Effectiveness of Therapeutic Non-operative Management of Wound Healing in Diabetic Foot Ulcer: A Systematic Review

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Abstract: Background: Therapeutic non-operative management is an important part in healing the wounds of diabetic foot ulcer but the most effective method among this remain questionable. This study aims to identify effective intervention to treat diabetic foot ulcer with therapeutic non-operative management by systematic review and followed the PRISMA statement guidelines. Methods: Scopus, PubMed, and Science Direct database from 2012 – 2018 were search for the relevant keyword. All included studies were access base on (1) random controlled trial, (2) case-control studies and (3) cohort studies. Results: 19 out of 1651 papers were including. Two articles suggest that advanced biologic therapy, the bioengineered living cellular construct (BLCC) of human fibroblast-derived dermal substitution (HFDS) and advanced skin substitution using graft have a significant. Five articles reported electrophysical therapy has significant. Two articles reported hyperbaric oxygen therapy (HBOT) had a significant and one article reported no effect. Five articles state that the NPWT has a significant influence on wound healing. Three studies reported that TCC resulted in a statistically significant to be an effective treatment of diabetic foot ulcers. Conclusions: NPWT should as promising therapeutic non-operative management in treating diabetic foot ulcer. Additional further randomized control trial design study needed to strengthen the finding.

1 BACKGROUND

Diabetes mellitus is not infectious disease issues figure high incidence of its victims and diabetes mellitus treatment if not done properly will cause complications of diabetes mellitus consisting of acute complications include Diabetic Ketoacidosis, hyperosmolar non ketotic, and hypoglycemia (Perkeni, 2011). Neuropathy is one of the complications that occur in the nervous system disorders of the foot and alirah peripheral blood which is early onset of diabetic foot ulcer (Waspadji, 2006). Patients with diabetes mellitus will evolve into a diabetic foot ulcer (DFU) is estimated to be 15-25% associated with venous insufficiency, neuropathy and peripheral artery damage and only about 24% of the wounds healed after 12 weeks of therapy, this causes ALOS lengthwise in the hospital, the costs incurred by the patient as well as the increased burden of the Government against health coverage also increases (Lavery, 2014). The treatment process for the DFU into a challenge for effective health workforce craft made proper wound care management to shorten the healing time and prevent further complications since DFU (Frykberg et al., 2017).

Prevelention of diabetes mellitus there are an estimated 382 million people living with diabetes in the world and in the year 2035 that number an estimated 592 million people stepped on the rise (International Diabetes Federation, 2014). Sufferers of diabetes mellitus a number of 382 million people, 175 million of them have not been terdiagnos, so that threatened developing progressively and unidentified become unwitting and complications and without any prevention of sufferers (Kemenkes RI, 2014). The prevalence in Indonesia there are around 7% of total population total number of 258 million people have diabetes mellitus (World Health Organization, 2016).

The impact of diabetic foot ulcer treatments that are not exactly very influential towards the quality of life, productivity, employment, depression due to the amputation to death. Risk factors as causes of DFU one is lack of management to prevention therapies that have not been appropriately and has not been used. DFU therapy can be done with the operative management and non-operative management (Cychosz, 2016).

Over recent decades, the significance of related research the healing of wounds in diabetics with non-operative management of therapeutics many do, some non-operative management strategies include such Advanced Biologics Therapy, Hyperbaric Oxygen Therapy, Electrophysical Therapy (HBOT), Negative Pressure Wound Therapy (NPWT), and the Total Contact Casting (TCC), the therapy is found in
all the review literary review Cychosz (2016) related preventive and therapeutic strategies for diabetic foot ulcer, but there has been no systematic review that discusses the effectiveness and excellence in the use of the therapy as a whole on the healing process of wounds so medical personnel can compare pengguaan therapy to each other so that right for granted. The purpose of this review is the systematic to know the effectiveness of non-operative management therapy therapeutic against healing in diabetic foot ulcer (DFU).

2 METHODS

This systematic review followed the Preferred Reporting Item for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Liberati et al., 2009).

Search strategy
Scopus, PubMed and Science Direct databases were searched for articles published from 2012 – 2018. The strategy had eight components which were combined: (1) non-operative management OR (2) negative pressure wound therapy OR (3) hyperbaric oxygen therapy OR (4) total contact casting OR (5) advanced biology therapy OR (6) electrophysical therapy AND (7) wound healing AND (8) diabetic foot ulcer.

Eligibility Criteria
Types of studies
(1) random controlled trial, (2) case-control studies and (3) cohort studies design were included.

Types of participants
The main inclusion criteria entailed adult (18 years or older), with a type I or type II diabetes.

Type of interventions
Any non-operative management for the treatment of diabetic foot ulcer was eligible. No studies were excluded on the basis of the comparator/control group used.

Type of outcomes measures
Primary outcomes of interest were any measure of wound healing. The timing of outcome measures was variable.

Study selection

The protocol standard for selecting research studies is suggested in the PRISMA method for systematic review followed by screening by removing duplicates, then three reviewers selecting titles, abstracts, and keywords, then deleting irrelevant quotes according to the selection criteria. Reviewers noted the reasons for choosing such research studies including selection of inclusion inclusion data. Selection of research studies that have been recorded by three reviewers and then compared to one another to be adjusted feasibility with the criteria set. Secondly, to minimize the risk of incorrect study entry in selection there are several research studies that have been applicable or can be applied in a review by one or two reviewers to be included in the next review stage. Full text of the articles is obtained if the title and abstract meet the inclusion criteria or if the feasibility study is clearly resolved by a joint discussion between the reviewers.

3 RESULTS

Literature search and study selection
A total of 19 studies were identified for inclusion in the review. The search of Scopus, PubMed and Science Direct databases provided a total of 1651 citations. After adjusting for duplicates 863 remained. Of these, 595 studies were discarded because after reviewing the abstract it appeared that these papers clearly did not meet the criteria. The full text of the remaining 268 citations was examined in more detail. It appeared that 250 studies did not meet the inclusion criteria as described. See flow diagram Figure 1.

Study Characteristic
Methods
19 studies finally selected for review were eight randomized controlled trial, eight cohort studies, and three case-control studies design.
Population
The included studies involved 2,304 participant. The main inclusion criteria entailed adult (18 years or older), with a type I or type II diabetes.

Intervention
Table 1 represents the characteristics and content of the interventions of the 19 studies.

Three studies evaluated Hyperbaric Oxygen Therapy/HBO (Fedorko et al., 2016; Chen et al., 2017; Hayes et al., 2017). Five studies evaluated Negative-Pressure Wound Therapy/ NPWT(Matsuzaki and Kishi, 2016; Kaushik et al., 2017; Mendame Ehya et al., 2017; Wang et al., 2017; Yang et al., 2017). Three studies evaluated Total Contact Casting/ TCC (Kashefsky and Marston, 2012; Arnold and Marmolejo, 2017; Merheb et al., 2017). Two studies evaluated Advanced Behaviour Therapy/ ABT (Lavery et al., 2014; Rice et al., 2015). Five studies evaluated Electrophysical Therapy (Keyl et al., 2013; Liani et al., 2014; Omar et al., 2014; Asadi et al., 2015; Wirsing et al., 2015).

Outcomes
In all studies the primary outcome assessed was wound healing. The timing of outcome measures was variable and could include monthly investigations, evaluations every three months or a single final evaluation.

Results of individual studies
Advanced Biologic Therapy
Two articles suggest that advanced biologic therapy, the Bioengineered living cellular construct (BLCC) of Human Fibroblast-derived dermal substitution (HFDS) and advanced skin substitution using Grafix have a significant effect on wound healing.

Lavery et al., (2014) reported that grafix can improve wound healing, shorten healing time and reduce complications. (Rice et al., 2015) reported that BLCC and HFDS can accelerate wound healing and lead to reduced maintenance costs.

Electrophysical Therapy
Five articles reported Electrophysical Therapy has significant effect on wound healing.

Asadi et al., (2015) reported that a cathode-direct current can increase skin temperature and accelerate wound closure or reduce injury to DFU ischemia by comparison of study groups showing significance at higher skin-temperature changes than in placebo groups in three sessions and and reduction of injured areas (52.68%) compared to the placebo group (38.39%). Keyl et al., (2013) suggest that electrical stimulation for sciatic nerve motor responses is increased in patients with DFU gangrene. Liani et al., (2014) reported that the Pulsating Electrostatic Field technique has influenced metabolic processes and accelerated wound healing in foot ulcers with type 2 diabetes. Wirsing et al., (2015) reported that Wireless Micro Current Stimulation (WMCS) technology significantly accelerated progress on wound healing and reduce the occurrence of expansion on the surface of the wound with wound healing achieved for 3 months in aetiologically difficult to recover patients. WMCS offers advantages over electrical stimulation because it is contactless, pain free from being easy to use

Hyperbaric Oxygen Therapy (HBOT)
Two articles reported Hyperbaric Oxygen Therapy (HBOT) had a significant effect on wound healing, and one article reported no effect.
Chen et al. (2017) reported that hyperbaric oxygen therapy can significantly improve the inflammatory index, blood flow and quality of life. Hayes et al. (2017) suggest hyperbaric therapy may reduce ulcers by 51% and pain reduction. Fedorko et al. (2016) reported that there is no significant influence on decreasing the risk of amputation and wound healing.

**Negative Pressure Wound Therapy (NPWT)**

Five articles state that the NPWT has a significant influence on wound healing.

Matsuzaki and Kishi (2016) reported that NPWT can accelerate wound healing time after debridement with an average of 31.3 days. Yang et al. (2017) reported that NPWT can increase protein and cFN and TGF-β1 levels compared with Advanced Moist Wound Therapy consisting of hydrogels, alginites, and dressings. Wang et al. (2017) reported that NPWT may decrease TNF-α, IL-6, iNOS, IkB-α and NF-kB P65 expression, increase ATF-3 levels, and provide anti-inflammatory effects by suppressing pro-inflammatory enzymes and cytokines as a result inhibition of IkB-α and the activation of ATF-3, which can prevent the activation of the NF-κB pathway in diabetic foot wounds and cause rapid injury to improve treatment with debridement. Mendame Ehya et al. (2017) reported NPWT reduces expenditures accumulated flap, reduces pain shorten wound healing time with good aesthetics, good mobility and satisfactory therapeutic results. Kaushik et al. (2017) reported that NPWT accelerates the wound healing period compared with gauze dressing.

**Total Contact Casting (TCC)**

Three studies reported that TCC resulted in a statistically significant to be an effective treatment of diabetic foot ulcers.

Arnold and Marmolejo (2017) reported there are similar healing rates and reduced rates of iatrogenic ulceration, amputation, recurrent ulceration were attained and an 85.6% healing rate was achieved with use of a prefabricated roll-on TCC. Kashefsky and Marston (2012) reported the percentage of wound healing using TCC at 75% complete and non-recurrent ulcer coverage during one year of follow-up and no surgery. Merheb et al. (2017) reported the average time of wound healing with TCC is 23.7 ± 16.3 days.

**DISCUSSION**

A systematic review is to find out about the effectiveness of the therapeutic management of non-operative against the wound healing in diabetic foot ulcer. The articles used to use heterogeneous research design. There are several related findings of various interventions concerning the advantage or disadvantage of some kind of intervention against the process of wound healing that is composed of several phases, and in this case the intervention of NPWT potentially as a treatment effective for wound healing in diabetic foot ulcer which will be discussed in detail as follows.

Diabetic foot ulcer treatment outcomes remains a challenge related effectiveness of treatment. Intervention or treatment should be assessed or reviewed, so that less proof of effectiveness of interventions should be avoided. Review update results Cychosz (2016), a literary review that discusses about strategies of preventive and therapeutic for diabetic foot ulcer management with operative or non-operative. The review contained an assessment of interventions that have advantages or effective in the process of wound healing at every phase. Wound healing there are three important phases include inflammatory phase, proliferasi, and remodelling. Inflammatory phase of wound healing is a process until the fifth day, acute inflammation occurs in 24-48 the first hour after injury. The process of epitilisation were formed then undergo constricting and reaction accompanied by the release and activate hemostase cytokines which act for the occurrence of cemoktasis retrofil, macrophages, mast cells, endothelial cells and fibrolas which are then This inflammatory reaction produces exsudation fluid (Ekaputra, 2013). In the inflammatory phase in NPWT have advantages and effective because of the application of the negative pressure can stimulate the activity of the cells in the wound, the migration of cells, eliminate excess fluid cuts, and decrease edema (Borgquist, 2011). In accordance with the results of the review of research studies conducted by Wang (2017) explained that NPWT enhances wound healing of diabetes due to inflammation of the soft and dense matrix cells are deposited. NPWT significantly lowered expression of TNF-α, IL-6 and iNOS (all P < 0.05). The results of PCR blotting and real-time PCR showed that NPWT decreases the level of IkB-α and NF-κB P65 and raise the level of ATF-3 (all P < 0.05) and can also provide anti-inflammatory effect with emphasis pro-inflammatory enzymes and cytokines due to inhibition of IkB-α and activation of ATF-3, which can prevent the activation of NF-κB pathways on
diabetic foot wounds and cause wounds quickly improved (Wang, 2017).

Compared to the four other interventions, such as advanced Biologics intervention therapy that has a weakness in the inflammation phase as it cannot reduce the exudate on the wound. Advanced Biologics therapy is a therapy of skin grafting on the wound the granting of appropriate research studies by Laverty (2014) that describes the advanced skin grafix substitution on diabetic foot. There are also similar things in therapy ESWT (extracorporeal shock wave therapy) is to respond to electrical stimulation of nerves, therapeutic research study conducted by Omar (2014) explained that ESWT therapy can improve perfusion and not on inflammatory processes. The next therapy HBOT only gives oxygen on peripheral, in accordance with the research study conducted by Fedorko (2016) that the results of the review describes the granting of hyperbaric oxygen therapy did not significantly effect against a decreased risk of amputation on the client with a diabetic foot ulcer (p = 0.846). Total contact casting is also a therapy that is designed to protect the ulcer by reducing pressure on the wounds, according to the research study by Arnold (2017) the results of the rate of healing using the TCC roll-on prefabricated reach 85%.

The second phase, i.e. poliferasi, this phase began on granulation, contraction of wounds and epitelisasi (Ekapatra, 2013). NPWT in it also have an important role in which excellence in improving growth of granulation. Yang (2017) that compares with NPWT AMWT therapy/advance moist wound therapy with hydrogel and alginates dressing as the control group, the results raise the levels of protein and NPWT cFN and TGF-β1 as compared to the control group (P. 01 < both), cFN and TGF-β1 granulation tissue through which so speed healing of wounds of diabetic foot.

Phases of remodeling is the last and longest phase in the process of wound healing. The dynamic processes occurring in the form of remodeling of collagen, scar maturation and wound contraction. This phase lasts from 3 weeks to 2 years. End of this healing grated ripe wounds obtained which has 80% of the strength of the normal skin (Ekapatra,2013). Advantages of the intervention research studies described in NPWT Mendame (2017) that there is a statistically significant difference in clinical endpoints in two groups (p < 0.001; p < 0.05). VAC combining perforating applications flap, flap accumulation reduce spending, reduce pain shorten the time healing wounds with the aesthetics of good, good mobility and therapeutic results are satisfactory.

**Limitations**

There are some potential limitations related to this systematic review. (1) Heterogeneity of study design. (2) What we considered as primary outcomes (wound healing) was not always the same as in the original study.

**5 CONCLUSIONS**

This review explains that systematic intervention NPWT potentially as effective therapy for DFU compared four other interventions such as advanced Biologics electrophysical therapy, therapy, HBOT, and total contact casting. Wound infections generally produce higher levels of exudate causes damage and localized edema. NPWT can reduce the bacterial load bed sores (Moues, 2004), besides NPWT also able to take excess fluid cuts and not only reduce the edema but also improve local blood flow and nutrients on the wound. The flow of new blood is able to reduce the formation of anti-inflammatory mediators such as metalloproteinase, which lose adhesion proteins needed to repair wounds. Clinical trial on diabetic foot wounds showed excellence in producing NPWT granulation than conventional dressings. NPWT also induces angiogenesis and vascular proliferation, further systemic endothelial cells mobilize NPWT progenitor (EPCs) which is a marker of the healing and repair. Design studies with randomized controlled trial is needed to strengthen the results of systematic.

**REFERENCES**


Chen, C.-Y. et al. (2017) ‘Adjunctive Hyperbaric Oxygen...


