REVIEW ARTICLE

REVISTA ENFERMAGEM ATUAL IN DERME

AUTOLOGOUS BLOOD CLOT THERAPY IN WOUND HEALING: SCOPE REVIEW

TERAPIA DO COÁGULO SANGUÍNEO AUTÓLOGO NA CICATRIZAÇÃO DE LESÕES: REVISÃO DE ESCOPO

TERAPIA DO COÁGULO SANGUÍNEO AUTÓLOGO NA CICATRIZAÇÃO DE LESÕES: REVISÃO DE ESCOPO

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ABSTRACT
Objective: To map and summarize scientific evidence on autologous blood clot therapy in wound healing. **Method:** This is a five-stage scope review, carried out in the Virtual Health Library (VHL) databases/search engines, PubMed, Google Scholar, Scientific Electronic Library Online (SCIELO) and in the Theses and Dissertations Portal of the Coordination for the Improvement of Higher Education Personnel (CAPES). The controlled descriptors were "healing" and "wounds and injuries" and the uncontrolled Autologous Blood Clot Therapy", with its derivations in English and Spanish. Articles in the last 10 years were included, and duplicate articles or articles that were not available in full were excluded. For the extraction, a synoptic table was built and the data were analyzed descriptively. **Results:** 246 publications were identified and the final sample consisted of 16 publications. The year 2022 was the one with the highest number of publications (5;33.4%), 15 (93.7%) studies were in English and 12 (75.0%) in US journals. No studies were located in Brazil on the subject. It was found that 11 (68.7%) studies evaluated the effect of therapy, of which 6 (37.5%) had a quasi-experimental design, three (18.7%) were case studies and two (12.5%) were %) case series study. **Conclusions:** The article achieved its objectives by mapping the scientific evidence on the subject, demonstrating that the therapy has good effectiveness in the treatment of pressure injuries. However, there are limitations due to the lack of research with methods with a higher level of evidence and with larger samples.
Keywords: Wound Healing; Wounds and Injuries; Therapeutics; Review; Nursing.

RESUMEN
Objetivo: Mapear y resumir la evidencia científica sobre la terapia de coágulos sanguíneos autólogos en la cicatrización de heridas. **Método:** Revisión de alcance en cinco etapas, realizada en las bases de datos/buscadores de la Biblioteca Virtual en Salud (BVS), PubMed, Google Scholar, SCIELO y en el Portal de la Coordinación para la Perfeccionamiento del Personal de Educación Superior (CAPES). Los descriptores controlados fueron "cicatrización" y "heridas y lesiones" y la no controlada Terapia de Coágulos Autólogos, con sus derivaciones en inglés y español. Se incluyeron articulos publicados en los últimos 10 años y se excluyeron los duplicados o que no estuvieran disponibles en su totalidad. Para la extracción se construyó un cuadro sinóptico y los datos se analizaron descriptivamente. **Resultados:** se identificaron 246 publicaciones y la muestra final estuvo conformada por 16 estudos. El año 2022 fue el de mayor número de publicaciones (5;33,4%), 15 (93,7%) estudios fueron en inglés y 12 (75,0%) en revistas estadounidenses. No se localizaron estudios en Brasil. Se encontró que 11 (68,7%) estudios evaluaron el efecto de la terapia, de los cuales 6 (37,5%) tuvieron un diseño cuasi-experimental, tres (18,7%) fueron estudios de casos y dos (12,5%) fueron estudios de series de casos. **Conclusiones:** El artículo logró sus objetivos al mapear la evidencia científica sobre el tema, demostrando que la terapia tiene buena efectividad en el tratamiento de las lesiones por presión. Sin embargo, existen limitaciones por la falta de investigaciones con métodos con mayor nivel de evidencia y con muestras más grandes.
Palabras clave: Cicatrización de Heridas; Heridas y Lesiones; Terapéutica; Revision; Enfermeria.

RESUMO
Objetivo: Mapear e sumarizar evidências científicas sobre a terapia do coágulo sanguíneo autólogo na cicatrização das lesões. **Método:** Trata-se de uma revisão de escopo construída em cinco etapas, realizada nas bases/motores de busca Biblioteca Virtual em Saúde (BVS), PubMed, Google Acadêmico, Biblioteca Scientific Electronic Library Online (SCIELO) e no Portal de Teses e Dissertações da Coordenação de Aperfeiçoamento de Pessoal de Nível Superior (CAPES). Os descritores controlados foram "cicatrização" e "ferimentos e lesões" e o não controlado Terapia do Coágulo Sanguíneo Autólogo", com suas derivações em inglês e espanhol. Foram incluídos artigos publicados nos últimos 10 anos, e excluídos os duplicados ou que não estivessem disponíveis na íntegra. Para a extração foi construído um quadro sinóptico e os dados foram analisados de forma descritiva. **Resultados:** Foram identificadas 246 publicações e a amostra final foi composta por 16 publicações. O ano de 2022 foi o que apresentou maior número de publicações (5;33,4%), 15(93,7%) estudos estavam em inglês e 12(75,0%) em revistas dos Estados Unidos. Não foram localizados estudos no Brasil sobre o tema. Verificou-se que 11(68,7%) estudos avaliaram o efeito da terapia, dos quais 6(37,5%) tiveram delineamento quase-experimental, três (18,7%) foram estudo de caso e dois (12,5%) estudo de série de casos. **Conclusões:** O artigo atingiu os objetivos ao mapear as evidências científicas sobre a temática, demostrando que a terapia possui boa efetividade no tratamento de lesões por pressão. Contudo, há limitações pela falta de pesquisas com métodos com maior nível de evidência e com amostras maiores.
Palavras-chave: Cicatrização; Ferimentos e Lesões; Terapêutica; Revisão; Enfermagem.

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INTRODUCTION

Chronic and complex wounds are lesions that are difficult to resolve, resulting from trauma or clinical conditions, whose healing process exceeds four to six weeks. They cause physical and psychological suffering for the patient, in addition to expenses for the health system, since they are long and costly treatments, especially in cases of infections by multidrug-resistant germs and/or bone involvement. Among the wounds that are difficult to heal are pressure injuries (LP), diabetic foot ulcers, infected surgical wounds, among others[1].

The incidence of PI among chronically ill patients has been a source of concern. PI is defined as damage that compromises the skin and adjacent tissues due to excessive pressure in areas over bony prominences, being related to intrinsic and/or extrinsic factors(1). They are progressively classified according to the degree of complexity, and may affect structures such as muscles, tendons and bones[2,3].

This type of injury is considered an incident related to health care and there are alarming data about the problem. The National Health Surveillance Agency (ANVISA) published a technical note in 2017, where it demonstrated the events reported from January 2014 to July 2017, with a total of 134,501 reported incidents, of which 23,722 (17.6%) corresponded to to PI notifications, becoming the third type of event frequently notified by patient safety centers. Of the 3,771 events that should never have occurred, 72.6% (2,739) were Stage 3 LP and 22.0% (831) were the result of Stage 4 LP[4].

Another type of chronic injury that is difficult to heal is ulcers resulting from diabetic foot. It is characterized by the destruction of the cutaneous tissue with the presence of infection and ulceration, associated with neurological disorders and peripheral arterial disease. The annual incidence of diabetic foot ulcers reaches 2% and people with Diabetes Mellitus (DM) have a 25% risk of developing foot ulcers throughout their lives. Diabetic foot ulcers are responsible for 50 to 70% of lower limb amputations, causing disability and affecting the capacity for daily activities of these individuals[5,6].

Faced with the seriousness of the problem generated by chronic and complex wounds, several therapeutic options have emerged to provide an improvement in the quality of life of affected patients, reducing the time of evolution of these wounds that cause morbidity and mortality. Therapies such as the use of specific concentrations of ozone, low power laser, negative pressure therapy associated with dressings, produce very promising effects, reducing infection, pain and providing faster healing. The aim is to provide a stimulation of physiological factors and thereby producing fewer side effects[6].

The use of autologous blood derivatives is also an innovative option, in the case of therapies that use the body's own products and substrates capable of creating an environment that resembles the extracellular matrix,

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reestablishing communication between cells and other components necessary for wound healing. wound[7].

Topical autologous blood clot therapy (ATTTC), marketed under the name of Actigraft®, consists of a whole blood clot created from the patient's own peripheral blood, which acts as a protective environment, mimicking the properties of the extracellular matrix, promoting a decrease in of pain intensity by modulating inflammation. This autologous clot is capable of converting M1 macrophages into M2 that secrete anti-inflammatory cytokines, progressing the wound to the proliferative phase of healing, thus providing a quick and more efficient closure than conventional treatment[7, 8].

This is an imported technology, expanding in the treatment of chronic and complex injuries, a fact that justifies the need to seek evidence in the scientific literature about what has already been published on the subject, as well as the effectiveness found, aiming at the production of knowledge on the subject. In this perspective, the present study aims to map and summarize the scientific evidence on TTCSA in wound healing. Measures that help in the treatment of chronic and complex injuries should be disclosed, seeking to improve the quality of life of patients affected by these damages.

METHOD

This is a scope review study, designed to measure research evidence, broadly map the existing literature on a specialty, and point out gaps in the scientific literature. The research was carried out as proposed by the Joanna Briggs Institute (JBI) and presents 5 essential steps: 1) identification of the research question; 2) identification of relevant studies; 3) selection of studies for review; 4) data mapping; and 5) collection, summary and reporting of results[9,10].

The guiding question was constructed with support from the PICO[11] strategy, where "P" corresponds to the population (adults with injuries); "I" for intervention (topical therapy of autologous blood clot); "C" for comparison (does not apply, as this is not a comparative study) and "O" for outcome (healing of the lesion). In this way, the guiding question was defined: "What evidence is available in the scientific literature on topical therapy of autologous blood clot in the healing of skin lesions and underlying tissues in adults?

The online identification of relevant studies took place in the first week of January 2023 using the Virtual Health Library (VHL), PubMed (Medical Literature Analysis and Retrieval System Online-Medline) and Google Scholar search engines, in the Scientific Electronic Library Online (SCIELO) and in the Theses and Dissertations Portal of the Coordination for the Improvement of Higher Education Personnel (CAPES). This choice considered the scope and affinity with the theme, in addition to making articles available in full. The research on the Capes Portal aimed to verify the presence of research that has not yet been published in the form of an article in Brazil.

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For expanded identification of research on the subject, the controlled descriptors "Wound Healing" and "Wounds and Injuries" were used, selected through research in Medical Subject Headings (MESH) and Descriptors in Health Sciences (DECS), and the uncontrolled "Autologous Blood Clot Therapy", chosen after reading publications on the subject. The combinations were performed in English and Portuguese, with Boolean operators AND and OR. For the selection of publications, the terms were searched in the title and abstract in the databases that allowed this choice. It should be noted that the current version of DECS has an interface with MESH and performs a search in all hierarchical terms of the chosen descriptors. Figure 1 presents the strategies for identifying the studies.

Figure 1- Search strategies used to identify publications for scope review. Porto Alegre, RS, Brazil, 2023.

Seekers/Database	Search Strategy
Pubmed	(autologous blood clot therapy) AND (wound healing) OR (wounds and injuries)
Google Schollar	(autologous blood clot therapy) AND (wound healing) OR (wounds and injuries) (terapia tópica com coágulo autólogo) AND (cicatrização de feridas) OR (ferimentos e lesões)
Scielo	(autologous blood clot therapy) AND (wound healing) OR (wounds and injuries)
BVS	((autologous blood clot therapy) AND (wound healing))
CAPES	(autologous blood clot therapy) AND (wound healing))

Source: Research Data, 2023

Articles from research, dissertations, theses, reviews, abstracts in events and protocols, in English, Portuguese or Spanish, available in full electronically, published in the last 10 years and referring to studies on skin lesions and underlying tissues were included. of adult patients.

Editorials, book chapters, qualitative research, articles with a dental focus, animal tests, as well as duplicate publications in the databases, which did not refer to the theme or population of the research or which did not answer the research question, were excluded. The publications indicated on the website of the company holding the patent were also analyzed and the inclusion and exclusion criteria were applied. We chose to exclude case studies published only on the website (which were not published in a journal) as they are not scientific publications.

There were three moments of exclusion: firstly, duplicated publications by evaluating the titles, in a second stage, by reading the title and abstract, and finally, after reading the texts in full. For mapping, publications were exported to Excel ® software and organized and summarized in a form constructed by the authors.

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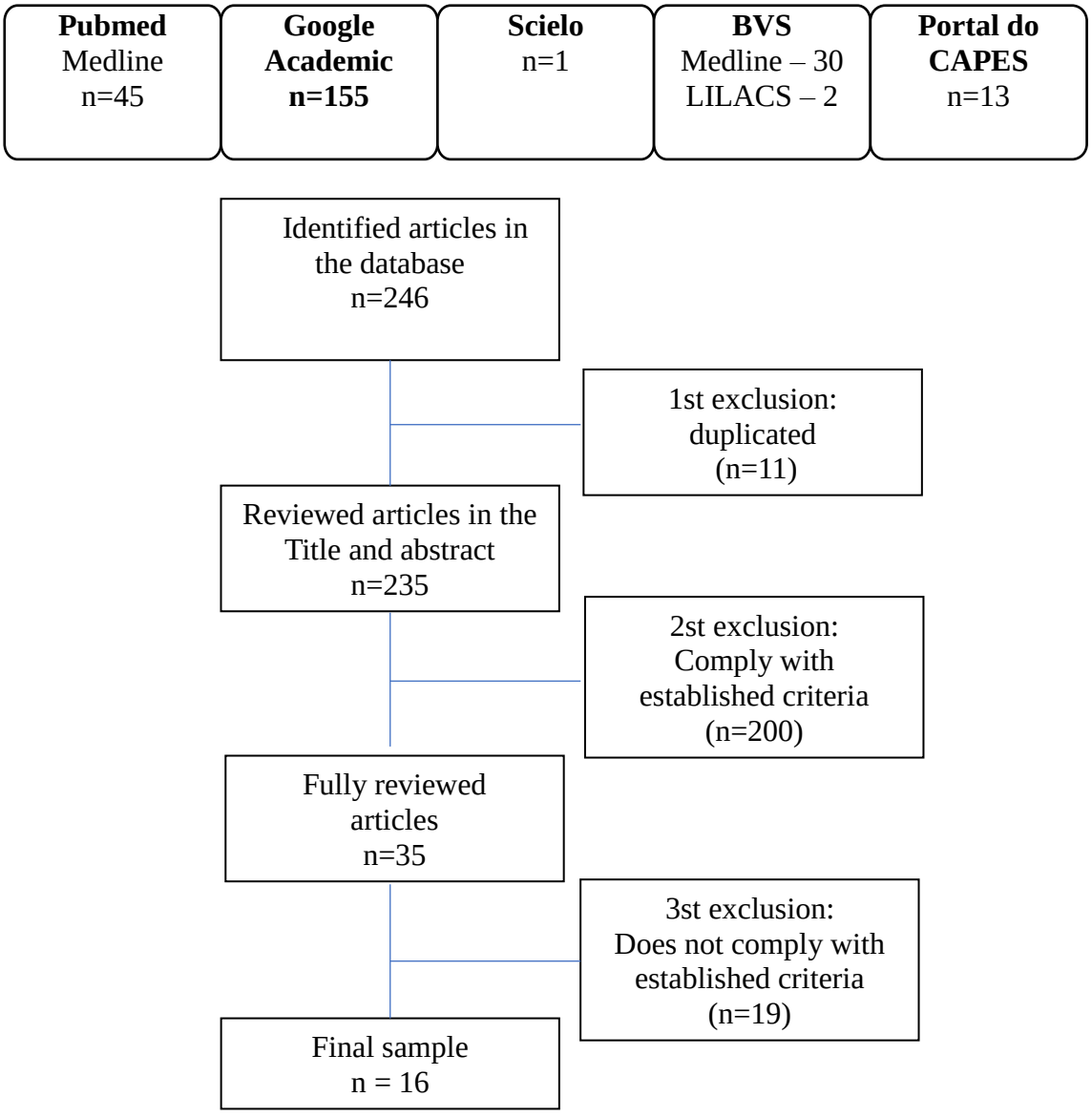
This study was built with the support of the Preferred Reporting Items for Systematic reviews and Meta-Analyses (extension for scoping reviews) (PRISMA-ScR) protocol [12] and the reporting of the results of the articles in tables with descriptive analysis. Ethical aspects were respected, with reliable citation of the authors' sources and definitions.

RESULTS

A total of 246 publications were identified, with Pubmed searching 45 studies in MEDLINE, the VHL tracking two 2 in Latin American and Caribbean Literature in Health Sciences (LILACS) and 30 in MEDLINE, Google academic were 155, in Scielo one and 10 dissertations and three theses on the Capes Portal. The final sample consisted of 16 publications. Figure 2 shows the stages of sample composition.

Figure 2. Study selection flowchart. Porto Alegre, RS, Brazil, 2



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The year 2022 was the one with the highest number of publications (5;33.4%), 15 (93.7%) studies were in English and 12 (75.0%) in journals from the United States (USA). No studies were located in Brazil on the subject and the theses and dissertations found came from tests with other types of blood derivatives. Other characteristics of the articles are shown in Figure 3.

Figure 3 - Characterization of studies according to authorship, journal, language and design. Porto Alegre, RS, Brazil, 2023

Cod.	Authorship and Year	Periodical Country of publishing	Language Delineation
P1	Kushnir I et al., 2016[13]	Wounds; EUA	English; QE
P2	Snyder RJ et al., 2018[14]	Wounds; EUA	English; QE multicentered
P3	Vallejo L; Achterberg J. 2020[15]	J Wound Care, Reino Unido	Spanish; QE
P4	Snyder, et al., 2020 [16]	JAPMA; EUA	English; Literature review
P5	Snyder RJ; Ead K., 2020[17]	Ann Rev Resear; EUA	English; Transversal
P6	Naude L et al., 2021[18]	Wounds International Inglaterra	English; QE
P7	Curtis RD; Wachuku CD., 2021[19]	Ann Rev Resear; EUA	English; Case study
P8	Emre OM; Wachuku CD., 2021[20]	Ann Rev Resear; EUA	English; Case study
P9	Gurevich et al., 2021[21]	Ann Rev Resear; EUA	English; Case series
P10	Landau et al. 2022[22]	Int Wound J.; Reino Unido	English; QE multicentered
P11	Williams et al., 2022[23]	Wounds; EUA	English; QE
P12	Dimitriou et al., 2022[24]	J Clin Images Med Case Rep; EUA	English; Case study
P13	Snyder RJ et al., 2022 [25]	Wounds; EUA	English; Descriptive
P14	Naude et al., 2022[26]	S Afr med j; África do Sul	English; Transversal
P15	Gurevich et al., 2023[27]	J Wound Care North American Supplement	English; Case study

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		EUA	
P16	Snyder RJ et al., 2023[28]	Wounds; EUA	English; Expert consensus

QE: Quase-experimental; Source: Research Data, 2023

It was found that 11 (68.7%) studies evaluated the effect of TCSA, 6 (37.5%) with a quasi-experimental design (QE), three (18.7%) of the case study type and two (12.5%) form a case series study. It was identified that the articles from the QE design also presented case studies during the presentation of the results.

All studies used the protocol recommended by the product manufacturer, with weekly TTCSA changes. The evaluation of the lesions was performed by physical examination, photographic record and measurement of measurements with a ruler. Figure 4 presents details of these publications.

Figure 4. Result of the use of Autologous Blood Clot Therapy in the treatment of lesions in quasi-experimental studies, case studies and case series. Porto Alegre, RS, Brazil, 2023

Cod.	Aim	Place and year of study	Sample and type of lesion	Results
P1[13]	Evaluate the efficacy and safety of a new method using an autologous whole blood clot	Israel; 2009/2010	Nine wounds (7 patients); LP stage 3 or 4 with more than a month of evolution,	Complete healing of 7 (78%) wounds within 7 weeks; Reduction of 77% and 82% of the area in the two unhealed areas. No adverse events.
P2[14]	To assess the safety and efficacy of a blood clot when applied to chronic neuropathic diabetic foot ulcers	USA; 2014/2016	Twenty patients started the protocol and 18 finished it; diabetic foot ulcer	Patients who completed the protocol had faster healing than those who were excluded. The average healing time was 56 days in the complete treatment and 59 in the others. Two adverse events, including a site infection.
P3[15]	Evaluate the effectiveness of the autologous matrix in the treatment of diabetic foot ulcers and analyze the	Porto Rico; 2020	Three patients; diabetic foot ulcer with more than 4 weeks of evolution, those with evolution of more	There was a 70% reduction in the size of the lesions after two applications and 97.6% after three applications, as well as an increase in tissue oxygen saturation. There were no adverse reactions.

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	response with an infrared scanner and a dermal pH meter.		than 9 months were excluded.	
P6[18]	Explore the use of TTCSA in difficult-to-heal wounds	South Afrika and Israel; 2020/2021	Twenty-nine patients; diabetic foot and vascular ulcer	Three lesions closed at week 4 and 8 more at week 12. At week 14 three lesions achieved closure and the remaining five achieved between 93% and 97% reduction.
P7[19]	presentation of a case of hand soft tissue reconstruction	No information	Single case; Gunshot wound to the hand	After one application, wound size decreased by 73% and use for 5 weeks enabled surgical closure
P8[20]	To present a case of therapy with ActiGraft, in a diabetic foot lesion with extensive necrotic tissue and exposed structures	No information	Single case; Diabetic foot	Granulation was promoted covering bone and tendon, necrotic tissue was reduced and the wound area was reduced, making it suitable for grafting.
P9[21]	Introducing ActiGraft treatment in complex wounds with exposed structures	No informatio	Three patients; complex injuries and exposure of bone and tendon	There was an increase in granulation, with coverage of vital structures and a reduction in the wound area.
P10[22]	Evaluate the effectiveness of TCSA in the treatment of LP	Place not informed; 2021	Twenty-four patients; LP ranging from stage 1 to 4, in any location	At week 4, 86.3% of patients exceeded 40% of the healing area and 8 (36.4%) had complete healing; in 12 weeks there was complete healing of 10 (45.5%) lesions.
P11[23]	Evaluated the effectiveness of TCSA in diabetic foot ulcers	USA and Israel Period not informed	Twenty-nine patients; diabetic foot ulcer	Twenty-two patients (75.86%) achieved 50% healing area at week 4; Complete closure was achieved in 28 wounds (95%) at week 12.
P12[24]	Discuss the features of	No	Single case;	Healing 60% in the first 6 weeks and complete after 16

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	ActiGraft for pain management and in the wound healing process.	information	vascular ulcer lasting one year	weeks
P15[27]	To present the effectiveness of ActiGraft in a case series of difficult-to-heal surgical wounds.	USA and Israel Period not informed	Fourteen patients; Complex surgical wounds	Week 4: area reduction of 72.33% and closure of 33.33%; Week 12: healing of 78.54% of the wounds.

Source: Research Data, 2023

Two cross-sectional studies evaluated cost and comparison with other therapies. The data can be found in Figure 5.

Figure 5. Description of cross-sectional studies with Autologous Blood Clot Therapy in injuries. Porto Alegre, RS, Brazil, 2023.

Cod.	Aim	**Results**
P5[17]	Analyze the cost-effectiveness of five (5) advanced skin substitutes, comparing TCSA with other technologies	ActiGraft was more economical when compared to the other products analyzed, as well as more effective in healing.
P14 [26]	To compare the social considerations and financial costs of TCSA versus Negative Pressure Therapy in the treatment of diabetic foot ulcers in South Africa.	The TCSA has a lower weekly cost than the vacuum in lesions with less and more exudate. At 12 weeks, healing was 75% for TCSA and 43% for NPT.

Source: Research Data, 2023

Research has demonstrated the effectiveness of TTCSA and reduced cost compared to other therapies. The sample also comprised three publications written by the same authors (P4[16]; P13[25]; P16 [28]), which were theoretical and literature review studies, one of which aimed to identify a potential mechanism of action of one autologous blood clot and two referring to the therapy use protocol.

DISCUSSION

Complex wounds tend to progress slowly or have their healing interrupted by a series of intrinsic and extrinsic factors [29,30]. In addition to the physiological impairments caused by this type of injury, such as pain, mobility difficulties and odor, there is a need to considering the psychosocial and economic impacts caused to patients: costs related to dressings, difficulties in maintaining daily/professional activities; psychic

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disorders such as self-image problems, depression, anxiety, for example [31,32].

This review identified 16 studies on TTCSA, of which 11 evaluated the effectiveness of the therapy. Five studies had as population of interest patients with diabetic foot[14,15,18,20,23]. Publications have shown rapid healing, in 2 to 4 weeks, on average 57.5 days[14]. A clinical trial tested hyperbaric oxygen therapy on the same type of lesion and achieved healing in 78% of patients in the intervention group, while no patient in the control group achieved complete closure ($p = 0.001$). However, the duration of lesions that used therapy was 8 months, on average, demonstrating success in healing, but slower than TTCSA[33].

Within the line of using human tissues, a study evaluated the healing of diabetic foot ulcers through amniotic membrane coverage, identifying 70% of healed lesions in 6 weeks, when compared to 15% with the use of debridement and conventional treatments[34]. These results demonstrate that a series of factors must be analyzed when indicating a therapy, such as costs and availability of technology, drugs or products, as well as the possibility of different patient responses.

Based on the results presented in the selected studies, vascular ulcers[18,24], pressure injuries[12,22], gunshot wounds[19], complex injuries with exposed structures[21] and complex surgical wounds[27] also showed a positive result with the use of TTCSA, even when compared to state-of-the-art technologies such as negative pressure therapy[26].

It is evident that the studies on TTCSA were developed with small samples, some with a single case, demonstrating that despite having presented effective results in the treatment of complex lesions, they leave doubt as to the sample power, preventing the generalization of the results and suggesting more studies. robust, such as randomized controlled trials. Another fact that draws attention in the selected publications is that some come from the same matrix study, or are authored by the same group of researchers, suggesting that the sample may have been segmented for publication purposes.

In addition, part of the studies found were developed by the company that registered the TTCSA, which was named Actigraft, which may represent a conflict of interest and bias in the results.

On the other hand, the study group that developed the therapy was concerned with standardizing its use, as shown by studies P4[16], P13[25] and P16[28]. The treatment of complex injuries requires knowledge and professionals specialized in wound care and alternative therapies to conventional ones. In this way, review publications, expert consensus and protocols for the use of new technologies can contribute to the use of the entire arsenal of treatments currently available on the market.

Finally, studies P4[17] and P14[26] analyzed costs and concluded that the use of TTCSA may have a lower cost compared to other treatments. Treatment of complex lesions represent 1 to 3% of costs for health systems, which justifies the need for less costly

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therapies[35]. Currently, the value of treatment with TTCSA from the Actigraft brand is still quite high in Brazil, due to import costs. Considering the average time for healing of the lesion with the use of the product, evidenced by the surveyed studies, the total cost of the treatment is high. However, when considering the difficulty in treating complex wounds, the use of alternative therapies to conventional ones is imperative. Thus, it is necessary to look for options to reduce the costs involved in the import process.

For greater reliability and possible generalization of data in Brazil, the development of national studies on the cost-effectiveness of the product is suggested, to be conducted by researchers without conflicts of interest. Carrying out more comparative studies with a solid methodological basis would provide certainty in the applicability of the product on a large scale.

CONCLUSION

This review fulfilled its objective by mapping and summarizing the existing scientific evidence on TTCSA, revealing that the literature points to the effectiveness of the therapy in the treatment of complex lesions, offering one more treatment option.

However, it is important to emphasize that the studies are limited in scope, as they are case studies, small samples or disclosure in different publications of data from a single matrix study, which may reduce the generalization of the results found. There is a need to promote research in this area to more widely evaluate the efficacy and safety of this therapy, in order to offer a safer and more effective treatment for patients with chronic wounds.

It is hoped that this article encourages further research and investment in this area, in order to improve the treatment of complex wounds, aiming to offer a better quality of life to patients affected by these conditions.

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