HYPODERMOCLYSIS FOR UNCONVENTIONAL PEDIATRIC TREATMENTS: AN INTEGRATIVE REVIEW*

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ABSTRACT
Objective: to describe the use of hypodermoclysis in unconventional pediatric treatments.
Method: an integrative review, with sampling period from 2010 to 2018, in five databases. Two independent reviewers selected the articles. Next, an evaluation of the level of evidence was performed, according to the Joanna Briggs Institute.
Results: Six international articles were selected, with levels of evidence 1 and 3. The unconventional diseases and situations for treatment via hypodermoclysis were: polyarticular juvenile idiopathic arthritis; prevention of hyponatremia during fluid restriction; sedation in dental treatment; rheumatic disorders; antibiotic therapy and refractory pulmonary arterial hypertension.
Conclusion: the procedure is an effective and safe option for the administration of medications in children, justified due to the minimization of pain intensity and the protection of the child, family and nursing staff from stress. However, more research is needed to substantiate it scientifically, and for its implementation in the professional practice.

DESCRIPTORS: Review; Technology; Hypodermoclysis; Child Health; Nursing.


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HIPODERMÓCLISE PARA TRATAMENTOS NÃO CONVENCIONAIS EM PEDIATRIA: REVISÃO INTEGRATIVA

RESUMO
Objetivo: descrever o uso da hipodermóclise em tratamentos pediátricos não convencionais.
Resultados: foram selecionados seis artigos internacionais, com evidência de nível 1 e 3. As doenças e situações não-convencionais para o tratamento via hipodermóclise foram: artrite idiopática juvenil poliarticular; prevenção de hiponatremia na restrição de fluidos; sedação em tratamento odontológico; desordens reumáticas; antibioticoterapia e hipertensão arterial pulmonar refratária.
Conclusão: o procedimento constitui-se como opcional efetivo e seguro para administração de medicamentos em crianças, justificada devido à minimização da intensidade da dor e proteção do estresse da criança, família e equipe de enfermagem. Contudo, são necessárias mais pesquisas para fundamentá-lo cientificamente, e para implementação na prática profissional.

DESCRITORES: Revisão; Tecnologia; Hipodermóclise; Saúde da Criança; Enfermagem.

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HIPODERMOCLISIS PARA TRATAMIENTOS NO CONVENCIONALES EN PEDIATRÍA: REVISIÓN INTEGRATIVA

RESUMEN:
Objetivo: Describir el uso de la hipodermoclisis en tratamientos pediátricos no convencionales.
Método: Revisión integrativa, con período muestral de 2010 a 2018, en cinco bases de datos. Dos revisores independientes se ocuparon de seleccionar los artículos. Luego se realizó una evaluación por nivel de evidencia, según Instituto Joanna Briggs.
Resultados: Fueron seleccionados seis artículos internacionales, con evidencia de nivel 1 y 3. Las enfermedades y situaciones no convencionales para tratamiento via hipodermoclisis fueron: artritis idiopática juvenil poliarticular; prevención de hiponatremia en la restricción de fluidos; sedación en tratamiento odontológico; desórdenes reumáticos; antibioticoterapia e hipertensión pulmonar refractaria.
Conclusión: El procedimiento se constituye como opción efectiva y segura para la administración de medicamentos en niños, justificada por la mínima intensidad de dolor y por proteger al niño, la familia y al equipo de enfermería del estrés. Sin embargo, serán necesarias más investigaciones para fundamentarlo científicamente, e implementarlo en la práctica profesional.

DESCRIPTORES: Revisión; Tecnología; Hipodermoclisis; Salud del Niño; Enfermería.
Administration of medications and infusion of fluids or electrolytes via the subcutaneous route is also known as hypodermoclysis (HDC)\(^1\). Its use dates from 1886, when it was used to treat dehydration in children and adults during the Cholera epidemic in Europe\(^2\).

At the time, the use of this route was not based on studies of its effectiveness and safety and various adverse events due to hypertonic solutions were registered, especially in children, leading to its disuse. Therefore, the use of the intravenous route for medication administration has been prevalent in the care practice provided by nursing professionals\(^3\).

Hypodermoclysis is currently considered an alternative technology for rehydration, nutrition and drug therapy in children, adults and older adults, especially in palliative care. Evidence of the safety and effectiveness of the route has been produced in situations where smaller volumes of infusion are needed, with absorption occurring through diffusion into the subcutaneous tissue\(^4\).\(^5\).\(^6\).

The advantages highlighted for this route of infusion are: greater convenience for the patient, family and health team; effective technique with a shallow puncture; reduction of infection rates; good tolerance for agitated patients; and quick and easy to perform in hospital and home environments, among others\(^5\).\(^6\).\(^7\).

Technically, the performance of HDC comprises the insertion of a catheter needle, SCALP (caliber 21 or 23G), into the skin, at an angle of 45°, aiming to reach the hypodermis. It is usually performed in specific regions of the body, with the largest amount of adipose tissue, such as: external arm, scapular, anterior thorax, abdomen and lateral thigh\(^6\).\(^7\).

It is well known that in pediatric patients the blood vessels are smaller, making it difficult to see and palpate, and there is capillary fragility, especially in younger children and/or those hospitalized due to chronic processes. Also the risk of failure to establish intravenous puncture on the first attempt, according to predictive variables such as visibility, palpability, prematurity, and skin tone, suggests the need for supporting resources\(^8\).

This anatomical and physiological context significantly overlaps the insufficient level of comprehension by the family, parents and caregivers regarding the need for a procedure characterized as invasive. It is concluded that the association of these factors related to difficult puncture experiences negatively impacts coping with the hospitalization and disease, which may lead to aggressive and agitated behavior from the children and caregivers\(^9\).\(^10\).

From this perspective, the HDC technology presents a potential for use in pediatric care. It has been confirmed as the route of choice for the treatment of childhood diabetes, with the first large group of studies with HDC, with a significant number of scientific publications. The second group of publications on diseases that use HDC for treatment include allergies. Therefore, HDC is the conventional route of choice for childhood diabetes and allergies, according to previous searches on the PUBMED/Medical Literature Analysis and Retrieval System Online (MEDLINE) portal.

As a possibility for developing this knowledge, there is an interest in recognizing the scientific production on the use of HDC in children, in order to identify unconventional diseases or situations, for which, more recently, the use of the route has been recommended nationally and internationally. It is believed that this investigation may support the professional practice of the nurse and nursing team, considering their technical-scientific responsibility for the comprehensive care of pediatric patients, focusing on medication administration. Therefore, the following aim was established: to describe the use of hypodermoclysis in unconventional pediatric treatments.

**METHOD**
This is an integrative literature review, which allows scientific findings to be gathered, identified and analytically synthesized, concerning any theme or issue, in published studies\(^{(11)}\), as well as allowing the analysis of knowledge gaps (gaps), which indicate the need for further research. Performed with methodological rigor, it is relevant to provide scientific knowledge to researchers, teachers, students and professionals, as well as to support the Evidence-Based Practice in health, standing out in the nursing practice sphere\(^{(12-13)}\).

Ganong’s Methodological Framework\(^{(12)}\) was used to perform this review, presented in six steps: selection of the hypotheses or questions for the review; sampling; representation of the characteristics of the primary studies; analysis of the findings; interpretation of the results; and presentation of the review. Based on the study design, the recommendations of the Preferred Reporting Items Checklist for Systematic Reviews and Meta-Analysis (PRISMA) statement\(^{(14)}\) were applied.

The problem was delimited according to the PICO strategy (population-intervention-comparison-outcomes), namely: in which pediatric diseases or situations, in addition to childhood diabetes and allergies (already conventional), according to the most recent scientific publications, has the treatment been implemented via hypodermoclysis?

To locate the primary studies, the search strategy was conducted from March to May 2018 in five health databases: PUBMED/Medical Literature Analysis and Retrieval System Online (MEDLINE); Web of Science; Scopus Info Site (Scopus); Cumulative Index to Nursing and Allied Health Literature (CINAHL); and Central (Cochrane Database). The search strategy was composed of Health Subject Descriptors (DECS), Medical Subject Headings (MESH) and, entry terms, combined by the Boolean operators “AND” and “OR”. Table 1 presents the different search strategies used in each database.

Table 1 - Search strategy using descriptors, entry terms and Boolean operators according to the databases. Curitiba, PR, Brazil, 2018 (continues)

<table>
<thead>
<tr>
<th>DATABASE</th>
<th>SEARCH STRATEGY</th>
</tr>
</thead>
<tbody>
<tr>
<td>Web of Science</td>
<td>TS=(child* OR infant* OR pediatric* OR paediatric OR preschool* OR school age OR school-aged OR school aged OR kid OR kids) AND TI=(child* OR infant* OR puericulture OR pediatric* OR preschool* OR school age OR school-aged OR school aged OR kid OR kids) AND TS=(hypodermoclysis OR subcutaneous hydration OR subcutaneous fluid administration OR infusions subcutaneous OR subcutaneous infusion* OR subcutaneous therapy OR subcutaneous OR subcutaneous treatment OR drug administration routes OR “fluid therapy” OR infusions parenteral OR injection subcutaneous OR subcutaneous absorption OR subcutaneous route) AND TI=(hypodermoclysis OR subcutaneous hydration OR subcutaneous fluid administration OR infusions subcutaneous OR subcutaneous infusion* OR subcutaneous therapy OR subcutaneous OR subcutaneous treatment OR drug administration routes OR “fluid therapy” OR infusions parenteral OR injection subcutaneous OR subcutaneous absorption OR subcutaneous route)</td>
</tr>
<tr>
<td>Scopus</td>
<td>TITLE-ABS-KEY (hypodermoclysis OR subcutaneous AND hydration OR subcutaneous AND fluid administration OR infusions, AND subcutaneous OR subcutaneous AND infusions OR subcutaneous AND therapy OR subcutaneous AND treatment OR fluid therapy OR infusions, AND parenteral OR subcutaneous AND absorption</td>
</tr>
</tbody>
</table>
The inclusion criteria were to be original articles available in electronic, full-text format, which answered the research question, regardless of the language of publication. These were published between 2010 and 2018, justifying this period due to the search for more recent and up-to-date publications. As the filter of the previous five years was insufficient for the analysis, the period was extended. This criterion observes the change in the profile of morbidity and mortality in childhood, with a significant reduction in infant mortality, especially in the previous decade.

The exclusion criteria were articles published in the format of accepted manuscript; randomized controlled trials (RCTs) without published results; systematic reviews, meta-analyses or integrative reviews; theses or dissertations. Studies with duplicate titles were counted only once.

To select the studies, two independent reviewers read the titles and abstracts of each of the publications identified in the search, totaling 559 studies, for analysis of those that met the inclusion criteria. In this process, there was no disagreement regarding the inclusion of articles in the sample, so the inclusion of a third reviewer was not necessary. As a result, the sample consisted of six scientific articles, as shown in Figure 1.
Figure 1 - Flowchart of the systematic search and selection of scientific articles that show the use of HDC in pediatric patients, adapted according to PRISMA\(^{14}\). Curitiba, PR, Brazil, 2018

To support the organization from the data collection, Excel\(^\circ\) 2016 was used as the predefined instrument and for the storage of the following information: sequence of inclusion of the article identified with letters from A to E; year; country; journal; its classification according to Qualis CAPES; study area; data base; general aim of the study; type of study; population data; level of evidence; variables and outcomes; and recommendations.

We sought to classify the articles included in the sample with the Evidence Level (EL) according to the classification, of international relevance, for studies of evidence synthesis of the Joanna Briggs Institute (JBI)\(^{15}\). Through this instrument it is possible to evaluate the quality of the method used and the evidence produced by the primary study, which guide the behaviors adopted in the health area, transforming the professional practice\(^{16}\).

**RESULTS**

The search resulted in six exclusively international articles published between 2011 and 2017, two (32%) publications from France and one article (17%) from each of the following countries: United States, Mexico, Canada, and Australia. Therefore, this review was developed with the five English and one French-language publications accessed via the internet, predominantly from the PUBMED portal. The selected articles covered the areas of medicine and dentistry, and four articles were classified above B1 regarding the Qualis CAPES ratings of the journals, as can be seen in Table 2.
Table 2 - Articles of the integrative review regarding the option for hypodermoclysis for the treatment of unconventional diseases in pediatrics according to year, country, journal, Qualis, professional area and database. Curitiba, PR, Brazil, 2018

<table>
<thead>
<tr>
<th>ORDER</th>
<th>YEAR</th>
<th>COUNTRY</th>
<th>JOURNAL</th>
<th>QUALIS</th>
<th>AREA</th>
<th>DATABASE</th>
</tr>
</thead>
<tbody>
<tr>
<td>B(18)</td>
<td>2016</td>
<td>Australia</td>
<td>Hemophilia</td>
<td>B1</td>
<td>Medicine</td>
<td>PubMed</td>
</tr>
<tr>
<td>D(20)</td>
<td>2014</td>
<td>Canada</td>
<td>Pediatric Rheumatology</td>
<td>B1</td>
<td>Medicine</td>
<td>PubMed</td>
</tr>
<tr>
<td>E(21)</td>
<td>2013</td>
<td>France</td>
<td>Archives de Pediatrie</td>
<td>B5</td>
<td>Medicine</td>
<td>PubMed</td>
</tr>
<tr>
<td>F(22)</td>
<td>2011</td>
<td>France</td>
<td>Journal of Pediatrics</td>
<td>A2</td>
<td>Medicine</td>
<td>PubMed</td>
</tr>
</tbody>
</table>

Table 3 shows the studies selected according to the type of study and the Evidence Level (EL) classification. Four observational studies were identified, three with cohort designs (50%) and one case study (17%). Regarding the two experimental studies (33%) both were randomized controlled trials (RCTs). Considering the EL classification, two articles (33%) presented evidence level 1 and the others (67%) level 3.

Table 3 - Articles of the integrative review regarding the option for hypodermoclysis for the treatment of unconventional diseases and situations in pediatrics according to the general objective, type of study, sample and scientific evidence level. Curitiba, PR, Brazil, 2018

<table>
<thead>
<tr>
<th>ORDER</th>
<th>GENERAL OBJECTIVE</th>
<th>TYPE OF STUDY AND SAMPLE</th>
<th>E.L.</th>
</tr>
</thead>
<tbody>
<tr>
<td>A(17)</td>
<td>To determine the safety, pharmacokinetics and efficacy of Golimumab (SC) for the treatment of polyarticular juvenile idiopathic arthritis.</td>
<td>Type of study Experimental (RCT) Sample: 173 children aged between 2-17 years.</td>
<td>1.c</td>
</tr>
<tr>
<td>B(18)</td>
<td>To evaluate the effectiveness of a defined fluid restriction protocol for the prevention of hyponatremia in children using perioperative Desmopressin (SC).</td>
<td>Type of study Observational, retrospective cohort. Sample: 69 children aged between 2-18 years.</td>
<td>3.c</td>
</tr>
<tr>
<td>C(19)</td>
<td>To evaluate the effectiveness of sedation (SC) using midazolam, associated or not with ketamine, in non-cooperative pediatric patients undergoing dental treatment.</td>
<td>Type of study Experimental (RCT) Sample: 13 children aged between 17-46 months.</td>
<td>1.c</td>
</tr>
<tr>
<td>D(20)</td>
<td>To quantify the amount of pain associated with methotrexate injections (SC) for treatment of rheumatic disorders.</td>
<td>Type of study Observational, retrospective cohort. Sample: 41 children (4 dropouts) aged between 4 and 17 years.</td>
<td>3.c</td>
</tr>
<tr>
<td>E(21)</td>
<td>To report the use of teicoplanin (SC) in antibiotic therapy to treat endocarditis.</td>
<td>Type of study Observational, case study. Sample 2 children, aged 5 and 11 years.</td>
<td>3.d</td>
</tr>
<tr>
<td>F(22)</td>
<td>To evaluate the efficacy and tolerability of Treprostinil (SC) in young children with refractory pulmonary arterial hypertension.</td>
<td>Type of study Observational, without control group Sample 8 children aged between 1.5 and 10 years.</td>
<td>3.e</td>
</tr>
</tbody>
</table>
The studies showed treatments with different medications administered by HDC, including: Golimumab; Desmopressin; Midazolam associated or not with Ketamine; Methotrexate; Teicoplanin; and Treprostinil. Table 4 presents the methodology and main results.

Chart 4 - Articles of the integrative review regarding the option for hypodermoclysis for the treatment of unconventional diseases and situations in pediatrics according to the methodology, the main results and recommendations. Curitiba, PR, Brazil, 2018

<table>
<thead>
<tr>
<th>No.</th>
<th>METHODOLOGY</th>
<th>MAIN RESULTS</th>
</tr>
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<tbody>
<tr>
<td>A(17)</td>
<td>All patients received Golimumab every four weeks, plus methotrexate weekly. Patients that improved according to the American College of Rheumatology Criteria (JIA ACR30) were selected for 1:1 randomization to continue Golimumab or to start placebo.</td>
<td>At the end of part one, out of 173 participants, 154 (89.0%) had a JIA ACR30 response. At week 48, the primary outcome was not fulfilled, as the groups had comparable IAB crisis rates (Golimumab Group 32 (41%) and Placebo Group 36 (47%)) p = 0.41.</td>
</tr>
<tr>
<td>B(18)</td>
<td>All medical records of children receiving desmopressin (SC-DDAVP) for the treatment of hemorrhagic disorders from January 2008 to December 2013 were analyzed.</td>
<td>A total of 69 patients received SC-DDAVP during the observation period. All patients receiving perioperative SC-DDAVP demonstrated excellent hemostasis, without the need for factor concentrate or blood products.</td>
</tr>
<tr>
<td>C(19)</td>
<td>Two forms of sedation were administered by the route (SC), Midazolam (M), and the combination of Midazolam-Ketamine (MK). Both for the same patient in two consecutive treatment sessions according to a randomized distribution.</td>
<td>The percentage of children who did not cry was higher in the MK treatment compared with the M treatment. Regarding body movement, the percentage of children who did not move was higher in the MK group in the first 10 minutes.</td>
</tr>
<tr>
<td>D(20)</td>
<td>The study included children using methotrexate injections (SC). The pain was evaluated on pain scales, the participants and those responsible were trained to apply the scales.</td>
<td>23 (62.1%) reported mild pain, 11 (31.0%) moderate pain and only 2 (5%) of the participants reported severe pain. With over 60% approval, the most effective techniques were ice, comfort positions and rewards.</td>
</tr>
<tr>
<td>E(21)</td>
<td>Case 1: Streptococcus gemella (SP) bacteria, treated for eight weeks with teicoplanin (SC). Case 2: Staphylococcus aureus bacteria, Teicoplanin dose (SC)</td>
<td>Treatment was effective in both cases. After six months there was no recurrence of endocarditis. Teicoplanin (SC) was sufficient to inhibit the bacterial growth of Staphylococcus aureus.</td>
</tr>
<tr>
<td>F(22)</td>
<td>Treprostinil (SC) treatment, catheter insertion into upper thigh. Initial dose of 1.25ng/kg/min, until hospital discharge, mean dose was 20ng/kg/min, and at home with monthly dose adjustment, up to 40ng/kg/min, depending on adverse events.</td>
<td>Administration in upper thigh and posterior arm presented greater tolerance. Case of one adverse event with pain and swelling at the puncture site. It is recommended to alternate the infusion site every 3 days.</td>
</tr>
</tbody>
</table>

DISCUSSION

Regarding the temporal distribution of the included studies, there was continuity in the publications of this theme, however, not in their number since only one study was published each year. Medicine and dentistry showed interest in exploring the HDC route, with a need for further scientific exploration in order to expand this knowledge, a strategy...
that would imply adherence to the professional practice\(^{(23)}\).

Although research groups favor the development of investigations, the development of the types of experimental studies that elucidate the effectiveness of HDC is still limited\(^{(24)}\). In this respect, it is emphasized that Nurses are responsible for administering medicines in their professional practice, and that no publications have been identified from this category or in Brazil. In the trajectory of the consolidation of nursing as a science, it is necessary that the care is performed with a theoretical basis coming from scientific research and that it is developed attending to the gaps that have been identified in the universe of its work.

It should be highlighted that the majority of the medications administered by HDC were considered off-label (use not described). This term refers to medication prescribed or administered differently from that recommended, either regarding the route of administration, the dose, the age range or the indicated treatment. In the case of this review, off-label use was related to the route of administration, which is different to the indicated route. Undescribed use is considered a common practice in pediatric patient care, whether in the hospital, outpatient and/or home environment, considering the difficulty of medications specifically for this age group\(^{(1,25)}\).

The results of the included studies showed that HDC technology is an alternative procedure for the administration of medications of various classes and types of treatment, and for pathologies and situations not restricted to diabetes and childhood allergy. Significant results for the children who participated in the studies of this review were related to rapid hemodynamic and symptomatic improvement, with less discomfort and absence of serious adverse events\(^{(17-22)}\).

The procedure studied is better tolerated by children and parents when compared to the intravenous route, with more control of puncture site discomfort\(^{(17-18,22)}\). In vulnerable patients, it is a viable therapeutic alternative, favoring treatment adherence as it is an easy to perform procedure, decreasing vascular, mechanical and tissue trauma, as well as stress and pain due to repeated and unsuccessful punctures\(^{(23,26)}\). This set of results indicates the contribution of care for the humanization and quality of assistance for the pediatric patients and their families.

Hypodermoclysis as an alternative technology for rehydration, nutrition and drug therapy in children and can be used for medication administration in patients with difficult venous access\(^{(26)}\). The use of this technology requires new care protocols for the nursing and multidisciplinary team, which guide the care in the administration for the categories of drugs, with expectation of positive impacts on the expansion of the use of this route in the hospital, outpatient and home contexts\(^{(27-28)}\).

For the behavioral control of children receiving dental treatment, especially for those who are more anxious and less cooperative regarding invasive procedures\(^{(18)}\), sedation medications administered via HDC were used. Procedures of this nature and complexity are diverse and frequent in pediatrics, requiring the child's collaboration, with reassuring monitoring of the family and professional support and guidance. Thus, the use of alternative pain and anxiety control procedures serves as a subsidy to ensure quality care and promotes faster recovery, while also being adequate\(^{(29-30)}\).

Regarding pain control, non-pharmacological techniques were employed before or after the procedure: application of ice at the puncture site; parental support for the child at the time of the procedure; and rewards received by children at the end of the procedure - play, toys and food\(^{(20)}\). Nursing is very interested in information on non-pharmacological measures for the management of pain and other symptoms in the application of HDC, as nurses act as a facilitator of this process and are more closely linked to the child and family\(^{(31)}\).

Interestingly, one study addressed the advantage of HDC for reducing the workload of the nursing staff, mainly due to the shorter time spent from the beginning to the end of the procedure\(^{(18)}\). This result is consistent with the classification of medication administration
activity and maintenance of venous access devices as a complex physiological intervention, in a descriptive study that mapped nursing activities in a pediatric clinic in a university hospital in the state of São Paulo.

In the area of pediatrics, due to the complexity and level of dependence of the patients, the difficulty of operationalizing the care process of nursing professionals is highlighted as one of the main factors that culminates in poor care and that impairs the implementation of safety measures and quality of the professional practice. From this perspective, this publication provokes reflection on the benefits of using HDC, not only for the children and their families, but also for nurses and the multidisciplinary team.

The main limitation of this integrative review was the small number of articles that answered the research question. A situation that has the potential to influence the comparative analysis of the results, which is a second limitation, is related to the heterogeneous characteristics of the articles analyzed, regarding the object, type of study, sample design and methodology.

CONCLUSION

This integrative review highlighted unconventional diseases and situations treated with the use of HDC for the administration of medications, in pediatric patients, such as: Golimumab (SC) for idiopathic arthritis; Desmopressin (SC) for the prevention of hemorrhagic disorders; Midazolam (SC) for the sedation of children undergoing dental treatment; Methotrexate (SC) for rheumatic disorders; antibiotic therapy for treatment of endocarditis; and Treprostinil (SC) for pulmonary hypertension. The use of HDC is considered conventional in treatments for diabetes and allergies, due to the large number of studies that show its effectiveness.

It was possible to identify that this is a practice used in various clinical procedures and well tolerated by the pediatric patient. Therefore, experimental studies with the use of HDC and analysis of its effectiveness need to be developed for the formulation of scientific evidence, as it has already been identified as a safe route. As a consequence, this would improve the quality of pediatric care, strengthen humanized care for children and their families and favor the minimization of work stress for the nursing staff.

Finally, it should be highlighted that the formulation of high quality evidence in the use of HDC in pediatrics can promote and support its inclusion in the practice of training of nursing professionals in the Brazilian scenario, contributing to its transformation.

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