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Review Paper

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WOUND HEALING: A REVIEW ON DESIGNING OF A RESEARCH PROTOCOL

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Declaration

The Declaration of the author for publication of Research Paper in Asian Journal of Modern and Ayurvedic Medical Science (ISSN 2279-0772) We Awadhesh Kr. Pandey,Prof. M. Sahu[and] Pathak Meenakshi S.N the authors of the research paper entitled Wound Healing: A Review on designing of a Research Protocol declare that ,we take the responsibility of the content and material of my paper as we ourself have written it and also have read the manuscript of our paper carefully. Also, we hereby give our consent to publish our paper in ajmams , This research paper is our original work and no part of it or it's similar version is published or has been sent for publication anywhere else.we authorise the Editorial Board of the Journal to modify and edit the manuscript. we also give our consent to the publisher of ajmams to own the copyright of our research paper.

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ABSTRACT:

Wound healing disorders present a serious clinical problem and are likely toincrease since they are associated with diseases such as diabetes, hypertension,and obesity The process of wound healing comprises of different biological changes, including inflammation,epithelial growth and its differentiation, fibrous tissue production ,collagen deposition and angiogenesis.

The combination of new and classic approaches has allowed the Researchers to make exciting results in the field of wound healing .The relevance of this field has generated great interest in designing of models and methods for the study of wound healing. The present study is to provide information about a combination of classic and new protocols of wound healing.

Keywords -Hypothesis, Sample size,Ethics committee,Consent

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INTRODUCTION Wound healing reasearch is especially dependent on the use of animal models perhaps more than the biologic study of other systems.This is the reason why researchers involved inthe complexities of wound healing research, struggling to find or develop reliable means of assessing the effectiveness of a wound healing drug .

So in planning of a wound healing research protocol various aspects need to be considered, including proposing a hypothesis (research question), Selection of Drug ,Toxic study of the drug ,choosing an appropriate design for both in experimental and clinical study, obtaining ethical approval, calculating sample size, , and addressing the source of funding,Thereafter report research findings as a means for dispersal of knowledge.

BACKGROUND

A completely healed wound can be defined as one that has returned to its normal anatomic structure, function and appearance within a reasonable period of time normally in about four to six weeks(Enoch and Price, 2004).

Any wound that has not reached the above state would be considered a chronic, non-healing wound. The problem may lie in disruption at one or more points in the phases of wound healing (haemostasis, inflammation, proliferation, or remodelling).

There is alteration in the inflammatory response of acute wound healing inj comparison to chronic wounds. On a molecular level, an alternation in the balance between various cytokines, growth factors, protease activity, matrix metalloproteinases (MMPs) and tissue inhibitors of matrix metalloproteinases (TIMPs) is observed in chronic wounds (Cook et al, 2000).

In addition, alteration in the morphology and proliferation rate of fibroblasts, keratinocyte activity, and accumulation of oxygen derived free radicals (Clark, 1996) and necrotic tissue (Clark et al, 1982; Enoch and Leaper, 2008) all play a role in inhibiting wound healing.

AIMS AND OBJECTIVES

Hypothesis is an essential initial requirement to plan for any effective research. The objective must be simple, focused and clear. The research question may arise from a specific problem, clinical or experimental or Biochemical , that has been previously identified.

If planning for assessment of drug is necessary then Toxicity study of drug is also important before trial. It is also required to establish the outcome measure (endpoint) of the study and the potential implications of the study.

Another requirement is to ensure adequacy of resources (money, materials, patients and staff), and this is often aided by performing a pilot study. A thorough literature search should then be performed and the study designed.

TRIAL DESIGN FOR EXPERIMENTAL STUDY

The Study design is based on two aspects :-

PART I.

Experimental Models of Wound Healing

A: In Vivo Animal Models

B: Reviews of Specific Model Systems

C: Human Wound Healing Models

D: In Vitro Models

PART II.

Analysis and Manipulation of Wound Healing

EXPERIMENTAL MODELS OF WOUND HEALING

Excisionalwound model

A circular wound of about 8 mm diameter (fullthickness, completely transdermal) will made on the pre-shaved, sterile (wiped with 70% alcohol) over dorsal thoracic region of mice.

The presented excisional wound model provides accessment to investigate

Histopathological changes in granulation tissue formation, reepithelialization, and angiogenic processes

Incisional wound model

In incision wound model ,6cm long para vertebral incisions will made through the full thickness of the skin on either side of the vertebral coloum of the mice ,the wound will closed with intruppted suture of 1 cm apart.

The skin breaking strength will be assesed on 10^{th} day

Breaking strength and tensile strengthare the two most commonly usedterms to describe the wound strength..

Tensile strength is defined as the load per unit of cross-sectional area at rupture.

Breakingstrength is simply the load required to break a wound and does not account forwound geometry.

Dead space wound model

The polyvinyl alcohol (PVA) sponge model is an extensively used modelfor wound-healing studies. In this model a biologically inert substance implanted subcutaneously and intowhich all phases of the healing process are expressed.

The PVA sponge model belongs to the class of dead-space models usedfor studying granulation and reparative tissue ingrowth.

The model is best used foracute studies because it begins to elicit foreign body reaction with giant cellaccumulation and fibrosis after about 2 wk in the rat and 4 wk in the mouse.

Within these time parameters, it remains a highly reproducible and biologicallyvalid model for studying acute healing responses.

Pig Graft Donor Site Model

Contraction and reepithelisationcan be evaluated by topical application on full thickness excisional wounds or in.

Chick Chorioallantoic Membrane or **Rabbit Cornea Model**

Induction of angiogenesis can be evaluated in chick chorioallantoicmembrane or rabbitcornea model.

Rat Linear Incision Model

Biomechanics or breaking strength can be evaluated in this model.

Impaired Healing Models

Impaired healing models can be used in irradiation, administration of corticosteroids or chemotherapeutic drugs or drug-induced or genetic diabetes mellitus in mice, rats,hamsters, guinea pigs and young pigs.

Rabbit Ear Dermal Ulcer Model

The rabbit ear dermalulcer model can be evaluated for ischemia in the wound.

The Fetal Model

The fetal model can be evaluated for scarless healing in mammals.

TRIAL DESIGN FOR CLINICAL STUDY

A wide range of clinical epidemiological methods or trial designs are available for evaluating wound healing such as case studies, clinical surveys, cohort studies, case-control studies, intervention trials, randomised controlled trials (RCTs) and cross-over trials.

The essential purpose in all designs must be to reduce all types of bias and in many instances this can be established via stratified randomisation.

Case studies

This type of study might be sufficient for evaluating a new device or dressing; for instance, a novel topical agent for treating burns. This could be carried out to test the efficacy and other unexpected possible side-effects of a treatment before planning a large trial. As such, this can be considered to be a pilot study.

Clinical surveys

These are also called 'cross-sectional' studies, often using samples, and are designed to measure the prevalence, and more particularly to study the associations between health status and various causing factors (e.g. association between spina bifida and pressure ulcerations).

The information gained from clinical surveys could be used to plan further studies and thus again be used as a pilot study.

Cohort studies

By first surveying, and then following a sample of people, it is possible to measure by how much the incidence of a particular disease differs between those who are exposed to an treatment or not exposed to an treatment.

For example in patients of deep venous thrombosis to find what proportion develop venous ulceration after the use of stockings can be evaluated by this study design.

Case-control studies

In these studies, people with a disease (cases) and people without (controls) are investigated, essentially to find out whether 'exposure' to a factor of interest is greater among the cases than the controls .(e.g. smoking and arterial ulceration).

It is a focused research design that allows measurement of the strength of the association between a disease and its possible cause, or factors (such as health interventions) that can afford protection.

Intervention trials

By taking a sample of people and intervening among some but not others, it is possible to assess how much the level of health or incidence of disease has been altered by the intervention (e.g. to evaluate the effect of a new silver-containing dressing in expediting wound healing); randomly selected patients are intervened (given silver-containing dressings) to find if this form of treatment is effective and superior as compared with non-silver dressings.

Evidence from such trials is powerful, especially if randomised, controlled and blinded. Since the investigator has much more control over the factor he/she wishes to test, in many respects it is an excellent research design.

Randomised controlled trials (RCTs)

These are widely acknowledged as a powerful research tool for evaluating health technologies .Their principal strength is that they minimise bias result . Protection from selection bias is provided by random allocation to alternative technologies and analyses based on the groups as allocated, thereby ensuring that the groups being compared differ only by chance.

Ascertainment bias can be avoided by arranging that the outcome is assessed in ignorance of the treatment allocated. Co-intervention bias is minimised by blinding treatments (where possible) and by employing clearly described treatment policies, which should be identical for each group apart from the intervention under examination in the RCT

Cross-over trials

This is a special type of RCT that uses subjects as their own controls and thereby reduces random error and the sample size required. During the course of the trial, each subject crosses over from receiving one treatment to receiving the other. This strength has to be balanced against the problem of 'carry over' and order effects, so it can only be used in certain types of interventions.

However, in a significant proportion of wound studies, the status of the wound and/or the wound bed at the start of the study is not the same 8–12 weeks later when the wound is exposed to the second form of treatment. In such instances, comparison between two forms of treatment might not be truly meaningful.

Determination ofsample sizes

Sample size calculation is a vital part of the planning of a trial, and together with advice from a statistician, these measures can reduce the chances of obtaining erroneous results on completion of the study.

In simple terms, if an appropriate significance levelis not chosen or there are not enough patients/subjects in a particular study, the results obtained are often incorrect.

The trial must therefore be designed to be large enough to avoid this mistake.

wound assessments parameter

Type of wound
Aetiology and original mechanism of wounding
Duration of wound
Location
Dimensions of wound e.g. length, width, depth, circumference
Clinical characteristics of wound bed e.g. agranular, granulation, epithelium,slough,necrosis, eschar, bone, tendon, fibrin, presence of foreign bodies.
Wound edge appearance: e.g. level, raised, rolled, undermined, colour.
Peri wound appearance: e.g. erythema, oedema, induration, maceration,desiccation, dermatitis/eczema, callus, hyperkeratosis, pigmentation,allergic reactions.
Exudate: Type and colour e.g. serous, haemoserous, sanguineous,seropurulent, purulent, consistency - thick or thin and amount.
Odour:
Inflammatory changes - Classic signs and symptoms include erythema, oedema,pain and heat.
Wound Infection: classic signs and symptoms include pain, heat, erythema,oedema and purulence which tends to be more evident in acute surgical or traumatic wounds. In chronic wounds and especially if host response is compromised, the signs and symptoms may be more subtle or differ according to wound type and aetiology
a) Covert infection: also known as critical colonisation, local infection, topical infection or increased bacterial

burden, signs and symptoms may include static healing, rolled edges, bridging of tissues,increased exudate or discomfort.
b) Spreading infection: involvement of adjacent or regional structures e.g.cellulitis.
c) Systemic infection: systemic signs and symptoms may include loss of appetite, general malaise, pyrexia, increased white cells, raised C-reactive protein.
Wound pain: pain intensity assessed with a validated pain scale and determine aetiology and presentation e.g.
a) Non-cyclic wound pain - suture removal or debridement
b) Cyclic wound pain - daily dressings
c) Chronic wound pain - not related to manipulated interventions
.

Biochemical parameters of assessment -

Histopathological changes
Growth factor estimation –FGF, PDGF,VEGF,EDGF,TGFbeta2
Microbial load
Neovascularization
Collagen Type III estimation
Hydroxyprolene estimation
Angiogenesis measurement
Inflammatory mediator estimation - CYTOKININ and INTERLUKIN 4

ETHICAL APPROVAL

Any form of study that needs access to patients (questionnaire, investigation or treatment), patient records, or involves collecting patient data in any form needs approval from the appropriate ethics committee. This may be at the level of the, the university, the Ethics Committee or the Multicentre Research Ethics Committee, as in the case for large trials and those involving various centres/hospitals.

ETHICS COMMITTEES

The objective of the ethics committees is to review and to act in agreement with good clinical practice so as to protect the rights of subjects, to ensure that any clinical investigation done is ethical and scientifically valid, and not at the expense of fellow human beings .

CONSENT FOR RESEARCH

Informed consent is a doctrine by which patients may protect themselves from unwanted interventions and take responsibility for shaping their lives as they see fit (Herbert, 1996). Consent is required by law and not to get consent is to violate the patient's moral right of respect for autonomy.

FUNDING

Funding for research can be obtained from a variety of sources. For small to medium scale projects, the research and development directorate within the NHS or the university have a range of grants to help both new and established researchers initiate projects (e.g. pump priming grants and young researcher grants). In addition, particularly in wound healing research, a substantial amount of funding is provided by the industries and commercial companies (Enoch et al, 2007). The relationship between academia and industry is well established, and a significant number of recent advances in wound healing have obtained fruition due to this partnership. Contract research, collaborative research and consultancy are the three major forms of collaboration between academia and industry in wound healing research.

DOCUMENTATION AND CONFIDENTIALITY

These requirements should be considered primarily as a set of management tools which ensure that data is correctly and properly recorded,

and that the rights of patients are protected by independent overview.

Proper documentation enables the sponsor and healthcare professional to monitor, and the assessor adequate means to assess, the verification of the manufacturers' claims of the devices' technical performance.

Moreover, it ensures that a structured and disciplined approach is undertaken for the effective management and execution of clinical investigation, and for the reliability of the clinical data.

REPORTING RESEARCH FINDINGS

It is clearly important to report the findings of any research or a trial to the wider world and to the scientific community. This serves not only in disseminating knowledge, but also provides an opportunity for other professionals to critically analyse and scrutinise the findings, allowing theories to be challenged, and identify any pitfalls or omissions of the study.

The usual medium of such dispersal of knowledge is via presentations in international and national scientific conferences or publication of the results in peer-reviewed journals. Needless to say, publication in journals is more significant since it reaches a wider audience, can be accessed globally, becomes embedded in the medical literature, thus providing reference for future work, and above all, is available for more intense examination and critical analysis by innumerable experts in that field.

DISCUSSION

With rapidly advancing understanding in wound science and technology, medical research is poised to play an ever crucial role in modern life. The collaborative efforts of healthcare professionals, patients, public, ethics committees, and the government are essential to develop the high standards that are needed to conduct ethical research for the betterment of the human race.

With regard to how research should be undertaken, the greatest emphasis should lie in the choice of the research question. Once identified, it should be evaluated on three important aspects:

1- The potential implications of the study

2- The type of study design required

3- The resource implications.

In addition, clear and meticulous planning is vital before embarking on any study or trial, since many research projects are never completed. This can occur if the study was more difficult than anticipated or the researchers lacked the resources. Resource does not just refer to money, but to all the materials needed to complete the study, including patients, staff with appropriate skills and expertise, filing systems and computers. As well as planning, the components of a study should be tested before the research is begun in earnest. It is advisable to start the main study only when it has been piloted and found to work, or suitably modified if it has failed. The guiding rule is: 'Do not begin unless you are sure to finish'.

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