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Transcutaneous electrical nerve stimulation (TENS) for treatment of constipation in children

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ABSTRACT

This is the protocol for a review and there is no abstract. The objectives are as follows:

The primary objective is to assess the efficacy and safety of TENS used for the treatment of childhood constipation.

BACKGROUND

Description of the condition

Constipation is a common problem in children. Globally, the prevalence ranges from around 0.7 to 30% of the paediatric population depending on diagnostic criteria (NICE 2010, van den Berg 2006). Less than five per cent of these children have an underlying organic cause for their constipation (Tabbers 2011). Around 3% of general paediatric outpatient visits and approximately 25% of paediatric gastroenterology consultations are related to a perceived defecation disorder, a major proportion of which is constipation (NASPGHAN 2006). Childhood constipation is associated with substantial financial and emotional burden for the affected children and their caregivers (Walia 2009). One report estimates the costs of constipation in children to be around USD 3.9 billion per year in the USA alone (Mugie 2011). The pathophysiology of constipation is multifactorial but the end result is disordered bowel movements with impacted faeces in the gut (NASPGHAN 2006).

Description of the intervention

Currently, there are several available interventions used to treat constipation as recommended in established guidelines such as the National Institute of Clinical Excellence (NICE), including various forms of laxatives (e.g. lactulose, milk of magnesia, liquid paraffin, senna and polyethylene glycol), non-pharmacological therapies such as biofeedback and behavioural therapy, and some newer treatment options like probiotics (NICE 2010). Most of the treatment options mentioned above have been assessed in Cochrane reviews that are either published or in development (Aboumarzouk 2011; Candy 2011; Coggrave 2006; Evans 2007; Gordon 2012; Lee-Robichaud 2010; Mowart 2007; Price 2001; Shariff 2009). None of these treatment options appear to be consistently effective for the majority of children. Continued exploration of treatment modalities with a favourable benefit-harm bal-
ance is therefore warranted to provide treatment options to suit different groups of affected children.

One of the newer modes of therapy for facilitating bowel motion in patients with constipation is transcutaneous electrical nerve stimulation (TENS) (Sluka 2003). Its use for other purposes, such as pain management from various conditions is more well-established (Dowswell 2009; Khadilkar 2005; Mulvey 2010; Nnoaham 2008; Rutjes 2009; Walsh 2009).

How the intervention might work

TENS is an electrical stimulation, usually an interferential current, used to stimulate the nerve. The TENS device consists of a voltage generator of electrical pulse, interconnecting wire or cable, and electrodes that are attached to the skin. The low voltage electrical impulse generated by this device travel across the skin and act as a stimulus to the appropriate peripheral nerves (Sluka 2003). Presently, the precise mechanism of the effect is unknown. One theory is that TENS acts centrally by re-balancing excitatory and inhibitory information and returning the neural drive to a more normal status (Sluka 2003).

An interferential stimulator is used for treating slow-transit constipation. The pad electrodes are placed over the skin surface of the abdomen and the paraspinal region. Four electrodes are placed, two on the anterior abdominal wall at the level of the umbilicus (i.e. navel), and two on the paraspinal region in between the distal thoracic and upper lumbar spine (i.e. T9 to L2) (Chase 2005). The TENS device produces one channel stimulation at a fixed frequency and the other at varying frequencies, resulting in the production of sinusoidal currents that cross within the body and stimulate the peripheral nerves. The mechanisms of action that lead to beneficial therapeutic effects are still unclear, although it is postulated that TENS improves bowel movement via neuro-modulation of the extrinsic neural control of the large bowel or modulation of reflexes that inhibit large bowel function. By using colonic manometry, it has been shown that TENS increases colonic propagating pressure waves (van Wunnik 2011; Clarke 2012).

The adverse events reported for TENS therapy include pain or discomfort at the electrode attachment site, electrode migration and infection (Norderval 2011; van Wunnik 2011, van Wunnik 2012), although some studies did not report any adverse effects (Eleouet 2010; Ismail 2009).

Why it is important to do this review

The current uncertainties on the role of TENS, a promising non-pharmacological mode of therapy, in treating childhood constipation, a generally difficult to treat disorder, warrants a regularly updated Cochrane systematic review to inform current practice and make recommendations for future research.

OBJECTIVES

The primary objective is to assess the efficacy and safety of TENS used for the treatment of childhood constipation.

METHODS

Criteria for considering studies for this review

Types of studies

We will include randomised controlled trials and randomised cross-over studies in which patients have their TENS device turned off at different periods in the study.

Types of participants

We plan to include studies that enrol children (aged 0 to 18 years) with a diagnosis of functional constipation with or without accompanying incontinence. We will accept various definitions of constipation in the included studies, which may be based on diagnosis by a physician or report by patient or caregivers or all three, or via the use of consensus criteria such as the ROME III criteria for functional gastrointestinal disorders (ROME III). We plan to exclude studies that assessed patients with constipation due to secondary causes, such as intestinal obstruction due to structural lesions, endocrine disorders such as hypothyroidism, metabolic or neurological problems, neuromuscular disorders, pregnancy or participants who were on medications that affect gastrointestinal motility as an adverse effect.

Types of interventions

Studies where a TENS treatment, administered either in clinical setting or at home, and applied either transabdominally, sacrally or via other means are compared to no treatment, a sham TENS treatment, other forms of nerve stimulation or any other pharmaceutical or non-pharmaceutical measures used to treat constipation will be considered for inclusion. We accept all types of devices used for the purpose of TENS and all dosing regimes (i.e. using TENS in different intensities such as number of times applied per day).

Types of outcome measures

Primary outcomes

Primary outcomes will include the following.
1. Global or clinical improvement in constipation as defined by the included studies. For example, clinical improvement could be
measured by the frequency of defaecations per week and could potentially be expressed as a mean number of defaecations or as the proportion of patients who meet a pre-specified threshold (e.g. greater than three defaecations per week).

2. Spontaneous bowel movements (SBM) and complete spontaneous bowel movements (CSBM). SBM is defined as the passage of a stool without the use of laxative, and CSBM is defined as SBM associated with a sense of complete evacuation (Mueller-Lissner 2010). SBM and CSBM could be measured by frequency per week and could be expressed as a mean number of SBM or CSBM or as the proportion of patients who meet a pre-specified threshold (e.g. greater than three SBM or CSBM per week).

Secondary outcomes

Secondary outcomes will include the following.
1. Improvement in symptoms associated with constipation (e.g. perceived ease of defaecation, abdominal pain or distension, stool consistency).
2. Improvement in bowel transit time, bowel activity or propagating contractions measured over a defined time period, for example, weekly.
3. Improvement in faecal soiling.
4. Improvement in growth (for example, weight in relation to centile or weight gain), measured at a defined intervals over the course of the study, for example, three monthly or six monthly.
5. The proportion of patients who experience an adverse event.
6. The proportion of patients who experience a serious adverse event.

Search methods for identification of studies

We will follow recommendations from the Cochrane Handbook for Systematic Reviews of Interventions for conducting the literature search (Lefebvre 2011).

Electronic searches

The following databases will be searched:
- The Cochrane Central Register of Controlled Trials (CENTRAL, part of The Cochrane Library);
- Cochrane Inflammatory Bowel Disease and Functional Bowel Disorders Group Specialized Trials Register;
- MEDLINE (PubMed, National Library of Medicine) (1950 to present); and
- Ovid EMBASE (1980 to present).

We will search MEDLINE (PubMed, National Library of Medicine) using the following search strategy:
1. Search child*[Title/Abstract]
2. Search Child[MeSH Terms]
3. Search Paediatric[Title/Abstract]
We will adapt this search strategy where appropriate for the other databases. We will not apply any restriction based on language.

We will also search the following trial registries for details of ongoing clinical trials and unpublished studies:

- ClinicalTrials.gov (http://www.clinicaltrials.gov/);
- Australia and New Zealand Clinical Trials Registry (http://www.anzctr.org.au/);
- WHO International Clinical Trials Registry Platform (http://apps.who.int/trialsearch/Default.aspx); and
- EU Clinical Trials Register (https://www.clinicaltrialsregister.eu/).

Additionally, we will search for conference proceedings that are not included in CENTRAL or the review group specialized trials register from the following sources:

- Digestive Disease Week (http://ddw.scientificposters.com/index.cfm);
- United European Gastroenterology Week (https://www.ueg.eu/week/past-future/future-ueg-week/); and

Searching other resources

We will search the reference lists of papers identified by the above strategies to identify studies that may have been missed by the electronic searches. We will also inspect the references lists of relevant Cochrane reviews for additional relevant studies.

Data collection and analysis

Two review authors (RTN and KMT) will independently screen titles and abstracts to identify potentially eligible studies. Two authors (KMT and NML) will independently assess the full-text of potentially eligible studies to determine eligibility for inclusion. We will record reasons for excluding ineligible studies. We will resolve any disagreement through discussion and consensus and if necessary we will seek the input of a third author (WSL) who will act as the arbiter. The process of study selection will be recorded in a PRISMA flow diagram.

Data extraction and management

We will extract data using a dedicated data collection form, which will be piloted on one included study. We include the following study characteristics and outcome data in the data collection form.

1. Methods: study design, location, setting and duration.
2. Participants: number, mean age, median age or age range, gender, underlying conditions, diagnostic criteria if applicable, inclusion and exclusion criteria.
3. Interventions: description of the components of the intervention and comparison.
4. Outcomes: description of primary and secondary outcomes specified and collected, and at which time points reported.
5. Notes: funding for trial, and notable conflicts of interest of trial authors.

Two review authors (KMT and RTN) will independently extract outcome data from included studies. We will note in the 'Characteristics of included studies' table if outcome data reported is not suitable for meta-analysis. Any disagreement will be resolved through discussion and consensus and if necessary we will seek the input of a third author (NML) who will act as the arbiter.

All review authors will participate in entering data into Review Manager (RevMan 5.2) (RevMan 2012) and the data entry will be double-checked for accuracy.

Assessment of risk of bias in included studies

Two review authors (NML and KMT) will independently assess the quality of each included study using the Cochrane risk of bias tool (Higgins 2011a). We will resolve any disagreements by discussion and consensus or by involving another author (WSL) when necessary. We plan to assess the following domains.

1. Random sequence generation.
2. Allocation concealment.
3. Blinding of participants and personnel.
5. Incomplete outcome data.
6. Selective outcome reporting.
7. Other bias.

Each item will be rated as high, low or unclear risk of bias, and a justification from the study report will be supplied to support the judgement as appropriate. We will summarise the risk of bias
judgements across different studies for each of the domains listed. Where necessary we will consider blinding separately for different key outcomes. Any information on risk of bias that relates to unpublished data or correspondence with a trialist will be noted in the 'Risk of bias' table. When considering treatment effects, we will take into account the risk of bias for the studies that contribute to that outcome.

**Measures of treatment effect**

We will calculate the risk ratio (RR) and corresponding 95% confidence interval (CI) for dichotomous outcomes. We will calculate the risk difference (RD) and corresponding 95% CI as appropriate. For continuous outcomes we will calculate the mean difference (MD) and corresponding 95% CI or standardised mean difference (SMD) and corresponding 95% CI as appropriate. If included studies only report effect estimates and 95% CI or standard errors we will enter these data into RevMan using the generic inverse variance method. If the outcomes are measured using a scale, we will standardise the direction of the scale in terms of the severity of the outcome and explain accordingly.

**Unit of analysis issues**

For cross-over studies, we include data only from the first interventional phase of the studies if possible, to avoid contaminating effect of the cross-over. If this is not possible, we will analyse data as presented by the authors, and perform sensitivity analysis to assess the impact of excluding data from such studies.

Where multiple trial arms are reported in a single trial, we plan to include only the relevant arms. If two comparisons (e.g. TENS method A versus a sham TENS procedure and TENS method B versus a sham TENS procedure) are combined in the same meta-analysis, we will halve the control group to avoid double-counting. In studies with repeated observations on participants, we plan to include data only at the level of the participants, for example, the number of participants who have experienced any adverse event (either single or multiple times). For participants who are enrolled multiple times, we will only include data only from the first enrolment. If this is impossible, we will include the data as reported by the authors, and perform a sensitivity analysis excluding studies in which the participants are enrolled multiple times.

**Dealing with missing data**

We will assess the drop-out rate from each study and look for explanations for non-completion of the studies. We will consider a drop-out rate higher than the control group event rate to be significant. If we find a significant drop-out rate with no reasonable explanation, we will judge the study to have a high risk of bias for incomplete outcome data. If necessary study authors will be contacted to request missing data and the reasons for non-completion. We will perform sensitivity analyses to evaluate the impact of excluding studies with significant drop-out rates on the magnitude and direction of the overall results.

After assessing drop-out rates and the reasons for drop-out, we will handle missing data based on the recommendations of the Cochrane handbook of Interventional Reviews, chapter 16.1.2 (Higgins 2011b). If drop-outs appear to occur at random, we will analyse only the available data. If drop-outs do not appear to be random, we will impute the missing data by assuming that all missing participants have a poor outcome for dichotomous outcomes and by imputing outcome values from the mean and standard deviation for continuous outcomes.

**Assessment of heterogeneity**

We will inspect the forest plots to globally assess the variation in the treatment effects of individual trials. We will then assess the included studies in terms of similarity of population, intervention, outcome and follow-up. We will consider populations to be similar when they are of similar age range and underlying pathology leading to constipation. We will consider interventions to be similar when they involve nerve stimulation through the skin. We will consider all outcomes that measure the same construct to be similar. For example, the number of bowel motions over a period of time or the amount of stool passed. However, we will regard objective measurement of outcomes such as the frequency of bowel movements and subjective report of outcomes such as the ease of bowel movements to be different. We will consider regard follow-up times of up to one month as short-term, one to six months as medium-term and more than six months as long-term. We will only pool data in a meta-analysis if studies are similar in terms of population, intervention, outcome and follow-up (to be determined by consensus). In cases where there are some differences among the studies and we are unsure of the significance of these differences, we will perform a sensitivity analyses to assess the impact of including and excluding these studies.

We plan to use the Chi-squared test and the I² statistic to evaluate statistical heterogeneity. If the Chi-squared test shows statistically significant heterogeneity, as indicated by a P value of less than 0.1, we will quantify the degree of heterogeneity using the I² statistic. In this review, we define an I² statistic of 50% or higher as substantial heterogeneity. In such cases, we will explore possible causes for the heterogeneity by prespecified subgroup analyses. If the degree of heterogeneity is excessive, as indicated by an I² statistic of more than 75% which is not contributed predominantly by a single study, we will consider not pooling the studies for meta-analysis.

**Assessment of reporting biases**

For each study, we will compare the outcomes reported in the results against the outcomes listed in the study protocol or the methods section of the manuscript. The study authors will be contacted for clarification where necessary. For studies where critical
outcomes are missing, we will search for the study protocol, either from PubMed, the relevant trial registry, the web link provided by the study or directly from the study authors, to establish whether these outcomes were prespecified.

Where possible, a sensitivity analysis will be performed to explore the impact of excluding studies with a high risk of reporting bias.

Assessment of publication bias
We plan to screen for publication bias by using a funnel plot if there are a sufficient number of studies (at least 10) included in the analysis. If publication bias is suspected as indicated by significant asymmetry of the funnel plot, we will include a statement in our results and the summary of findings table with a corresponding note of caution in the discussion.

Data synthesis
For dichotomous outcomes we will calculate the pooled RR and corresponding 95% CI. In the case of statistically significant results, we will calculate the pooled risk difference (RD) and 95% CI and the number needed to treat for an additional beneficial outcome (NNTB) or for an additional harmful outcome (NNTH) as appropriate. For continuous outcomes we will calculate the pooled MD or SMD and corresponding 95% CI as appropriate. We plan to use a fixed-effect model to pool data. A random-effects model will be used when significant heterogeneity is identified. If possible, we will analyse all data on an Intention-to-treat basis. We will provide a narrative description of any skewed data reported as medians and interquartile ranges.

Summary of findings table
We will use the GRADE approach to assess the overall quality of evidence for the primary outcomes and selected secondary outcomes of interest. We will create a ‘Summary of findings’ table using the GRADEpro software to report the results of the GRADE analysis. Outcomes from pooling of randomised trials start as high quality evidence, but may be downgraded due to risk of bias, inconsistency of effect, imprecision, indirectness and publication bias. Reasons for downgrading the quality of the included studies will be reported in the footnotes of the ‘Summary of findings’ table.

Subgroup analysis and investigation of heterogeneity
We plan to conduct the following subgroup analyses if data are available.
1. Studies that enrol patients with the purpose of achieving bowel clearance (i.e. remission) and studies that enrol patients with the purpose of maintaining regular bowel clearance (i.e. maintenance).
2. Studies that employ TENS differently, for instance, transabdominally versus sacrally.
3. Studies that assess different comparisons, for example, medication or other form of nerve stimulation.
4. Studies that employ TENS in different doses or intensities (i.e. current frequency and amplitude).
5. Studies with different duration of treatment.
6. Patients of different age groups, for instance, infants, young and older children

Sensitivity analysis
We will perform sensitivity analysis defined a priori to assess the robustness of our conclusions. Potential sensitivity analyses will include the following.
1. Fixed-effect versus random-effects models.
2. Excluding studies judged to be at high risk of selection bias.
3. Excluding studies judged to be at high risk of attrition bias.
4. Excluding studies judged to be at high risk of performance or detection bias.
5. Excluding studies judged to be at high risk of reporting bias.
6. Excluding cross-over studies and studies with multiple enrolment of the same participants.

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Transcutaneous electrical nerve stimulation (TENS) for treatment of constipation in children (Protocol)

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CONTRIBUTIONS OF AUTHORS
WSL and NML conceived the review.
NML and RTN drafted the search strategy.
RTN, NML, KMT, HLA and WSL wrote and revised the protocol.

DECLARATIONS OF INTEREST
None known.

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