Review Article

Comprehensive economic studies on sickle cell anemia treatments

Estudos econômicos completos sobre tratamentos da anemia falciforme

Estudios económicos completos sobre tratamientos para la anemia falciforme

Andréia Insabralde de Queiroz Cardoso[1] https://orcid.org/0000-0002-9431-7484
Marcos Antonio Ferreira Júnior[1,2] https://orcid.org/0000-0002-9123-232X
Carolina Mariano Pompeo[1] https://orcid.org/0000-0003-4454-0140
Caroline Neris Ferreira Sarat[1] https://orcid.org/0000-0003-1232-2026
Mayk Penze Cardoso[1] https://orcid.org/0000-0003-2130-5738
Maria Lúcia Ivo[1] https://orcid.org/0000-0003-2993-4758

How to cite:
Cardoso AI, Ferreira Júnior MA, Pompeo CM, Sarat CN, Cardoso MP, Ivo ML, et al. Comprehensive economic studies on sickle cell anemia treatments. Acta Paul Enferm. 2021;34:eAPE01641.

DOI
http://dx.doi.org/10.37689/acta-ape/2021AR01641

Keywords
Sickle cell disease; Hemoglobin, sickle; Health economics; Costs and cost analysis; Cost-benefit analysis

Descritores
Anemia falciforme; Hemoglobina falciforme; Economia da saúde; Custos e análise de custo; Análise custo-benefício

Descriptores
Anemia de células falciformes; Hemoglobina falciforme; Economía de la salud; Costos y análisis de costo; Análisis costo-beneficio

Submitted
July 8, 2019

Accepted
June 29, 2020

Corresponding author
Andréia Insabralde de Queiroz Cardoso
E-mail: andreia.cardoso@ufms.br

Abstract

Objective: To analyze complete economic studies focusing on sickle cell anemia treatments.

Methods: Integrative literature review developed by collecting data in the electronic databases National Library of Medicine - Medline via PubMed; Elsevier's Scopus; Current Index to Nursing and Allied Health Literature; Science Direct and Web of Science with descriptors indexed in Medical Subject Headings. The studies were selected by the relevance test and analyzed according to the classification of economic analyses in health and the classification system of evidence quality and strength of recommendations.

Results: Nine articles were part of this review, seven of which were retrieved from *Elsevier's Scopus* and two from Medline via PubMed. All articles reported on studies focusing on the perspectives of using hydroxyurea and blood transfusion in the treatment of sickle cell anemia.

Conclusion: No studies were identified that were conducted in Brazil and involved this type of analysis for sickle cell anemia. Much remains to be done worldwide to assess existing technologies, reassess the technologies currently used and implement continuous diagnosis and treatment, by means of a system that guarantees an active and efficient care network for the patients.

Resumo

Objetivo: Analisar os estudos econômicos completos com enfoque nos tratamentos da Anemia Falciforme.

Métodos: Estudo de revisão integrativa de literatura desenvolvido mediante coleta de dados nas bases eletrônicas *National Library of Medicine* - Medline via PubMed; *Elservier's Scopus*; *Current Index to Nursing and Allied Health Literature*; *Science Direct* e *Web of Science* com descritores indexados no *Medical Subject Headings*. Os estudos foram selecionados pelo teste de relevância e analisados de acordo com a classificação das análises econômicas em saúde e o sistema de Classificação da qualidade das evidências e a força das recomendações.

Resultados: Fizeram parte desta revisão 09 artigos, dos quais sete recuperados na base *Elservier's Scopus* e dois na Medline via PubMed. Todos estudos com enfoque nas perspectivas do uso da Hidroxiureia e da transfusão sanguínea no tratamento da Anemia Falciforme.

Conclusão: Não foram identificados estudos realizados no Brasil com este tipo de análise para Anemia Falciforme. Há muito a ser feito mundialmente para avaliação das tecnologias vigentes, reavaliação das utilizadas atualmente e implementação de diagnóstico e tratamento contínuo, com um sistema que garanta uma rede de atenção ativa e eficiente aos pacientes.

[1]Universidade Federal do Mato Grosso do Sul, Campo Grande, MS, Brazil.
[2]Universidade Federal do Rio Grande do Norte, Natal, RN, Brazil.
Conflicts of interest: nothing to declare.

Resumen

Objetivo: Analizar los estudios económicos completos con enfoque en tratamientos para la anemia falciforme

Métodos: Estudio de revisión integradora de la literatura desarrollado mediante la recolección de datos en las bases electrónicas *National Library of Medicine* - Medline vía PubMed; *Elservier's Scopus*; *Current Index to Nursing and Allied Health Literature*; *Science Direct* y *Web of Science* con descriptores indexados en *Medical Subject Headings*. Los estudios fueron seleccionados mediante la prueba de relevancia y analizados de acuerdo con la clasificación de análisis económicos en salud y con el sistema de clasificación de la calidad de las evidencias y la fuerza de las recomendaciones.

Resultados: Nueve artículos formaron parte de esta revisión, de los cuales siete fueron encontrados en la base *Elservier's Scopus* y dos en Medline vía PubMed. Todos son estudios completos con enfoque en las perspectivas del uso de hidroxiurea y transfusión sanguínea para el tratamiento de anemia falciforme.

Conclusión: No se identificaron estudios realizados en Brasil con este tipo de análisis de anemia falciforme. Hay mucho por hacer a nivel mundial para evaluar las tecnologías vigentes, revaluar las que se utilizan en la actualidad e implementar el diagnóstico y tratamiento continuo, con un sistema que garantice una red de atención activa y eficiente para los pacientes.

Introduction

Sickle Cell Anemia (SCA) is the most severe form of sickle cell disease, involving clinical conditions resulting from genetic, hereditary and recessive changes with structural variations of hemoglobin. In this condition, the low oxygen pressure leads to erythrocyte alteration and the polymerization of hemoglobin S (HbS), which becomes drepanocyte or sickle-shaped.[1]

The clinical effect on the alteration of HB S culminates in hemolysis or vaso-occlusion, with inflammatory processes and tissue lesions in the first years of life, which tend to enhance and increase the severity over time years, when they injure tissues and organs, a condition that can be fatal.[2]

SCA is known as the most common monogenic hereditary disease in Brazil. Its prevalence was described as higher in the North and Northeast, affecting between 6% and 10% of the population, against only 2 to 3% in the South and Southeast, respectively.[3]

The highest mortality rate in hospitalizations due to SCA occurs in young adults and children, mostly due to heart disease, sepsis, stroke, acute respiratory failure and multiple organ failure.[4,5]

One treatment option is allogeneic hematopoietic stem cell transplantation, with limited donor availability for less than 14% of the patient, being an unconventional treatment. The main alternatives are chronic blood transfusions or exchange transfusions as adjuvant treatment or the use of non-curative drug therapy with hydroxyurea (HU), approved worldwide.[6]

It is noteworthy that the challenge to improve the treatment of SCA patients consists in manager's planning, based on economic assessments to improve care. Thus, the scientific evidence guides decision-making for reliability, recovery, diagnosis and treatment accessible to the various populations worldwide.[5,7]

There are recommendations for new cost-effectiveness research from the social perspective, with a view to better grounding the care, diagnosis, treatment, direct and indirect costs related to SCA.[8]

This integrative review is part of a research to analyze the cost-effectiveness of the treatment of SCA patients using HU, in which a computer modeling system will be developed to prospect a hypothetical cohort in order to analyze the need for investment, improvements in services and to serve as evidence for managers' proper decision making.

Thus, this review aims to analyze the economic studies that are considered complete and are focused on the treatments used in SCA patients.

Methods

This is an integrative literature review, a strict method with defined criteria that is used in evidence-based practice. The stages followed were: problem identification and elaboration of the guiding question; literature search with application of inclusion and exclusion criteria; data collection using previously structured tool; data analysis and presentation of the review.[9,10]

To elaborate the guiding question, the PVO strategy was adopted,[11] in which the letter P refers to the population/context (patients with sickle cell anemia), the letter V deals with the variable of interest (complete economic studies) and the letter

O, refers to the *outcome* (treatment of sickle cell anemia). Thus, the guiding question was defined: "What complete economic studies have been conducted focused on the treatments of patients with sickle cell anemia?".

Two independent reviewers undertook the search between January and February 2019, using the proxy of the Federal University of Rio Grande do Norte, to access the CAPES journal portal (<http://www-periodicos-capes-gov-br.ez51.periodicos.capes.gov.br/>).

The electronic databases used were the National Library of Medicine (Medline via PubMed); Elsevier's Scopus (SCOPUS); Current Index to Nursing and Allied Health Literature (Cinahl); Science Direct and Web of Science.

The following controlled descriptors indexed in *Medical Subject Headings* (MeSH) were used: 1# (Anemia, Sickle Cell); Entry Terms – 2# (Sickle Cell Disease); 3# (Costs and Cost Analysis); Entry Terms – 4# (Cost Analysis); 5# (Cost Benefit Analysis); Entry Terms – 6# (Cost Effectiveness). To execute the database search, the descriptors were crossed twice (A and B), using the Boolean operators AND and OR, namely: *A)* #1 OR #2 AND #3 OR #4 e *B)* #1 OR #2 AND #5 OR #6.

Articles were included in any language, without time limit, complete and relevant to the research proposal. Duplicate articles were excluded, which were considered only once, as well as reviews, editorials, letters to the editor, abstracts, expert opinions, reviews, books, theses, dissertations, monographs and course conclusion papers.

To preselect the articles, the relevance test was applied, which consists of inclusion and exclusion criteria, reading the titles and abstracts. For the selected articles, we read the full text and extracted the data. For the analysis, we used a Microsoft Excel® spreadsheet, according to The Critical Evaluation of Evidence: Part I.[12]

To analyze the research, we used the Classification of Economic Analyses in Health[13] and, for the quality of evidence, the Classification of Quality of Evidence and Strength of Recommendations (GRADE).[14]

Data collection included four stages, namely: identification, selection, eligibility and inclusion, represented in Figure 1.[15]

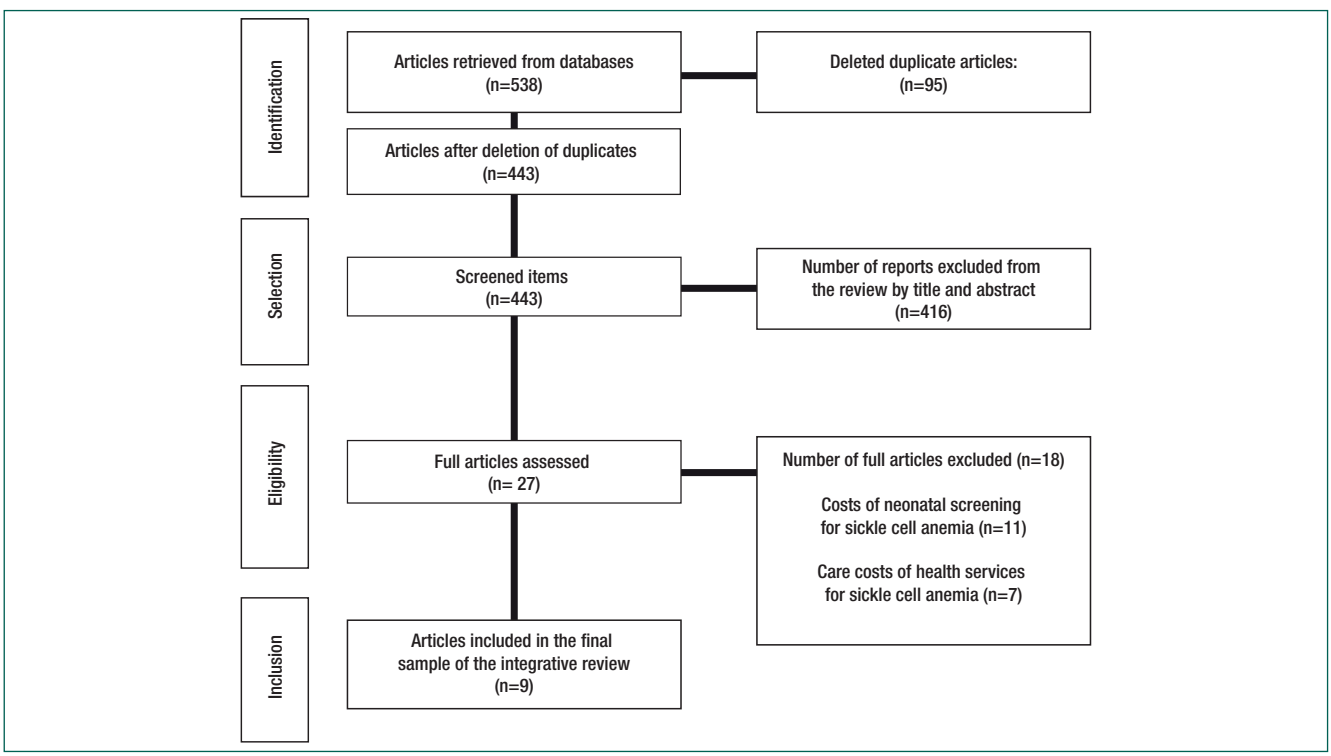

Figure 1. Phases of the search process and composition of the final sample of cost-effectiveness studies focused on sickle cell anemia treatment.

Results

In the analyzed databases, initially, we retrieved 443 articles, all screened by reading their titles and abstracts. The selection based on the relevance test and careful analysis resulted in nine articles for the final sample, seven of which from the Scopus database and two from Pubmed.

The countries of origin of the studies were the United States of America with four publications (44.50%), the United Kingdom with two publications (22.20%), followed by Jamaica, Uganda and Puerto Rico with one publication each (11.10%).

Two journals stood out, the *American Journal Hematology* and *Transfusion* with two publication each (22.25%). One publication (11.10%) was found in *BMC Health Services Research, Pediatric Blood Cancer, European Journal of Haematology, Health Technology Assessment and Boletín de la Asociación Médica de Puerto Rico*. The studies in the final sample were published in English, initially dating back to 2000, with an increase in studies as from 2010.

As for the type of study, [13] five dealt with cost-benefit (55.56%), two cost-utility (22.22%), one cost-minimization (11.11%) and another cost-effectiveness (11.11%). Computer modeling simulations with the Markov model were used in four studies (44.44%) and one Monte Carlo simulation (11.11%). Two studies (22.22%) were based on randomized clinical trial, three (33.33%) were based on retrospective cohort data and four (44.45%) performed a hypothetical computational cohort.

When we analyzing the level of evidence by means of the GRADE system,[14] eight study was considered moderate level (88.89%) and one low level (11.11%).

The treatments of SCA patients found in the studies were blood transfusion in five stud-

Chart 1. Characterization of cost-effectiveness studies for the treatment of patients with Sickle Cell Anemia and respective strengths of recommendation (N = 9)

Author/year	Type of economic analysis	Classification GRADE	Methodological design	Recommendations and limitations
Moore et al., 2000[16]	Cost-effectiveness	Moderate	Based on a randomized controlled clinical trial in pediatrics (N = 299). Wilcoxon test. Control group (N = 147) and HU Group (N = 152)	HU decreased painful seizures in sickle cell anemia (SCA) and reduced hospitalization costs, a fact that compensated for the use, but requires clinical monitoring and investigations. Limitations: quality of life or years of life saved were not evaluated.
Stallwort; Jerrell; Tripathi, 2010[17]	Cost-effectiveness	Moderate	Based on pediatric retrospective cohort (N = 523). Rate ratio. Control group (N = 348) and HU Group (N = 175)	Need for new long-term observational research for the use of HU in children. Lesser pain episodes, hospitalizations and total costs. Limitations: retrospective data, not controlled, without interviews and analysis of dropouts.
Prados et al., 2010[18]	Cost-minimization	Low	Based on pediatric retrospective cohort (N = 14). Non-paired *t* test. Pump method (N = 10) group and automated blood cell separator (N = 4) group	Exchange transfusion using a pump is realistic, economical and effective. Ideal for social contexts with difficulties. Limitations: retrospective data from a hospital and small sample.
Cherry et al., 2012[19]	Cost-utility	Moderate	Pediatric hypothetical cohort (N = 1000). Markov model. Quality Adjusted Life Years (QALYs). Transcranial Doppler (DTC) altered with transfusion group and DTC altered without transfusion group.	The practice of DTC and identification of the risk for stroke with blood transfusion seems to be cost-effective, improving the living and development condition. Limitations: few clinical data related to blood transfusion in stroke prevention.
Spackman et al., 2014[20]	Cost-utility	Moderate	Based on a randomized, adult and pediatric study (N = 70). Monte Carlo simulation. QALYs Preoperative blood transfusion group and control group.	Preoperative blood transfusion seems to be cost-effective in low-cost and moderate-risk surgeries. Increased acute chest syndrome in control group with direct effects in the short term. Limitations: number of patients, lack of QALYs in children.
Kacker et al., 2014[21]	Cost-effectiveness	Moderate	Hypothetical cohort (N = 8000). Markov model. Prospective antigen matching group, history-based antigen group, perfect matching group and imperfect antigen matching group.	A specific screening test for alloimmunization, even if imperfect could provide support for clinical benefits in blood transfusion. Limitations: simplified alloimmunization model, did not incorporate dynamic population and represents local realities.
Kacker et al., 2014[22]	Cost-effectiveness	Moderate	Hypothetical cohort (N = 8500). Markov model. Antigen group based on history and prospective antigen matching group.	The cost of specific antigen tests for alloimmunization would be high. Need for research in the area. Limitations: simple model, underestimated costs, no indirect costs.
Cunningham-Myrie et al., 2015[23]	Cost-effectiveness	Moderate	Based on a pediatric cohort study (N = 42). Incremental cost-effectiveness and student's *t* test. Control group (N = 32) and hydroxyurea group (N = 10).	HU is cost effective for preventing recurrent strokes. Can be beneficial in environments with limited resources. Limitations: analysis restricted to direct costs, without indirect costs.
Kuznik et al., 2016[24]	Cost-effectiveness	Moderate	Pediatric hypothetical cohort (N = 228,169). Markov model and disability-adjusted life years (DALYs). Control group and neonatal screening group and prophylactic intervention.	Neonatal screening and prophylactic prevention would be cost-effective in some countries with higher incidence rates of the disease. Specialized diagnosis and treatment centers are needed. Limitations: non-generalizable estimates and costs. Did not observe the intervention throughout life.

ies (55.56%), drug treatment in three other studies (33.33%) and one study focused on neonatal screening for SCA and the treatment (11.11%). Pediatric patients were the most investigated target population with six studies (66.67%).

Discussion

The studies analyzed in this review demonstrated that economic assessments are recently used tools and are important for prospecting the potential risks, benefits and costs arising from the treatment of SCA patients.

Further research at this level will support the development of effective guidelines as references for a structured care network for SCA patients.[16-18,25]

All studies analyzed were economic evaluations, although only five used the computer modeling system for data analysis, which evidences that this is a relatively new area. Using to the GRADE system, we classified eight studies as moderate, which means that future studies may modify the confidence in the referred estimated effect. Several authors have focused on these allusions in different studies.[17,20,23,25]

New research should consider the social conditions, background and form of access to specialized care for the treatment of SCA patients.[18,24] Currently, sociodemographic conditions still interfere in the late diagnosis and, consequently, in the treatment of patients, a fact that alerts to the strengthening of health management actions.[26]

Both the diagnosis and the prophylactic and drug treatment of SCA patients are still considered a public health problem in several countries, especially in some countries of Sub-Saharan Africa. Improving child survival and interventions should be reconsidered. In some areas, life expectancy is estimated at 1.7 years for children with SCA, or who die even before getting diagnosed.[24]

Economic studies involving hydroxyurea

After introducing the use of HU in the treatment of children with SCA, a decrease in the number of hospitalizations, recurrent painful crises and complications of the disease was perceived.[8,16,17,27]

Although the studies analyzed in this review did not evaluate the improvement in the quality of life and the years of life saved, they pointed to the improvement of children's clinical condition. The outpatient, inpatient and emergency service costs decreased after two to three years of treatment, from US$ 12,842.00/year/patient to US$ 8,839.00 in the third year.[17] This fact was also appointed in another study that reported a total drop in annual expenses by US$ 5,210.00 per pediatric patient treated with HU.[16]

It is important to implement the use of HU in children with SCA, as it is a feasible, viable and effective practice to prevent future complications. Nevertheless, health services should conduct and monitor this practice well and prospectively from birth to avoid treatment losses and complications.[8,27]

The use of HU is also reported as positive to reduce recurrent strokes and death in children with SCA, being described as cost-efficient and with benefits for society in terms of maintaining their productivity capacity in the stages of life. But it is known that the treatment of choice is blood transfusion for the prevention of recurrent stroke in children.[23] There is currently no strong evidence to guarantee the use of HU in stroke prevention.[28]

New studies are needed for the implementation of public policies that enhance bone marrow transplantation in SCA patients, as HU is considered a palliative rather than curative treatment. [16] Nevertheless, in some countries, not even an effective diagnosis is reached and infant mortality is high and demonstrates socioeconomic disparities.[24]

Economic studies involving blood transfusion

The treatment with traditional or exchange blood transfusion is intended to decrease HbS levels. This method is discussed as safe and reduces the risks of iron overload, hyperviscosity and hypocalcemia, among other changes.[29,30]

The automated exchange transfusion technique using the "*pump method*" is a realistic, safe and effective procedure, more feasible than automated apheresis systems, especially in remote locations with limited geographical, technological and financial resources.[18] In 2017, a study analyzed the

new automated apheresis system for incorporation in England, reducing the treatment costs of SCA children who require blood transfusion by £ 12.9 million (US$ 16.3 million) per year.[30]

The cost-benefit relationship of DTC to identify high stroke risks in children over two years of age was described, using prophylaxis by means of blood transfusions.[19] Children without earlier long-term transfusions and diagnosed as at risk for strokes need to be analyzed, whose risk would probably drop when using prophylactic transfusions. The risks and adverse effects of chronic transfusions should be considered though, as no time limit is set for this type of treatment, nor interruption when the DTC tests are normalized.[23,28]

Preoperative blood transfusion was indicated for SCA patients undergoing low to moderate risk surgery, considered in the study as a cost-effective procedure.[20] There is not enough evidence though as to whether this conduct is an effective indication for SCA patients who will undergo surgery, so further research should be developed.[25]

The articles on alloimmunization resulting from blood transfusions in SCA patients highlighted important points. A specific phenotyping test for alloimmunization, even if imperfect, could provide clinical benefits and be cost-effective. Safety is a top priority in transfusion services, but it requires investment in technologies for quality assurance when compared to other health areas.[21,22] A long course is needed to reduce the prevalence of red blood cell alloimmunization, as research in this scenario tends to be cost-effective.[31]

Conclusion

We did not identify research related to complete economic studies conducted in Brazil with this focus on SCA patients. The studies focused on HU and blood transfusion treatments, with technologies to be implemented and structured in health services. Much remains to be done to assess the existing technologies, reassess the technologies currently used and implement early and continuous diagnosis and treatment, using a system that guarantees an active and efficient care network for SCA patients. Therefore, comprehensive and robust research should be developed on the direct and indirect financial resources related to SCA, aiming to consider the context of patients, their families and society.

Acknowledgements

The authors are grateful for the support of the Interdisciplinary Study Group on Sickle Cell Disease - NEIDF at the Federal University of Mato Grosso do Sul. This study was developed with funding from the Federal University of Mato Grosso do Sul, the Coordination for the Improvement of Higher Education Personnel-Brazil (CAPES) - Funding Code 001 and the Mato Grosso do Sul Support Foundation for the Development of Education, Science and Technology (FUNDECT). Obtained through FUNDECT call 06/2017 - UNIVERSAL-MS, under protocol 39136.570.1362.14022018.

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