Biochemical test as an efficient system to improve safety in parenteral nutrition for premature infants

Análisis bioquímico como método eficiente para aumentar la seguridad de la nutrición parenteral en neonatos

Objective: The biochemical test validation process of parenteral nutrition bags is described to verify the correct composition of critical compounds before its administration, as well as its impact on safety after two years since its implantation in a population of premature infants.

Method: For the validation of the technique, 35 samples of parenteral nutrition without lipids were processed by the emergency laboratory, following the routine procedures used to measure the concentrations of glucose and electrolytes in plasma and urine. To analyze its impact on safety, pre-implantation and post-implantation risk analysis was carried out using failure mode, effects and criticality analysis (FMECA). Likewise, all out-of-range results and their potential repercussions on patient safety were evaluated.

Results: Regression analysis showed no systematic measurement error for glucose, calcium and potassium; however, there is a constant systematic error for sodium and magnesium, thus both were discarded for routine analysis. Failure mode, effects and criticality analysis results showed a decrease in the risk of the process of 11% for the biochemical test. We tested 1,734 parenteral nutrition from 218 premature neonates; 58 (3.3%) results were out of the acceptance range, and 7 were considered to be potentially dangerous compounding errors.

Conclusions: The biochemical test of glucose and electrolytes is an efficient and reproducible method that prevents possible compounding errors from reaching the patient.

KEYWORDS
Chemical analysis; healthcare failure mode, effect and criticality analysis; Infant; Parenteral nutrition; Quality control; Premature; Safety.

PALABRAS CLAVE
Análisis modal de fallos y efectos; Análisis químico; Control de calidad; Nutrición parenteral; Prematuro; Seguridad.
Introduction

Parenteral nutrition (PN) is essential to the survival of neonates whose nutritional requirements cannot be met via the oral route. Scientific societies, such as the European Society of Pediatric Gastroenterology, Hepatology, and Nutrition (ESPGHAN) and the European Society of Clinical Nutrition and Metabolism (ESPEN), provide specific guidelines for the prescription of PN in this group of patients. However, PN is associated with a high risk of adverse effects, such as infections or metabolic imbalances, which can put intrinsically very vulnerable patients at risk. Any prescription error, compounding error, or microbiological contamination could prove lethal for such vulnerable patients.

Furthermore, the complexity of compounding PNs constitutes a risk in itself. The main causes of this complexity are the handling of a large number of compounds in very small volumes, physicochemical stability issues, and a high risk of contamination during the compounding process. In recent years, the introduction of semi-automated systems for the compounding of PN mixtures has strongly improved traceability and the safety of the process. However, the implementation of these systems for compounding PN for low-birth-weight preterm neonates is challenging because it entails dealing with components of less than 1 mL in volume. For this reason, PN for preterm neonates is typically compounded by hand. Thus, it is essential to implement quality controls to reduce the likelihood of errors and to guarantee patient safety. In-process controls, such as double-checks or systems that ensure the traceability of the ingredients, are valid alternatives in the absence of semi-automated compounding systems. Microbiological testing is also needed to ensure that the final product is sterile. A gravimetric test with an acceptance margin of 5% for the final weight of the bags is the most widespread type of test of the finished product. However, given that most of the compounds are used in very low volumes, its ability to detect compounding errors is quite limited.

Parenteral nutrition typically contains amino acids, glucose, lipids, electrolytes (sodium, potassium, calcium, phosphorus, and magnesium), trace elements, vitamins, and drugs such as carnitine and heparin. The biochemical analysis of the composition of PNs could be an effective control method to ensure the correct composition of critical compounds, such as glucose or some potentially dangerous electrolytes, and to prevent compounding errors. The concentrations of these compounds in PN can be measured by adapting conventional techniques used in clinical laboratories to measure their concentrations in biological samples. This is a simple alternative that is available in almost all hospitals. Emergency laboratories already work within short response times, and the measurement procedures used can rapidly obtain results at a very low cost.

The aim of this study was to describe the validation of the procedure used in the biochemical testing of PN for preterm neonates, and to assess the impact on patient safety of its implementation in a tertiary hospital.

Methods

Validation of the procedure

The most clinically relevant compounds measured in this process were glucose, sodium, potassium, magnesium, and calcium. They were measured in the emergency laboratory of our hospital using the Dimension EXL automatic analyser (Siemens Diagnostics), which allows us to measure, for example, glucose and electrolyte concentrations in plasma and urine.

Glucose and calcium were measured by molecular absorption spectrometry using the Dimension EXL (GLUC Ref D40 and CA Ref D23A, respectively). Sodium and potassium concentrations were measured by the indirect potentiometry method using the Dimension QuikLyte (Ref S600). The procedures used to measure calcium, magnesium, sodium, and potassium concentrations in PN were not modified, whereas glucose was measured after diluting the PN samples with distilled water at a ratio of 1:20.

To validate the measurement procedures, we used 35 samples of lipid-free PN, which were replicas of real samples and were compounded using double-checks to guarantee their correct composition. The in-process double-checks and the use of volumetric and weighing material with negligible measurement uncertainty allowed us to assume that the samples used for validation were free of compounding errors. Measurement inaccuracy was calculated using Passing-Bablok non-parametric linear regression to analyse the difference between theoretical concentrations and measured concentrations.

In order to interpret the results obtained in daily practice, we also reached a consensus with neonatologists on the clinically acceptable margins of error for each compound.

Assessment of the implementation

Risk analysis

The failure mode, effect, and criticality analysis (FMEA) method was used to quantify the pre-implementation and post-implementation risks of the process. This analysis was based on a global redesign of the paediatric PN prescription and compounding process, which included an electronic prescription program and a double-check system in addition to the implementation of biochemical mixture tests.

A multidisciplinary team of pharmacists and pharmacy technicians with expertise in compounding paediatric PN used an Ishikawa diagram to identify all possible errors during the prescription, validation, and compounding of the mixtures. Subsequently, they assigned a value to each possible error in terms of its likelihood (from 1 to 10), severity of its consequences for the patient (from 1 to 10), and difficulty in detecting the error during the process (from 10 to 1). These three items were multiplied to obtain the criticality index (CI), which quantifies the magnitude of the risk of the process.

The difference between the pre- and post-implementation CI provides an estimate of the impact of the implementation on overall risk reduction.

Assessment of effectiveness

We assessed all paediatric PNs compounded in the first 2 years post-implementation. The mixtures did not contain lipids because they are administered separately in our hospital. We recorded the following variables: patient weight on day PN started, gestational age, and duration of nutrition. We also quantified the response time from the moment a laboratory analysis was requested until the time of its validation in the hospital’s computer system, as well as the mean cost of analysis. Finally, we assessed all preparations with out-of-range results and analysed their causes and possible impact on patient safety.

Results

Validation of the procedure

The neonatologists used a theoretical concentration of ± 10% as the clinically acceptable range for the components under analysis, although larger deviations could be acceptable depending on the characteristics and clinical situation of the preterm neonate.

Tables 1 and 2 show the mean concentrations of the samples used for validation and the regression lines for each compound, respectively.

The regression analysis obtained a correlation coefficient of more than 0.975 for all parameters. No systematic measurement errors were found for glucose and calcium. A positive systematic proportional error of 3.7% was found in the case of potassium; however, this result was not considered to be clinically relevant. A positive systematic constant error of 3 mmol/L was found in the case of sodium. This level of error is irrelevant at high concentrations, but can be significant at small concentrations. Thus, sodium was not included in the biochemical test. A mixed systematic error was found in the case of magnesium, with a proportional error of 11.3%.

Table 1. Mean concentration of each ingredient in the samples analysed.

<table>
<thead>
<tr>
<th>Ingredient</th>
<th>Mean</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Calcium</td>
<td>32.29 mg/dl</td>
<td>12.90-92 mg/dl</td>
</tr>
<tr>
<td>Glucose</td>
<td>10,397 mg/dl</td>
<td>7,894-12,888 mg/dl</td>
</tr>
<tr>
<td>Magnesium</td>
<td>2.28 mg/dl</td>
<td>1.08-3.28 mg/dl</td>
</tr>
<tr>
<td>Potassium</td>
<td>12.84 mmol/L</td>
<td>7.39-70 mmol/L</td>
</tr>
<tr>
<td>Sodium</td>
<td>28.50 mmol/L</td>
<td>14-90 mmol/L</td>
</tr>
</tbody>
</table>
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Table 2. Regression lines for the relative inaccuracy of the different measurement procedures and their correlation coefficients

<table>
<thead>
<tr>
<th>Substance</th>
<th>Regression line Conc Theo = a (CI a) Conc Med + b (CI b)</th>
<th>Correlation coefficients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Calcium</td>
<td>Conc Theo = 1.067 (1.000-1.097) Conc Med - 0.77 (-124-0.26)</td>
<td>0.997</td>
</tr>
<tr>
<td>Glucose</td>
<td>Conc Theo = 0.940 (0.797-1.034) Conc Med + 896 (-77-2514)</td>
<td>0.975</td>
</tr>
<tr>
<td>Magnesium</td>
<td>Conc Theo = 1.113 (1.052-1.217) Conc Med + 0.28 (0.16-0.35)</td>
<td>0.978</td>
</tr>
<tr>
<td>Potassium</td>
<td>Conc Theo = 1.037 (1.015-1.056) Conc Med + 0.15 (-0.04-0.21)</td>
<td>0.999</td>
</tr>
<tr>
<td>Sodium</td>
<td>Conc Theo = 1.041 (0.996-1.083) Conc Med + 3 (2.1-4.4)</td>
<td>0.987</td>
</tr>
</tbody>
</table>

a: proportional error; b: constant error; CI: confidence interval; Conc Med: measured concentration; Conc Theo: theoretical concentration.

Assessment of effectiveness

A total of 1734 PN bags were used in the analysis, involving 218 neonates with a gestational age of 30 ± 4 weeks. On the first day of PN, mean weight was 1.35 ± 0.8 kg. In total, 94 patients (43%) weighed less than 1 kg. The mean duration of PN was 7.93 days.

Of the 1734 samples analysed, 58 (3.3%) were found to be out-of-range for glucose, calcium, and potassium ± 10%. In 34 of the 58 cases, the deviation was slightly above the acceptance range (between 10% and 15%), however, the neonatologists considered that the deviation would not have any clinical repercussions, and so the compounding was accepted as correct. In 17 cases, the out-of-range result was identified either as a transcription error when using the software to enter the request, or as an identification error regarding the patient for whom the request was made. Finally, the 7 remaining cases were identified as potentially dangerous compounds, and so the bags were discarded and the PN was compounded again. Of these 7 errors, 3 were related to the calcium concentration in the sample, 3 to the potassium concentration, and 1 to the glucose concentration.

Discussion

The complexity of the mixtures and the fragility of the patient make the prescription and compounding of paediatric PNs a critical process that requires continuous review to guarantee safety. The biochemical analysis of nutrition can provide great added value to this process by ensuring the correct composition of critical ingredients, such as sodium, potassium, calcium, and glucose.
as glucose or potassium. The fact that it is not a standard practice in hospitals may be due to either the difficulty of integrating it into daily routines or its high cost, depending on the measurement instruments used.

However, tests are randomly conducted on a specific percentage of PNs. This study shows that it is feasible to implement biochemical test for all PN bags at a genuinely affordable cost, due to interdisciplinarity collaboration between the emergency laboratory and pharmacy services. The response time, which is less than 1 hour in most cases, means that possible errors can be detected before the time of administration and the PN can be compounded again if needed.

Although the risk analysis showed that the implementation of a biochemical test reduces the overall risk inherent to the process, other measures, such as electronic prescription or the introduction of in-process controls (e.g. double-checks in the present study), could have the same or an even greater effect on risk reduction.

It is relevant to note that despite the introduction of the new measures, a certain level of risk always remained (34% in our case). These risks should be studied, their causes clearly determined, and suitable measures implemented with the aim of reducing or eliminating them.

Although the results of the FMEA cannot be extrapolated to other hospitals, various institutions such as the Joint Commission or the Council of Europe have recommended the integration of risk analysis into standard practice in hospitals as a support tool for continuous improvement.

Although we did not collect data on PN medication errors that reached the patient before or after the implementation of the biochemical test, we consider that the results corroborate the benefits of the intervention in relation to risk reduction in the PN compounding process and error avoidance.

The data show that the study population mainly consisted of preterm neonates weighing less than 1.5 kg, whose indication for PN is, by definition, their prematurity. The challenge of compounding these PNs resides in the high number of ingredients and small volumes involved in their preparation. This well-known problem has been approached in various ways. These approaches include the appropriate training and periodic assessment of the professionals who compound PNs, although other authors have investigated the advantages of automation or the use of standardized mixtures. Future research will undoubtedly determine the performance of these options in clinical practice. Until then, interdisciplinary teams responsible for neonatal PN should continue to innovate and apply continuous improvement strategies to meet the challenge of improving the safety of the process.

In conclusion, the biochemical test of glucose and electrolytes is an efficient and reproducible method. This kind of biochemical testing can be used to analyse critical ingredients in all PNs. The results would be known before the administration of PN, thus preventing potential compounding errors from reaching the patient. In our 2-year experience, the use of biochemical testing allowed us to detect 7 compounding errors with potentially severe consequences in these neonatal patients.

**Statement of authorship**

All the authors have contributed to writing the article, as stated in the journal’s publication guidelines. They have also approved the final version of the article, thus fulfilling the authorship requirements. I would like to state on their behalf that this study has not been previously published, nor is it under peer review by any other journal.

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**Conflicts of interests**

No conflict of interest.

- Part of this work was awarded the third prize for the best communication at the 21st EAHP Congress.
- It was also partially presented as a poster at the 31st Congress of the Sociedad Española de Nutrición Parenteral y Enteral (SENPE).

**Contribution to the scientific literature**

This study investigated a technique to reduce the risks inherent to the process of compounding parenteral nutrition for extremely vulnerable patients, such as neonates. To this process we added a biochemical test to current quality controls, such as microbiological and gravimetric tests. Unlike these tests, the biochemical test has the added value of detecting errors in the composition of the mixture. In our hospital, the biochemical analysis of parenteral nutrition bags allowed us to identify 7 potentially dangerous errors before they reached the patient. Before implementing the biochemical test, we conducted a risk analysis that allowed us to improve the safety of the process by identifying its critical points. The description of the steps followed to implement this biochemical test in our hospital may be of help to other hospital pharmacy services that wish to include this type of quality control in their standard procedures.
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Bibliography


