ABSTRACT
Objective: To analyze the cost-effectiveness of the intravenous medication mixing center in reducing dose errors in the preparation of injectable medications in neonatal intensive care.
Method: mathematical model proposed in 2017 to assess cost-effectiveness by comparing two health technologies in hypothetical scenarios using the TreeAge® 2011 Pro Suite Software. A Monte Carlo simulation was used to analyze the robustness of the model.
Results: the model predicted that the intravenous medication mixing center was cost-effective, with a mean effectiveness of 0.96 in avoiding dose errors in intravenous drug administration, with an incremental cost-effectiveness ratio of R$26,785.61.
Conclusion: the use of an intravenous medication mixing center was the most cost-effective alternative, considering the willingness to pay assumed in the model. The study may contribute to reducing uncertainty in decision making regarding the incorporation of dose error reduction technologies in medication administration in pediatric and neonatal ICUs.

DESCRIPTORS: Medication errors; Patient safety; Cost-effectiveness analysis; Neonatal intensive care units; Evaluation of biomedical technology.


HOW TO REFERENCE THIS ARTICLE:

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CUSTO-EFETIVIDADE DA CENTRAL DE MISTURA DE MEDICAMENTOS INJETÁVEIS EM UNIDADE DE TERAPIA INTENSIVA NEONATAL

RESUMO
Objetivo: analisar o custo-efetividade da central de mistura intravenosa na redução de erros de doses no preparo de medicamentos injetáveis em terapia intensiva neonatal. 
Resultados: o modelo prediz que a central de mistura de injetáveis é custo-efetiva, com efetividade média de 0,96 para se evitar erros de dose na administração de medicamentos intravenosos, com razão de custo-efetividade incremental de R$ 26.785,61.
Conclusão: o uso da central de mistura intravenosa foi a alternativa mais custo-efetiva, considerando a disposição de pagar assumida no modelo. O estudo pode contribuir para reduzir incertezas na tomada de decisões acerca da incorporação de tecnologias para redução de erros de dose na administração de medicamentos em UTI pediátrica e neonatal.

DESCRITORES: Erros de medicação; Segurança do paciente; Análise de custo-efetividade; Unidades de terapia intensiva neonatal; Avaliação da tecnologia biomédica.

COSTO EFECTIVIDAD DE LA CENTRAL DE MEZCLA DE PRODUCTOS MEDICINALES INYECTABLES EN UNA UNIDAD DE TERAPIA INTENSIVA NEONATAL

RESUMEN:
Objetivo: analizar el costo efectividad de la central de mezcla intravenosa en la reducción de errores de dosis, en la preparación de medicamentos inyectables, en terapia intensiva neonatal.
Método: modelo matemático, propuesto en 2017, para evaluar el costo efectividad comparando dos tecnologías de la salud, en escenarios hipotéticos utilizando el programa Software TreeAge® Pro Suite 2011. La Simulación de Monte Carlo analizó el grado de robustez del modelo.
Resultados: el modelo predice que la central de mezclas de inyectables es costo efectivo para evitar errores de dosis en la administración de medicamentos intravenosos; la efectividad media fue de 0,96 y la razón de costo efectividad incremental de R$ 26.785,61.
Conclusión: el uso de la central de mezcla intravenosa fue la mejor alternativa costo efectiva, considerando la disposición de pagar asumida en el modelo. El estudio puede contribuir para reducir incertidumbres en la toma de decisiones acerca de la incorporación de tecnologías para reducción de errores de dosis, en la administración de medicamentos en UTI pediátrica y neonatal.

DESCRIPTORES: Errores de medicación; Seguridad del paciente; Análisis de costo efectividad; Unidades de terapia intensiva neonatal; Evaluación da tecnología biomédica.
INTRODUCTION

The medication process can be defined as a complex system in which errors can occur, causing avoidable patient injuries and expenses. The larger neonate is more susceptible due to various factors and particularities of the newborn (NB), such as the calculation of dose based on age, weight and physiological immaturity, which alters the capacity for absorption and excretion of drugs(1).

Possibly 66% of errors that occur in the Neonatal Intensive Care Unit (NICU) are drug related, with 38% being dosage errors(2). During some stages of the preparation and administration process, errors in administration (72-75%), documentation (17-21%), dispensing (5-58%) and prescription (3-37%) have been documented(3).

The Unit Dose Drug Distribution System (UDDDS) has enabled the pharmacotherapeutic monitoring of the user, as well as providing safe and traceable drug distribution. The medications are distributed in a ready-to-use form, according to the prescription and without the need for manipulation(4-7).

A breakthrough in the Hospital Pharmacy service is the Intravenous Medication Mixing Center, which can ensure the rational use of the medications, which are manipulated and dispensed individually by pharmacists, reducing errors and improving infusion safety(8).

According to Anvisa RDC No. 67/2007, drug manipulation should follow the Good Pharmacy Practice guidelines. Choosing this type of system can guarantee the quality of health care, reducing the chance of errors(9-10).

The American Society of Health-System Pharmacists (ASHP) recommends the use of unit dose distribution and the pharmacy intravenous drug preparation system to prevent medication errors in a hospital(11).

However, there are no studies that have evaluated the costs and consequences of incorporating this technology into the NICU. It seems relevant to evaluate the best strategy for mixing intravenous drugs in these units, as a way to contribute to the prevention and/or reduction of harm related to the infusion of medications.

The research question was: in the preparation of injectable drugs, is the intravenous medication mixing center cost-effective to reduce errors when compared to the preparation performed by nurses in the NICU? The aim of this study was to analyze the cost-effectiveness of the incorporation of the intravenous medication mixing center for the preparation of injectable drugs in an NICU.

METHOD

The cost-effectiveness assessment was performed from a mathematical model using the decision tree software. In mathematical modeling, the term scenarios is used to refer to hypothetical situations based on assumptions that may be similar to those that eventually happen in the real world. Therefore, no physical scenario was used in this study.

The parameters imputed into the model were based on a hypothetical cohort of patients and cost and effectiveness estimates, drawn from primary and secondary studies. There was no need for the Ethics Committee to appraise the study protocol, as it was mathematical modeling based on hypothetical data and theoretical assumptions.

Health Technology Assessment (HTA) is a comprehensive way to study the short- and long-term technical, economic and social consequences of the use of health technologies, as well as their direct and indirect effects(12-16).
Models are representations of reality and, in the context of cost-effectiveness analysis, can be very useful for providing data for making informed decisions. They are analytical tools that allow, from a base-case, health strategies to be compared. This modeling followed the recommendations of the Methodological Guideline for Economic Evaluation, of the Ministry of Health\(^\text{17}\).

In the design of the model, the study problem began with the possibility of manipulating intravenous medications in two different scenarios: in the reference scenario, in which the nurse manipulates the medications within the NICU, this being the usual standard in Brazil. Alternatively, the Intravenous Medication Mixing Center is used and the manipulation is performed by the Pharmacist, in a place designed for this purpose.

The base-case was composed of these two scenarios. In the reference scenario, the medication map is written according to a standard form in the sector, varying from hospital to hospital, generally containing the following information: name of mother and newborn, medication, prescribed dosage, administration route and time. Inconsistencies in the identification of the NB and medication data interfere with the Patient Safety dynamics proposed by the nine rights of medication administration for administration of the medication to the correct patient\(^\text{12-13}\).

Newborns are more vulnerable to misidentification due to their inability to participate in the identification process, cases of twins, similarity between infants in the first days of life, similarity in hospitalization registration numbers and surnames, and loss or removal of identification bracelets\(^\text{14-15}\).

In the alternative scenario, also hypothetical, the pharmacist uses equipment and software to manipulate the maps and prescriptions, in compliance with the Collegiate Board Resolution No. 67 of October 08, 2007 items 6.2.1 through 6.2.11, which establishes, among other things, that the physical area of the intravenous medication mixing center must be located, designed, constructed or adapted with appropriate infrastructure for the activities to be developed.

The room for the preparation and filling of sterile preparations must be independent and exclusive\(^\text{1-4}\). The room for cleaning and sanitizing pharmaceuticals, health products and packaging materials used in the preparation of intravenous mixtures has a Grade D rating (100,000 particles/cubic foot air). In the preparation areas all surfaces must be coated with a material that is resistant to sanitizing agents, which is smooth and impervious to prevent the accumulation of particles and microorganisms, and must have rounded corners\(^\text{1-3}\).

In both scenarios, with different probabilities and different outcomes, errors and successes may occur in the drug preparation. Adverse drug events (ADEs), specifically dosage errors in the preparation of the medication, were considered as complications in the proposed model (Figure 1). Therefore, the outcome of interest of this analysis was the avoidance of dose errors.

Figure 1 - Decision tree model structure. Rio de Janeiro, RJ, Brazil, 2017
Source: Author, with the aid of the TreeAge® software
Primary data from the reports generated by EpiMedSolutions and secondary data from a systematic literature review were used to estimate the effectiveness, and the Bank of Prices in Health and the State Department of Labor and Income to estimate the costs.

The uncertainties were addressed by probabilistic sensitivity analysis using Monte Carlo simulations (10,000 simulations), considering the cost variables, for which Gamma distributions were assigned, and the probability effectiveness variables, for which Beta distributions were assigned.

The following assumptions were considered in the model: the perspective was of the Brazilian Nation Health System (SUS); the time horizon was 1 year; and no discount or inflation rate was applied for the cost or effectiveness. The mean length of stay in the NICU was estimated to be 20 days\(^{15-18}\).

Each preterm infant receives 15 to 20 doses of injectable medication daily (mean of 18 doses)\(^{19}\) and between 15.0% and 69.6% of drug errors occur during the preparation phase. The effectiveness in the reference scenario was estimated at between 30.4% and 85.0% and in the alternative, between 63.5% and 81.1%\(^{4,20,23}\).

Dose error rates and increase in length of stay after the error occurred were 14% to 38% and 26%, respectively\(^{2,21,22}\). In the event of a serious adverse drug event, ICU hospitalization could last for a further 17.0 to 28.3 days\(^{24-25}\).

The daily costs ranged from R$3,002.40 to R$8,893.37 (State Department of Health - SES-RJ), and the cost with preventable adverse events, R$3,200.00 per day of hospitalization. For each error that resulted in a prolonged length of hospitalization, an additional 17 days were added to the total length of hospitalization\(^{26}\). The daily cost of the Intravenous Medication Mixing Center was R$475.92. This cost included the cost of 24 hours of work for 02 pharmacists that would prepare 18 doses of injectable drugs (daily mean number of doses given to the NB hospitalized in the NICU, as found in the literature) and the monthly cost of using the filter of the laminar flow cabinet.

The Willingness to Pay (WTP) was estimated at 01 GDP per capita R$28,105.41, considering 2016 (GDP per capita of US$8,649.95) and the exchange rate for the dollar on 12/29/2016, which was R$3.2492.

The TreeAge® 2011 Pro Suite software (TreeAge software, Willianstown, MA, USA) was used for the construction of the model, in the decision tree format and for the cost-effectiveness analysis.

**RESULTS**

The Intravenous Medication Mixing Center may be the best alternative to avoid intravenous drug preparation errors. The cost-effectiveness graph (Figure 2) reveals that it is possible, in the base-case, to achieve a mean effectiveness of up to 0.96 using the Intravenous Medication Mixing Center, at a cost ranging from R$17,400.00 to R$17,600.00.
An avoided ADE can represent a significant economy of resources and lives saved, given the potential for death related to these events. The cost-effectiveness analysis revealed an incremental cost-effectiveness ratio (ICER) of R$26,785.61, slightly below the willingness to pay threshold defined in the base-case.

The acceptability curve (Figure 3) shows that the probability of the Intravenous Medication Mixing Center being cost-effective is only greater from a willingness to pay of more than R$87,000.00, well above the WTP threshold assumed in the model (R$28,105.41). With the WTP assumed in the model, the probability of being cost-effective is just over 35%.
The probabilistic analysis carried out from 10,000 second order Monte Carlo simulations to address the uncertainties related to the variability of the parameters imputed in the model, considered a confidence interval, represented by the ellipse in the Scatterplot (Figure 4), of 95% and the WTP threshold, of R$56,000.00 (twice the GDP per capita that would be R$28,105.41).

It was possible to verify in the Scatterplot that the effectiveness of the Intravenous Medication Mixing Center ranged from 75% to 95% (blue circle on the graph), with little dispersion. Regarding costs, the dispersion was slightly higher, with a higher concentration of simulations between the ranges of R$10,000.00 to R$56,000.00. It also revealed a large dispersion in relation to the effectiveness of the traditional preparation performed by the Nurse (red triangle on the graph), ranging from 10% to 100%, with a higher concentration of simulations in the range of 50% to 100%. Regarding the costs, the dispersion was very similar to the dispersion observed in the Intravenous Medication Mixing Center, however, with a slightly higher variability.

The probabilistic analysis showed that the Intravenous Medication Mixing Center is very likely to be actually more cost-effective than the traditional preparation by the Nurse, confirming what had already been revealed by the acceptability curve, which showed that the Intravenous Medication Mixing Center becomes more likely to be cost-effective compared to the traditional preparation performed by the Nurse, from a threshold of approximately R$10,000.00.

**DISCUSSION**
Economic evaluation in health is a type of research that uses a slightly unconventional methodological approach and design that are difficult for those unaware of the approach to interpret. In Brazil, this type of study is still very incipient and scarce.

One of the major challenges for the SUS is the implementation of solutions with high functional impact, coupled with low operating costs, which can contribute to improving the quality of the sector, facilitating access and providing organization and agility in the health care. Resistance to the need for great financial investment, without considering the justifiable benefits offered, has shown the non-occurrence of the implementation of intravenous medication mixing centers, one of the requirements in the adoption of the unit dose distribution system.

In this evaluation, the results of a doctoral thesis, developed by a nurse with expertise in the area of neonatology, it was possible to estimate the ICER of the use of the Intravenous Medication Mixing Center as a cost-effective alternative, predicted in the decision tree model. This should therefore be incorporated as the best technology option to avoid dose errors in NICU intravenous drug preparation, however, considering the willingness to pay threshold.

The American Society of Health-System Pharmacists (ASHP) cites the use of unit dose distribution and the pharmacy intravenous drug preparation system as important recommendations to prevent medication errors in a hospital(11).

The results of this study should serve as a warning for nurses and health service managers to rethink traditional intravenous drug preparation systems, as they bring into question the preparation of injectable drugs by the nursing team. This is from both a technical perspective and from a legal perspective, considering the Law of Professional Practice of Nursing Professionals, the physical spaces intended for manipulation and preparation, and the technical skill and knowledge that may lead to the incorrect use of the material, compromising safety, effectiveness, effectiveness and efficiency of preparing the doses of these drugs.

The existence of the Intravenous Medication Mixing Center requires greater interaction of the multidisciplinary team in the unit, as the pharmacist discusses with the medical team the prescribed drug and later with the nursing team, the drug having been previously prepared, providing an improvement in the quality of the patient care(27).

Economically, the centralization of the preparation of intravenous medications influences the cost reduction, especially with the rational use of the drugs. Studies conducted by the Instituto da Criança showed that, with the availability of unitarized medications, pharmacies can reduce internal consumption by up to 35%(5).

The expenses related to the implementation of the Intravenous Medication Mixing Center, in relation to the total costs of the hospital, can represent around 5% to 20%, with an average growth of 25% per year. Therefore, the existence of drug distribution systems that rationalize this process is of utmost importance(28).

In practice, the implementation of the Intravenous Medication Mixing Center can directly impact the nursing staff. In the traditional scenario, where the nurse prepares the medicine within the NICU, the extremely agitated environment due to the complexity of the care can lead to drug administration errors. In this situation, it is necessary to provide a safe environment for the preparation of the medications. The Intravenous Medication Mixing Center can reduce the time spent by nurses for the administration of injectable medicines from 8 to 2 hours, providing these professionals with time to perform their activities more safely(4).

For the clients, in this case the great majority being premature NBs, the implantation of the Intravenous Medication Mixing Center represents greater safety and quality in the treatment. For the institution it provides a substantial savings and for the nursing professionals, an expansion of knowledge, greater integration of the team with safer
service and more time to spend at the bedside of the patient. Specifically in the Pharmacy, this implementation allows the return of the activity of drug preparation, which is in fact its responsibility.

As with any economic analysis developed from mathematical modeling, structural, analytical and parametric uncertainties present in the model can impose limitations, especially regarding the external validity and extrapolation power of its results.

Since the models are representations of reality and, as such, are created in an attempt to simulate scenarios that come as close as possible to the real world, it must be highlighted that one of the main limitations of this and any other modeling for economic analysis in health is the difficulty of interpretation of the results by managers and health providers that want data to support their decisions based on the results. The difficulty in interpreting the ICER is a good example.

In this economic evaluation, the model predicts that the cost to additionally avoid a dose error in the preparation of injectable drugs (ICER) is R$26,785.61, using the intravenous medication mixing center. At first this cost seems extremely high, however, it must be considered that, in the evaluated model, the total cost of the alternative scenario (scenario that uses the intravenous medication mixing center) included the cost of equipment acquisition and work necessary on the physical space, for the implantation of the center.

Budgetary impact analysis, which could not be done due to the time available for the conclusion of the thesis, could facilitate and better guide the interpretation of the results of this evaluation. The impossibility of realizing the budgetary impact should therefore be considered a limitation of the study. It is important to emphasize that any attempt to extrapolate the results of this evaluation to scenarios that may be very different from the assumptions assumed in the model, must be made with caution.

Economic analyses in health and its different types of studies and approaches is a unique opportunity for the nursing field to expand the scope of methodological approaches in the area. The difficulties encountered in estimating the effectiveness of the scenarios analyzed in the study should be mentioned, which was due to the scarcity of studies addressing this theme, especially ones developed in Brazil.

**CONCLUSION**

The incremental cost-effectiveness ratio was R$26,785.61, which allows the inference that, in the base-case, the use of the intravenous medication mixing center proved to be cost-effective, considering the willingness to pay.

Extrapolation of the results of this analysis should be performed with caution, given the structural and parametric uncertainties of the model that were not addressed in the sensitivity analysis. Regarding the internal validity of the results of the studies used as assumptions in the model, considering a scale for valorizing the reliability of the scientific evidence, although the value of observational studies and reviews may be reduced, in the absence of more consistent data and for effectiveness evaluation their contribution was very useful in the model.

This economic analysis may represent a new perspective for addressing the problem of ADEs related to the preparation of intravenous drugs in NICUs, normally approached in the scientific literature from two focuses that are almost always dissociated from each other. The first based on the concern with increasing ADE rates in these units, which has contributed to the advance of scientific knowledge about the best strategy to reduce them, and the second related to increasing hospital costs associated with the incorporation of technologies and with the adverse event itself, becoming explicit in the growing number of studies published on the subject. Their results, however, do not have the strength of
evidence to provide solid support for behaviors regarding this situation, and in Brazil, they are still incipient.

By avoiding ADEs, gains and benefits are provided for the population studied, with the size of this benefit being directly proportional to the size of the effectiveness. The study showed that, when using the Intravenous Medication Mixing Center, the cost-effectiveness is higher when compared to the scenario where the nurse prepares the intravenous drugs in the NICU space.

As a necessary complement to the study in order to provide data for informed decision making, it is suggested that budget impact analyses of the adoption of the most cost-effective strategy be carried out according to the target population and the institutional reality, which was not possible in this economic analysis.

The study may contribute to reducing uncertainty in decision making regarding the incorporation of dose error reduction technologies in medication administration in pediatric and neonatal ICUs.

REFERENCES


10. Silva MJS da, Magarinos-Torres R, Oliveira MA, Osorio-de-Castro CGS. Avaliação dos serviços de


12. Vásquez AR, Montoya JIE. Apreciaciones de trabajadores de la salud sobre la implementación del sistema de seguridad en la utilización de medicamentos. Rev Univ. salud. [Internet]. 2017 [access 01 maio 2019];19 (1). Available at: http://dx.doi.org/10.22267/rus.171901.64.


