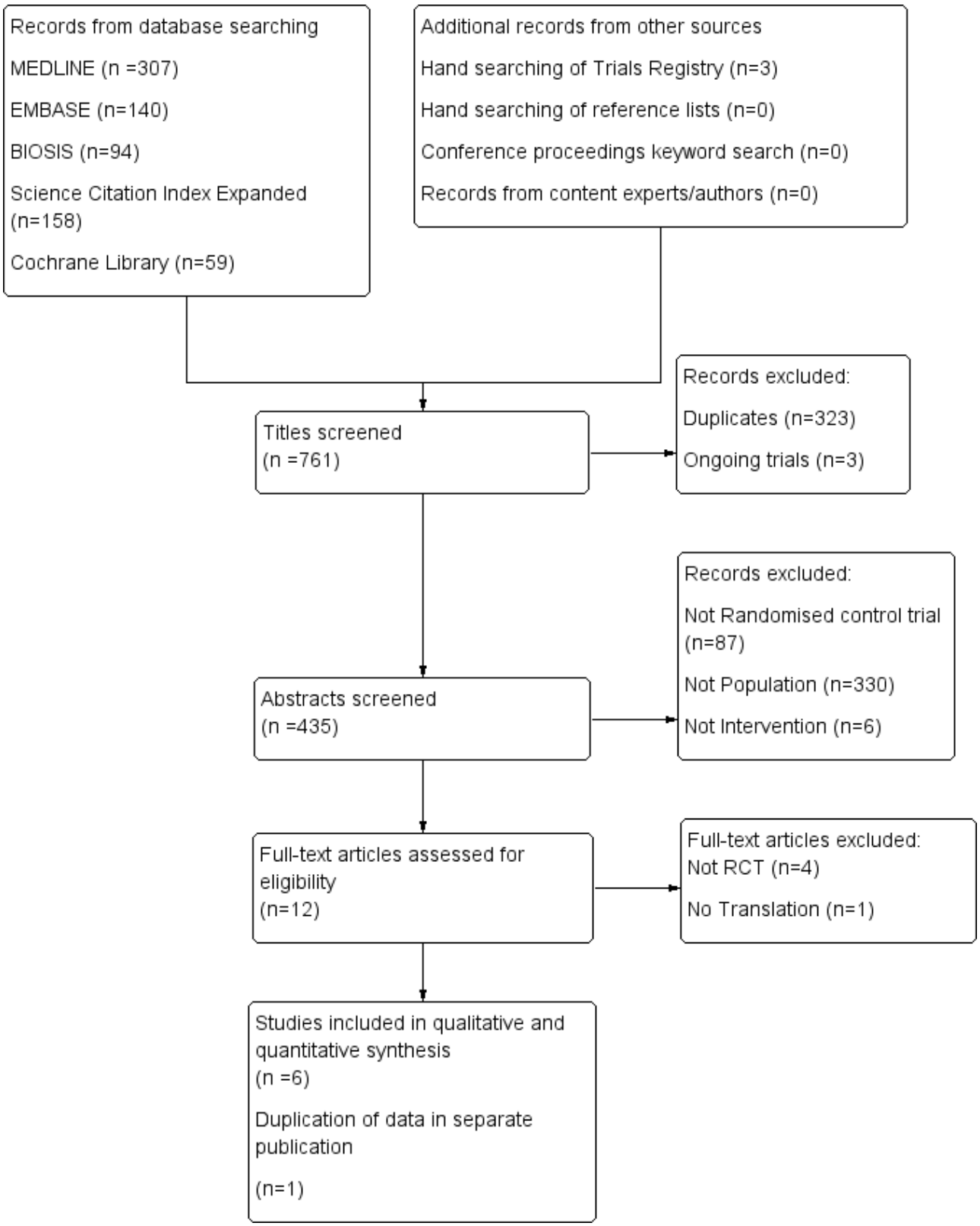
Figure 1. Study flow diagram for identification of randomised trials exploring management of intussusception in children.



Electronic searches of the Conchrane Central Register of Controlled Trials (n = 59), MEDLINE (n = 307), Embase (n = 140), BIOSIS (n = 94), and the Science Citation Index (n = 158) yielded a total of 758 publications. We identified three additional ongoing trials

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through trial registries and found no additional trials by searching conference proceedings and reference lists, or by contacting content experts. After exclusion of duplicates and ongoing trials, 435 unique records remained. Of these, we excluded 423 after reviewing titles and abstracts. We examined the full text of the remaining 12 publications and excluded five additional trials - four because they were not RCTs (Diaz-Aldagalan 2012; Guo 2010; Hsiao 1988; Morrison 2009) and one because we could not obtain a translation of the trial and classification is pending (Zhang 2014a). Two of the seven remaining publications were duplicates; thus we included them as one trial (Lin 2000). In summary, we included six RCTs (Essa 2011; Franken 1983; Hadidi 1999; Lin 2000; Meyer 1993; Mortensson 1984) in the review. These six completed trials were published in five different journals.
Searches for ongoing trials revealed three (El Fiky 2016; Mehraeen 2011; Zhang 2015), for which no results were available.

No disagreements about trial selection among review authors required adjudication.

Included studies

Included trials assessed a wide range of treatments.

- Essa 2011 compared use of saline enema plus dexamethasone versus saline enema alone in 75 participants.
- Franken 1983 and Mortensson 1984 compared use of liquid contrast enema plus glucagon versus liquid contrast enema alone in 30 and 188 participants, respectively.
- Hadidi 1999 and Meyer 1993 compared use of liquid contrast enemas versus air enemas in 147 and 101 participants, respectively.
- Lin 2000 compared use of air enema plus dexamethasone versus air enema alone in 281 participants.

All six included trials recruited participants referred for management of intussusception in a hospital setting. Two of these studies were performed in the USA (Franken 1983; Meyer 1993). One trial was performed in Taiwan (Lin 2000), two in Egypt (Essa 2011; Hadidi 1999), and one in Sweden (Mortensson 1984).

Only one trial (Essa 2011) reported adverse outcomes for surgical interventions, including number of participants requiring manual reduction and number requiring bowel resection.

This review used subsets of data from two trials (Meyer 1993; Mortensson 1984). Meyer 1993 examined liquid enema versus air enema; however, not all participants who were initially randomised had intussusception at the time of intervention. Therefore, it was necessary to extrapolate data from those with confirmed intussusception. Mortensson 1984 conducted this study in three stages. We have included data only for the first stage, as this was the only stage that met our inclusion criteria (Characteristics of included studies).

Hadidi 1999 conducted a three-arm trial to assess the efficacy of air, barium, and saline enemas. Review authors combined barium and saline into a liquid enema group for comparison with air enema.

Excluded studies

We excluded five full-text articles (see Characteristics of excluded studies).

Risk of bias in included studies

Reporting of methods was incomplete for most trials, as shown in Figure 2 and Figure 3. We judged five trials as having at least one domain at high risk of bias, and we judged Franken 1983 as having unclear risk of bias.

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Figure 2. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.

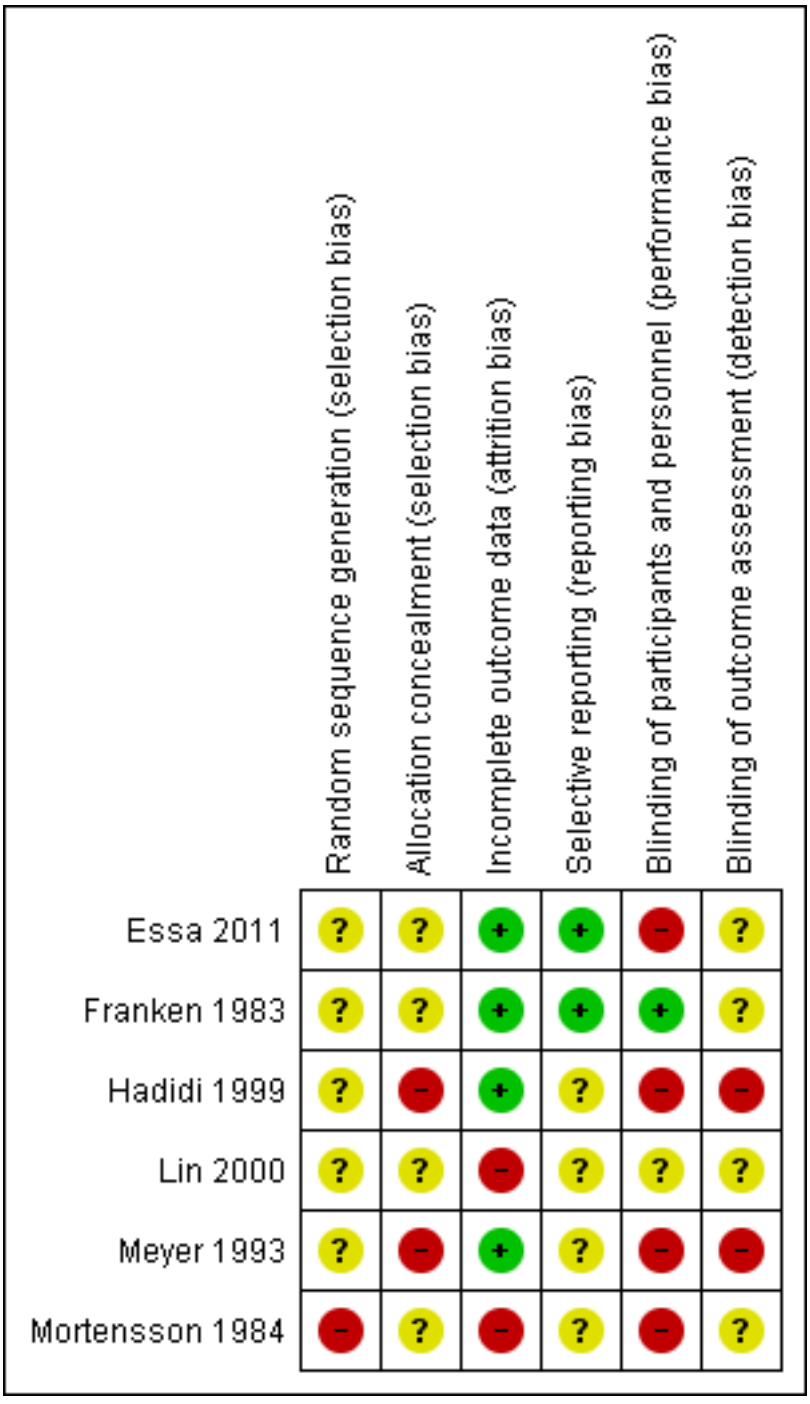

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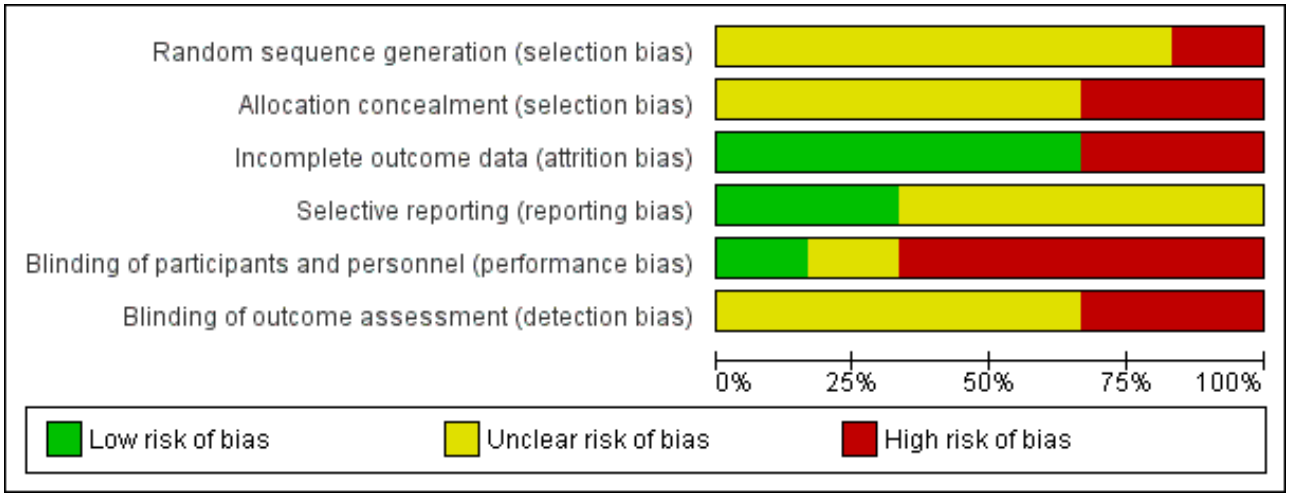
Figure 3. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.



Allocation

No study reported adequate sequence generation or adequate allocation concealment. Both Hadidi 1999 and Meyer 1993 used random number tables that may have allowed for prediction of intervention by participants. It is unclear whether this was adequate to ensure random sequence generation in Hadidi 1999; in Meyer 1993, the randomisation process was compromised by the need to extrapolate data for participants with confirmed intussusception; and Mortensson 1984 applied inadequate sequence generation by using birth dates to randomly allocate participants. The remaining studies (three studies for sequence generation and five for allocation concealment) used unclear methods. Both Essa 2011 and Franken 1983 referred to the random allocation used but provided no details.

Blinding

Owing to the nature of some treatments, blinding was not possible, for example, liquid versus air enema in Hadidi 1999 and Meyer 1993. Therefore, we reported four trials as having inadequate blinding of participants and personnel. One trial (Franken 1983) successfully blinded participants and personnel through the use of pre-made identical appearing vials of drug and placebo. The remaining trial used unclear methods.

We judged two trials as having inadequate blinding of outcome assessors because treating personnel recorded the results and thus were unable to be blinded (Hadidi 1999; Meyer 1993). For the remaining four trials, it was unclear whether outcome assessors were study personnel (i.e. paediatricians, radiologists, or surgeons) or independent assessors.

Incomplete outcome data

Four studies adequately addressed incomplete outcome data (no missing data in the trials). Essa 2011 explicitly referred to reporting on all participants included in this trial, and Franken 1983, Hadidi 1999, and Meyer 1993 avoided attrition bias by randomising participants after completing an exclusion process. Two studies reported incomplete outcome data inadequately (Lin 2000; Mortensson 1984), when data were not available for unexplained reasons.

Selective reporting

We judged only two studies (Essa 2011; Franken 1983) as being free of selective reporting bias (all outcomes were reported). We judged the remaining four trials as having unclear risk. None of the trials included a protocol. Lin 2000 did not report how data were collected after participants were discharged, and Meyer 1993 and Mortensson 1984 did not report all expected outcomes.

Other potential sources of bias

No other biases were evident as judged by review authors (e.g. pharmaceutical funding).

We attempted to contact study authors to clarify all areas of unclear risk, but we received no replies and acquired no new information.

We could not assess publication bias as planned because of the small number of included studies.

Effects of interventions

See: **Summary of findings for the main comparison** Enema plus glucagon versus enema alone; **Summary of findings 2** Enema plus dexamethasone versus enema alone; **Summary of findings 3** Air enema versus liquid enema

Interventions and outcomes reported across trials varied greatly; therefore, meta-analysis was not possible for many outcomes.

Enema plus glucagon versus enema alone

1. Primary outcomes

1.1 Number of children with successfully reduced intussusception

It is uncertain whether use of liquid enema plus glucagon improved the rate of successful reduction of intussusception when compared with enema alone because the quality of the evidence is low (reported in two trials, 218 participants; RR 1.09, 95% CI 0.94 to 1.26; I^2 = 0%; Analysis 1.1).

1.2 Number of children with bowel perforation or perforations

This outcome was not reported for this comparison.

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1.3 Number of children with recurrent intussusception

This outcome was not reported for this comparison.

2. Secondary outcomes

2.1 Number of children who undergo a bowel resection

This outcome was not reported for this comparison.

2.2 Number of children with a diagnosis of sepsis

This outcome was not reported in any trial.

2.3 Radiation exposure from intervention

This outcome was not reported in any trial.

2.4 Length of hospitalisation

This outcome was not reported in any trial.

2.5 Intraluminal pressure

This outcome was not reported in any trial.

2.6 Number of attempts required to achieve successful reduction

This outcome was not reported in any trial.

2.7 Length of operation, in the case of surgical intervention

This outcome was not reported in any trial.

2.8 Number of intraoperative complications

This outcome was not reported in any trial.

2.9 Number of postoperative complications

This outcome was not reported for this comparison.

2.10 Number of intraoperative conversions

This outcome was not reported in any trial.

2.11 Time to resumption of full diet

This outcome was not reported in any trial.

Enema plus dexamethasone versus enema alone

1. Primary outcomes

1.1 Number of children with successfully reduced intussusception

It is uncertain whether use of liquid enema plus dexamethasone improved the rate of successful reduction of intussusception when compared with enema alone because the quality of the evidence is low (reported in two trials, 356 participants; RR 1.01, 95% CI 0.92 to 1.10; I^2 = 0%; Analysis 2.1).

1.2 Number of children with bowel perforation or perforations

It is uncertain whether use of enema plus dexamethasone reduced the number of participants with bowel perforation or perforations because the quality of the evidence is low (reported in one trial, 75 participants; RR 2.63, 95% CI 0.11 to 62.66; Analysis 2.2).

1.3 Number of children with recurrent intussusception

Treatment with enema plus dexamethasone compared with enema alone may reduce the recurrence rate of intussusception (reported in two trials, 299 participants; RR 0.14, 95% CI 0.03 to 0.60; I^2 = 0%; Analysis 2.3). This equates to an NNTB of 13 (95% CI 8 to 37).

2. Secondary outcomes

2.1 Number of children who undergo a bowel resection

It is uncertain whether use of liquid enema plus dexamethasone reduced the number of participants who underwent bowel resection (an unwanted complication) (reported in one trial, 75 participants; RR 0.88, 95% CI 0.19 to 4.06; Analysis 2.4).

2.2 Number of children with a diagnosis of sepsis

This outcome was not reported for this comparison.

2.3 Radiation exposure from intervention

This outcome was not reported in any trial.

2.4 Length of hospitalisation

This outcome was not reported in any trial.

2.5 Intraluminal pressure

This outcome was not reported in any trial.

2.6 Number of attempts required to achieve successful reduction

This outcome was not reported in any trial.

2.7 Length of operation, in the case of surgical intervention

This outcome was not reported in any trial.

2.8 Number of intraoperative complications

This outcome was not reported in any trial.

2.9 Number of postoperative complications

Only one trial reported on postoperative complications (Essa 2011) when comparing use of enema plus dexamethasone versus enema alone. We did not perform a quantitative analysis of this outcome owing to poor reporting and high risk of bias. A small sample of 15 children underwent surgical intervention - nine underwent manual reduction and the remaining six had a bowel resection. However, data on postoperative complications for the nine children undergoing manual reduction were not available. We contacted the study authors for clarification but received no response.

2.10 Number of intraoperative conversions

This outcome was not reported in any trial.

2.11 Time to resumption of full diet

This outcome was not reported in any trial.

Air enema versus liquid enema

1. Primary outcomes

1.1 Number of children with successfully reduced intussusception

Air enema may be superior to liquid enema for successfully reducing intussusception in children (reported in two trials, 199 participants; RR 1.28, 95% CI 1.10 to 1.49; I^2 = 0%; Analysis 3.1). This equates to an NNTB of 6 (95% CI 4 to 17).

1.2 Number of children with bowel perforation or perforations

This outcome was not reported for this comparison.

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1.3 Number of children with recurrent intussusception

This outcome was not reported for this comparison.

2. Secondary outcomes

2.1 Number of children who undergo a bowel resection

This outcome was not reported for this comparison.

2.2 Number of children with a diagnosis of sepsis

This outcome was not reported in any trial.

2.3 Radiation exposure from intervention

This outcome was not reported in any trial.

2.4 Length of hospitalisation

This outcome was not reported in any trial.

2.5 Intraluminal pressure

This outcome was not reported in any trial.

2.6 Number of attempts required to achieve successful reduction

This outcome was not reported in any trial.

2.7 Length of operation, in the case of surgical intervention

This outcome was not reported in any trial.

2.8 Number of intraoperative complications

This outcome was not reported in any trial.

2.9 Number of postoperative complications

This outcome was not reported for this comparison.

2.10 Number of intraoperative conversions

This outcome was not reported in any trial.

2.11 Time to resumption of full diet

This outcome was not reported in any trial.

GRADE analysis indicated that the quality of evidence supporting all reported outcomes was low (see Summary of findings for the main comparison, Summary of findings 2, and Summary of findings 3).

Although none of the included trials reported Outcome 2.3, four trials made use of fluoroscopy (Franken 1983; Hadidi 1999; Meyer 1993; Mortensson 1984), and one trial made use of ultrasound guidance alone (Essa 2011). One trial did not stipulate whether fluoroscopy or ultrasound guidance was used (Lin 2000).

DISCUSSION

Summary of main results

We identified six completed trials of 822 participants in which all children had presented for management of intussusception. Investigators used a wide range of treatments, and this prevented meta-analysis for most of our outcomes. In particular, many review outcomes related to adverse effects (e.g. number of intraoperative complications) were not reported.

We could make few direct comparisons of interventions. However, air enema may be superior to liquid enema for successfully reducing intussusception in children. Use of dexamethasone as an adjunct may reduce the rate of recurrence of intussusception. No other results were statistically significant. See summary of findings tables (Summary of findings for the main comparison; Summary of findings 2; Summary of findings 3). Of note, we downgraded many of the recommendations provided in these tables owing to the small numbers of included trials and the small participant numbers.

It is important to note that surgical intervention was not the primary study question for any of the included studies. Lack of trials on surgical management might reflect the nature of treatment of children with intussusception, and might suggest that cases are managed largely by non-surgical means, although this suggestion does not seem to be based on trial evidence.

Overall completeness and applicability of evidence

The internal validity of the design, conduct, and analysis of included studies was difficult to assess because important methodological details were omitted from the study reports. No single study adequately reported all domains of the risk of bias assessment (Figure 2). We judged most trials as having high risk of bias in at least one domain, and omissions in methods were evident in all included studies. Selection bias was generally addressed adequately.Although detection and performance biases are difficult to mitigate for researchers in this field, it may be possible to overcome such biases, for example, Franken 1983 used identical appearing vials for injection in both intervention and control groups. Reporting bias was also difficult to address, although with adequate reporting of protocols and reporting of all expected outcomes, as in Essa 2011 and Franken 1983, this may be mitigated. Although postoperative complications were reported (Outcome 2.9), Essa 2011 presented data in such a way that analysis was not possible. Data for one subgroup of children, specifically those undergoing manual reduction, were not available. We attempted to contact study authors but received no response. Thus data were provided by only one study, and for only a subgroup of children receiving surgical intervention, and data were not sufficient to permit an analysis of this outcome. Again, trials infrequently reported data related to adverse events and harms. These situations might reflect missing data, which may have implications for analysis.

Included trials largely assessed participants of varied ethnic and cultural backgrounds from single centres; this fact may influence the comparability of results between studies. However, given the small quantity of evidence and our inability to perform a meta-analysis, we could not assess the implications of population differences for applicability of the evidence.

Again we wish to highlight the lack of evidence on surgical interventions and on different imaging modalities and protocols used for delayed repeat enemas.

Quality of the evidence

We have summarised the quality of evidence for each outcome in summary of findings tables (Summary of findings for the main comparison; Summary of findings 2; Summary of findings 3), which present evidence of low quality for all outcomes examined. We obtained only data for the outcomes 'liquid enema plus glucagon versus liquid enema alone' and 'air enema versus liquid enema'

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from two trials each, and data for all other outcomes from single trials only, most with small sample sizes. In Summary of findings for the main comparison, Summary of findings 2, and Summary of findings 3, we downgraded quality of trial evidence for serious to very serious concerns of imprecision or wide confidence intervals, or because trials were subject to serious to very serious concerns of high risk of bias. This limits the strength of our conclusions and our ability to investigate both clinical and statistical heterogeneity. The limited number of included studies and the heterogeneity between them precluded performance of sensitivity and subgroup analyses.

As all examined outcomes were subject to a GRADE assessment of low quality, the true effect of outcomes measured may be substantially different from the estimates; therefore, these estimates can be accepted only with limited confidence.

Potential biases in the review process

We undertook an extensive literature search to examine different aspects of surgical and non-surgical management of intussusception in children, and we sought data from each identified study. In particular, we attempted to contact study authors to gain further information, and we identified ongoing trials. Two independent review authors undertook searching and data extraction and analysis, and a third review author provided arbitration. However, we could not contact study authors to obtain the data that we required. Individuals who apply the results of this review need to acknowledge the limitations of available data derived from few trials.

Agreements and disagreements with other studies or reviews

To the best of our knowledge, this is the only systematic review of RCTs related to this topic, including unpublished data and ongoing trials. However, several narrative reviews have included comparative studies and RCTs (Applegate 2009; Cachat 2012; Daneman 2003; Ko 2007; Sadigh 2015). Applegate 2009 included comparative trials as well as RCTs to examine the role of ultrasonography, air versus liquid enema for reduction, and risk of bowel perforation in children with intussusception. This review concurred that air enema was superior to liquid enema for successful reduction of intussusception in children - a fact that review authors attribute to speed, cost of the procedure, and safety. Daneman 2003 similarly included comparative studies and RCTs, highlighting in their review the ongoing debate regarding fluoroscopy versus ultrasound-guided enema reduction, suggesting that greater accuracy can be afforded with ultrasound-guided reduction. Ko 2007 also examined the role of fluoroscopy versus ultrasound-guided enema reduction by examining both comparative studies and RCTs; these review authors concluded that ultrasound-guided reduction is superior to fluoroscopy owing to its greater accuracy, lack of ionising radiation, lower costs, and no need for sedation. The authors of the current review could not perform the comparison offered in both Daneman 2003 and Ko 2007 but agree with the findings of Ko 2007, which suggest that lack of standardisation among single studies makes objective comparison difficult. Cachat 2012 performed a meta-analysis of studies examining children with radiologically confirmed intussusception, including RCTs and retrospective comparative studies, to compare rates of recurrence. Although Cachat found that dexamethasone was beneficial in reducing rates of recurrence of intussusception among children, review findings suggest that risk of recurrence of intussusception is low, and that regardless of the technique used for successful reduction, it is safe to discharge a patient after performing successful reduction. Sadigh 2015 compared the efficacy of air versus liquid enema for reduction of intussusception in children and found that air enema was superior to liquid enema. These results are similar to those of the current review. Applegate 2009, Cachat 2012, Daneman 2003, Ko 2007, and Sadigh 2015 included no relevant randomised trial that was not included in our review.

AUTHORS' CONCLUSIONS

Implications for practice

Low-quality evidence suggests that air enema may be more effective than liquid enema for reducing intussusception in children. Evidence is insufficient to show whether adjuncts such as glucagon or dexamethasone influenced intussusception reduction rates. Low-quality evidence suggests that use of dexamethasone as an adjunct may be associated with lower rates of recurrent intussusception when compared with enema alone. Evidence on any of the interventions examined was insufficient to allow us to draw any conclusions regarding rates of bowel perforation or other adverse effects.

We found no data on surgical interventions that were suitable for analysis, and no evidence regarding the relative effectiveness and safety of different imaging modalities or protocols for delayed repeat enemas.

Implications for research

The evidence base for this topic is lacking and must be developed further. Clinical trials in children present specific challenges, although randomised controlled trials in surgery are well documented. Researchers must address these concerns. Populations studied should include people in low- and middle-income countries, where the burden of disease is greatest; and trials should be more adequately powered. Interventions utilised must be standardised and clearly defined. In particular, research on the surgical management of intussusception is needed. Outcomes should be standardised and data related to safety and harm should be included. In addition, future investigators should consider how blinding of participants and personnel might be achieved to minimise bias. Further clinical research is needed to determine the most effective and least harmful non-surgical and surgical approaches to management of intussusception in children.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Essa 2011

Methods	• Study design: randomised controlled trial; 2-arm study • Study duration: August 2006 until July 2010
Participants	• Setting: single-centre study • Location: Assuit University Children's Hospital, Egypt • Health Status: "clinical features of intussusception" • Number (treatment group/control group): 75 (40/35) • Age: 5 to 24 months • Sex (M/F): 59/16 Exclusion criteria: pathological lead points, late neglected intestinal obstruction, bowel perforation or shock
Interventions	**Treatment group** • IM dexamethasone sodium sulphate: 0.5 mg/kg/8 h, immediately before the start of enema reduction and every 8 hours thereafter, for a total of 3 doses, plus nasogastric tube, IV fluids, antibiotics, and ultrasound-guided saline enema reduction **Control group** • Nasogastric tube, IV fluids, antibiotics, and ultrasound-guided saline enema reduction alone
Outcomes	• Complete reduction by ultrasound-guided saline enema • Incidence of recurrence during first 24 hours in hospital and during first week (early recurrence) and 6 months post reduction (late recurrence)

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Essa 2011 *(Continued)*

Notes	**Procedure details:** The technique of ultrasound-guided saline enema reduction involved the following: "a reservoir filled with warm, normal saline was placed at a maximum height of 120cm above the table, with its upper end opened connected to a 10-18-Fr Foley's catheter." The enema could be repeated twice more, after a 30-minute rest, if the initial attempt failed (i.e. lack of reduction within 5 minutes) The ratio of participants requiring non-surgical reduction to those requiring surgical reduction was 60:15. In other words, 4/5 participants had successful reduction achieved with non-surgical techniques

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	“The cases were randomly classified into two groups…”. No further details supplied
Allocation concealment (selection bias)	Unclear risk	“The cases were randomly classified into two groups…”. No further details supplied
Incomplete outcome data (attrition bias) All outcomes	Low risk	All 75 cases were reported, including those that failed initial intervention: "Cases who failed ultrasound guided saline enema reduction underwent surgical exploration, with operative details and postoperative complications also reported"
Selective reporting (reporting bias)	Low risk	Study includes all expected outcomes
Blinding of participants and personnel (performance bias) All outcomes	High risk	No placebo treatment used in control group
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not specified who assessed outcomes

Franken 1983

Methods	• Study design: randomised controlled trial; 2-arm study • Study duration: not stated
Participants	• Setting: not stated • Location: not stated • Health status: referred for reduction of ileocolic intussusception • Number (treatment group/control group): 30 (15/15) • Age: 3 years or younger • Sex (M/F): not stated • Exclusion criteria: suspicion of attending physician of peritonitis, clinical or radiographic evidence of peritonitis or intestinal perforation, radiographic evidence of small-bowel obstruction, indication that intussusception had been present for over 48 hours, fever over 40° C, hypovolaemic shock, blood loss anaemia (haemoglobin < 80 g/L), contraindication to administration of glucagon (suspected pheochromocytoma, insulinoma, glucagon sensitivity, or uncontrolled diabetes)
Interventions	**Treatment group**

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Franken 1983 *(Continued)*

- Glucagon: 0.05 mg/kg with barium enema injected IV (over 1 minute) when intussusception was identified at fluoroscopy

Control group

- Placebo: 0.05 mg/kg with barium enema injected IV when intussusception was identified at fluoroscopy

Outcomes	• Reduction of intussusception by barium enema • Failure of procedure at the end of the time limit, but ultimately successful hydrostatic reduction • Failure of procedure, but intussusception reduced at surgery • Failure of procedure, and intussusception un-reduced at surgery
Notes	**Procedure details:** The enema consisted of barium sulphate suspension of approximately 20% w/v concentration, with the enema bag 1 metre above the table top. The enema could be repeated twice more if the initial attempt failed (i.e. lack of reduction within 5 minutes) **Other details:** Glucagon and placebo were supplied by the Eli Lilly Company

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"The injections were given in randomized, double-blind fashion"; no further details supplied
Allocation concealment (selection bias)	Unclear risk	"The injections were given in randomized, double-blind fashion"; no further details supplied
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing data (randomisation post exclusion)
Selective reporting (reporting bias)	Low risk	Reporting included all outcomes and explained outcomes that were unexpected: "eight of 15 intussusceptions...were successfully reduced" - "two patients in the study suffered complications of intussusception...before full recovery ensued"
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"The injections were given in randomized, double-blind fashion...Glucagon and the placebo were supplied in identical vials"
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not specified who assessed outcomes

Hadidi 1999

Methods	• Study design: randomised controlled trial; 3-arm study • Study duration: July 1994 until December 1999
Participants	• Setting: single-centre study • Location: Cairo University Children's Hospital (Abu El Rich) • Health status: "All patients whose clinical and radiological data confirmed the diagnosis of intussusception were eligible for the study"

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Hadidi 1999 *(Continued)*

- Number (treatment group/control group): 147 (50/97)
- Mean age, months (SD):
  - **Treatment 1:** 15 (12)
  - **Treatment 2 (barium/saline):** 17 (16)/16 (15)
- Sex (M/F): 93/54

Exclusion criteria: more than 48 hours of symptoms, general or abdominal signs of toxicity, peritonism or peritonitis, or unreasonable electrolyte levels

Interventions	Participants were prepared in the same manner. Preparation included a nasogastric tube with drainage of the stomach, intravenous fluid deficit replacement, and intravenous metronidazole and cefotaxime All air insufflations were performed by the paediatric surgeon, who was experienced in the technique, and all barium and saline reductions were done by the radiologist, who was experienced in those 2 techniques **Treatment 1** • Pneumatic reduction via air enema **Treatment 2** • Hydrostatic reduction, via liquid enema; 50 participants were allocated to barium enema; 47 were allocated to ultrasound-guided saline enema
Outcomes	• Amount of fluoroscopic time • Rate of successful reduction
Notes	**Procedure details:** Diagnosis and treatment were provided by a dedicated “intussusception clinical team,” consisting of a single paediatric surgeon, a single paediatric radiologist, and 3 residents; all data were recorded on a specially designed protocol sheet The study protocol allowed a maximum of 3 attempts at reduction for each participant. An attempt was defined as pneumatic or hydrostatic pressure for 5 minutes Barium enemas were prepared by routine methods During enemas administered with liquid contrast material, the top of the bag of liquid contrast agent could be raised to a maximum of 1.5 m above the table top. For air insufflation, the maximum pressure used was 120 mmHg. After 3 unsuccessful attempts, the examination was considered a failure. No sedation was used Sonographic criteria for successful reduction were disappearance of intussusception and visualisation of passage of fluid and air bubbles from the caecum well into the terminal ileum. After successful reduction, saline solution was replaced by gastrografin, and a single abdominal radiograph was taken again to document the successful reduction **Other details:** All air reductions and barium reductions were performed with a GE DRS Prestilix 1600X x-ray machine. All saline reductions were done under sonographic guidance with Tochiba SSA 140 ultrasound machine

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"...randomisation was based on a table of random numbers, wherein 15 consecutive random numbers were selected and assigned to cases 1 through 15. This list of 15 cases was used repeatedly throughout the study (10 times) with random sequence every time.” This allocation sequence is predictable

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Hadidi 1999 *(Continued)*

Allocation concealment (selection bias)	High risk	"...randomisation was based on a table of random numbers, wherein 15 consecutive random numbers were selected and assigned to cases 1 through 15. This list of 15 cases was used repeatedly throughout the study (10 times) with random sequence every time." This allocation sequence is predictable
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing data (randomisation post exclusion). "Only 76 patients came to follow up examinations"; however these data were not used in this review
Selective reporting (reporting bias)	Unclear risk	No protocol available
Blinding of participants and personnel (performance bias) All outcomes	High risk	By definition, the paediatric surgeon or radiologist was aware of the procedure each was conducting
Blinding of outcome assessment (detection bias) All outcomes	High risk	Outcome assessment involved a treating surgeon or radiologist capable of interpreting sonographic criteria for successful reduction (disappearance of intussusception and visualisation of the passage of fluid and air bubbles from the caecum well into the terminal ileum)

Lin 2000

Methods	• Study design: randomised controlled trial • Study duration: not stated

Participants	• Setting: single-centre study
	• Location: Chang Gung Memorial Hospital, Keelung, Taiwan
	• Health status: "intussusception patients"
	• Number (treatment/control): 281 (144/137)
	• Mean age:
	  ◦ Treatment group: 18.2 months ± 5.1
	• ◦ Control group: 20.3 months ± 4.7
	• Sex (M/F):
	• ◦ Treatment group: 96/48
	  ◦ Control group: 99/38
	• Exclusion criteria: not stated

Interventions	**Treatment group** • Dexamethasone sodium phosphate: 0.5 mg/kg injected IM immediately after patient met inclusion criteria, before air enema reduction by radiologist team **Control group** • Normal saline: 0.5 mg/kg injected IM before air enema reduction by radiologist team
Outcomes	• Initial successful reduction • 72 hours post reduction recurrence of intussusception (early recurrence) • 1 week post reduction recurrence of intussusception (early recurrence) • 6 months post reduction recurrence of intussusception (late recurrence)
Notes	**Procedure details:** no details on procedure provided

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Lin 2000 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"We designed a randomised, double-blind study"
Allocation concealment (selection bias)	Unclear risk	"We designed a randomised, double-blind study"
Incomplete outcome data (attrition bias) All outcomes	High risk	Data on participants lost to follow-up not reported
Selective reporting (reporting bias)	Unclear risk	Method of data collection post discharge not reported
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	"We designed a randomised, double-blind study"
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	It was not specified who assessed outcomes

Meyer 1993

Methods	• Study design: randomised controlled trial; 2-arm study • Study duration: July 1989 until December 1991
Participants	• Setting: single-centre study • Location: Children's Hospital, Boston • Heath status: patient's physicians requested examination to rule out intussusception; 52 of 101 children undergoing investigation had intussusception • Number (treatment 1/treatment 2): 101 (50/51) • Mean age: • ○ Treatment group 1: 17 months ± 16 ○ Treatment group 2: 15 months ± 12 • Sex (M/F): • ○ Treatment group 1: 30/20 ○ Treatment group 2: 34/17 • Exclusion criteria: patient required a specific contrast, refused consent, required a stronger contrast agent to show mucosa, had increased bowel gas, had indications for water-soluble contrast agent (risk of perforation), had recent unsuccessful examination of intussusception, or had a language barrier
Interventions	• Both study groups were prepared in the same manner. Sedation was usually achieved with IV pentobarbital sodium (Abbott Labaratories, North Chicago, Illinois), but occasionally with IM meperidine HCL (Sanofi Winthrop, New York, New York) given alone or in combination with IV pentobarbital sodium. A Foley catheter was inserted, and a balloon was inflated in the rectum **Treatment group 1** • Hydrostatic reduction via liquid enema (barium or water-soluble contrast media) at the radiologist's discretion

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Meyer 1993 *(Continued)*

	Treatment group 2 • Pneumatic reduction via air enema
Outcomes	• Confirmation of intussusception • Rate of successful intussusception reduction • Recurrence of intussusception • Fluoroscopy time
Notes	**Procedure details:** During the first 1.5 years of the study, barium was the only liquid contrast agent used. During the final year, owing to evolving concepts in intussusception management and changes in personnel, the type of liquid contrast material (water-soluble or barium) used was determined at the radiologist's discretion The study protocol allowed a maximum of 3 attempts at reduction for each participant. An attempt was defined as pneumatic or hydrostatic pressure applied for a total of 5 minutes. After 3 unsuccessful attempts, the examination was considered a failure The concentration of barium used in individual cases was not recorded Cysto-Conray II (Iothalamate meglumine 17.2%; Mallinckrodt Medical, St Louis, Missouri) was the water-soluble enema administered The air insufflation device included an electronic pop-off valve that could be set to pressure of 60, 80, or 120 mmHg **Other details:** This study examined the accuracy of diagnosis with air versus liquid enema, and thus included participants who did not have intussusception. It was necessary to extrapolate the data of those who did have confirmed intussusception for our review

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"Randomization was based on a table of random numbers, wherein 20 consecutive random numbers were selected and assigned to cases 1 through 20. Cases assigned even random numbers were to undergo examination with liquid contrast material and those assigned odd random numbers were to be examined with air." This allocation sequence is predictable and is compromised by the need to extrapolate data for participants with confirmed intussusception
Allocation concealment (selection bias)	High risk	Central randomisation table (n = 20) Used repeatedly throughout the study. Repetative use of the random number table may have allowed prediction of intervention for participants
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing data (randomisation post exclusion). Successful diagnosis of intussusception not significantly different between air and liquid contrast groups
Selective reporting (reporting bias)	Unclear risk	No protocol available. Not all expected outcomes were reported
Blinding of participants and personnel (performance bias) All outcomes	High risk	By definition, the radiologist was aware of the procedure he was conducting
Blinding of outcome assessment (detection bias)	High risk	Radiologist who conducted the procedure recorded results

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Meyer 1993 *(Continued)*
All outcomes

Mortensson 1984

Methods	• Study design: quasi-randomised controlled trial (allocation via date of birth); 2-arm study • Study duration: not stated
Participants	• Setting: not stated • Location: St Goran's Children's Hospital, Stockholm, Sweden • Health status: intussusception radiologically confirmed by barium enema • Number (treatment/control): 188 (69/119) • Age (median): 1 month to 5 ½ years (9 months) • Sex (M/F): not stated • Exclusion criteria: intestinal obstruction and clinical suspicion of bowel gangrene, clinical and radiological manifestations of peritonitis, high fever with gross bowel obstruction
Interventions	• Following diagnosis by barium enema, groups were allocated to 2 groups **Treatment group** • Glucagon: 0.05 mg/kg injected IM, 5 minutes before barium enema reduction **Control group** • Barium enema reduction, 5 minutes after diagnosis by barium enema, similar to treatment group
Outcomes	• Rate of successful intussusception reduction • Number of attempts until successful enema reduction of intussusception • Time until successful reduction of intussusception with enema
Notes	**Procedure details:** The pressure of the enema employed was kept as uniform as possible, corresponding to 100 to 120 cm of barium suspension Reduction was considered a failure when an intussusception could no longer be moved in an oral direction after several minutes of effective pressure 5 minutes after a first attempt had failed, a second and later a third attempt was made. Failure after this point meant that the participant was prepared for operation. Participants in the control group with 3 failed attempts were administered IV glucagon, as in the treatment group, and an attempt at hydrostatic reduction was repeated. After a fourth attempt, these participants were prepared for operation **Other details:** Study was undertaken in 3 steps (Step 1: initial 3 attempts at reduction as per treatment group; Step 2: participants belonging to the control group were administered glucagon and a fourth attempt was made at reduction; participants with reduction regarded as a failure were prepared for surgery; Step 3: all other participants otherwise not reduced were given a final attempt at reduction before they were prepared for surgery). We have included data only for Step 1, as this step pertains to our outcomes and criteria for inclusion

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Allocation of material to a test group and a reference group according to date of birth; participants born on an even calendar date were given an intramuscular injection of 0.05 mg glucagon/kg body weight

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Mortensson 1984 *(Continued)*

Allocation concealment (selection bias)	Unclear risk	Unclear who allocated participants, and who administered treatment
Incomplete outcome data (attrition bias) All outcomes	High risk	Not stated why some participants from reference group or control group progressed to steps 2 and 3, and why others were excluded
Selective reporting (reporting bias)	Unclear risk	No protocol available. Not all expected outcomes were reported
Blinding of participants and personnel (performance bias) All outcomes	High risk	No placebo given Treatment group given intramuscular injection; control group given no injection
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	It was not specified who assessed outcomes

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Diaz-Aldagalan 2012	Not a randomised controlled trial
Guo 2010	Not a randomised controlled trial
Hsiao 1988	Not a randomised controlled trial
Morrison 2009	Not a randomised controlled trial

Characteristics of studies awaiting assessment *[ordered by study ID]*

Zhang 2014

Methods	
Participants	
Interventions	
Outcomes	
Notes	Translation pending

Characteristics of ongoing studies *[ordered by study ID]*

El Fiky 2016

Trial name or title	Effect of hydrocortisone on improving outcome of pneumatic reduction of infantile intussusception

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El Fiky 2016 *(Continued)*

Methods	• Study design: randomised single-blind controlled; 2-arm study • Study duration: April 2015 until December 2016
Participants	• Setting: single-centre study • Location: Cairo University Pediatric Hospital • Health status: diagnosis of infantile intussusception • Number: 80 • Age: 3 months to 4 years of age • Exclusion criteria: peritonitis, pneumoperitoneum, morbid patient
Interventions	**Treatment group 1** • Hydrocortisone; hydrocortisone IV 10 mg/kg with resuscitation before attempted reduction, single dose with resuscitation before attempted reduction **Treatment group 2** • Saline; saline IV 100 mL with resuscitation before attempted reduction, single dose with resuscitation before attempted reduction
Outcomes	• Primary outcome: success of pneumatic reduction • Secondary outcomes: number of trials required before successful reduction, number of complications
Starting date	April 2015
Contact information	Mahmoud El Fiky, Lecturer of Pediatric Surgery, Cairo University
Notes	ClinicalTrials.gov Identifier:NCT02691858

Mehraeen 2011

Trial name or title	The effect of midazolam in decreasing time of hydrostatic reduction of childhood intussusceptions
Methods	• Study design: randomised single-blind controlled; 2-arm study • Study duration: not stated
Participants	• Setting: single-centre study • Location: Amirkola Children's Hospital • Health status: diagnosis of ileocolic intussusception • Number: 32 • Age: 6 months to 4 years of age • Exclusion criteria: any pathological lead points, known case of chronic gastrointestinal disease, history of chronic pulmonary disease or any hypoxic disease, any signs of peritonitis or bowel perforation, such as dehydration or lethargy
Interventions	**Treatment group** • Liquid enema with midazolam (0.1 mg/kg, up to 3 mg) **Control group** • Liquid enema with IV injection of distilled water (0.1 mg/kg, up to 3 mg)
Outcomes	• Time of reduction

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Mehraeen 2011 *(Continued)*

	• Successful reduction
Starting date	Date of registration: 26 August, 2011
Contact information	Dr. Raheleh Mehraeen sany_monzavi@yahoo.com
Notes	

Zhang 2015

Trial name or title	Open reduction of paediatric intussusception through inferior umbilical skin fold incision
Methods	Study design: randomised single-blind controlled; 2-arm study Study duration: 1 May 2014 until 30 June 2015
Participants	• Setting: not stated • Location: Tongji Hospital, Wuhan, Hubei, China • Health status: within 48 hours of diagnosis of intussusception • Number (treatment group 1/treatment group 2): 60 (30/30) • Age: 14 years of age and younger • Exclusion criteria: clinical instability, severe dehydration, peritonitis, intestinal perforation, inability for air enema to show the intussusception, apex can retreat to the ascending colon or ileocaecal junction
Interventions	**Treatment group 1** • Transumbilical incision intussusception reduction **Treatment group 2** • Laprascopic intussusception reduction
Outcomes	• Reduction rate • Operation time • Time to first oral intake • Time to full feeds • Complications • Actual cost • Scars
Starting date	Date of registration: 26 April 2014
Contact information	Wen Zhang wenzhang09@126.com
Notes	Randomisation procedure involves flipping a coin

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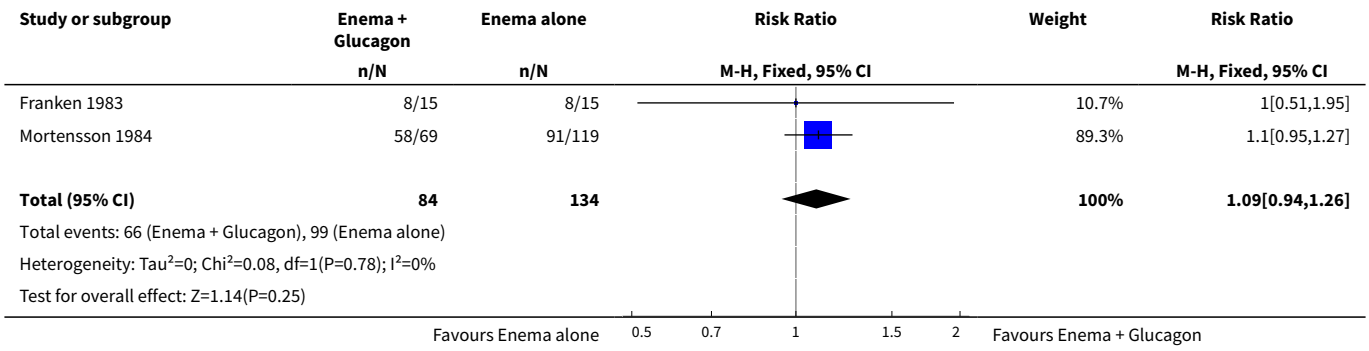
DATA AND ANALYSES

Comparison 1. Enema plus glucagon versus enema alone

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Successfully reduced intussusception	2	218	Risk Ratio (M-H, Fixed, 95% CI)	1.09 [0.94, 1.26]

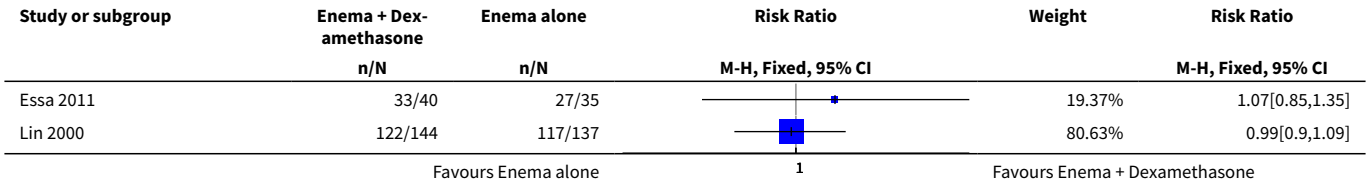
Analysis 1.1. Comparison 1 Enema plus glucagon versus enema alone, Outcome 1 Successfully reduced intussusception.



Comparison 2. Enema plus dexamethasone versus enema alone

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Successfully reduced intussusception	2	356	Risk Ratio (M-H, Fixed, 95% CI)	1.01 [0.92, 1.10]
2 Bowel perforation(s)	1	75	Risk Ratio (M-H, Fixed, 95% CI)	2.63 [0.11, 62.66]
3 Recurrent intussusception	2	299	Risk Ratio (M-H, Fixed, 95% CI)	0.14 [0.03, 0.60]
4 Bowel resection	1	75	Risk Ratio (M-H, Fixed, 95% CI)	0.88 [0.19, 4.06]

Analysis 2.1. Comparison 2 Enema plus dexamethasone versus enema alone, Outcome 1 Successfully reduced intussusception.



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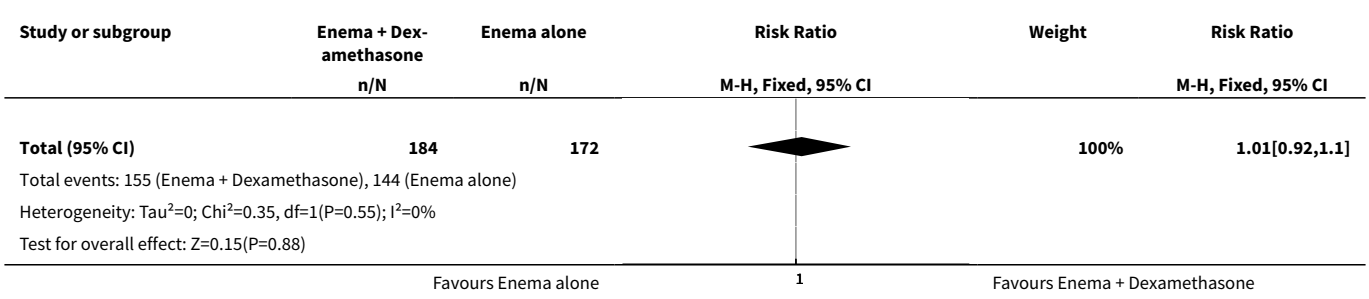
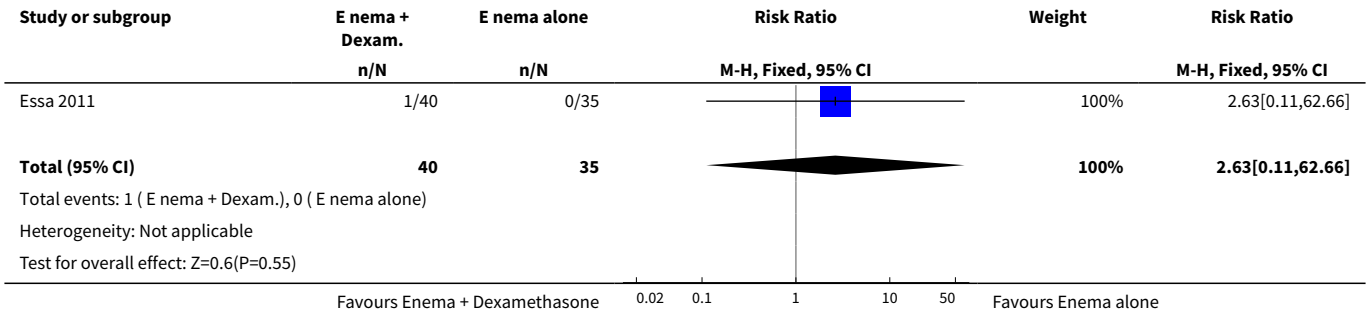
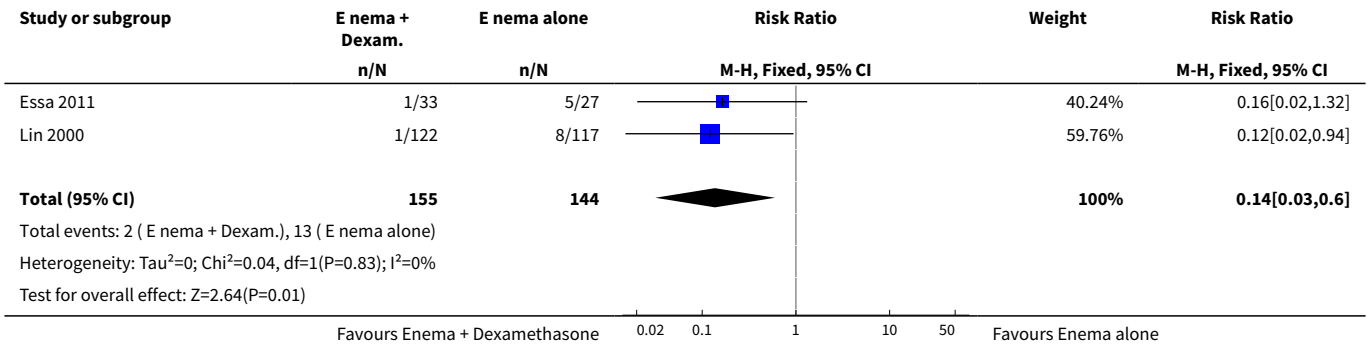


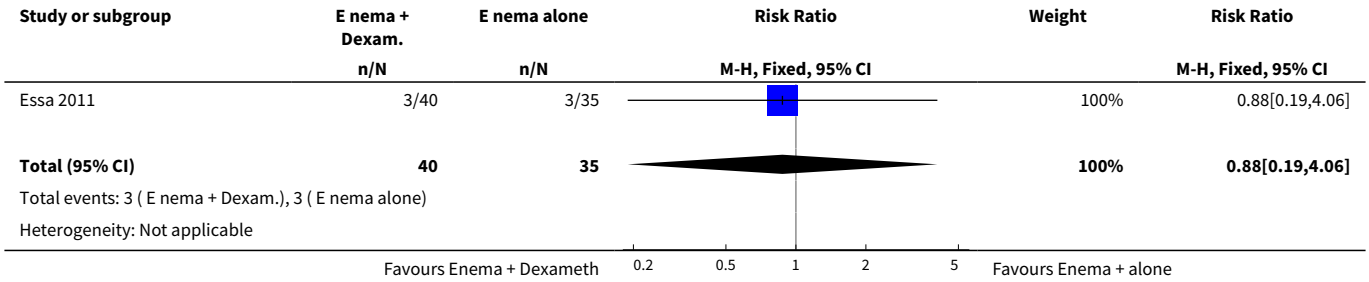
Analysis 2.2. Comparison 2 Enema plus dexamethasone versus enema alone, Outcome 2 Bowel perforation(s).



Analysis 2.3. Comparison 2 Enema plus dexamethasone versus enema alone, Outcome 3 Recurrent intussusception.



Analysis 2.4. Comparison 2 Enema plus dexamethasone versus enema alone, Outcome 4 Bowel resection.



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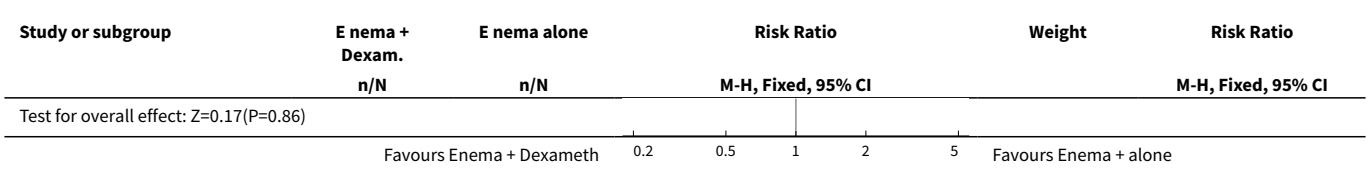
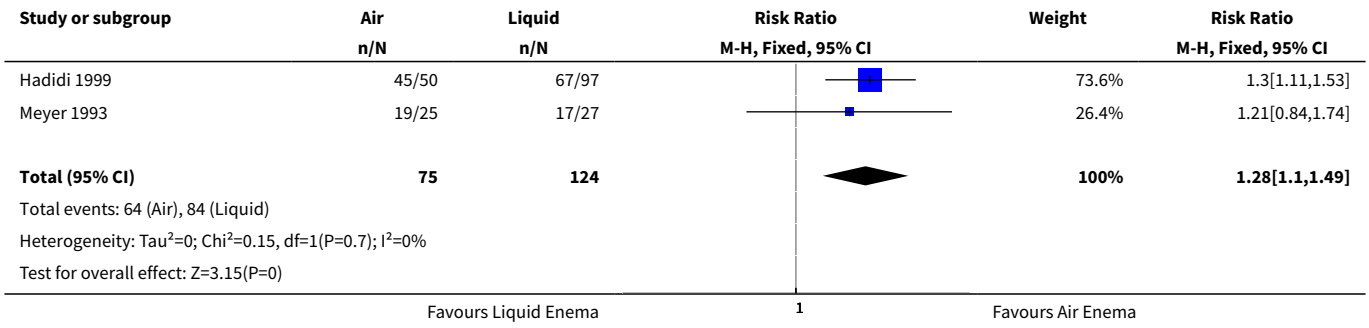


Comparison 3. Air enema versus liquid enema

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Successfully reduced intussusception	2	199	Risk Ratio (M-H, Fixed, 95% CI)	1.28 [1.10, 1.49]

Analysis 3.1. Comparison 3 Air enema versus liquid enema, Outcome 1 Successfully reduced intussusception.



APPENDICES

Appendix 1. CENTRAL search strategy

CENTRAL (2016, Issue 8)

#1 MeSH descriptor Intussusception explode all trees
#2 ((intestin* and invagination*) or intususcep* or intussuscep*):ti,ab,kw
#3 (#1 OR #2)
#4 MeSH descriptor Infant explode all trees
#5 MeSH descriptor Child explode all trees
#6 (infant* or child* or newborn*):ti,ab,kw
#7 (#4 OR #5 OR #6)
#8 (#3 AND #7)

Appendix 2. MEDLINE search strategy

MEDLINE (Ovid 1950 to September 2016)

1. exp Intussusception/
2. ((intestin* and invagination*) or intususcep* or intussuscep*).mp.

3. 1 or 2
4. exp Infant/
5. exp Child/

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6. (infant* or child* or newborn*).mp.

7. 4 or 5 or 6
8. 3 and 7
9. randomized controlled trial.pt.
10. controlled clinical trial.pt.
11. randomized.ab.
12. placebo.ab.
13. drug therapy.fs.

14. Randomly.ab.
15. trial.ab.
16. groups.ab.
17. 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16
18. exp animals/ not humans.sh.
19. 17 not 18
20. 8 and 19

Appendix 3. Embase search strategy

Embase (Ovid, 1974 to September 2016)

1. exp intussusception/
2. ((intestin* and invagination*) or intususcep* or intussuscep*).mp.
3. 1 or 2
4. exp child/
5. (infant* or child* or newborn*).mp.
6. 4 or 5
7. 3 and 6
8. CROSSOVER PROCEDURE.sh.
9. DOUBLE-BLIND PROCEDURE.sh.
10. SINGLE-BLIND PROCEDURE.sh.
11. (crossover* or cross over*).ti,ab.
12. placebo*.ti,ab.
13. (doubl* adj blind*).ti,ab.
14. allocat*.ti,ab.
15. trial.ti.
16. RANDOMIZED CONTROLLED TRIAL.sh.
17. random*.ti,ab.
18. 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17
19. (exp animal/ or exp invertebrate/ or animal.hw. or nonhuman/) not (exp human/ or human cell/ or (human or humans or man or men or wom?n).ti.)
20. 18 not 19
21. 7 and 20

Appendix 4. Science Citation Index search strategy

Science Citation Index Expanded (via Web of Science) (1900 to September 2016)

#1 Topic=(((intestin* and invagination*) or intususcep* or intussuscep*))
#2 Topic=((infant* or child* or newborn*))
#3 Topic=((controlled trial or controlled clinical trial or placebo or clinical trial or random* or trial or cct or rct))
#4 (#3 AND #2 AND #1)

Appendix 5. Biosis Previews search strategy

Biosis Previews (via Web of Science) (1969 to September 2016)

#1 Topic=(((intestin* and invagination*) or intususcep* or intussuscep*))
#2 Topic=((infant* or child* or newborn*))
#3 Topic=((controlled trial or controlled clinical trial or placebo or clinical trial or random* or trial or cct or rct))
#4 (#3 AND #2 AND #1)

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Appendix 6. Criteria for judging risk of bias in the 'Risk of bias' assessment tool

RANDOM SEQUENCE GENERATION	
Selection bias (biased allocation to interventions) due to inadequate generation of a randomised sequence	
Criteria for a judgement of 'Low risk' of bias	The investigators describe a random component in the sequence generation process such as: • Referring to a random number table; • Using a computer random number generator; • Coin tossing; • Shuffling cards or envelopes; • Throwing dice; • Drawing of lots; • Minimization*. *Minimization may be implemented without a random element, and this is considered to be equivalent to being random.
Criteria for the judgement of 'High risk' of bias.	The investigators describe a non-random component in the sequence generation process. Usually, the description would involve some systematic, non-random approach, for example: • Sequence generated by odd or even date of birth; • Sequence generated by some rule based on date (or day) of admission; • Sequence generated by some rule based on hospital or clinic record number. Other non-random approaches happen much less frequently than the systematic approaches mentioned above and tend to be obvious. They usually involve judgement or some method of non-random categorization of participants, for example: • Allocation by judgement of the clinician; • Allocation by preference of the participant; • Allocation based on the results of a laboratory test or a series of tests; • Allocation by availability of the intervention.
Criteria for the judgement of 'Unclear risk' of bias.	Insufficient information about the sequence generation process to permit judgement of 'Low risk' or 'High risk'.
ALLOCATION CONCEALMENT	
Selection bias (biased allocation to interventions) due to inadequate concealment of allocations prior to assignment.	
Criteria for a judgement of 'Low risk' of bias.	Participants and investigators enrolling participants could not foresee assignment because one of the following, or an equivalent method, was used to conceal allocation: • Central allocation (including telephone, web-based and pharmacy-controlled randomization); • Sequentially numbered drug containers of identical appearance; • Sequentially numbered, opaque, sealed envelopes.
Criteria for the judgement of 'High risk' of bias.	Participants or investigators enrolling participants could possibly foresee assignments and thus introduce selection bias, such as allocation based on: • Using an open random allocation schedule (e.g. a list of random numbers); • Assignment envelopes were used without appropriate safeguards (e.g. if envelopes were unsealed or nonopaque or not sequentially numbered); • Alternation or rotation; • Date of birth;

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(Continued)

	• Case record number; • Any other explicitly unconcealed procedure.
Criteria for the judgement of 'Unclear risk' of bias.	Insufficient information to permit judgement of 'Low risk' or 'High risk'. This is usually the case if the method of concealment is not described or not described in sufficient detail to allow a definite judgement – for example if the use of assignment envelopes is described, but it remains unclear whether envelopes were sequentially numbered, opaque and sealed.
BLINDING OF PARTICIPANTS AND PERSONNEL Performance bias due to knowledge of the allocated interventions by participants and personnel during the study.	
Criteria for a judgement of 'Low risk' of bias.	Any one of the following: • No blinding or incomplete blinding, but the review authors judge that the outcome not likely to be influenced by lack of blinding; • Blinding of participants and key study personnel ensured, and unlikely that the blinding could have been broken.
Criteria for the judgement of 'High risk' of bias.	Any one of the following: • No blinding or incomplete blinding, and the outcome is likely to be influenced by lack of blinding; • Blinding of key study participants and personnel attempted, but likely that the blinding could have been broken, and the outcome is likely to be influenced by lack of blinding.
Criteria for the judgement of 'Unclear risk' of bias.	Any one of the following: • Insufficient information to permit judgement of 'Low risk' or 'High risk'; • The study did not address this outcome.
BLINDING OF OUTCOME ASSESSMENT Detection bias due to knowledge of the allocated interventions by outcome assessors.	
Criteria for a judgement of 'Low risk' of bias.	Any one of the following: · No blinding of outcome assessment, but the review authors judge that the outcome measurement is not likely to be influenced by lack of blinding; · Blinding of outcome assessment ensured, and unlikely that the blinding could have been broken.
Criteria for the judgement of 'High risk' of bias.	Any one of the following: • No blinding of outcome assessment, and the outcome measurement is likely to be influenced by lack of blinding; • Blinding of outcome assessment, but likely that the blinding could have been broken, and the outcome measurement is likely to be influenced by lack of blinding.
Criteria for the judgement of 'Unclear risk' of bias.	Any one of the following: • Insufficient information to permit judgement of 'Low risk' or 'High risk'; • The study did not address this outcome.
INCOMPLETE OUTCOME DATA Attrition bias due to amount, nature or handling of incomplete outcome data.	
Criteria for a judgement of 'Low risk' of bias.	Any one of the following: • No missing outcome data;

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(Continued)

	• Reasons for missing outcome data unlikely to be related to true outcome (for survival data, censoring unlikely to be introducing bias); • Missing outcome data balanced in numbers across intervention groups, with similar reasons for missing data across groups; • For dichotomous outcome data, the proportion of missing outcomes compared with observed event risk not enough to have a clinically relevant impact on the intervention effect estimate; • For continuous outcome data, plausible effect size (difference in means or standardized difference in means) among missing outcomes not enough to have a clinically relevant impact on observed effect size; • Missing data have been imputed using appropriate methods.
Criteria for the judgement of 'High risk' of bias.	Any one of the following: • Reason for missing outcome data likely to be related to true outcome, with either imbalance in numbers or reasons for missing data across intervention groups; • For dichotomous outcome data, the proportion of missing outcomes compared with observed event risk enough to induce clinically relevant bias in intervention effect estimate; • For continuous outcome data, plausible effect size (difference in means or standardized difference in means) among missing outcomes enough to induce clinically relevant bias in observed effect size; • 'As-treated' analysis done with substantial departure of the intervention received from that assigned at randomization; • Potentially inappropriate application of simple imputation.
Criteria for the judgement of 'Unclear risk' of bias.	Any one of the following: • Insufficient reporting of attrition/exclusions to permit judgement of 'Low risk' or 'High risk' (e.g. number randomized not stated, no reasons for missing data provided); • The study did not address this outcome.
SELECTIVE REPORTING Reporting bias due to selective outcome reporting.	
Criteria for a judgement of 'Low risk' of bias.	Any of the following: • The study protocol is available and all of the study's pre-specified (primary and secondary) outcomes that are of interest in the review have been reported in the pre-specified way; • The study protocol is not available but it is clear that the published reports include all expected outcomes, including those that were pre-specified (convincing text of this nature may be uncommon).
Criteria for the judgement of 'High risk' of bias.	Any one of the following: • Not all of the study's pre-specified primary outcomes have been reported; • One or more primary outcomes is reported using measurements, analysis methods or subsets of the data (e.g. subscales) that were not pre-specified; • One or more reported primary outcomes were not pre-specified (unless clear justification for their reporting is provided, such as an unexpected adverse effect); • One or more outcomes of interest in the review are reported incompletely so that they cannot be entered in a meta-analysis; • The study report fails to include results for a key outcome that would be expected to have been reported for such a study.
Criteria for the judgement of 'Unclear risk' of bias.	Insufficient information to permit judgement of 'Low risk' or 'High risk'. It is likely that the majority of studies will fall into this category.
OTHER BIAS	

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(Continued)
Bias due to problems not covered elsewhere in the table.

Criteria for a judgement of 'Low risk' of bias.	The study appears to be free of other sources of bias.
Criteria for the judgement of 'High risk' of bias.	There is at least one important risk of bias. For example, the study: • Had a potential source of bias related to the specific study design used; or • Has been claimed to have been fraudulent; or • Had some other problem.
Criteria for the judgement of 'Unclear risk' of bias.	There may be a risk of bias, but there is either: • Insufficient information to assess whether an important risk of bias exists; or • Insufficient rationale or evidence that an identified problem will introduce bias.

HISTORY

Protocol first published: Issue 2, 2007
Review first published: Issue 6, 2017

Date	Event	Description
4 August 2015	New search has been performed	New search performed. One new trial included
28 October 2013	Amended	New review author team. Major changes and new citation
5 October 2013	Amended	Copy edited and ready for publication

CONTRIBUTIONS OF AUTHORS

SG: running searches, selecting studies, extracting data, analysing results, and writing the main review.

JK: drafting the protocol, identifying studies, and providing content area advice.

ACW: drafting the protocol and providing methodological advice.

RGM: drafting the protocol, running searches, selecting studies, extracting data, analysing results, and writing the main review.

DECLARATIONS OF INTEREST

Review authors have no conflicts of interest to declare.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

In contrast to our published protocol, we decided to conduct the analysis using fixed-effect meta-analysis because it is more conservative in the presence of heterogeneity and small-study effects. Although not specifically stipulated in the protocol, we saw both quasi-RCTs and cluster RCTs as fit for inclusion in this review.

When data were missing, and intention-to-treat analysis was not possible, we planned to use available-case or per-protocol analysis.

Although we did not discuss these matters in the protocol, we used the GRADE approach and 'Summary of findings' tables to summarise our findings.

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INDEX TERMS

Medical Subject Headings (MeSH)

Air; Dexamethasone [*therapeutic use]; Enema [*methods]; Gastrointestinal Agents [*therapeutic use]; Glucagon [*therapeutic use]; Glucocorticoids [*therapeutic use]; Intestinal Perforation [etiology]; Intussusception [surgery] [*therapy]; Postoperative Complications; Randomized Controlled Trials as Topic; Recurrence; Secondary Prevention [methods]

MeSH check words

Child; Humans

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