INPLASY PROTOCOL

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None declared.

Protocol: Systematic Review on Individualized Versus Standardized Parenteral Nutrition in Preterm Infants

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Review question / Objective: **Population Infants born preterm, up to 28 days after their due birth date. Intervention Any standardized approach to providing parenteral nutrition. Comparison Any individualized parenteral nutrition solutions (bespoke prescriptions). Outcomes: Protein intake. Adverse events: 1. Sepsis; 2. NEC; 3. Mortality; Duration of hospital stay; Growth/anthropometric measures; Neurodevelopmental outcomes.**
Information sources: **Search strategies - A literature search was performed from 2015 up to 11/2022 in PubMed and Cochrane database for clinical trials on parenteral nutrition in preterm infants. The search strategy for each electronic database is given in Supplement 1.**

INPLASY registration number: This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 21 February 2023 and was last updated on 21 February 2023 (registration number INPLASY202320094).

INTRODUCTION

Review question / Objective: **Population Infants born preterm, up to 28 days after their due birth date. Intervention Any standardized approach to providing parenteral nutrition. Comparison Any individualized parenteral nutrition solutions (bespoke prescriptions). Outcomes: Protein intake. Adverse events: 1. Sepsis; 2. NEC; 3. Mortality; Duration of hospital stay; Growth/anthropometric measures; Neurodevelopmental outcomes.**

Rationale: **Parenteral Nutrition (PN) is a lifesaving therapy for preterm infants. PN is indicated when oral or enteral nutrition is not possible, insufficient, or contraindicated in order to avoid**

undernutrition and related adverse consequences. The nutrient stores of very low birth weight (VLBW, birth weight < 1500g) and extremely low birth weight (ELBW, birth weight < 1000g) preterm infants are low. Bridging PN ensures adequate fluid intake and nutrient supply for weight gain and possibly neurodevelopmental long-term outcome. VLBW infants are vulnerable to postnatal growth failure because the gut is immature and provision of nutrients is challenging. The evidence showing the beneficial effects of enhanced PN to VLBW infants is accumulating. Providing amino acids and energy immediately after birth with PN is a standard practice to promote positive nitrogen re-tention[1]. PN can be provided as a standard pre-specified formulation or individually prescribed solutions.

Individual prescriptions for PN are ordered and prepared every 24-48 h. The main advantage of individually prescribed PN is that it is tailored to suit a specific patient, thereby assuring the best possible nutrition and biochemical control[2]. However, several limitations such as errors, stability issues and risk of infections have been reported[2]. Batch-produced standardized PN bags can be readily available as ward stocks in neonatal intensive care units, enabling initiation of early PN immediately after delivery of a premature infant. Moreover, standard PN solutions incorporate expert nutritional knowledge and support[2].

Both techniques have been employed. Based on low level of evidence, limited randomized controlled trials (RCTs) and some retrospective observational studies, in 2015 the combined working group on pediatric parenteral nutrition of ESPGHAN, ESPEN, ESPR, and CSPEN conditionally recommended that standard PN solutions (SPN) should generally be used over individualized PN solutions (IPN) in the majority of pediatric and newborn patients, including VLBW premature infants[3]. This recommendation has re-cently been endorsed by the UK National Guideline Alliance[4].

The optimal PN management, SPN or IPN, is still controversial. The provision of PN is highly complex, requiring high-quality pharmacy aseptic manufacturing services. The proposed practical benefits of SPN were as follows:

- Improved patient safety (minimization of procedural incidents),
- Provision of higher early intakes of amino acids and glucose, and better calcium phosphate ratio during the first week of life[5,6],
- Prevention of ordering and compounding errors - due to the complexity of the supply chain much of the variations in actual nutrient intake are un-intended[7],
- Improved pharmaceutical control of the physicochemical stability and aseptic manufacturing[8] by large scale industrial production and
- Reduction of costs[9].

Variation in PN macronutrient intake (glucose, protein or lipid intake) results also from differences in nutritional policy[10] and use of central instead of peripheral venous catheters which enabled the use of more concentrated PN solutions. PN is recognized as a high risk and complex treatment. There is a need to compare outcomes including adverse events (sepsis, due to a less complex aseptic preparation, and mortality), growth (in-cluding weight gain) and protein intake, particularly influential on growth, as a surrogate measure of all other PN components, where the evidence base is still incomplete and questioned. One would expect to achieve better nutritional goals with IPN, tailored to the individual needs. The ready-to-use triple-chamber SPN solutions with the option to add additional nutrients such as vitamins, trace elements, or amino acids are possibly easier to use by less experienced doctors. The aim of the present systematic review was to update the available evidence and investigate the effect of SPN vs. IPN on protein intake, im-mediate morbidities, growth and long-term outcome in preterm infants.

Condition being studied: This review was designed to update the 2015 conditional recommendation of the combined working group on pediatric parenteral nutrition of ESPGHAN, ESPEN, ESPR, and CSPEN that standard PN solutions (SPN) should generally be used over individu-alized PN

solutions (IPN) in the majority of preterm infants[3] using standard methods[11] and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) criteria[12,13]. The level of evidence of eligible studies and the degree of recommendation were assessed following the recent guideline approach[1,3]. The research questions were defined following the PICO framework[14] (Tab 1). Primary outcomes were defined as protein intake, immediate in hospital complications such as mortality, sepsis incidence, necrotizing enterocolitis (NEC) incidence, duration of PN (days), growth, and neurode-velopmental long-term outcome. The NEC data were defined and extracted as stage >2 NEC[15]. Growth was assessed as weight gain in g/kg/d during the study period, weight standard deviation score (SDS) at discharge, head circumference (HC) SDS at discharge, or weight and occipitofrontal circumference (OFC) SDS change from birth to 36 weeks postmenstrual age.

METHODS

Search strategies:
A literature search was performed from 2015 up to 11/2022 in PubMed and Cochrane database for clinical trials on parenteral nutrition in preterm infants. The search strategy for each electronic database is given in Supplement 1. Gray literature was assessed by hand search.
Selection criteria
Inclusion criteria included all clinical trials published in any language however providing an English language abstract. All retrieved records were imported into EndNote X9, and duplicates were removed automatically and by manual checking. The titles and abstracts of the outputs were screened independently by two reviewers (MS and WM) to select the potential trials. Then, the full text of each potential trial was further assessed for eligibility. The reviewers also screened the reference lists of eligible trials to identify further relevant eligible trials. All eligible trials were finally included after discussions between the reviewers. Two reviewers (MS and WM) extracted the following information: author, year of publication or update, country or region, population, in-tervention, comparison, and outcomes. The GRADE approach was used to assess the quality of evidence and to interpret findings. Authors evaluated the level of evidence (LoE), the grade of recommendation (GOR), and the form of recommendation as described previously[11]. The SIGN classification was used to assign both the evidence level and the recommendation grade. The scales used to evaluate LoE, GOR, and form of recom-mendation are summarized in Tables 2 to 4[11,16].

Participant or population: Infants born preterm, up to 28 days after their due birth date Intervention.

Intervention: Any standardized approach to providing parenteral nutrition.

Comparator: Any individualized parenteral nutrition solutions (bespoke prescriptions).

Study designs to be included: Any controlled trials.

Eligibility criteria: None.

Information sources: Search strategies - A literature search was performed from 2015 up to 11/2022 in PubMed and Cochrane database for clinical trials on parenteral nutrition in preterm infants. The search strategy for each electronic database is given in Supplement 1.

Main outcome(s): Outcomes: Protein intake. Adverse events 1. Sepsis; 2. NEC; 3. Mortality; Duration of hospital stay; Growth/anthropometric measures; Neurodevelopmental outcomes.

Additional outcome(s): None.

Data management: Statistics - Outcomes for categorical data are presented as odds ratio with respective 95% con-fidence intervals. For continuous data, the weighted mean difference with 95% confidence interval was used. The treatment effects of individual trials and heterogeneity between trial results were

examined by inspecting the forest plots. The impact of heterogeneity in any meta-analysis was assessed using a measure of the degree of inconsistency in the studies' results (I- squared statistic). A random effects model for metanalyses was used. Review Manager (RevMan) Version 5.4 software, Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014 was used for data analysis.

Quality assessment / Risk of bias analysis: All studies used historical controls. Therefore the risk of bias was very high by design of the studies. Further use od the Cochrane risk of bias tool would not improve the judgement and was not used.

Strategy of data synthesis: Selection criteria - Inclusion criteria included all clinical trials published in any language however providing an English language abstract. All retrieved records were imported into EndNote X9, and duplicates were removed automatically and by manual checking. The titles and abstracts of the outputs were screened independently by two reviewers (MS and WM) to select the potential trials. Then, the full text of each potential trial was further assessed for eligibility. The reviewers also screened the reference lists of eligible trials to identify further relevant eligible trials. All eligible trials were finally included after discussions between the reviewers. Two reviewers (MS and WM) extracted the following information: author, year of publication or update, country or region, population, in-tervention, comparison, and outcomes. The GRADE approach was used to assess the quality of evidence and to interpret findings. Authors evaluated the level of evidence (LoE), the grade of recommendation (GOR), and the form of recommendation as described previously[11]. The SIGN classification was used to assign both the evidence level and the recommendation grade. The scales used to evaluate LoE, GOR, and form of recom-mendation are summarized in Tables 2 to 4[11,16].

Subgroup analysis: Statistics - Outcomes for categorical data are presented as odds ratio with respective 95% con-fidence intervals. For continuous data, the weighted mean difference with 95% confidence interval was used. The treatment effects of individual trials and heterogeneity between trial results were examined by inspecting the forest plots. The impact of heterogeneity in any meta-analysis was assessed using a measure of the degree of inconsistency in the studies' results (I- squared statistic). A random effects model for metanalyses was used. Review Manager (RevMan) Version 5.4 software, Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014 was used for data analysis.

Sensitivity analysis: Not done.

Language restriction: Language was restricted to English.

Country(ies) involved: Germany and Spain.

Other relevant information: None.

Keywords: Preterm infant, parenteral nutrition, standardised, individualised, protein, growth, necrotising enterocolitis.

Dissemination plans: Publication in Nutrients.

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