Study of the effectiveness of papain in wound healing and specific approach to its application in patients with venous ulcers: a systematic review

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Abstract

Purpose: The aim of this study was to research and analyse the medical data about the use of papain and its effectiveness in wound healing.

Methods: Searches were performed in the following databases: LILACS, COCHRANE, EMBASE, Science Direct, Web of Science, Scielo and Pubmed/Medline. Descriptors and terms searched were: papain x wound and papain x ulcer. Inclusion criteria: nonspecific wounds, clinical and laboratory trials in human and animal patients.

Results: 5549 scientific papers were found, and after criteria merge 12 of them were selected. The most part of the relevant publications occurred in 2012 and in 2015 and the greatest number was literature review.

Conclusions: The use of papain gel in the healing process of venous ulcers has shown great therapeutic potential. Researches with greater methodological accuracy are still necessary in order to give scientific evidence about papain effectiveness and standardization.

Keywords: Papain; Wound Healing; Venous ulcer; Wounds

Introduction

Wounds are defined as interruption of continuity in a body tissue, mainly caused by trauma or triggered by clinical diseases [1, 2].

Wounds are considered a public health problem, due to the psychological, social and economic impact for their patients and family. Costs to the health system are also high and rising, reaching people regardless of gender, age or ethnicity [1, 2].

Wounds can also be classified by complexity, lifetime and etiology. As for complexity, simple wounds are defined as those that progress to spontaneous resolution, following the three main stages of physio-logical healing: inflammation, cell proliferation and tissue remodeling [2].

Complex wounds are those involving extensive and/or deep areas that require special features for their resolution and have changed their natural evolution process, threatening the viability of a member or reopening recurring wounds that require more elaborated treatment. Criteria to consider a complex wound are: a) extensive and deep loss of tegument; b) presence of local infection; c) compromising the viability of necrosis tissue; and d) association with systemic diseases that hinder the physiological process of tissue repair [1, 2].

As for the lifetime, wounds can be acute and easily healing or chronic when take longer than six weeks to heal and can present beyond the skin breakdown and subcutaneous tissue, in some cases, injuries to muscles, tendons and bones [1, 2].
Regarding to etiology, despite the wide variety of factors, the main causes of chronic leg ulcers are venous and arterial diseases. 60 to 70% of these ulcers are of venous origin. Arterial insufficiency represents between 10 to 25% and may coexist with venous disease, being called mixed ulcers. In approximately 3.5% of patients the cause of the ulcer is not identified [3].

Accurate incidence of venous ulcers origin is still unknown, but its prevalence is approximately 1% of the Western world’s population. When not properly managed, about 30% of healed venous ulcers relapse in the first year and this rate rises to 78% after two years [3, 4, 5].

Venous ulcers treatment includes clinical and surgical methods, and dressing is the most often used clinical approach to help the tissue repair. The choice of suitable material stems from pathophysiologic knowledge and biochemical mechanisms of healing and tissue repair [1].

Among the various materials available for wounds treatment, papain, which originates from the latex of Carica papaya, is easily found in Brazil and at affordable cost. It is a complex mixture of proteolytic enzymes and peroxidase, causing degradation of proteins into amino acids (proteolysis) of devitalized tissue and necrosis. Papain does not alter the healthy tissue due to a plasmatic antiprotease - the α1-antitrypsin, a human globulin; only present in that tissue that inactivates the proteases [6, 7, 8].

The enzymatic activity of papain is derived from a sulphydryl radical (SH) belonging to the amino acid cysteine and after dilution has odor similar to sulfur [2].

Besides it is a debriding agent, papain has anti-inflammatory action, acting in contraction and joining the wound healing edges by secondary intention. Papain can be used in several healing stages with different concentrations according to the type of wound tissue [2, 9]. Studies show that papain gels at 2% and 4% were effective in the healing of venous ulcers, and can be safely used in granulation tissue and slough with no adverse events. Papain can still reduce the pH of the wound bed stimulating the production of cytokines that promote cellular reproduction and turns the environment unfavorable to the growth of pathogenic microorganisms [2, 10].

In Brazil, reports on the literature about the use of papain as active ingredient in the treatment of ulcers are available since 1983, but with no scientific evidences regarding to its indications, method of use and shelf life after dilution [11, 12, 13].

Considering the need to search for information on the use of papain and its effectiveness in wound healing, this study proposes a systematic review to assist future decisions regarding its application with scientific criteria. Due to the growing interest in the application of papain in the treatment of chronic wounds, the healing process of venous ulcers was also approached in this paper.

Methodology

This study was previously approved by the Ethical Committee of Hospital das Clínicas - CAAE 35417614.1.1001.0068.

Systematic review was performed by electronic literature, including papers published in the following databases: Latin American and Caribbean Health Sciences (LILACS); Evidence Portal focused on Cochrane (Cochrane); EMBASE; Science Direct; Web of Science; Scielo and Medical Literature Analysis and Retrieval Sistem Online (MEDLINE) via Pubmed, describing the exclusive interest of the papain application in the wound treatment. The following descriptors and term search were used: papain x wound; papain x ulcer. Languages used for search were Portuguese and English.

Inclusion criteria were all wound types, clinical and laboratory studies in human patients and animals, in which papain is used in the wound healing process.

Exclusion criteria were the use of papain as debriding agent and / or use of papain in patients with diabetes mellitus.

Selected studies were analyzed for relevance to the objective of this research, source, title, journal, authors, type of study, sample, scope, methodological design, results and conclusions.

Results

5549 scientific papers were found published between 1940 and 2015, distributed in databases sources as shown in Figure 1.

Figure 1: Number of the papers distributed in the respective databases.

From the total number of papers initially found, just 12 (0.22%) matched closely to the selection criteria in this study, as shown in Figure 2.

Impact factor of the journals where papers were published is presented in Figure 3.

![Impact factor of journals](image)

**Figure 3:** Impact factor of the journals of the 12 selected papers.

Publications by countries are shown in Figure 4.

![Publications by countries](image)

**Figure 4:** Countries of origin of the 12 selected papers.

Regarding the etiology of the wounds reported in the papers, most of them refered to general wounds followed by venous ulcers, as shown in Figure 7.

![Wounds etiology](image)

**Figure 7:** Wounds etiology in the 12 selected papers.

Figure 5 shows that the predominant distribution of authors professions according to the publications was nurses (59%).

![Incidence of author professions](image)

**Figure 5:** Incidence of author professions for 12 selected papers.

Figure 8 presents the classification of the 12 selected papers and Table 1 shows the classification of types of studies.

![Classification](image)

**Figure 8:** Classification of the 12 selected papers.
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Table 1: Classification of types of studies in the 12 selected papers (A1 to A12).

<table>
<thead>
<tr>
<th>Prospective</th>
<th>Retrospective</th>
<th>Randomized</th>
<th>N/Randomiz.</th>
<th>Clinical</th>
<th>N/Controlled</th>
<th>Laboratorial</th>
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Discussion

Number of papers found is quite significant, showing that the issue of papain and wounds was cited by many authors in the literature. Highest number of citations occurred in the databases Science Direct and EMBASE that publish scientific papers just in English. Most of the studies described the use of papain as a debriding agent, in diabetic patients, or used in combination with other substances. It is important to notice that Brazilian databases (Scielo and LILACS) showed the most relevant papers selected, representing 58% of the total amount.

Five papers were published in journals whose impact factor is currently B4, showing that most publications is based on more empirical use of papain in wounds and chronic ulcers. Three papers were A2 factor journals (international publications), showing that national studies need to reach the scientific community more effectively. This is also evident when analyzing the publications by countries, as shown in Figure 4. Brazil had the highest number of publications with 59% of the papers and the predominant language was Portuguese.

The largest number of relevant publications for the purpose of this study occurred in 2012 and 2015 (3 studies in each year), as presented in figure 6, showing that the use of papain in wound healing has raised again the attention of the scientific community, although it is a subject known since the 40’s.

Papain was applied according to the needs of health care due to their low cost and availability in Brazil looking for more practical results in the wounds treatment. Use of papain in the healing of venous ulcers has shown recent interest with plenty of potential for future research. Among these publications, the greatest number was literature review (42%), followed by human clinical studies. This result shows that further research may be made to satisfy the scientific gap in the use of papain in the treatment of wounds in human patients. This evidence is also seen by the classification of types of studies that presented five papers (42%) of literature reviews.

Several studies have demonstrated the positive effect of the papain in the stimulation of the healing process, the removal of sloughs as well as a good proteolytic agent. It is a valuable therapeutic source in the treatment of skin lesions and do not present risks to the patient or side effects despite some reports of pain and burning. Papain has been used in various etiologies wounds in different stages of the healing process and in patients of different age groups, such as newborns, adults and the elderly. Some studies have shown that treatment with papain resulted in the decrease of the healing time and epithelization of the injury. In the wounds therapeutic, papain has been used in various dosage forms such as powder, gel, cream and solution at a concentration of 2 to 5% [2, 6, 9, 12].

Studies have also suggested that the use of papain in different concentrations, according to the phase of the contaminated tissue damage may help positively to the debridement of the wound, reducing the residence time of the blood fibrinous crust and reducing time for neoformation of the epidermis with dermis reorganization during the process of wound healing [14].

According to some authors, papain gels were effective in reducing wound area of 20 cm² (66.6%) and in wounds larger than 20 cm² (23.7%). There was an increase in epithelialization tissue and significant reduction of slough and ulcer depth, as well as the amount of exudation and edema. It was found that the gels of papain at 2% and 4% were effective in the healing of venous ulcers. For the gel at 2% wound was significantly reduced between the 5th and the 12th week of treatment [10, 15].

There are references in the literature of the use of papain carbopol gel in the treatment of burns, promoting greater deposition of collagen to the wound when compared to normal skin dermis without treatment. However, results of clinical trials are still required to support its effectiveness [11, 13].

It was observed that the gel formulation although standardized since 1993 was not used/evaluated with respect to the comfort, pain, ease of application and wound development. Analysed studies were purely descriptive and case studies, and often omitted patient’s data, their wounds and how to evaluate them [12, 13, 16].

Conclusions

Use of papain in wounds remains a subject of recent interest, despite being largely investigated for decades. Use of papain gels in...
in the healing of venous ulcers has shown great potential for future studies.

Despite the consensus on the topical application of papain in the treatment of wounds, researches conducted with greater methodological accuracy are required in order to obtain scientific evidences of its effectiveness and standardization of their use in different stages of healing as a result of randomized controlled clinical, experimental studies or even controlled clinical studies in humans.

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Conflict of interest: None