Study Protocol

Title:

Effectiveness of acupuncture therapy for the prevention of emergence agitation in children: A meta-analysis with trial sequential analysis

Registration information:

Pre-registration site: University hospital Medical Information Network (UMIN)
Registration number: 000040775

Purpose:

Effectiveness of acupuncture therapy for the prevention of emergence agitation in children remains unclear. The purpose of this study is to assess the effect and possible adverse events of the acupuncture therapy for the prevention of emergence agitation events in children undergoing general anesthesia.

Methods:

This study is a systematic review and meta-analysis with trial sequential analysis.
We followed the recommendations of the PRISMA statement and Cochrane Handbook.

Search strategy

Databased searched

MEDLINE, CENTRAL, Embase, and Web of Science; the reference lists of the retrieved full articles are also searched. Further, we conduct a search of the Clinicaltrial.gov, the European Union Clinical Trials Register (EU-CTR), the WHO International Clinical Trials Registry Platform (ICTRP), and the University Hospital Medical Information Network linical Trials Registry (UMIN).

Date of search

We planned to search these databases at July 1, 2020.

The following search strategy combining free text and MeSH terms was set up for PubMed: This information is confidential.

Two authors independently scan the titles and abstracts of reports identified by the variety of search strategies described above. If eligibility cannot be determined from the title or abstract, the full paper is retrieved. Potentially relevant studies, chosen by at least one author, are retrieved and evaluated in full-text versions. The articles that meet the inclusion criteria are assessed separately by two authors, and any discrepancies are resolved through discussion.

Inclusion and Exclusion Criteria

We will include RCTs that evaluated the effect of acupuncture therapy on the prevention of emergence agitation compared with no treatment, placebo/sham, or standard care in children undergoing general anesthesia. We will exclude RCTs that did not evaluate the effect of acupuncture therapy, in which the subjects were not children (aged more than 18), and in which the incidence of emergence agitation was not evaluated using a specific assessment tool. We will also exclude data from case reports, observational studies, comments, reviews, and animal studies. Eligibility was not restricted by language, type of surgery, or anesthetic technique.

Primary and secondary outcomes

The primary outcome is the incidence of emergence agitation evaluated using a specific assessment tool. We followed the definitions of the incidence of emergency agitation to the criteria established in each study. When emergence agitation was classified according to severity or points, we extract the data from the severe category. When emergence agitation was evaluated at several time points, we extract the data evaluated immediately after emergence (e.g. data evaluated on the PACU or in the recovery room) in order to extract the data that represented acute emergence agitation.

The secondary outcomes are the absolute value of the emergence agitation score evaluated using a specific assessment tool score, and the pain score evaluated using a specific assessment tool score. Incidence of adverse events such as nausea and vomiting, delayed awakening (Time to extubation, PACU stay duration) are also analyzed.

Data Collection

Titles and abstracts of studies retrieved using the search strategy and those from additional sources will be screened independently by two review authors to identify studies that potentially meet inclusion criteria outlined above. The full text of these potentially eligible studies will be retrieved and independently assessed for eligibility by two review authors. Any disagreement between them over the eligibility of particular studies will be resolved through discussion.

A standardized, pre-piloted form will be used to extract data from the included studies for assessment of study quality and evidence synthesis. The extracted information will include: (i) number of patients in the study, (ii) age, (iii) sex, (iv)American Society of Anesthesiologists' (ASA) physical status, (v) risk factors for EA, (vi) type of anesthesia, (vii) type of surgery, (viii) method of acupuncture therapy, (ix)duration and the onset of acupuncture therapy, (x) a number of cases of EA (xi) absolute value of the emergence agitation score evaluated using a specific assessment tool, (xii) absolute value of the pain score evaluated using specific assessment tool (xiii) Time to extubation, (xiv) PACU stay duration (xv) adverse effects of acupuncture therapy. Two review authors will extract data independently, discrepancies will be identified and resolved through discussion (with a third author where necessary). Missing data will be requested from study authors.

Assessment of risk of bias in individual studies

We assess the risk of bias using Cochrane's Risk of Bias tool (RoB 2) for randomized, controlled trials. The RoB 2.0 assessment for individually randomized trials (including cross-over trials) has five domains, as follows.

(1) Bias arising from the randomization process.

(2) Bias due to deviations from intended interventions.

(3) Bias due to missing outcome data.

(4) Bias in measurement of the outcome.

(5) Bias in selection of the reported result.

Trials with ≥1 risks of bias classified as "some concerns" or "high" are trials with a high risk of bias.

Assessment of quality of evidence

We grade the quality of evidence of the main outcomes using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) approach with

GRADEpro software. Judgments of the quality of evidence are based on the presence or absence of the following variables: limitations in study design, inconsistency, indirectness, imprecision of the results, and publication bias. The quality of evidence for the main outcomes was graded as very low, low, moderate, or high.

Statistical Analysis

We will compare the incidence of the emergence agitation with risk ratio. We will summarize the risk ration with 95% confidence interval. If the 95% CI includes 1, we consider the difference not to be statistically significant. We will use a random effect model to combine the result. Heterogeneity is quantified with I^2 statistic. We consider that significant heterogeneity existed when the I2 statistic exceeded 50%. We plan to conduct subgroup analyses according to the following predefined factors when the I2 statistic exceeded 50%: (1) method of acupuncture therapy, (2) selection of points (unilateral or bilateral) (3) type of surgery. Forest plot is used to graphically represent and evaluate the effect of treatment. Small study effect is assessed using a funnel plot and Egger's regression asymmetry test and is considered positive if $p < 0.1$ in the regression asymmetry test. Sensitivity analysis are performed for primary outcomes according to the risk of bias (low vs high or unclear). For the primary outcome, Trial Sequential Analysis (TSA) is performed to correct for random error and repetitive testing of accumulating and sparse data. TSA monitoring boundaries (i.e. monitoring boundaries for meta-analysis) and required information size (RIS) are quantified, and adjusted CIs are calculated. Risk of type 1 error is maintained at 5% with a power of 90%. The reduction of risk ratio by 25% is considered clinically meaningful. If the TSA-adjusted CI included the value of 1, we consider the difference not statistically significant.

Software used for statistical analysis

Statistical analyses are performed using the R statistical software package, version 3.6.3 (R Foundation for Statistical Computing, Vienna, Austria). TSA is performed using TSA viewer version 0.9.5.10 β (www.ctu.dk/tsa).