WOUND REGENERATION ON INFECTIVE DIABETIC ULCER PATIENTS AFTER THERAPY WITH PSIDIUM GUAJAVA, LYNN AS PRIMARY DRESSING

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SOAK THERAPY with PSIDIUM GUAJAVA, LYNN. EFFECTIVE IN STIMULATING WOUND REGENERATION

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ABSTRACT

Infection is a frequent complication in diabetic foot ulcer that contributed in increased morbidity and mortality of diabetic patients with ulcers, so that ulcer treatment innovation is needed. Psidium Guajava, Lynn (PGL) is presumed to help wound healing through an emphasis α-PDGF. This research aimed to identify the effect of Psidium Guajava Lynn to the process of wound healing diabetic ulcer on infective patients in Makassar. This research was a quantitative research with experimental design, with the controlled group design with pre and post test. The research sample was taken by accidental sampling and divided into two groups, there were 3 samples for the intervention group and 3 samples for the control group. The intervention group soaked the wound with a combination of NS-PGL for 10 minutes and then closed by the moist gauze primary dressing of PGL-NS, 10 times in three days. Psidium guajava lynn processed by boiling 10 grams in 1 L of water until it remained 0.5 L, then filtered and put into a sterile bottle. The wound washing in the control group was in the standard way. Intake of scar tissue for RT-PCR examination of MMP-9 was conducted 2 times before the 1st intervention and after the 6th intervention. Wilcoxon sign rank test found there was effect of Psidium Guajava Lynn to wound healing scoring (p = 0.048). NS wound treatment side effects in combination with Psidium guajava lynn was not found.

Keywords: Psidium Guajava Lynn, Wound Regeneration

INTRODUCTION

Infection is a common complication in diabetic foot ulcer, with incidence rates as high as 40% - 80%, and most require costly than other complications, so many cases of infection in diabetic foot ulcers unhandled and continues into gangrene. Survey shows cases of these infections contribute the most to the morbidity and mortality in patients with DM (Richard et al, 2011). Diabetic ulcers have become a financial problem in the health care system by spending an average cost of 4500 US dollars per patient in addition to the psychosocial issues that must be borne by the patient due to a decrease in quality of life. Ulcers can be a port d'entry of infection and can cause progressive tissue damage and delayed healing. Therefore, it is necessary to push the boundaries for wound healing time in every phase to prevent amputation (Wu et al, 2007).

Principles of infection control management in addition to the eradication of bacteria is improve the blood flow, to prevent occlusion of blood vessels in the injured area that can lead to gangrene (Bowen, 2007). A period of 10-15 years, 50% of patients with diabetic foot ulcers infective experienced occlusion, especially vascular wound area (Rodrigues & Mitta, 2011). Karyocyte platelet mega systems that are specifically activated in patients DM with exudation fibrin-like substances (FLS), play an important role in the cascade clotting is initiated early phase of wound healing diabetic. FLS exudation is found to be increased to DM patient with infective ulcers than non infective (Agale, 2013). FIS excessive exudation in the ulcer infective triggers total occlusion (Alexiadou & Doupis, 2012).
Infective wound care in general using antibiotics, but the Infectious Disease Society of America (IDSA) in 2012 advocated the using of antibiotics only in cases of ulcer infection with osteomyelitis, while in the case without osteomyelitis do debridement. The FIS management can help diabetic ulcer infection with or without osteomyelitis to reduce the risk of gangrene (Lipsky, 2012). Exudation FIS can be suppressed by pressing the cascade clotting is initiated by platelet derived growth factor (PDGF). PDGF is the most important growth factor in the transition process to the inflammatory phase of wound healing proliferative phase. PDGF is a glycoprotein composed of two chains A or two B chains or a combination of both, while specifically in wound healing PDGF is PDGF α-chain consisting of 2 AA (Lobman et al., 2005).

Drugs currently used to suppress α-PDG is Beclapermins, by binding to the zinc binding site on MMP-9 in which the activation of pro MMP-9 to initiate the activity of MMP-9 α-PDG (Muller et al., 2008). Beclapermin, is one example of modern topical hydrogel dressing with platelet composition of 0.01% that is currently recommended, but is not an option because it is a commercial treatment besides remains controversial, although their effectiveness has been proven in several studies. When this beclaparmins is combined with gel and hyperbaric oxygen, it will produce cellulose that will bind MMP-9 (Liu et al., 2009). Therefore, the FIS management can be done through the epithelialization management by specific proteolysis control diabetic ulcers namely MMP-9.

Plants that had the effect of such a combination beclaparmins with gel and hyperbaric oxygen are the leaves of guava (Psidium guajava, Linn.) Easy and very easily processed into medicines. According to Patil et al. (2008) on guava leaves are known contained flavonoids, tannins, essential oils, fatty oils, psidioklacet acid, tannin substances, quercetin and tannin (flavonoid), saponins guajaverin acid, oleanolat acid and Ursolic acid. Flavonoid has the effect of lowering the working ratio of MMP-9 and TIMP-1, which is a prognostic factor of wound healing by binding zinc thus inhibiting the activation of MMP-9 so as to suppress angiogenesis and reduce cascade activation clotting by α-PDG.

Flavonoid will be excreted Psidium guajava, linn when heated to the temperature of 100°C. The boiling water is currently used by a community of wound care to wash wounds DM, which is based on research Oktiarni et al. (2005) that the flavonoid component when administered as a topical burned wound in the female mice then Flavonoid will bind pro-MMPs-9 passing through the blood wound under the scar tissue by osmosis. The boiling water is made by boiling 10 grams of guava leaves in 1 L of water until it is boiled and remain 0.5 L (Abubakar, 2009, & Mundi et al., 2014). The results of the testing laboratory test quality and food safety of UB 2014, the boiling water filter of Psidium guajava Lynn contains 90.04% water, 8.95% quercetin, 0.84% essential oil, 0.08% fat oils, 0, 05% acids psidioklat, and 1.78% tannin.

Washing the wound with the boiled water of Psidium guajava, lynn has been examined by Fernandez et al. (2010) in patients with diabetic ulcers proliferative phase is conducted twice a week for four weeks, showed the effect in reducing biofilm. Fernandez et al. (2010) also found that Psidium guajava lynn as wound washing with no adverse effects or disadvantages. This is consistent with research patil et al. (2008) found Psidium guajava lynn does not cause side effects in Wistar rats wound. The toxicity test by Traul et al. (2008), the water filter of Psidium guajava, linn essentially non-toxic in some animals, there is no irritant either the eyes or the skin, and does not have the capacity to cause hypersensitivity.

The use of topical Psidium guajava, lynn on human chronic wound with flavonoid content was up to 10.98% has been confirmed in several clinical studies. Guava leave is included kingdom Plantae, divisi Magnoliophyta. Class magnoliopsida, ordo Myrtaeae, family Myrtaceae, genus Psidium and species Psidiumguajava (Mundi et al., 2014). In accordance with the decision of PPI RS Hasanuddin Makassar (2013), the wound care should be conducted 3 days. According to the research, it was found that the wound care is conducted every day with conventional dressings increases the risk of infection (Linger,
Based on Karimi et al (2007), wound care with Normal Saline on burned wound on mice was not significantly associated with cascade, clotting angiogenesis and extracellular matrix degradation.

OBJECTIVES

This research aimed to identify the effect of PGL to prognostic factors in wound healing specific diabetic ulcers, namely wound scoring. This research was expected to provide benefits to the health care provider in Indonesia, both in hospitals, health centers or health services more to take the policy and make the procedure how to do the wound care, so that it can provide direct benefits to society across Indonesia, by accelerating the wound healing process with infection control.

RESEARCH METHODS

This research was a quasi-experimental design with pre and post test with a control group. In this population screening appropriate inclusion criteria: 1) the wound with granulation at least 30%, 2) wound grade 3/4/5 on Wagner criteria, 3) DM suffered less than 10 years. Samples in this research determined accidentally. To determine the treatment and control groups performed the allocation of the sample. The exclusion criteria of this research were: 1) respondents who have treated the wound with Psidium guajava lynn, 2) have undergone major surgery. The Criteria dropped out of this research were 1) patients who are unable or resign within the research period, 2) patients during the research underwent major surgery, and 3) have an infection or discomfort in the wound during the research period. Samples in this research was calculated using the Frederer formula, there were 4 samples of intervention group and 4 samples of control group.

RESEARCH PROCEDURES

Researchers screened samples according to the criteria through the patient’s medical record of public health centers and wound polyclinics in Makassar area, went to the prospective respondents door to door to validate the suitability condition of patients with the research criteria. Having ascertained the criteria, then the prospective respondents were given an explanation of the research and informed consent. Respondent, consisted of three intervention groups and three control groups. Intervention group was given wound care by soaking the wound with liquid and PGL-NS and PGL-NS primary dressing, while the intervention group performed a standard wound care. Wound care will be carried out once every three days up to 10 treatments. Wound scoring with the instrument of Bates-Jensen assessment identified each wound care up to 10 treatment sessions, which will be taken as this scoring pretest data is the first day of wound care and day 10 wound care. During treatment responder would do, check GDS and will fill dit observation sheet.

RESULTS AND DISCUSSION

Characteristics of respondents include gender, GDS mean, the use of insulin and nutrition intake conducted univariate analysis. All the respondents were in the range of mature age and 3th grade of wound (Wagner).
Table 1  
Characteristics Distribution of Respondents with Ulcers Diabetic in Makassar  
(n1 = 3; n2 = 3)  

<table>
<thead>
<tr>
<th>Variable</th>
<th>Control Group</th>
<th>Intervention Group</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>%</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>1</td>
<td>33.3</td>
</tr>
<tr>
<td>Female</td>
<td>2</td>
<td>66.7</td>
</tr>
<tr>
<td>Average GDS</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>High</td>
<td>3</td>
<td>100</td>
</tr>
<tr>
<td>Insulin</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Regular</td>
<td>1</td>
<td>33.3</td>
</tr>
<tr>
<td>Irregular</td>
<td>2</td>
<td>66.7</td>
</tr>
<tr>
<td>Diet Intake</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SR</td>
<td>2</td>
<td>26.7</td>
</tr>
<tr>
<td>TSR</td>
<td>1</td>
<td>6.7</td>
</tr>
</tbody>
</table>

All respondents in this research both the control and intervention groups were adults. Goodson (2014) stated that an open wound contraction that occurs at a young age faster than the elderly. The majority of survey respondents were women. Gilliver et al (2008) in his research found that wound to the female rats more rapid expansion of wound than male rats. It is clear that gender, men and women have different responses to wound, and the factors that most influence are sex hormones. The majority of respondents in this research had a high GDS and MMP-9 in respondents with high GDS tends to increase higher than normal GDS. Normal GDS appropriate referral is less than 200 mg / dl (Leuwen & Poelhuis-Leth, 2009). Increased MMP-9 showed higher epithelialization slower. This is consistent with research Rai et al (2005), that the respondent with blood sugar levels are not controlled showed a significant increase in apoptosis occur ulceration and subsequent microangiopathy contribute to wound healing compounds. More than 60% of diabetic ulcer experiencing neuropathic. The development of neuropathy was seen in in-vitro experimental animals induced hyperglycemia. Conditions of hyperglycemia increases the activity of the enzyme aldose reductase and sorbitol dehydrogenase thus altering the intracellular glucose into sorbitol and fructose, which in turn decreases the synthesis of myoinositol by nerve cells and lead to oxidative stress, so that the scar tissue oxygen deficiency (Clayton et al, 2009). But in this research actually showed improvement hyperglycemia respondents wound with a greater propensity score than respondents with normal GDS. It is as ever described above that wound mending is influenced by diet and gender. Hyperglycemia respondents were respondents interventions which can be caused by the effect of the intervention Psidium guajava lynn described later. Respondents in this research did not use insulin regularly in the intervention group and mostly use regular insulin in the control group. The results of further analysis, scoring wounds tended to regenerate the insulin groups using irregular. It is not in accordance with Schuiler (2011) who found that insulin therapy orally or intravenously in patients with DM led to decrease expression of IL-6 which is a stimulator of expression of MMP-9. MMP-9 is expressed as a response other than an expression of IL-6, also can reduce the risk of hyperglycemia and oxidative stress response (Baugh et al, 2003). Nutritional intake survey respondents, the majority were in the appropriate categories and respondents with dietary recommendations according to the recommendations tend to change a score greater than unsuitable recommendation. Nutrient intake recommended by the ADA (2010) in
Tatti and Barber (2011) for DM patients with ulcer is in the range of 20-25 kcal / kg / day. Nutritional management is a very important aspect in the management of diabetes. Recommendations to the nutritional components, expressed in Kelley (2003), the intake of carbohydrates and saturated fatty acids diabetic patients is limited to 60-70%. The theory was proven in the results of this research, where score wounds respondents with appropriate dietary recommendations tend to be larger.

Table 2
Differences Wound Scoring Before and After Intervention
($n_1=3; n_2=3$)

<table>
<thead>
<tr>
<th>Group</th>
<th>Variable</th>
<th>SD</th>
<th>Mean</th>
<th>P Value (Paired T Test)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intervention</td>
<td>Pre Scoring</td>
<td>4.58</td>
<td>27</td>
<td>0.20</td>
</tr>
<tr>
<td></td>
<td>Post Scoring</td>
<td>6.24</td>
<td>19</td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>Pre Scoring</td>
<td>1.00</td>
<td>35</td>
<td>0.45</td>
</tr>
<tr>
<td></td>
<td>Post Scoring</td>
<td>1.00</td>
<td>31</td>
<td></td>
</tr>
</tbody>
</table>

Table 5
Differences of Wound Changes Scoring in Intervention and Control Group
($n_1=3; n_2=3$)

<table>
<thead>
<tr>
<th>Group</th>
<th>Mean</th>
<th>SD</th>
<th>Mann Whitney U</th>
<th>P Value</th>
<th>Mean Ranks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intervention</td>
<td>8</td>
<td>3.46</td>
<td>0.043</td>
<td>5</td>
<td>2</td>
</tr>
<tr>
<td>Control</td>
<td>4.33</td>
<td>0.58</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

can not measure up to the level of microbiological cells. In accordance with the results of Chuan-Yang et al (2009) about the changing dynamics of wound healing in diabetic mice 21 and 21 non-diabetic mice that wound healing occurs faster in non-diabetic than diabetic mice after wound in week 6. This was supported by variable microbiological examined through biopsy scar tissue both groups of mice to identify MMP-9 and TIMP-1 by the method of RT-PCR for mRNA and ELISA for protein, showed that the mRNA of MMP-9 protein and MMP-9 in group diabetic rats was higher than non-diabetic (p <0.05) and TIMP-1 mRNA and protein TIMP-1 was lower in diabetic than non-diabetic group. The research is in line with the research in which all respondents are DM patient, ie in this research, all respondents in both groups to regenerate wounds. Histological changes and cell function in patients with DM may increase susceptibility to exogenous factors such damage. Therefore, DM patients are more vulnerable get wound and experience healing old wounds.

Research Davis et al (2006) found that the mRNA levels of MMP-9 in diabetics patients were higher with non diabetic, even before the damage, whereas the mRNA levels TIMP-1 is lower, so the ratio of MMP-9 and TIMP-1 DM patients more higher than non DM since before the wound. Decrease in TIMP-1 in diabetic wounds, will lead to disorganization of connective tissue and widen the distance between collagen. Adequate inflammation have a role in the process of wound healing, excessive inflammation in patients with DM will cause a buildup of cytokines, namely TNF-α and IL-1β which then stimulates macrophage and fibroblast to secrete
MMP-9 and TIMP-1 inhibits the production. An imbalance of MMP-9 and TIMP-1 will lead to excessive degradation of extracellular matrix and ended in delayed healing after 3rd day wound. So that the necessary therapy with consideration of components that can reduce or suppress the ratio of MMP-9 and TIMP-1. It is also recommended by Rosch et al (2014) which finds that the increase in MMP-9 and TIMP-1 decline will make redundant the proteolytic environment that inhibit wound healing diabetic, so that therapies aimed at decreasing MMP-9 akan very helpful healing.

The result of differences of wound changes scoring in intervention and control group showed there was significant difference \((p = 0.043)\). *Psidium Guajava Lynn* (PGL) was presumed to help regenerate wounds by inhibiting the production of MMP-9 through one of its components, namely the flavonoid quercetin, by binding zinc in pro MMP-9. PGL contains essential oil with quercetin component 18,81% caryopyllene, copaene 11.80%, 10.27% and 7.36% Azulene Eucallyptol. Quercetin is also called avicularin a 3-L-4-4-arabinofuransid other than an anti-inflammatory is also an antibacterial (Begum et al, 2012). PGL on research Muruganandan et al (2010) proved to have anti-inflammatory effects by inhibition percentage of 58.27% in topical use. Ticzon (2011) proved also that PGL young and fresh has antispasmodic effect on the oral use. Water boiled PGL has also gone through the research Suzuki et al (2010) among respondents with atopic dermatitis that turns this water contains allergenic activity after 4-8 weeks of treatment.

In this research PGL have a role to help perfect the proliferative phase of wound healing, which theoretically MMPs play a lot in it, especially MMP-9 degrades collagen denatured partially or referred to gelatin. MMP-9 dispose of collagen and other extracellular matrix component which partially denatured during injury. This is very important because the collagen must interact specifically to form fibrils was perfect. Partially degraded collagen that will not be interacting perfectly with new collagen molecules formed during the proliferative phase so that the newly formed tissue wall brittle (Wadood etal, 2015).

Dysregulation between MMP-9 and TIMP-1 in DM patients if not treated will develop into cardiovascular disease, in addition to causing a long healing wound. Research Wadood et al (2015) on 24 patients with DM without dyslipidemia with old DM less than five years, 30 diabetic patients with dyslipidemia with old DM more than 10 years and 26 healthy people, proving that a significant increase in MMP-9 is a risk factor of cardiovascular complications DM with and without dislipideifi and long suffering from diabetes for less than five years old or over 10 years compared with healthy people.

Wound care treatment by immersion or irrigation using a combination of NS PGL can stimulate the regeneration of wound. However, cure rates related to such interventions cannot be separated from patient characteristics that should be communicated to be controlled in addition to wound care routine according to the procedures and moist principles. Mendes and Neves (2012) wrote in their literature review hat severe ulcers requires a multidisciplinary approach, due care should be in harmony go hand in hand with medication, diet and physical
therapy so that optimal wound healing. Further research is needed to find innovation in the provision of PGL as dressing primary a variety of preparations, so hopefully with the research ratio of MMP-9 and TIMP-1 in diabetic patients with ulcers not only lowered, but can be lowered to less than 0.39. So it is still necessary to analyze the RT-PCR of mRNA of MMP-9 in this research.

**CONCLUSIONS AND SUGGESTIONS**

*Psidium Guajava Lynn* can stimulate the regeneration of wounds in patients with infective diabetic ulcers. Suggestions for further research is needed to find innovation in the provision of PGL as primary dressing in a variety of preparations, so hopefully with the research could occur maturation on day 28 in accordance with the theory of wound healing. In addition, there needs to control the characteristics of the respondent i.e. diet, gender, use of insulin and blood sugar levels.

**REFERENCES**


