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Effectiveness of Maggot Debridement Therapy (*Luciliacuprina*) In the Treatment of Diabetic Foot Ulcer

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Abstract: *Chronic wound such as diabetic foot ulcer (dfu) is commonly resistant to conventional methods andassociated with foot complications. Delay in the healing of diabetic foot ulcers could lead to devastating complications such as infection, gangrene and lower limb amputations. Thus, effective management of dfu is crucial to expedite healing. Management of dfu requires efficient wound debridement to remove slough, necrotic tissue, prepare the wound for healing and closure. Maggot debridement therapy or MDT has been widely used in the debridement of chronic wounds and shown promising findings. However, MDT studies in the treatment of dfu remained less in number. Consequently, the comparison study between MDT and conventional method in dfu remained limited and inconclusive. The aim of the study was to evaluate the efficacy of MDT using local species Luciliacuprinaas compared to the non-surgical conventional method in the treatment of dfu based on slough percentage and size of ulcer on day 3, 6,9. The study also assessed the relationship between patients' demography, clinical characteristics, and slough percentage. The study was conducted in UMMC, tertiary healthcare setting on 110 adult diabetics (55 in each group) with sloughy ulcer below 40cm^2, less than 2cm deep, ankle-brachial index ABI of 0.8 or higher. Slough and size were measured using NDKare^{TM} app.The result showed a significant difference in slough percentage on day 3,6 and 9 between both groups ($p<0.001$). Reduction of slough was faster in MDT group on day 3, complete debridement on day 6 whereas there was still 67.31% of slough in the conventional group on day 9. However, size reduction was not significantly different between both groups. The site of ulcer was shown to have a significant relationship with slough percentage in the study. Due to rapid in time to debridement with MDT, it is highly recommended that MDT is integrated into the treatment of dfu to prevent foot complications especially lower limb amputations.*

Background*: The prevalenceof diabetesmellitusisincreasingrapidlyworldwide.Diabetic foot complications are devastatingwhichinclude infection, gangrene, and lowerlimb amputations. Managingdfu has been a costlyaffairespecially in developing countriessuch as Malaysia. Complication of dfuincreasedhealthcareburden and reducedquality of life dordiabetics.MDT hadshowntremendousoutcomes in the debridement of chronicwounds for decadessince World War 1. Mostly, MDT has beenusedworldwideas the last option in limbsalvaging for patients withdfu.Studies on the effectiveness of MDT in the treatment of dfu are stilllacking and remaininconclusive. Benefits of MDT has been demonstrated in previousstudies in removingslough, necrotic tissue and acceleratingchronicwoundhealing.Successfuloutcomeswith MDT couldpreventfoot complications, reduceincidences of infection, gangrene and lowerlimb amputations. Despiteadvancements in wound care technology, the management of dfu has been resistant to conventionalmethods and challenging for clinicians.Hence, MDT could serve as an effective debridement method to manage DFU.*

Materials and Methods*: In this prospective controlled study, 110 adult diabetic patients with sloughy DFU of Grade II, III and ABI>0.8 were included. The 110 patients were allocated into 2 groups of 55 patients each (MDT Group and Conventional Group). The patients were followed for 9 days. The efficacy of MDT was compared to a non-surgical conventional method based on slough percentage and size of ulcer at baseline, day 3, day 6, day 9 using the validated wound monitoring system NDKare^{TM}. The relationship between patient socio-demography, diabetes and ulcer clinical characteristics were evaluated.*

Results*: Time to debridement was shorter in MDT Group as compared to Conventional Group. Rapid reduction in slough percentage within 3 days was observed in MDT Group (200 maggots) as compared to the conventional method. Complete debridement was achieved in 6, 9 days in ulcers treated with MDT (400 maggots) whereas there was still a mean 67.31% slough in the conventional group in the Conventional Group. The differences in the mean slough percentage between the two groups were statistically significant ($p<0.001$). However, the mean size of ulcer was not significantly different between MDT and Conventional group due to non-homogeneity of size at baseline. The site of ulcer was significantly associated with a slough percentage in the study population.*

Conclusion: *MDT was significantly more effective than conventional method in the treatment of DFU*

Key Word*: Diabetic foot ulcer; Debridement; Maggot debridement therapy*

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I. Introduction

Incidences of DFU had been on an upward trend due to the increase of diabetes prevalence worldwide. As TheInternational Diabetes Federation (2017) reported, there are more than 400 million adult diabetics globally and the numbers are on the rise. It was estimated 25% of diabetics with poor control of glucose will develop a foot ulcer in their lifetime and DFU has been the major indication for lower limb amputation.[1] Complications of DFU has become a healthcare burden for developing countries, negatively affected the patients' economic standpoint and quality of life.[2]Majority of the complications of DFU includes infection, gangrene and lower limb amputation that can be prevented with effective chronic wound management as stated in T.I.M.E framework (T=tissue management/debridement, I=infection/inflammation, M=moisture balance, E=advancing edges).[3,4,5] Tissue management via effective debridement is crucial in wound bed preparation to accelerate healing. [6,7] The purpose of debridement is to remove slough, necrotic, non-viable tissue, promote granulation, and eventually epithelialization. In addition, debridement also plays a pivotal role in controlling infections. Therefore, the benefits of debridement are irrefutable in the management of chronic wounds.[8] MDT had been effective in debriding chronic and infected wounds, DFUs, venous ulcers, and pressure ulcers since its inception in the 19th century. Initial investigations had revealed that the healing of chronic wounds was expedited due to the debridement effect of sterile maggots in removing 25mg of slough and necrotic tissue within 24 hours. [9,10] In view of the chronicity of DFU, the usage of the century-old MDT had gained momentum and been advocated for debridement purposes in healthcare settings.[11]Due to this effect, MDT had been explored in chronic wound debridement when the conventional method failed to achieve the targeted outcomes. Nevertheless, MDT is mostly utilized as a last option for limb salvaging in actual clinical settings as demonstrated in a majority of clinical observations with MDT.[12,13,14] MDT had been prescribed as bio-surgery, larval therapy, maggot debridement therapy or maggot therapy referring to the application of medical-grade sterile larvae on chronic wounds.[15,16,17,18]Selection of an effective debridement tool could optimize wound bed preparation to prevent delay in healing.[19] MDT using sterile maggots of *Luciliasericata*had shown promising outcomes for decades in removing slough and necrotic tissue as revealed in previous studies. [20,21]However, comparison studies between MDT and conventional method (surgical and non-surgical) in the treatment of non-healing DFUs remain sparse. [23]Despite advancements in technology, MDT had stood the test of time and emerged as a promising tool for debridement in chronic wounds.[24]However, not all species of flies were safe and effective for wound debridement. The sterile larvae of greenbottle blowflies, *Luciliasericata* and *Luciliacuprina* (Diptera: Calliphoridae) have been used for the debridement of chronic wounds. [25,26]However, the majority of the MDT studies were conducted with *Luciliasericata* which is abundantly present in Europe. Less studies had been published with *Luciliacuprina* which is mainly found in Asia and Africa. [27,28]When conventional debridement methods failed to yield positive outcomes, MDT had been an alternative debridement modality for limb salvaging used by clinicians mainly in Europe and the USA.[29,30]The striking effect of MDT was based on its three major modes of actions which include debridement, disinfection, and stimulation of wound healing.[31,32,33]In Malaysia, the investigation into the efficacy of MDT using *Luciliacuprina* did not produce significant outcomes and inconclusive.Hence, the main objective of the study is to evaluate the effectiveness of MDT in the treatment of DFU as compared to conventional method based on reduction in slough percentage on day 3, 6, 9 and size of ulcer in 9 days.

Material And Methods: This prospective controlled study was conductedin University Malaya Medical Centre, Malaysia from September 2018 to April 2019 on a total 110 adult diabetic patients aged ≥ 18 years with sloughy Grade II, Grade III DFU (both male and females) with ankle brachial index ABI>0.8.
Study Design: Prospective controlled observational study
Study Location: Tertiary care teaching hospital, UMMC
Study Duration: September 2017 to November 2019.
Sample size: 110 patients.
Sample size calculation: The sample size was calculated based on a previous MDT study by Opletalová et al. (2012) with an assumption of a 20% mean reduction in slough or necrotic tissue using MDT with an error estimate of 5% and 80% probability of detecting the effect of application with MDT. The calculation of sample size in the present study revealed a minimum of 55 participants in each group (MDT and conventional group).
Subjects & selection method: The participants for the study were selected when based on their consent for MDT. Patients consented for MDT are allocated into the MDT Group and others in the conventional group at the Orthopaedic Ward in UMMC. Patient socio-demography data such as age, gender and diabetes history, HbA1c, type of diabetes are documented during the admission of patients to the ward.

Inclusion criteria:
1. Adult diabetic patients with sloughy, Wagner DFU Grade II,III
2. Both male and female

3. No profuse bleeding
4. ABI>0.8
5. Single wound in each limb
6. No sepsis and require urgent debridement

Exclusion criteria:

1. Non-diabetic based foot ulcers
2. Less than 18 years of age
3. ABI<0.8
4. Multiple ulcers in the same limb.
5. Sepsis and require urgent debridement

Procedure methodology

The selection of patients for the study was selected by doctors in the Orthopaedic Ward based on the inclusion and exclusion criteria. After getting informed consent from the patients, they were admitted to the ward. Baseline characteristics of the patients (age, gender), diabetes history, HbA1c, type of diabetes and ulcer characteristics (grade, size, site, and duration of ulcer) was documented. Size of ulcer and slough percentage was measured using the wound monitoring app NDKare™ at baseline, day 3, day 6 and day 9.

Statistical analysis

Data were analyzed using SPSS version 23 (SPSS Inc., Chicago, IL). Normality in the distribution of data was tested with skewness and kurtosis test. If the numerical values of skewness and kurtosis were between -1.96 and 1.96 and were established as normal distribution of data Repeated measures Rm-ANCOVA with size as covariate was applied to ascertain the difference between the two groups in relation to slough percentage. Independent sample*t*-test was used to determine the significance of differences between the two groups in relation to mean size of ulcer. In addition, Spearman, Pearson and Mann-Whitney statistical test was used to determine the relationship between age, gender, diabetes history, HbA1c, type of diabetes and ulcer characteristics grade, size, site and duration of ulcer. The level $p< 0.05$ was considered as the cutoff value or significance.

II. Result

After 9 days of follow up, rapid debridement was observed MDT from baseline (80%) to day 3 (13%) with 1 cycle of MDT and complete debridement in 6 days whereas there was still 67.3% slough in the ulcers treated with conventional method (saline moistened gauze, paraffin gauze). The differences between the mean percentage of slough was statistically significant ($p<0.001$). However, the reduction of size was not significantly different between both groups from baseline to day 9. The site ulcer had shown significant relationship with slough percentage in the study population.

Figure 1: Profile plot showing the efficacy of MDT as compared to conventional method in DFU

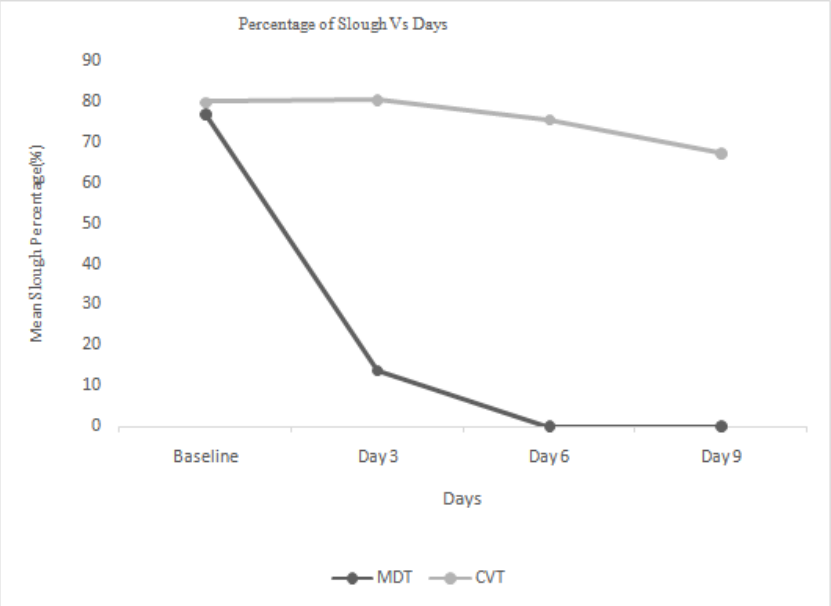

Figure 1: Significant slough reduction in the shortest time was achieved in the ulcers treated with MDT as compared to ulcers treated with the conventional method from baseline to day 3, 6, 9. The findings of Rm-ANCOVA with Bonferroni adjustments showed the average slough percentage at baseline was homogenous between both groups and not significantly different (p=0.522). However, the differences in the mean percentage of slough were demonstrated to be statistically significant (p<0.001) across different time points; day 3, day 6, and day 9 between the MDT and Conventional groups. At day 3, the percentage of slough reduced to 13.71% in MDT compared to 80.25% of slough in the conventional group. The data analysis showed that there were almost no changes in the percentage of slough at baseline and day 3 in the conventional group. In comparison to the percentage of slough in the conventional group (75.62%), the ulcers in MDT group were successfully debrided on day 6 (zero slough). On day 9, ulcers in MDT still maintained with no slough whereas there was still 67.31% slough percentage in the conventional group. Overall, the ulcers in MDT group achieved a significant reduction in slough percentage on day 3 and continued to achieve complete debridement on day 6 as compared to ulcers in the conventional group. Hence, ulcers treated with MDT achieved significant reduction in slough percentage and complete debridement faster than the conventional method.

Table 3: Relationship between independent variables and percentage of slough (n=110)

Research variables	Statistical test	p value
Age	Pearson's correlation, r =0.095	p=0.323
Gender	Independent sample Mann-Whitney U test	p=0.61
Type of diabetes	Independent sample t test	p=0.292
HbA1c	Pearson's correlation, r = -0.119	p=0.215
Duration of diabetes	Spearman's correlation, r_s = 0.13	p=0.893
Grade of ulcer	Independent samples Mann-Whitney U test	p=0.326
Size of ulcer	Pearson's correlation, r =-0.115	p=0.232
Site of ulcer	Spearman's correlation, $\boldsymbol{r_s}$**= 0.269***	**p=0.004**
Duration of ulcer	Spearman's correlation, r_s = 0.095	p=0.321

*Correlation is significant at the 0.05 level (2 tailed)

The secondary objective of the present study was to evaluate the relationship between selected independent variables such age, gender, type of diabetes, HbA1c, duration of diabetes, grade of ulcer, duration of ulcer, site of ulcer with the dependent variable (percentage of slough) among the 110 participants in the study. The findings revealed no significant relationship between selected research variables such as age, gender, type of diabetes, HbA1c, duration of diabetes, grade of ulcer, size of ulcer, duration of ulcer, and slough percentage in the study population. The only variable which indicated a significant relationship with slough percentage was the site of ulcer. The site of ulcer showed a positive correlation with the percentage of slough (Spearman's correlation, r_s=0.269, p=0.004).

III. Discussion

The study population of 110 adult patients with DFU comprised of more males than females with an average age 61.5 years. Majority of study population had been diabetic for more than 10 years whereas diabetes history of 5 years. Type I and Type II diabetes were equally represented in the study population with poor control of glucose (8%). Most of the DFU fell under Grade 3 Wagner classification with a ulcer history of more than 6 months, the least was less than 6 weeks. DFUs in the study were predominantly represented at the plantar region followed by forefoot, dorsum and hindfoot (least). All the baseline characteristics such as age, gender, type of diabetes, HbA1c, duration of diabetes, grade of ulcer, site and duration of ulcer were homogenous between both groups except for size of ulcer. The average size of ulcer in MDT group was 2x bigger than conventional group at baseline. The statistical analysis showed normal distribution of data in the study population based on the numerical value of skewness and kurtosis. In view of the normal distribution of data, repeated-measure (Rm)ANCOVA was performed (size as covariate) to compare mean slough percentage between MDT and conventional group at baseline, day 3, day 6 and day 9. The findings indicated there were

significant differences between both groups in relation to slough percentage at day 3, day 6, and day 9 in the present study. Slough reduction was significantly faster in 3 days with MDT as compared to conventional method. Complete debridement was achieved on day 6 and maintained zero slough till day 9 whereas there was still 67.31% of slough in the conventional group on day 9. Independent sample t-test was performed to compare average wound size between both groups from baseline to day 9. Due to the non-homogeneity of wound size at baseline, therefore the wound size was not concluded to be significant at day 3, day 6 and day 9. However, the wound size reduction was shown to be higher in MDT group as compared to conventional group ($1.42cm^2$vs $0.45\ cm^2$) from baseline to day 9. The findings also indicated the site of ulcer had a significant relationship with the slough percentage in the present study. Overall, the result showed MDT was significantly more effective than conventional method in the treatment of DFU based on slough reduction at day 3, day 6 and day 9.

Slough is a common phenomenon in DFU and prolonged existence of slough promotes infection, biofilm, and impede healing. Therefore, slough must be removed from the wound bed to promote granulation and wound closure. Reduction in slough could lead to faster healing and lesser foot complications among diabetics.[33] The primary outcome of the present study showed that reduction of slough percentage was higher in the MDT group as compared to the conventional method. Time to debridement was proven to be shorter in MDT group as compared to conventional group at day 3, day 6 and day 9. Time to debridement is defined as time taken to remove slough/necrotic tissue from the wound bed. Rapid debridement was achieved in 3 days and complete debridement in 6 days. The ulcers in the conventional group did not even 50% slough reduction on day 9, whereby there was still 67.31% average mean slough on day 9. The differences in slough percentage between MDT and conventional method was statistically significant ($p<0.001$). Based on the result, MDT is more effective than the conventional method in the treatment of DFU than conventional method from baseline to day 3, day 6 and day 9. Since there is the difference in slough percentage was statistically significant, therefore Alternative hypothesis is accepted.

To the researcher's knowledge, the findings in the present study were the first to demonstrate significant shorter time to debridement with MDT on day 3 and complete debridement on day 6, 9 in DFU treated with MDT using *Luciliacuprina.* Undoubtedly, the findings of the present study corroborate with previous comparison studies between MDT and conventional method in DFU as mentioned in the literature review.[34,35] However, the findings in the study by Sherman (2003) and Azad et al (2016) showed time taken to achieve complete debridement was one month as compared to 6 days in the present study. In one study by Opletalová et al. (2012)[36] on non-diabetic based foot ulcer, significant slough reduction with MDT was observed on day 8 (54.5%) as compared to control group (66.5%). In a similar finding[37], complete debridement was achieved in 1.9 weeks in 10 patients treated with MDT. Averagely,the time taken to achieve rapid debridement was within 2 weeks and complete debridement within 4 weeks as reported in previous studies with MDT in previous studies.[37,38] The finding in the present study is considered to be the shortest significant time to debridement observed with MDT using *Luciliacuprina*. Ultimately, the outcome of the present study demonstrated the superior efficacy of MDT in debriding DFUs as compared to the conventional method (non-surgical). The significant reduction in slough percentage within 3-6 days with 1-2 cycle of maggot application (200 maggots each cycle) had revealed the excellent potential benefit of MDT in the debridement of DFU.

IV. Conclusion

Chronic wounds such as dfu will not be able to heal without effective debridement. Debridement enables devitalized tissue to be removed from the wound bed which is a barrier for granulation of tissue and further treatment of the wound for. Rapid and effective debridement of diabetic foot ulcer with MDT had been demonstrated as compared to conventional method in the present study. Most of the published articles supported the use of MDT for debridement but without conclusive outcomes with statistical significance. The significant findings in the present study had increased the evidence base for MDT with *Luciliacuprina* in the treatment of dfus in Malaysia. This may bring MDT a step closer to be integrated into debridement protocol of dfuin healthcare settings to improve healing outcomes. Since the site of ulcer was the only factor which had been shown in the study to affect the slough percentage, consideration of the offloading needs to be implemented for plantar regions to enhance faster healing. Based on the findings, MDT should be considered as the first line in the debridement protocol of indicated diabetic foot ulcers with sloughy, necrotic tissue and not as the last option in chronic wound management. Delay in debridement could imminently prolong wound healing which ultimately cause foot complication and in worst case, lower limb amputation. However, there were a few limitations.Due to the time and cost constraints, the present study was a short-term prospective controlled study for 9 days. A longer period of study could have been helpful to determine the continuous effect of MDT in the reduction of slough percentage till wound closure. Furthermore, recurrent of slough presentation in diabetic foot ulcers and the effect of maintenance debridement with MDT could have been investigated if the study was conducted for a minimum of 4 weeks. Another limitation was the size of the diabetic foot ulcer. The size of ulcer in the MDT group was double the size of ulcers in the conventional group. Homogenous size of ulcer

between MDT and CVT group could have enhanced precision in the evaluation of size reduction in the present study. Furthermore, it was difficult to recruit participants with similar size of ulcer in the actual clinical setting in a short span of time. Therefore, future studies with MDT should consider a minimum of 4 week study duration to investigate the efficacy

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