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Evidence for Clinicians
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Dietary interventions for recurrent abdominal pain in childhood

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For the current issue of the *Journal*, we asked Dr. Mathew W. Carroll to comment on and put into context the recent Cochrane dietary interventions for recurrent abdominal pain in childhood.

BACKGROUND

This is an update of the original Cochrane review, last published in 2009 (Huertas-Ceballos 2009). Recurrent abdominal pain (RAP), including children with irritable bowel syndrome, is a common problem affecting between 4% and 25% of school-aged children. For the majority of such children, no organic cause for their pain can be found on physical examination or investigation. Many dietary inventions have been suggested to improve the symptoms of RAP. These may involve either excluding ingredients from the diet or adding supplements such as fibre or probiotics.

OBJECTIVES

To examine the effectiveness of dietary interventions in improving pain in children of school age with RAP.

SEARCH METHODS

We searched CENTRAL, Ovid MEDLINE, Embase, eight other databases, and two trials registers, together with reference checking, citation searching and contact with study authors, in June 2016.

SELECTION CRITERIA

Randomised controlled trials (RCTs) comparing dietary interventions with placebo or no treatment in children aged five to 18 years with RAP or an abdominal pain-related, functional gastrointestinal disorder, as defined by the Rome III criteria (Rasquin 2006).

DATA COLLECTION AND ANALYSIS

We used standard methodological procedures expected by Cochrane. We grouped dietary interventions together by category for analysis. We contacted study authors to ask for missing information and clarification, when needed. We assessed the quality of the evidence for each outcome using the GRADE approach.

MAIN RESULTS

We included 19 RCTs, reported in 27 papers with a total of 1453 participants. Fifteen of these studies were not included in the previous review. All 19 RCTs had follow-up ranging from one to five months. Participants were aged between four and 18 years from eight different countries and were recruited largely from paediatric gastroenterology clinics. The mean age at recruitment ranged from 6.3 years to 13.1 years. Girls outnumbered boys in most trials. Fourteen trials recruited children with a diagnosis under the broad umbrella of RAP or functional gastrointestinal disorders; five trials specifically recruited only children with irritable bowel syndrome. The studies fell into four categories: trials of probiotic-based interventions (13 studies), trials of fibre-based interventions (four studies), trials of low FODMAP (fermentable oligosaccharides, disaccharides, monosaccharides and polyols) diets (one study), and trials of fructose-restricted diets (one study).

We found that children treated with probiotics reported a greater reduction in pain frequency at zero to three months postintervention than those given placebo (standardised mean difference (SMD) -0.55, 95% confidence interval (CI) -0.98 to -0.12; 6 trials; 523 children). There was also a decrease in pain intensity in the intervention group at the same time point (SMD -0.50, 95% CI -0.85 to -0.15; 7 studies; 575 children). However, we judged the evidence for these outcomes to be of

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low quality using GRADE due to an unclear risk of bias from incomplete outcome data and significant heterogeneity.

We found that children treated with probiotics were more likely to experience improvement in pain at zero to three months post intervention than those given placebo (odds ratio (OR) 1.63, 95% CI 1.07 to 2.47; 7 studies; 722 children). The estimated number needed to treat for an additional beneficial outcome (NNTB) was eight, meaning that eight children would need to receive probiotics for one to experience improvement in pain in this timescale. We judged the evidence for this outcome to be of moderate quality due to significant heterogeneity.

Children with a symptom profile defined as irritable bowel syndrome treated with probiotics were more likely to experience improvement in pain at zero to three months post intervention than those given placebo (OR 3.01, 95% CI 1.77 to 5.13; 4 studies; 344 children). Children treated with probiotics were more likely to experience improvement in pain at three to six months post intervention compared to those receiving placebo (OR 1.94, 95% CI 1.10 to 3.43; 2 studies; 224 children). We judged the evidence for these two outcomes to be of moderate quality due to small numbers of participants included in the studies.

We found that children treated with fibre-based interventions were not more likely to experience an improvement in pain at zero to three months post intervention than children given placebo (OR 1.83, 95% CI 0.92 to 3.65; 2 studies; 136 children). There was also no reduction in pain intensity compared to placebo at the same time point (SMD -1.24, 95% CI -3.41 to 0.94; 2 studies; 135 children). We judged the evidence for these outcomes to be of low quality due to an unclear risk of bias, imprecision, and significant heterogeneity.

We found only one study of low FODMAP diets and only one trial of fructose-restricted diets, meaning no pooled analyses were possible.

We were unable to perform any meta-analyses for the secondary outcomes of school performance, social or psychological functioning, or quality of daily life, as not enough studies included these outcomes or used comparable measures to assess them.

With the exception of one study, all studies reported monitoring children for adverse events; no major adverse events were reported.

AUTHORS' CONCLUSIONS

Overall, we found moderate- to low-quality evidence suggesting that probiotics may be effective in improving pain in children with RAP. Clinicians may therefore consider probiotic interventions as part of a holistic management strategy. However, further trials are needed to examine longer-term outcomes and to improve confidence in estimating the size of the effect, as well as to determine the optimal strain and dosage. Future research should also explore the effectiveness of probiotics in children with different symptom profiles, such as those with irritable bowel syndrome.

We found only a small number of trials of fibre-based interventions, with overall low-quality evidence for the outcomes. There was therefore no convincing evidence that fibre-based interventions improve pain in children with RAP. Further high-quality RCTs of fibre supplements involving larger numbers of participants are required. Future trials of low FODMAP diets and other dietary interventions are also required to facilitate evidence-based recommendations

The full text of the Cochrane Review is available in *The Cochrane Library*: Newlove-Delgado TV, Martin AE, Abbott RA, Bethel A, Thompson-Coon J, Whear R, Logan S. Dietary interventions for recurrent abdominal pain in childhood. Cochrane Database of Systematic Reviews 2017, Issue 3. Art. No.: CD010972. DOI: 10.1002/14651858.CD010972.pub2.

EXPERT COMMENTARY: M.W. CARROLL, BMed (Hons) MHSC FRACP

Abdominal pain in childhood remains a common clinical presentation to general practice, general paediatrics, and paediatric gastroenterology. With a broad differential diagnosis, most recurrent abdominal pain in children is benign in nature falling into the 'functional' category, meaning that there is no serious or progressive underlying organic pathology driving the clinical presentation (1).

Recurrent abdominal pain has gone by many names over the years and this has led to confusion, misclassification, and heterogeneity in data collection and analysis. In an attempt to address this, the ROME Foundation developed criteria to provide practitioners with a symptom-based guide by which childhood and adolescent functional gastrointestinal disorders (FGIDs) could be diagnosed and researched. The latest iteration, Rome IV, divides abdominal pain FGIDs (AP-FGID) into four main diagnoses: functional dyspepsia; irritable bowel syndrome; abdominal migraine; and functional abdominal pain—not otherwise specified (FAP-NOS) (2). The understanding of the etiology of AP-FGIDs has evolved over time also with a greater appreciation of the so-called 'brain-gut axis' and it's sensitization by triggering events (inflammation, infection, psychosocial factors) leading to visceral hyperalgesia and functional disability. The role of psychological distress, genetic predisposition, and abnormalities of gastrointestinal motor function is acknowledged. In turn, this has led to a move away from AP-FGIDs being considered simply 'nonorganic' in etiology and to recognize their complex, heterogenous pathophysiology (2,3).

The use of the ROME IV criteria may allow a practitioner to confidently make a diagnosis of an AP-FGID and forego

many unnecessary, costly, and often invasive investigations driven by a desire to sufficiently rule out an alternative etiology (2,4,5). It is critical, however, to highlight the concept of 'red flags' when assessing a patient for AP-FGIDs. Presence of such signs and symptoms should prompt practitioners to investigate further and screening tests for conditions such as celiac disease and inflammatory bowel disease should be considered. That said, a diagnosis of AP-FGID should be a reassuring one for patients and families with a focus on the absence of a serious underlying disease process. A reassuring diagnosis should be a relief in itself, yet practitioners and families are often frustrated with a lack of therapeutic strategies. There are few randomized control trials in the paediatric literature that examine therapy for FGIDs and many studies have simply lumped all AP-FGIDs together, reducing precision and introducing heterogeneity.

The Cochrane Review by Newlove-Delgado et al. (6) assesses the evidence for probiotics; a low fermentable carbohydrate diet (low fermentable oligosaccharide, disaccharide, monosaccharide, and polyol (FODMAP) diet); fibre supplements; and a fructose-restricted diet in the management of AP-FGIDs. Evidence was synthesized from 19 randomized controlled trials comprising 1,453 patients aged 5 to 18 years. Probiotics (13 trials) were found to reduce pain frequency and intensity, but would be considered low quality evidence due to significant heterogeneity. The benefit in terms of a number needed to treat for an additional beneficial outcome (NNTB) was eight, meaning eight children would require treatment for one to experience improvement in the 0- to 3-month timeline assessed (odds ratio [OR] 1.63, 95% confidence interval: 1.07 to 2.47; 7 studies; 722 children). Fortunately, serious adverse events are very rare with probiotics so a trial of therapy would be quite reasonable and certainly is a common part of my practice. There is insufficient data currently to recommend which strain or dose of probiotic should be used. However, *Lactobacillus rhamnosus* GG, and *Lactobacillus reuteri* were the most common species studied (five and three studies, respectively).

Fibre-based supplements do not appear to improve pain in the four studies reviewed. There was only one study each for low FODMAP and fructose-restricted diets that met the inclusion criteria and so, no pooled data analyses were possible. I judiciously use the low FODMAP dietary approach in my practice and have found it to be somewhat useful in patients with predominant symptoms of bloating and colicky pain. The fermentable carbohydrate restriction, in theory, leads to less gaseous distension of the bowel and less pain as a result. This dietary approach is becoming one of the most widespread clinical approaches despite the lack of available high-quality evidence.

Both pharmacological and nonpharmacological therapies for AP-FGIDs exist and with the right combination many patients can find symptom relief or control. Recent Canadian guidelines in adult Irritable Bowel Syndrome reflect the fact that evidence-based practice is possible in AP-FGIDs (7). With dietary interventions such as psyllium supplementation (moderate quality of evidence), peppermint oil (low-quality evidence) or probiotics (low-quality evidence) to improve Irritable Bowel Syndrome symptoms being suggested or recommended based on the quality of the evidence. However, Newlove-Delgado's conclusions highlight the comparative dearth of available data in children and emphasize the need for more research in this field. If one approaches treatment from the same biopsychosocial model that now underpins out conceptualization of etiology, a range of possible therapies are available and an integrative approach is well advised (2,3,8). Ultimately, more research in the dietary treatment AP-FGIDs is clearly required.

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