The hierarchy of evidence

In this chapter, the selected pieces of literature obtained from the research process will be critically appraised and analyzed. Critical appraisal is a systematic method of evaluating the strengths and limitations of a piece of evidence in order to establish its credibility, value and applicability into practice (Valente, 2003 as cited in Coughlan, Cronin & Ryan, 2007). The tools developed by CASP will used to critique literature in this dissertation. These include checklists for the major study designs including randomized controlled trials and cohort studies (See appendix). A hierarchy of evidence will also be established to classify the literature according to its strength and methodological approach.

3. 2 – Hierarchy of Evidence

Evidence-based practice is a way to ensure the integration of best research evidence with clinical expertise and patient values (Sackett, Strauss & Richardson, 2000 as cited in Akobeng, 2004). Diffent study designs and methodologies offer different strength and validity in answering clinical questions on the effectiveness of interventions. A hierarchy of evidence therefore needs to be obtained. The hierarchy serves as a framework for ranking evidence and indicates which studies should be given more importance in the evaluation of the PICO question (Akobeng, 2005). The hierarchy framework developed by Evans (2003) relies on three important elements which are effectiveness, appropriateness and feasibility (See appendix).

When evaluating a health care intervention, Randomised Controlled Trials (RCT’s) are regarded to provide the most powerful forms of evidence. The RCT is “ the most scientifically rigorous method of hypthesis testing

available” (Last, 2001, as cited in Akobeng, 2005, pg 840) and is considered as “ the gold standard trial for evaluating the effectiveness of interventions” (McGovern, 2001, as cited in Akobeng, 2005, pg 840). This is because the random assignment of participants in an RCT minimizes the risk of confounding factors that may influence findings thus obtaining less biased and more reliable results (Evans, 2003). Evidence is also provided by other designs such as non-randomsied controlled trials and uncontrolled trials but the degree of error or bias is high (Dawson-Saunders & Trapp, 1994 as cited in Evans, 2003).

3. 3 – Appraisal of Literature

This dissertation will include six studies: four RCT’s, a retrospective chart review and a quasi-experimental research. The RCT’s are ranked as ‘ Good’ in all elements of effectiveness, appropriateness and feasbility according to Evans (2003) framework. The retrospective chart review (non-randomised controlled trial) is classified as ‘ Fair’ in the only element of effectiveness. The quasi-experimental research (uncontrolled trial) is placed at the same level of the non-randomised controlled trial. ‘ Good’ level of evidence forms a good basis for clinical practice and embraces a low risk of error. On the other hand ‘ Fair’ level of evidence may contain some degree of error and does not provide strong evidence-based practice. The selected clinical studies will be critically appraised according to their strength level and validity in descending order as identified by the hierarchy of evidence.

3. 3. 1 – Maggot Therapy for Wound Debridement – A Randomized Multicenter Trial – Opletalova, K., Blaizot, X., Mourgeon, B., Chene, Y., Creveuil, C., Combemale, P., Laplaud, AL., Sohyer-Lebreuilly, I., & Dompmartin, A. (2012).

Opletalova et al (2012) carried out a prospective, double-blinded, randomized controlled trial to examine the effectiveness of bagged larvae on wound debridement in comparision with conventional therapy. This trial carries numerous strengths which make the whole study relevant, valid and reliable. It involved 105 patients with a chronic sloughy ulcer on the lower limb. The study was carried out in two hospital referral centers in France (Caen and Lyon) between March 2005 and December 2008. Recruiting subjects from a wider population may have increased the generalisability of the subsequent results.

Participants selected had sloughy venous leg ulcers with a surface area of 40cm2 or smaller, less than 2cm2 deep and an ankle brachial index of 0. 8 or higher. Participants included willingly gave their informed consent. Exclusion criteria included pregnancy and lactation, neuropathic and perforated foot wounds, dementia and previous hospitalization for chronic ulcers. Patients were allocated into two groups: an experimental group with larval dressings (51) and a control group with conventional dressings (54) using a randomisation list that was stratified by center. Such stratified randomisation helps to strengthen the credibility of the study.

For the experimental group, eighty sterile maggots of the Lucilia sericata species were applied to the wound bed using the contained technique. MDT was carried out twice weekly for 2 weeks. One or two dressings were applied

during each change depending on the size of the wound. Participants within the control group had their wound surgically debrided three times a week by means of a scalpel. Topical anesthesia was applied 30 minutes before the debridement. The quality of surgical debridement provided was high owing mainly to hospitalization in the dermatology department and a team of highly-trained nursing staff specialized in wound care. Such increased quality of debridement in the control group may have reduced the differences between the two groups improving the reliability of the results. Debridement was considered complete when all slough was removed and red granulating tissue started to appear. Hydrogel covered with a hydrocolloid dressing was used on dry wounds and an alginate or fiber-based dressing was used on oozing wounds.

Digital photographs were taken to determine the quantification of percentage of slough and surface of the wounds. The main outcome of the study was percentage of slough at day 15. This was calculated by dividing slough area by wound area; both measured using computerized planimetry software (Canvas, version 10; ACD Systems). The software also calculated the circumference of traced boundaries, the area inside the boundaries and the percentage of slough areas within the wound. Secondary outcomes include wound healing, ulcer pain, swab cultures for detection of MRSA and Pseudomonas aeruginosa and time needed for wound care.

This trial is the most valid in this dissertation. It is based on rigorous methods in an attempt to eliminate possible subjective bias. Patients were unaware of wound care schedules and were blindfolded during the treatment to ensure that they did not know which treatment was being provided. To

make sure patients were blinded only enclosed dressings could be used. The authors assumed that the efficacy of bagged and free larvae was equal since their effect is not related to the crawling action on wound surface. Outcome measures were also evaluated with a blinded assessment by a single observer increasing the validity of the results. All patients were discharged after 15 days of treatment with a follow-up visit after another two weeks. The only weak point is the short duration of the trial. This RCT was probably not long enough to assess the complete healing of leg ulcers and concentrated on short-term goals such as wound debridement as a result.

3. 3. 2 – Larval Therapy for Leg Ulcer (VenUS II): Randomised Controlled Trial – Dumville, JC., Worthy, G., Bland, JM., Cullum, N., Dowson, C., Iglesias, C., Mitchell, JL., Nelson, EA., Soares, MO., & Torgerson, DJ. (2009).

Dumville et al (2009) conducted a large study comparing the clinical effectiveness of MDT with a standard conventional treatment (hydrogel). The study has a very clear and focused question. It involved 267 patients with at least one venous or mixed venous and arterial ulcer covered by at least 25% slough or necrotic tissue. This was a pragmatic multicentre, randomised, open trial with equal randomisation, carried out in 22 centres in the UK between July 2004 and May 2007. The fact that data was obtained from different medical settings may have increased the reliablity of the results. This is because a wider range of healthcare providers would deliver care decreasing the chance of variability. The main outcome measures of the study were time to healing, time to debridement, health related quality of life, presence of bacteria especially MRSA, adverse events and ulcer related pain.

Elegible patients had non-healing leg ulcers with an area of 5cm2 or less. In case of multiple ulcers, the largest ulcer was selected as the ulcer of reference. Those patients who were pregnant or lactating, allergic to hydrogel, had oedematous legs or were taking anticoagulants were excluded. After participants consented to the trial they were randomized to receive loose larvae (94), bagged larvae (86) or hydrogel (87). Randomisation was achieved using permuted blocks with stratification by trial centre and ulcer area (â‰¤5 cm2 or > 5 cm2). This approach was useful in balancing randomness, thereby increasing the validity of the study.

Larvae of Lucilia sericata were used for about 3-4 days with nurses assessing the participant during this time period. If more MDT was required, hydrogel and bandage were applied while more larvae were ordered. Participants within the hydrogel control group received a knitted viscose dressing with hydrogel and compression depending on the ankle brachial pressure index and patient tolerance. The frequency of application was determined by the nurse overseeing the patient. After debridement, all participants received a standard knitted viscose dressing with or without compression. The maximum length of follow-up was about 12 months.

Time to complete healing of the reference ulcer was the primary outcome. Photographs were taken by nurses every week for six months and then continued on a monthly basis for the duration of the treatment. An ulcer was considered healed when there was complete epithelial coverage in the absence of eschar. These photographs were examined to establish healing status by two independent assessors who were masked to the treatment group. This blinded outcome assessment helped to protect against observer

bias. While this increases the validity of the study there was no information regarding blinding in participants.

This study is believed to be the first RCT investigating the effects of MDT on wound healing. It contains high quality evidence due to VenUS II team's participation and large population size but there are several limitations to the study. These include the lack of follow up on how many ulcers remained debrided in the long-term. Another problem is the level of autonomy of nursing staff with regards to treatment which could have had an influence on the measured outcomes. The researchers also did not explore any other bacterial burdens except for MRSA, so are unable to draw conclusions on the effects of MDT on other types of bacteria found within the wound bed.

3. 3. 3 – Cost Effectiveness Analysis of Larval Therapy for Leg Ulcers – Soares, MO., Iglesias, CP., Bland, JM., Cullum, N., Dumville, JC., Nelson, EA., Torgerson, DJ., & Worthy, G. (2009).

Soares et al (2009) undertook an economic evaluation to assess the cost effectiveness of MDT versus hydrogel in the treatment of leg ulcers. This was a randomized open trial with equal randomization carried out in the UK with the help of the VenUS II team. It involved 267 patients with venous or mixed venous and arterial ulcers with at least 25% slough or necrotic tissue. The main outcome measure was cost effectiveness over a time horizon of 12 months.

Participants consented to the trial and were randomly allocated to receive bagged larvae, loose larvae or hydrogel. Larvae were left in the wound for about 3 to 4 days. During this time patients received nursing care for wound

assessment and rehydration. The amount of slough or necrotic tissue remaining on removal of larvae was assessed by the nurse to decide whether further application of MDT was needed. Full details of the trial are mentioned above in the accompanying study carried out by Dumville et al (2009).

Cost effectiveness and a cost utility analysis were carried out using patient level data collected within the leg ulcer trial (VenUS II). Cost effectiveness analysis was expressed in terms of incremental costs per ulcer-free day while cost utility in terms of incremental costs per quality adjusted life years. The year of pricing was 2006 and the time horizon was 12 months after recruitment. The time horizon of the economic analysis was restricted to the duration of the trial and this could have limited the study. Analyses were conducted using Stata 10 (StataCorp 2007, TX, USA). Larval groups were analyzed as a single group, that is data from both groups was pooled. Data on use of resources was gathered from nurse completed and patient completed questionnaires. Health benefits were measured in terms of ulcer-free days and quality adjusted life years (QALYs).

This is the first full economic evaluation investigating the value for money for a single phase of MDT compared to hydrogel. The only other existing analysis is a partial cost consequences analysis carried out by Wayman et al (2000) which will be critiqued later. Although the results of this study have a strong external validity for the UK NHS, the applicability of these findings around the world may need further consideration. This is because variations on the use of debriding agents in different settings may have an impact on the cost effectiveness of these treatments.

3. 3. 4 – The Cost Effectiveness of Larval Therapy in Venous Ulcers – Wayman, J., Nirojogi, V., Walker, A., Sowinski, A., & Walker, MA. (2000).

Wayman et al (2000) conducted a prospective randomised trial comparing the efficacy and cost of MDT with a conventional pharmaceutical agent in the treatment of necrotic venous leg ulcers. The two therapies tested were MDT versus hydrogel dressings. The study which involved 12 patients with sloughy venous leg ulcers was carried out in Cumbria, UK.

Patients reported to the leg ulcer service and were seen by a leg ulcer specialist nurse. Exclusion criteria were presence of arterial insufficiency and previous failed therapy undergone by the patient. Twelve patients with venous ulceration were recruited to participate in the study. Participants were randomized by the sealed envelope technique to receive either hydrogel (Group 1) or MDT (Group 2). This is not a good method for achieving true randomisation as it cannot be certain that the allocation was concealed. Any health care provider may have held envelopes to a strong light to read the next allocation. Alternatively, envelopes may have been opened prior to placing the patient.

Patients in the control group received a standard hydrogel dressing (Intrasite gel). The gel was applied to the wound, then topped with an appropriate secondary dressing (Melolin or Telfa) and left in place for a maximum of 3 days. Sterile Lucilia sericata larvae were used for Group 2. A specially designed containment dressing made up of a fine nylon mesh laid across an adhesive hydrocolloid border was used to cover the larvae to prevent them from migrating. Larvae were removed after 3 days and replaced if required.

For each patient, details such as age, sex, ulcer size and duration were recorded. Patients were reviewed every 72 hours for a maximum of one month or until debridement was complete. The outcome measure used for clinical effectiveness was time to debridement which depends on amount of discharge from the ulcer. Success of debridement was determined by the nurse applying the dressings. Dressings in the control group, however, were better than the other at absorbing exudates. This may have hindered the balance between groups influencing the results. The differences made by secondary dressings were minimized by standardizing their application by the same health care provider. An ulcer was considered debrided when the percentage area of slough was less than 5%. Slough percentage area was calculated as a percentage of the total ulcer surface area by mapping the ulcer onto a clear centimetre grid. The outcome measures for cost-effectiveness were number of nursing visits, cost of nursing time and cost of dressings to achieve debridement or for one month of treatment. Dressings were purchased at the standard UK costs and nursing time was calculated according to the pay scale of an ‘ F’ grade nurse. The non-parametric Mann-Whitney U test was utilized for statistical analysis. When p <0. 05 significance was regarded to have been reached.

A deficiency of this study is the small sample size which may have decreased the reliability of the results. Assessments of debridement and exudates were not blinded which make study findings prone to an element of bias. The study also does not take into account healing rates as the main outcome measure which undoubtedly for the patient is the most important outcome.

Also, costs mentioned in the study do not include travel expenses incurred and cost of in-patient stay.

3. 3. 5 – Maggot Therapy for Treating Diabetic Foot Ulcers Unresponsive to Conventional Therapy – Sherman, RA. (2003).

Sherman (2003) performed a cohort study investigating the effectiveness of MDT in the treatment of chronic leg and foot ulcers initially failing conventional therapy. It involved a retrospective comparision of changes in 18 diabetic patients with 20 non-healing ulcers treated with either MDT or standard surgical or non-surgical treatments. The study was carried out in California, USA.

The participants were chosen from 143 applicants referred to MDT between 1990 and 1995. Only unhealed ulcers and ulcers whose contours could be measured by planimetry within the first two weeks of treatment were made eligible for this study. In this cohort, six ulcers were treated with conventional therapy, six with MDT and eight with conventional therapy then MDT. This study has methodological limitations as it did not employ a randomisation method to establish which intervention group participants would be in. Also being a retrospective study, it can leave room for selection bias compromising the generalisability of the findings.

MDT consisted of sterile Lucilia sericata larvae applied to the wound at a density of 5-8 maggots/cm2 with loose gauze. A hydrocolloid ring was added around the wound margins to protect the surrounding skin. A porous Dacron chiffon or nylon stocking was glued or taped to the hydrocolloid ring to create a cage-like dressing for maggots. A gauze pad was placed on top of

the dressing to absorb liquefied necrotic drainage. Maggots were replaced in cycles of 48 hours but the top layer of gauze was changed every 4-6 hours. One or two cycles of maggots were used each week with saline or sodium hypochlorite-drenched gauze dressing applied between MDT cycles and after treatment was complete. Patients receiving conventional therapy had treatment prescribed by their primary care or wound care providers.

The study had four main outcome measures: amount of necrotic tissue debrided, amount of granulating tissue noted, change in wound surface area and time to complete wound healing. A retrospective study was in this case the most adapt way of carrying this research since it is better at analyzing multiple outcomes. The healing of ulcers was evaluated via digital photographs looking at the length, width circumference and surface area of wounds. Repeated measures of ANOVA were used to further assess the clinical efficacy of MDT. Ulcers that were treated by conventional therapy first and then MDT were compared through paired t tests. Ulcers treated by MDT had a larger surface area (~9. 7cm2) while conventional therapy wounds had a smaller surface are (~3. 8 cm2). However, according to the authors this does not make a significant statistical difference.

The authors suggest that further investigation using a larger population group and participants with less advanced disease should be done to obtain better results about the impact of MDT on total wound debridement. The study also does not consider the cost effectiveness of the treatment or investigate the environment in which MDT can become ineffective.

3. 3. 6 – Biosurgery Supports Granulation and Debridement in Chronic Wounds – Clinical Data and Remittance Spectroscopy Measurement – Wollina, U., Liebold, K., Schmidt, WD., Hartmann, M., & Fassler, D. (2002).

Wollina et al (2002) carried out a trial investigating 30 patients with chronic leg ulcers of mixed origin treated with MDT. The purpose of the study was to determine the clinical efficacy, side effects and possible modes of action of biosurgery by a clinical wound score and contact-free spectroscopy. The study, however, included a number of weak components that lessened the clinical trial's overall strength and validity. It was conducted in Dresden, Germany.

Patients investigated were aged between 18-89 years (mean age 66. 3 ± 16. 0 years) and had chronic leg and foot ulcers. Further inclusion and exclusion criteria were not mentioned, so any other factors that may have influenced the results cannot be discussed. The lack of random assignment makes it difficult to eliminate confounding variables hence increasing the threats to internal validity.

Debridement was performed using biosurgery. Two day old Lucilia sericata larvae combined with vacuseal gel (Coloplast) were applied. A sterile mesh net was placed on top of the gel sheets to cover the wounds and another dressing was added to absorb the exudates. Larvae were removed by shower after 3-4 days. The lack of a control group also decreases the validity of the study. Without a comparision group, it is difficult to establish the significance of an observed change. The change could be the result of

historical changes unrelated to the treatment, the maturation of the subject, or an artifact of testing.

Presence of granulating tissue including quantity, colour and consistency were documented by means of a wound score. Wound scores were read before and after application of maggots making this study a pre-test pos-test quasi-experimental research. Remittance spectroscopy which registers the proportion of remitted light from the skin was used in monitoring. Remitted light includes regular reflected light and light which is scattered or absorbed within the tissue penetrating the skin surface again in the opposite direction. These spectroscopic measurements of the skin were performed with the equipment SKINREM®VIS/NIR consisting of two couple diode-array spectrometers. This may have increased the reliability of the results due to the contact-free measuring nature of the device which prevents the impairment of microcirculation by pressure. Spectroscopic readings were taken in eight patients before and after biosurgery. Measurements were taken above the ulcer and above the granulating tissue respectively.

The quasi-experimental design of this study, however, helps to reduce artificiality and minimize threat to external validity which enables research findings to be applied to other settings and generalized to other populations.

3. 4 – Ethical Issues

Written informed consent was obtained in four studies (Sherman, 2003; Dumville et al, 2009; Soares et al, 2009 & Opletalova et al, 2012). Three of these studies (Dumville et al, 2009; Soares et al, 2009 & Opletalova et al, 2012) were also approved by the local ethics committee. An RCT, despite

being the gold standard trial for assessing the effectiveness of interventions presents a range of ethical problems (Clinical Research Centre [CRC], 2011). One problem is when comparing treatment interventions. Participants within the control group can be deprived of potential beneficial experimental interventions. Another ethical issue is when the practitioner has a dual role and is also the investigator besides delivering the treatment. Other ethical considerations include randomisation and blinding. The question is whether it's ethical that the process of randomisation is carried out by a computer program rather than based on the participant's needs and characteristics. Another enquiry is that in some studies, neither the participants (single-blinded) nor the investigators (double-blinded) knew which treatment the subject was undergoing.

3. 5 – Conclusion

The selected pieces of literature were critically appraised on their methodologies, in order to establish which research was most valid in the derivation of information to promote evidence based practice. A summary of the clinical trials that were reviewed is listed in Table 3. In the next chapter the overall findings both in the form of data and indications will be discussed in relation to the PICO question.

Table 3: Summary of clinical trials reviewed regarding the effectiveness of MDT

Author/s

Year Published

Country

Type of Study

Population

Intervention

Comparision

Outcome

Wayman et al

2000

UK

Randomised controlled trial

12 patients with sloughy venous ulcers.

MDT

Hydrogel

Rapid debridement of venous ulcers and cost-effective compared to hydrogel.

Wollina et al

2002

Germany

Quasi-experimental research

30 patients with chronic lef ulcers of mixed origin.

MDT

Debridement was rapid and selective. An increase in tissue oxygention recored by remittance spectra.

Sherman

2003

USA

Retrospective Chart Review

18 diabetic patients with 20 non-healing leg and foot ulcers.

MDT

Conventional treatment

MDT was more effective and efficient in debriding foot and leg ulcers than conventional care.

Dumville et al

2009

UK

Randomised controlled trial

267 patients with at least one venous or mixed venous and arterial ulcer, with at least 25% coverage of slough or necrotic tissue and an ankle brachial pressure index of 0. 6 or more.

Bagged larvae and loose larvae

Hydrogel

Time to healing was not improved by MDT but time to debridement was significantly reduced.

Soares et al

2009

UK

Randomised controlled trial

267 patients with a venous or mixed venous and arterial ulcers with at least 25% coverage of slough or necrotic tissue.

Bagged larvae and loose larvae

Hydrogel

Healing time of sloughy or necrotic leg ulcers was faster with MDT and at similar cost to treatment with hydrogel.

Opletalova et al

2012

France

Randomised controlled trial

119 patients with a sloughy leg ulcer 40 cm2 or smaller, less than 2

cm deep and an ankle brachial index of 0. 8 or higher.

Bagged larvae

Conventional treatment

Debridement by MDT is significantly faster and occurs during the first week of treatment.