

Abstinence syndrome in Pediatric Intensive Care Unit: a systematic review protocol*

Síndrome de abstinência em Unidade de Tratamento Intensivo Pediátrico: protocolo de revisão sistemática

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ABSTRACT

Objective: To verify the most appropriate treatment for the prevention and reduction of the signs and symptoms of abstinence in critically ill children through a systematic review of the world literature. **Method:** The systematic review will be conducted according to the PRISMA and Cochrane methodology, with registration at PROSPERO, under the ID number CRD42021274670, in the respective databases, PubMed, LILACS, Embase, Web of Science, Cochrane, CINAHL, Cochrane Database Systematic Review, and CENTRAL, searches will be carried out by two independent evaluators, and a third party will perform the intermediate if necessary. The data will be entered into the Zotero software program that will delete duplicate articles after the selected material is transferred to an Excel spreadsheet on its instrument. The studies will be classified according to their level of evidence, bias, and risk factors. The results will be analyzed, tabulated, and discussed to understand the results better. If possible, meta-analyses will be carried out for the aggregated results.

Descriptors: Substances Abstinence Syndrome, Pediatric Intensive Care Unit, Nursing.

RESUMO

Objetivo: Verificar qual o tratamento mais indicado para a prevenção e redução dos sinais e sintomas de abstinência em crianças criticamente doentes por meio de uma revisão sistemática da literatura mundial. **Método:** A revisão sistemática será conduzida conforme a metodologia PRISMA e Cochrane, com registro no PROSPERO, sob o número de ID CRD42021274670, nas respectivas bases de dados PubMed, LILACS, Embase, *Web of Science*, Cochrane, CINAHL, *Cochrane Database Systematic Review* e CENTRAL. As buscas serão realizadas por dois avaliadores independentes, um terceiro realizará o intermédio se necessário. Os dados serão inseridos no programa de *software* Zotero que irá excluir os artigos duplicados, após o material selecionado será transferido para planilha Excel em instrumento próprio. Os estudos serão classificados quanto ao seu nível de evidência, viés e fator de risco. Os resultados serão analisados e tabulados e discutidos a fim de melhor compreensão dos resultados. Se possível, serão realizadas meta-análises para os resultados agregados.

Descritores: Síndrome de Abstinência a Substâncias; Unidade de Terapia Intensiva Pediátrica; Enfermagem.

INTRODUCTION

Pediatric patients requiring admission to a pediatric intensive care unit (PICU) are most often submitted to painful and traumatic procedures, and sedation and analgesia are necessary⁽¹⁻³⁾. From this perspective, the use of sedatives and analgesics is aimed at providing safe and effective care to minimize pain and anxiety, facilitating the care provided in the PICU⁽⁴⁻⁵⁾.

However, it is difficult to achieve adequate sedation and analgesia in children, and it is observed that only 60% of this population can maintain moderate levels of sedation and analgesia⁽⁶⁾. This condition is related to increased hospitalization, prolonged use of mechanical ventilation (MV),

increased morbidity and mortality, inadequate pain management, increased risk of nosocomial infections, and occurrence of abstinence syndrome (SA).

SA usually occurs within the first 24 hours after interruption of its infusion of sedoanalgesia, manifested by unpleasant signs and symptoms in various systems of the organism. The central nervous system is uncompetitive by irritability, tremors, anxiety, convulsions, delirium, hallucinations, and mydriasis; signs and symptoms such as tachycardia, tachypnea, hypertension, fever, sweating, and cough can affect the sympathetic nervous system; in addition to food intolerance with vomiting, diarrhea and uncoordinated sucking in the gastrointestinal system⁽⁷⁻⁸⁾.

The signs and symptoms of SA show significant variability and can be influenced by factors such as age and health status, which are easily confused with other clinical conditions of the patient⁽⁹⁾.

Although there is a broad consensus that SA requires attention in the treatment of children in PICUs, its diagnosis and monitoring are still a challenge⁽¹⁰⁾.

It is estimated that approximately one fifth of the admissions to the PICU will result in SA. In one study, 50% of patients admitted to PICU who received continuous midazolam and fentanyl infusions for 48 hours developed withdrawal symptoms, this number increases to 80% when infusions remain for more than five days⁽¹¹⁾.

It is observed that the incidence of SA may vary between 7.5% and 100% in pediatric patients, and these factors are found in the absence of an instrument classified as a gold standard for the diagnosis of SA, in addition, the incongruent weaning of opioids and/or benzodiazepines and the lack of protocols related to the dosage, administration, and weaning of sedoanalgesia makes it impossible the homogeneity in the incidence of SA in critical pediatric patients^(3,12).

In addition to the difficulty of SA recognition and diagnosis, there still needs to be a consensus on its treatment and prevention. Some articles point out that a trained team, administration protocols, the withdrawal of established sedoanalgesia, and the careful evaluation of each patient are necessary for its treatment and prevention^(9,12-13).

It is observed that the basis of the treatment for SA is gradual weaning and the management of abstinence with rescue therapies, in which continuous short-acting infusion is replaced by

sedative and long-acting analgesic agents, preferably in enteric presentation. Administering short-acting drugs only as rescue therapy when acute symptoms of abstinence arise^(14,15). That said, it is observed that the basis of the SA treatment is the gradual reduction of analgesia and sedation, although the methodologies are widely heterogeneous, requiring further studies on the subject.

Previous research was carried out in the PROSPERO (The International Prospective Register of Systematic Reviews), MEDLINE (Medical Literature Analysis and Retrieval System Online), the Cochrane Database of Systematic Reviews, and the JBI Evidence Synthesis, which evidenced the need to review the scope or systematic, current, or ongoing regarding the subject matter. Thus, the present study aims to verify the strategies for the prevention and treatment of withdrawal syndrome in a PICU.

METHOD

The systematic review will be conducted according to the recommendations of the main items for the Report Systematic Reviews and Meta-analyses (PRISMA)⁽¹⁶⁾ and the Cochrane Handbook⁽¹⁷⁾. The protocol was registered in the PROSPERO under ID CRD42021274670. The review protocol is registered on the Open Science Framework (OSF) platform and can be accessed at <https://osf.io/u6hfc>.

Review question

The elaboration of the main research question was conducted through the PEAKS strategy, with the population (P) critically ill children, the intervention (I) the approaches for the prevention and reduction of symptoms, the comparison (C) the types of treatment or intervention, the outcome (O) the abstinence syndrome, and the study designs (S) were observational or experimental. The following question was therefore reached: "What are the most suitable approaches for prevention and reduction of Abstinence Syndrome symptoms in critically ill children?"

And as sub-questions: What are the most appropriate approaches for prevention and reduction of SA related to the use of opioids? What are the most appropriate approaches for the prevention and reduction of SA related to the use of benzodiazepines? What are the most appropriate approaches for the prevention and reduction of SA related to the use of other sedative drugs?

Research strategy

A three-step search strategy will be used for review. Initially, an initial research limited to MEDLINE (PubMed) was carried out on July

19th, 2021, using the “advanced search” feature with the keywords MeSH (Medical Subject Headings) and Boolean operators “or” and “and” (Figure 1).

Consultation	Mapping of terms	Records Retrieved
1#	"Substance Withdrawal Syndrome/therapy"[mh] OR "Substance Withdrawal Syndrome/prevention and control"[mh] OR Withdraw*[tw] OR Abstin*[tw]) AND	437 results
2#	"Iatrogenic Disease/therapy"[mh] OR "Iatrogenic Disease/prevention and control"[mh] OR "Analgesics, Opioid/therapeutic use"[mh] OR "Benzodiazepines/therapeutic use"[mh] OR "Morphine Derivatives/therapeutic use"[mh] OR "Fentanyl/therapeutic use"[mh] OR "Dexmedetomidine/therapeutic use"[mh] OR "Ketamine/therapeutic use"[mh] OR "Iatrogen"*[tw] OR "Hospital-Acquired"[tw] OR "Opioid"*[tw] OR "Benzodiazepin"*[tw] OR "Morphine"[tw] OR "Codeine"[tw] OR "Hydrocodone"[tw] OR "Oxycodone"[tw] OR "Dihydromorphine"[tw] OR "Ethylmorphine"[tw] OR "Hydromorphone"[tw] OR "Oxymorphone"[tw] OR "Thebaine"[tw] OR "Phentanyl"[tw] OR "Fentanyl"[tw] OR "Alfentanil"[tw] OR "Sufentanil"[tw] OR "Midazolam"[tw] OR "Dexmedetomidine"[tw] OR "Ketamine"[tw]) AND	
3#	"Critical Illness"[mh] OR "Critical Care"[mh] OR "Intensive Care Units, Pediatric"[mh] OR "Critical Illness"*[tw] OR "Critically Ill"[tw] OR "Critical Care"[tw] OR "Intensive Care"[tw] OR "ICU"[tw] OR "NICU"[tw] OR "PICU"[tw]) AND	
4#	"Child"[mh] OR "Infant"[mh] OR "Child"*[tw] OR "Preschool"*[tw] OR "School"*[tw] OR "Infant"*[tw] OR "Newborn"*[tw] OR Neonat*[tw] OR "Paediatric"*[tw] OR "Pediatric"*[tw])	

Figure 1 – Database search strategy via PubMed, Porto Alegre, RS, 2021

After identifying the articles in PubMed, the terms will be translated into the other selected databases. The temporal cut-off will be articles published from 2010 onwards to find a search in the current literature, with the availability of text in at least one of the following three languages: Portuguese, English, and Spanish. The other databases used, besides PubMed, were the Latin American and Caribbean Health Sciences literature (LILACS) of the Virtual Health Library (VHL), EMBASE, Web of Science, Cumulative Index to Nursing and Allied Health Literature (CINAHL), Cochrane Database Static Review (CDSR) and CENTRAL. Every stage of searches will be carried out independently by two reviewers, ensuring the most rigorous criteria for the review.

Font types

This systematic review will include randomized clinical trials (RCTs) and non-randomized (non-RCTs), prospective and retrospective studies.

In addition, studies with observational design, including cohort studies and control case studies.

Inclusion Criteria

Studies with pediatric patients aged > 28 days and < 21 years will be included in the use of sedoanalgesia, aiming at identifying strategies for the treatment, reduction and prevention of SA. Also, original RCTs and non-RCTs available in Portuguese, English, and/or Spanish languages, with full text available, will be included. No restrictions will be imposed on the design of studies, including observational and experimental studies.

Exclusion Criteria

Literature review articles, which address the treatment of childhood abstinence syndrome at home, exclusive studies with adult or neonatal populations, and incomplete or unpublished

data in full will be excluded. Studies with a retrospective design with a < 50 sample, due to their lower methodological quality, will also be excluded in order to reduce research bias. Finally, studies published before 2010, abstracts of congresses or articles portrayed by fraud in data.

Context

Patients admitted to a general or specific PICU who need to use intravenous sedoanalgesia included in weaning protocols of sedation and analgesia will be included.

Evidences selection

Initially, the records will be exported to the Zotero version 5.0 reference manager software. Two reviewers, independently, will conduct the initial evaluation of the relevant records after the deletion of duplicate articles by the program, which will begin by reading the titles, followed by reading the abstracts and after the full text. From this action, the studies to be examined by the reviewers were tabulated. In case of disagreement in the choice, they shall be determined by means of a consensus, or if necessary, by means of a third reviewer. References of included studies and relevant reviews will be checked in order to find new studies. If necessary, the Kappa concordance test will be used to evaluate the discordance rate among the reviewers.

Data extraction and quality of evidence

The data will be extracted and compiled into an Excel spreadsheet version 16.0 (Microsoft), the main items being: study identification, title, journal, authors, year of publication, study country, study design, population age, sample size, inclusion and exclusion criteria, results, SA identification instrument, outcome. In possession of the collected data, the tabulation of the information will be performed, including analysis, interpretation and elaboration of the work.

The results of the selection will be presented in a flowchart of PRISMA. The quality of the studies will be evaluated using the *Risk of Bias* 2.0 (Rob 2) tool for RCTs, while the Robins tool will be used for non-RCTs and JBI levels of evidence for observational studies. If possible, a meta-regression technique will be performed to identify potential sources of variability between the studies and Egger's regression test to evaluate

the asymmetry between the studies, demonstrating visually through the funnel chart⁽¹⁸⁾.

Data analysis

The extracted data will be presented in the form of tables and diagrams, in a way that aligns with the objective of the review. The data shall inform the characteristics of the studies selected for review; the information about the protocols used, drugs, weaning characteristic, dosages, sedation assessment tool, pain and abstinence syndrome. A descriptive and narrative analysis will follow the tabulated and mapped results, describing the relation of the findings with the objective of this research. If possible, meta-analyses will be carried out to evaluate which prevention and treatment strategies of abstinence syndrome are effective in pediatric ICUs. To do this, if studies provide sufficient data, two types of meta-analyses will be performed: 1-meta-analysis of RCTs, the results being presented as mean and standard deviation; 2-meta-analysis of observational studies, with the results expressed in *Odds Ratio* (OR). In both, the results will be presented with a 95% confidence interval (95%CI), while heterogeneity will be estimated through Higgins I2 statistics, considering values above 50% and $p < 0.05$ as high heterogeneity⁽¹⁹⁾. If there is high heterogeneity, random effect models will be calculated so that fixed effect models will be used for analyzes without heterogeneity. If more than one study uses the same database, the most recent one will be maintained. Where possible, the most adjusted templates will be used for the or meta-analysis. If any observational study presents the results as relative risk (RR) or Hazard Ratio (HR), the values will be converted to or by the following formula $OR = (1 - p) * RR / (1 - RR * p)$. Analyzes will be performed using the R language, using the Meta package⁽¹⁹⁾.

*Paper extracted from the master's dissertation "Prevention and treatment of abstinence syndrome in pediatric intensive care unit: systematic review", presented to the Federal University of Rio Grande do Sul, Porto Alegre, RS, Brazil.

CONFLICT OF INTERESTS

The authors have declared that there is no conflict of interests.

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