

Parenteral nutrition: overview of the samples analyzed at the National Institute for Quality Control in Health

Nutrição parenteral: visão geral das amostras analisadas no Instituto Nacional de Controle de Qualidade em Saúde

Nutrición parenteral: resumen de las muestras analizadas en el Instituto Nacional de Control de Calidad en Salud

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ABSTRACT

Background and objectives: Total parenteral nutrition (TPN) has great clinical importance in malnutrition treatment and prevention in patients with digestive problems. Although good practices for handling TPN are well established, contamination of these products still occurs, and this product remains listed as a higher risk drug by the Institute for Safe Medication Practices. The present study aimed to obtain an overview of the documentary data of the parenteral nutrition samples sent to the National Institute for Quality Control in Health (INCQS) of *Fundação Oswaldo Cruz*. **Methods:** This is a qualitative descriptive and quantitative study carried out based on a cross-section of TPN samples analyzed from 2000 to 2016. **Results:** A total of TPN 134 samples were sent during the study period. 11.20% of the samples were sent in 2001, 0.80% in 2005, 8.20% in 2006, 16.40% in 2007, 63.40% in 2013. Six samples (4.5%) were canceled and 113 submitted to sterility testing, resulting in 13.3% unsatisfactory samples. **Conclusion:** During the study period, four suspected events of enterobacterial contamination in TPNs administered to patients were reported, three of which have not yet been described in the scientific literature. For the safety of patients using TPN to be guaranteed, it is suggested that the norms that regulate TPN therapy be reviewed and updated, and programs to monitor the quality of these preparations should be established.

Keywords: Parenteral Nutrition. Health Surveillance. Quality Control. Contamination.

RESUMO

Justificativa e objetivos: A nutrição parenteral total (NPT) tem grande importância clínica no tratamento e prevenção da desnutrição em pacientes com problemas digestivos. Embora as boas práticas para o manuseio da NPT

estejam bem estabelecidas, a contaminação desses produtos ainda ocorre, e este produto continua listado como um medicamento de alto risco pelo Institute for Safe Medication Practices. O presente estudo teve como objetivo obter um panorama dos dados documentais das amostras de nutrição parenteral enviadas ao Instituto Nacional de Controle de Qualidade em Saúde (INCQS) da Fundação Oswaldo Cruz. **Métodos:** Trata-se de um estudo qualitativo descritivo e quantitativo realizado a partir de um corte transversal de amostras de NPT analisadas de 2000 a 2016. **Resultados:** Foram enviadas 134 amostras de NPT no período do estudo. 11,20% das amostras foram enviadas em 2001, 0,80% em 2005, 8,20% em 2006, 16,40% em 2007, 63,40% em 2013. Seis amostras (4,5%) foram canceladas e 113 submetidas a ensaio de esterilidade, resultando em 13,3% amostras insatisfatórias. **Conclusão:** Durante o período do estudo, foram relatados quatro eventos suspeitos de contaminação por enterobactérias em NPT administradas a pacientes, três dos quais ainda não descritos na literatura científica. Para que a segurança dos pacientes em uso de NPT seja garantida, sugere-se que as normas que regulam a terapia com NPT sejam revistas e atualizadas e sejam estabelecidos programas de monitoramento da qualidade dessas preparações.

Palavras-chave: Nutrição Parenteral. Vigilância de Saúde. Controle de qualidade. Contaminação.

RESUMEN

Fundamento y objetivos: La nutrición parenteral total (NPT) tiene una gran importancia clínica en el tratamiento y prevención de la desnutrición en pacientes con problemas digestivos. Aunque las buenas prácticas para el manejo de TPN están bien establecidas, aún se produce la contaminación de estos productos, y este producto sigue figurando como un fármaco de mayor riesgo por el Instituto de Prácticas Seguras de Medicamentos. El presente estudio tuvo como objetivo obtener una visión general de los datos documentales de las muestras de nutrición parenteral enviadas al Instituto Nacional de Control de Calidad en Salud (INCQS) de la Fundação Oswaldo Cruz. **Métodos:** Se trata de un estudio cualitativo descriptivo y cuantitativo realizado a partir de un corte transversal de muestras de TPN analizadas entre 2000 y 2016. **Resultados:** Se enviaron un total de 134 muestras de TPN durante el período de estudio. El 11,20% de las muestras se enviaron en 2001, el 0,80% en 2005, el 8,20% en 2006, el 16,40% en 2007, el 63,40% en 2013. Se cancelaron seis muestras (4,5%) y 113 se sometieron a pruebas de esterilidad, lo que resultó en un 13,3% insatisfactorio muestras. **Conclusión:** Durante el período de estudio, se informaron cuatro eventos sospechosos de contaminación por enterobacterias en TPN administradas a pacientes, tres de los cuales aún no se han descrito en la literatura científica. Para garantizar la seguridad de los pacientes que utilizan NPT, se sugiere que se revisen y actualicen las normas que regulan la terapia con NPT y que se establezcan programas para monitorear la calidad de estas preparaciones.

Palabras clave: Nutrición parenteral. Vigilancia de la salud. Control de calidad. Contaminación.

INTRODUCTION

Total parenteral nutrition (TPN) has great clinical importance in the treatment and prevention of malnutrition when patients present a condition that does not allow them to absorb and digest food through the digestive system. TPN is prepared exclusively for each patient. Its composition contains amino acids, carbohydrates, lipids, vitamins and minerals in amounts adjusted to their metabolic needs for the synthesis and maintenance of tissues, organs, and systems.¹

As it is an intravenous infusion, TPN must be sterile and pyrogenic to ensure the health of users. TPN is an extemporaneous product, not subjected to terminal sterilization, which makes the production process critical. Consequently, these preparations must be produced and handled under aseptic conditions according to the parameters established by standards. In Brazil, parenteral nutrition therapy is regulated by Ordinance 272 of April 8, 1998. According to Ordinance 272, TPNs must be produced in a clean grade-C or B area, surrounded by a clean grade-C area. Cleaning and sanitizing of pharmaceutical products and other materials used in handling must be

carried out in a D-grade area.²

Although good handling practices for TPN are well-established, contamination of these products is still observed and may occur due to contaminated industrialized components, during preparation, storage and administration, demonstrating the importance of establishing updated standards. Several publications have reported bacterial, fungal contamination and the damage caused to patients. One of the most relevant complications is bloodstream infection related to intravenous therapy, which represents an important factor in mortality and morbidity, generating increased hospital costs. High rates of bacteremia caused by using contaminated TPN have led the American Society for Parenteral and Enteral Nutrition to publish some guidelines, such as suggestion to restrict TPN use during the first seven days after admission to Intensive Care Units (ICUs) in healthy and well-nourished patients.³⁻¹²

Although TPN remains a high-risk drug by the Institute for Safe Medication Practices, there are few scientific articles published in Brazil on the topic. As it is a product that poses a risk to users, any suspicion of

quality deviation should generate a health surveillance action to ascertain the situation. In this regard, the Brazilian National Institute for Quality Control in Health (INCQS - *Instituto Nacional de Controle de Qualidade em Saúde*) of *Fundação Oswaldo Cruz* (Fiocruz), a component of the National Network of Health Surveillance Laboratories, analyzes TPN to assess the quality of samples from inspection actions by health surveillance agencies. Producing establishments must have implemented a quality management system, where TPNs are handled according to current regulations, meeting all requirements, from prescription to administration.^{13,14}

The present study aimed to obtain an overview of the characteristics of the TPN samples sent to INCQS/Fiocruz from 2000 to 2016 and to report events of possible microbial contamination or outbreaks of infection that occurred in the period. Moreover, this study aimed to carry out an assessment of the standards of preparation and analysis of the quality of TPN, since there are few studies assessing this product.

METHODS

A descriptive and quantitative qualitative documentary study was carried out based on a cross-section of TPN samples sent and analyzed at INCQS from January 2000 to December 2016. The cut-off period was established considering the availability of computerized data. During this period, there was no change in the laboratory method of TPN analysis.

The quantitative survey of TPNs sent to INCQS, in the established period, was carried out by consulting the Laboratory Sample Management System (SGAweb and Harpya) by searching for the expression "parenteral nutrition". The qualitative data came from the archived documentary processes regarding the samples and the respective Sample Collection Report (SCR) were collected. The studied samples were coded in order to maintain the confidentiality of the information used.

Analysis mode, region of origin, reason for seizure, result of sterility testing, time between collection and entry of the sample at INCQS, sample volume, canceled samples were the variables defined for this study. This information was collected in spreadsheets generated by the systems used, and through the analysis of documentary processes. At INCQS, for each sample received, a process is created with a registration form and all the documentation that accompanies it.

There was no need for an appraisal by a Research Ethics Committee, due to the nature of the study, as data were not collected from patient records.

RESULTS

According to the data survey, a total of 134 TPN samples were sent to INCQS from January 2000 to December 2016. Among the 134 TPN samples, six samples were canceled (4.5%). The reasons for canceling analysis

were: sample envelope violation (four samples), product not recognized by the company on the label (a sample), and broken syringe needle cap (a sample).

The samples were sent for analysis in syringes when collected from the bag just after the production of TPN (volumes from 3 mL to 10 mL) or in manipulated bags of 130, 250 and 1250 mL. One hundred twenty-seven (94.8%) samples were collected in syringes, the majority (46.3%) containing 5 mL of the TPN produced.

Of the total of 134 samples, 113 TPN samples were submitted to sterility testing, with 98 samples showing satisfactory results and 15 samples were unsatisfactory (nine had a volume of 5 mL, 60.0%, and six, 40.0%, the volume of 10 mL). The time between collection and entry of the TPN sample at INCQS ranged from 0 to 8 days, with 0 days (1.5%), 2 days (60.5%), 3 days (1.5%), 7 days (10.5%), 8 days (26.0%).

To facilitate assessment, TPN samples were organized into five groups according to the seizure period and the data collected in the respective processes (Table 1). After verifying table 1, only the samples from Group 1 were not sent to perform sterility testing, as the suspicion was not bacterial contamination. The samples were referred to INCQS Department of Chemistry for insulin research. According to table 1, the remaining samples could be grouped into 4 four possible bacterial contamination events, which are Groups 2, 3, 4 and 5. Each sample group was associated with bacterial contaminants, identified as enterobacteria.

DISCUSSION

The present study showed an overview of the characteristics and data associated with the TPN samples sent for analysis at INCQS over a 17-year period. The analysis carried out showed some situations that need to be addressed and questioned.

The guidance analysis was not regulated at the time; however, in this study, the importance of this type of analysis was highlighted. For the samples of Group 5 (Table 1), a higher percentage of contamination of the samples sent for analysis of guidance was observed than for the samples referring to fiscal analyzes. This data shows the importance of the guidance analysis both to be used as a relevant support tool to support the actions of the Health Surveillance and to routinely monitor the quality of this product.¹⁵

Another issue to be highlighted is the inclusion of the reason for seizure in SCR in a standardized way to facilitate the direction of quality control analysis, as the samples are seized as single samples and the quantity is usually not sufficient to carry out various analyzes. In the present study, despite the reasons for seizure being related to bacterial contamination, the description was incomplete or with incomprehensible terms, which highlights the need for uniformity in the description of the reason for seizure in SCR by supervisory agents.

Data analysis suggests that some technical parameters, such as sampling, sample volume and the period of

Table 1. Data assessed in the present study regarding TPN samples received at INCQS from 2000 to 2016.

Group	Date of entry of the sample at INCQS	Place	Reason for seizure	N° of patients	Symptoms reported	Analysis modality (N°)	Sample volume (N°)	Time between taking the sample and entering INCQS (N°)	Test (N°)	Test results	Contamination
1 (n=15)	Oct/2001	São Paulo	Suspected of causing hypoglycemia and adverse event in neonates	NR	Hypoglycemia	Supervision (n = 7) Guidance (n = 8)	Syringe 3 mL (n = 15)	8 days (n = 15)	Insulin detection (n = 15)	100% S (15/15)	NA
2 (n=12)	27/12/05 Jan and Feb/2006	Curitiba	Death in neonates	3 neonates, three deaths	Hyperemia, redness and abdominal wall edema	Supervision* (n = 12)*	Bags 250 mL (n = 4) ^a Syringes 10 mL (n = 8) ^b	7 days (n = 1), 3 days (n = 2), 2 days (n = 1) 2 days (n = 8)	Sterility (n = 7)	57.1% S (4/7) 42.9% (3/7)	Enterobacteria (3 samples) isolated and identified by INCQS and <i>Enterobacter agglomerans</i> by the TPN producing company
3 (n=20)	04/04/07	Rio de Janeiro	Suspected bacterial contamination	4 neonates	NR	Supervision (n = 20)	Syringe 3 mL (n = 20)	8 days (n = 20)	Sterility (n = 20)	100% S (20/20)	Gram negative bacillus. by the producing company
4 (n=2)	06/04/07	Rio de Janeiro	Death in a patient using TPN	1 patient, one death**	Septic shock and positive blood culture	Supervision (n = 2)	Bag 1250 mL (n = 2)	0 days (n = 2)	Sterility (n = 2)	100% S (2/2)	<i>Klebsiella pneumoniae</i> isolated from blood culture by the hospital
5 (n=85)	Nov/2013	Paraná	Investigation of hospital infection outbreak	15 patients (adults, children, and neonates), three deaths	Infectious conditions, bacteremia, and sepsis	Supervision (n = 41) Guidance (n = 44)**	Bag 130 mL (n = 1) Syringes 10 mL (n = 12) Syringes 5 mL (n = 28) Syringes 10 mL (n = 10) Syringes 5 mL (n = 33)	7 days (n = 13) 2 days (n = 28) 2 days (n = 43)	Sterility (n = 84)	92.7% S (38/41) 7.3% U (3/41) 79.1% S (34/43) 20.9% U (9/43)	<i>Pantoea</i> spp. (11 samples), <i>Rhizobium radiobacter</i> (1 sample) isolated from TPN by INCQS and blood culture by the hospital

Caption: ^afive samples were canceled; ^basample was canceled; four canceled samples; ^cGram negative bacillus of the Enterobacteriaceae family, possibly belonging to the following species: *Enterobacter intermedius*, *Rahnella aquatilis*, *Enterobacter/Pantoea agglomerans* or *Enterobacter cloacae*. S: satisfactory; U: unsatisfactory; TPN: total parenteral nutrition; NR: not reported; NA: not applicable.

time between sample collection and the beginning of microbiological analyzes, need to be revised in the current legislation that was established 21 years ago. The volume of TPN in the control sample is a factor that can impact the result of sterility testing. A statistically low volume can generate a false negative result, as the collected part may not contain viable cells from the contaminating microorganism. In this study, all unsatisfactory TPN samples had a volume between 5 mL and 10 mL. But it is important to consider that several fiscal samples of TPNs, in which the patient made use and developed infection, presented satisfactory results and had a volume of 5 mL. Other parameters are also involved. Thus, we concluded that, it would be of sanitary relevance that the current legislation included that the TPN sampling must be statistically significant considering the final volume produced to increase the sterility testing's accuracy.^{2,13}

The retention of a control sample and a sample for quality control (the latter is not mandatory for all TPN produced) are essential to take precautionary measures or elucidate an outbreak, even if they are not directly related to cases of infection. Currently, by Ordinance 272/1998, sampling is done by handling session, and samples are not taken from all bags produced.² Each TPN bag produced has a different formulation; therefore, different batches are considered, even if they have been filled in the same handling session. Therefore, sampling is important for the quality control of all bags produced. We consider that the sampled volume of each TPN bag, both for sample and quality control, also deserves to be reassessed in the current legislation.

The period of time between the collection of samples and the performance of the analysis can impact the result of sterility testing. The longer the time between sample collection and analysis, the lower the chance of detecting viable microorganisms, which is the basis of that test. Moreover, the short time between notification of an outbreak due to bacterial contamination and test performance allows Health Surveillance agencies to take faster actions. Most unsatisfactory TPN samples (93.3%) had a two-day delay between collection and entry into INCQS.

Although sterility testing is highly recommended worldwide and has been described in several pharmacopoeias, it only performs well when there are high levels of contamination. Probably for this reason, several TPN samples, which were administered to patients who developed bloodstream infection, were assessed as satisfactory by sterility testing. Given this fact, it is extremely important that analytical laboratories have more sensitive analysis techniques for detecting low concentration of microorganisms in sterile products, especially in cases of large outbreaks.^{16, 17}

The samples belonging to Group 3 (Table 1), exemplify issues addressed here. The samples had a satisfactory analytical report and the company declared that it identified the contaminating bacteria. Probably, the contamination in these samples sent to INCQS was below the detection limit of sterility testing. This difference in result can also be justified by using alternative methods

for detecting contamination. Furthermore, other reasons may have impacted the results of the sterility testing of these samples, such as small volume. They were sent in syringes containing 3 mL of TPN, or due to the time of 8 days for the samples to be sent for analysis.

Another technical issue that needs to be updated is where TPN is handled. Good Manufacturing Practices and Normative Instruction 35/2019 establishes that the filling of sterile drugs must be done in a unidirectional flow cabinet or in an isolator (both considered grade A), being surrounded by area grade B. Therefore, one must consider that Ordinance 272/1998 is not updated, as it says that TPN must be handled in a grade-A or B clean area surrounded by grade-C area.² This consideration broadens the need for review and harmonization of the standard regarding TPN production.¹⁸

In this study, the percentage of unsatisfactory samples in sterility testing was 13%, a relatively high value, even considering that it can be overestimated in a global assessment, as they referred to samples suspected of causing damage to patients. Although this data is an important indication of the quality of TPNs produced in Brazil, it does not represent the real value of contaminated TPNs, as it does not include the great diversity of handling pharmacies, and, also, the samples did not come from all regions of the country. In this regard, it would be of great importance to carry out studies that analyze the microbiological quality of TPN in the country, since they are scarce and, generally, limited to a certain region due to the occurrence of outbreaks. Thus, this study shows the need to carry out a national program for TPN assessment and supervision of its production.^{5,19,20}

In the data referring to the region of origin of the TPN samples determined in this study, the absence of samples from Center-West, Northeast, and North regions was verified (Table 1). Such an occurrence suggests the possibility that cases of TPN contamination are unnoticed by healthcare professionals in Brazil and are not being notified or that the samples have been sent to the nearest public health laboratories that perform sterility testing.

According to Ordinance 272/98, it is important that healthcare professionals involved with TPN use are attentive and aware of the risks of this therapy. TPN is considered a critical intravenous product and has the highest mortality rate from infections around 50%. According to a survey conducted by the Institute for Safe Medication Practices in 2012, only 64% of the professionals interviewed considered TPN to be a high alert medicine. Therefore, the continuing education of all healthcare professionals involved with TPN use is essential for the effective prevention of nosocomial infections.^{2,21,22}

In this work, it was evidenced the occurrence of four events of possible microbial contamination or outbreaks of infection that are described in Table 1. It is possible to observe the difficulty in identifying the source of contamination, since sterility testing was satisfactory in all samples from Group 3 and Group 4, even if the documents of the processes were indicating TPN as the only possible source of contamination. In the case of Group 3 samples,

the TPN producing company detected contamination in its samples. This may have been due to the method used to assess TPN sterility. In the samples of Groups 2 and 5, the contamination of TPN was confirmed by sterility testing; however, additional experiments would be needed to verify the clonality of isolated strains of blood culture and TPN. This information was not present in the analyzed processes.

In the study carried out on a national outbreak in Brazil in early 2013, several geographically distant states were involved. The authors analyzed strains of *R. radiobacter* isolated from patients who had received TPN using the PFGE (Pulsed Field Gel Electrophoresis) technique. They found that a bacterial strain referring to an inpatient patient a month before the outbreak started belonged to the same clonal group as the outbreak. This demonstrates that the outbreak started a month before Health Surveillance was notified. Additionally, this finding also shows that healthcare professionals did not immediately check the quality of TPN with the producing pharmacy when a patient had a bloodstream infection having received TPN, emphasizing, again, the need to raise healthcare professionals' awareness of this problem.^{23,24}

Considering the period and the contamination found, it is possible that the samples sent to INCQS in 2013 have involvement with an outbreak of infection already described in the scientific literature.²³ However, this fact cannot be stated so far, as molecular typing was not performed to verify the similarity between the bacterial strains detected at INCQS and those isolated from patients at the time of the referred outbreak.²³

Based on the present study, we verified the need for several adaptations of Ordinance 272/1998. Some countries, after problems caused by bacterial contamination in TPN, have made regulatory changes regarding the production and quality control of TPN. The supervision carried out by the state and municipal Health Surveillance agencies, in companies producing TPN, is also essential for the safety of these products. An effective supervisory program, in addition to ensuring the safety of patients who make use of them, can reduce the risk of bloodstream infection, improving clinical results and spending on hospital expenses.^{2,6,21,25}

Finally, this study took an unprecedented approach to show the relevance of TPN quality control for human health. It involves not only norms for the prescription, preparation, storage, transport and administration of this product, as described in the current regulation. In this study, several important technical aspects for microbiological assessment were highlighted, such as sampling, time from collection to analysis, detection techniques and identification of microorganisms that are not included in Ordinance 272/1998, needing to be included in the regulation for improvement of TPN quality.

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AUTHORS' CONTRIBUTIONS

Mariana Bruno Rodrigues Benitez and Verônica Viana Vieira contributed to the conception, design of the article, analysis, writing, revision and final approval of the article; **Célia Maria Carvalho Pereira Araujo Romão** contributed to the planning and design of the article, writing, review and final approval of the article.

All authors have approved the final version to be published and are responsible for all aspects of the work, including ensuring its accuracy and integrity.