FACTORS ASSOCIATED WITH CHRONIC WOUNDS AMONG SURGICAL WOUNDS IN WOUND CLINIC FROM 2016 till 2019 IN HOSPITAL UNIVERSITI SAINS MALAYSIA.

By

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ABSTRAK

Latar belakang: Penjagaan luka telah menjadi antara aspek utama dalam bidang perubatan. Sejak kebelakangan ini penjagaan luka mendapat perhatian khusus dari syarikat farmaseutikal. Kaedah dan produk pencucian luka moden telah diperkenalkan untuk mempercepatkan proses penyembuhan luka. Pesakit yang mengalami luka pembedahan memerlukan rawatan and penjagaan luka untuk jangka masa panjang terutamanya dalam kes-kes luka kronik. Klinik penjagaan luka HUSM ditubuhkan pada tahun 2016 dan aktif menyediakan perkhidmatan penjagaan luka untuk pesakit di HUSM serta kawasan sekitarnya. Kajian ini adalah untuk mengenalpasti faktor-faktor yang berkaitan dengan luka kronik di kalangan luka pembedahan dari 2016 hingga 2019 di HUSM. Dengan mengenal pasti faktor yang berkaitan, penukaran luka pembedahan kepada luka kronik dapat dikurangkan.

Kaedah: Seramai 147 orang pesakit telah dipilih melalui data retrospektif dari klinik luka HUSM antara bulan Jun 2016 sehingga bulan Disember 2019. Mereka semua telah menjalani rawatan cuci luka untuk luka pembedahan di klinik luka HUSM. Data pesakit dikumpul di dalam borang data.

Keputusan: Seramai 147 pesakit telah dimasukkan ke dalam kajian ini, dan sebahagian besar daripada mereka adalah Melayu (96.6%). 80 daripadanya berusia kurang daripada 55 tahun, dan lebih separuh adalah Lelaki (52.4%). Dari segi komorbiditi, lebih separuh

daripada mereka menghidap diabetes mellitus (72.8%) dan tekanan darah tinggi (60.5%), dan hanya 23.1% mempunyai penyakit kardiovaskular**.**

Untuk ciri-ciri luka, terdapat 15 pesakit dengan luka yang bersih dan bersih tercemar. 5 luka pesakit didapati tercemar dan 115 pesakit mengalami luka kotor. Median saiz luka awal adalah 52cm^3 (julat interquartile: 18cm^3, 193.5cm^3). Bagi pesakit yang mengalami luka kronik, median saiz luka selepas 3 bulan adalah 4.5cm^3 (julat interquartile: 2.3cm^3, 8.5cm^3). Perkaitan penting ditemui di antara masa penyembuhan luka dengan status merokok (p=0.018), diabetes mellitus (p=0.008), dan tekanan darah tinggi (p=0.025). Terdapat lebih ramai perokok yang didapati mengalami luka kronik (57.1%) berbanding dengan pesakit yang luka sembuh dalam masa kurang daripada 3 bulan (35.7%).

Selain itu, perbezaan ketara ditemui dalam saiz luka awal antara pesakit dengan masa penyembuhan luka kurang daripada 3 bulan berbanding lebih daripada 3 bulan (p<00.001). Pesakit dengan luka kronik diperhatikan mempunyai saiz luka awal yang lebih besar berbanding pesakit yang luka sembuh dalam tempoh 3 bulan.

Hanya saiz luka yang signifikan dalam analisis multivariate. Peningkatan unit dalam saiz luka (cm3) akan meningkatkan kemungkinan luka kronik sebanyak 1%

Rumusan: Kajian ini menunjukkan pengaruh tabiat merokok yang ketara, comorbid seperti kencing manis dan tekanan darah tinggi sebagai faktor yang mempengaruhi proses penyembuhan luka dan menyebabkan luka yang lebih kronik di kalangan pesakit. Perkaitan penting yang terdapat di antara masa penyembuhan luka dengan status merokok (p=0.018), diabetes mellitus (p=0.004), dan tekanan darah tinggi (p=0.029). Terdapat lebih ramai perokok yang didapati mengalami luka kronik (57.1%) berbanding dengan pesakit yang luka sembuh dalam masa kurang daripada 3 bulan (35.7%). Selain itu, pesakit diabetes diperhatikan untuk menyumbang kepada bahagian yang lebih tinggi dalam luka kronik (91.4%) berbanding dengan luka akut (67.0%). Perkaitan penting

ditemui antara tekanan darah tinggi dan masa penyembuhan luka di mana 77.1% pesakit yang menghidap tekanan darah tinggi diperhatikan mengalami luka kronik berbanding 55.4% pada pesakit yang mengalami tekanan darah normal. Selain itu, perbezaan ketara ditemui dalam saiz luka awal antara pesakit dengan masa penyembuhan luka kurang daripada 3 bulan berbanding 3 bulan ($p<0.001$). Pesakit dengan luka kronik diperhatikan mempunyai luka awal yang lebih besar berbanding pesakit yang luka sembuh dalam 3 bulan.Hanya saiz luka yang signifikan dalam analisis multivariate. Peningkatan unit dalam saiz luka (cm3) akan meningkatkan kemungkinan untuk luka kronik sebanyak 1%

Kata Kunci: Luka pembedahan , luka pembedahan kronik, klinik luka HUSM

ABSTRACT

Background: Wound management have been a cornerstone in medical field. Wound management have taken leaps and bounds over the years with the latest advancement and products to improvise the healing process. Patients with surgical wounds require wound dressing and long term follow up especially in cases of chronic wound. Patients with chronic wound will undergo wound dressing for long term. Wound care clinic HUSM was establish in 2016 and have actively providing wound care service for patients in HUSM as well as the surrounding neighbourhood. This study is to establish factors associated with chronic wounds among surgical wounds from 2016 till 2019 in HUSM. By identifying the associated risk factors, progression of surgical wound to the chronic wound could be reduced.

Methods: A retrospective secondary data of total 147 patients who underwent wound dressing for surgical wounds in wound clinic at HUSM between Jun 2016 and December 2019 was carried out. Initially the data of patients were gained from patient's wound clinic assessment records and entered in a data collection form. Simple random sampling using random number generator(using Microsoft Excel) of all surgical patients with acute surgical wound underwent dressing at wound clinic at HUSM from 2016 till 2019 was done to choose the patients. The demographic and medical history data was obtained from patients summary from the medical record. The primary outcome were to describe the prevalence of chronic surgical wound among acute surgical wound under wound clinic follow up . Outcome parameters were: healed wound and chronic wound after duration of 3 months. Demographic and medical history of patients (diabetes mellitus, hypertension

and coronary artery disease, smoking habits and type of wounds were analysed as the factors influencing the wound healing of the patients

Results: A total of 147 patients were included into the study, and vast majority of them were Malay (96.6%). Eighty of them were less than 55 years old, and more than half were Male (52.4%). Sixty patients out of hundred forty seven patients were active smoker. More than half of them had diabetes mellitus (72.8%) and hypertension (60.5%), and only 23.1% had cardiovascular disease.

There were 15 patients with clean and clean contaminated wound each. Five patient wound was found to be contaminated and 115 patients had dirty wound. The median initial wound size was 52cm^3 (interquartile range: 18cm^3, 193.5cm^3). For patients with chronic wound, the median wound size after 3 months were 4.5cm^3 (interquartile range: 2.3cm^3, 8.5cm^3). Significant associations were found in between wound healing time with smoking status ($p=0.018$), diabetes mellitus ($p=0.004$) and hypertension ($p=0.029$). There were more smokers found to have chronic wound (57.1%) compared to patients which wound healed in less than 3 months (35.7%).

Besides, patients with diabetes were observed to contribute to higher proportion in chronic wounds (91.4%) compared to acute wound (67.0%). Significant association was found between hypertension and wound healing time where 77.1% of patients with hypertension were observed to have chronic wound compared to 55.4% in patients with normal blood pressure. Apart from that, significant difference was found in initial wound size between patients with wound healing time of less than 3 months vs more than 3 months ($p<0.001$). Patients with chronic wound were observed to have bigger initial wound compared to patients which wound healed in 3 months.

Conclusions: This study showed significant influence of smoking habit, comorbid like diabetes and hypertension as factor that influence the wound healing process and causing more chronic wounds among patients. Significant associations found in between wound healing time with smoking status (p=0.018), diabetes mellitus (p=0.004), and hypertension (p=0.029). Apart from that, significant difference was found in initial wound size between patients with wound healing time of less than 3 months vs more than 3 months (p<0.001). A unit increase in wound size (cm^3) will increase the odds for chronic wound by 1%.

Keywords: surgical wounds, chronic surgical wound, wound clinic HUSM

CHAPTER 1

INTRODUCTION

1.1 LITERATURE REVIEW

Wound healing is a dynamic process consisting of four continuous, overlapping, and precisely programmed phases. The events of each phase must happen in a precise and regulated manner. Interruptions, aberrancies, or prolongation in the process can lead to delayed wound healing or a non-healing chronic wound(Guo and Dipietro, 2010a).

In adult humans, optimal wound healing involves the following events: (1) rapid hemostasis; (2) appropriate inflammation; (3) mesenchymal cell differentiation, proliferation, and migration to the wound site; (4) suitable angiogenesis; (5) prompt re-epithelialization (re-growth of epithelial tissue over the wound surface); and (6) proper synthesis, cross-linking, and alignment of collagen to provide strength to the healing tissue(Gosain and DiPietro, 2004).

An acute wound is an injury to the skin that occurs suddenly due to accident or surgical injury. It heals at a predictable and expected time frame usually within 8-12 weeks depending on the size, depth and the extent of damage in the epidermis and dermis layer of the skin(Schreml *et al.*, 2010).

Chronic wounds or non healing wound on the other hand fail to progress through the normal stages of healing and cannot be repaired in an orderly and timely manner to produce anatomic and functional integrity within a period of 3 months or that has proceeded through the repair process without establishing a sustained, anatomic and functional result(Lazarus *et al.*, 1994).

Systemic Factors That Influence Healing

Age

The elderly population (people over 60 years of age) is growing faster than any other age group (World Health Organization), and increased age is a major risk factor for impaired wound healing. Many clinical and animal studies at cellular and molecular level have examined age-related changes and delays in wound healing. It is commonly recognized that, in healthy older adults, the effect of aging causes a temporal delay in wound healing, but not an actual impairment in terms of the quality of healing(Gosain and DiPietro, 2004; Keylock *et al.*, 2008). Overall, there are global differences in wound healing between young and aged individuals. A review of the age-related changes in healing capacity demonstrates that every phase of healing undergoes characteristic age-related changes, including enhanced platelet aggregation, increased secretion of inflammatory mediators, delayed infiltration of macrophages and lymphocytes, impaired macrophage function, decreased secretion of growth factors, delayed re-epithelialization, delayed angiogenesis and collagen deposition, reduced collagen turnover and remodelling, and decreased wound strength(Gosain and DiPietro, 2004). Several treatments to reduce the age-related impairment of healing have been studied. Interestingly, exercise has been reported to improve cutaneous wound healing in older adults and is associated with decreased levels of pro-inflammatory cytokines in the wound tissue. The improved healing response may be due to an exercise-induced anti-inflammatory response in the wound(Emery *et al.*, 2005).

Sex Hormones in Aged Individuals

Sex hormones play a role in age-related wound-healing deficits. Compared with aged females, aged males have been shown to have delayed healing of acute wounds. A partial explanation for this is that the female oestrogens (estrone and 17β-oestradiol), male androgens (testosterone and 5α-dihydrotestosterone, DHT), and their steroid precursor dehydroepiandrosterone (DHEA) appear to have significant effects on the wound-healing process(Guo and Dipietro, 2010a). The differences in gene expression between elderly male and young human wounds are almost exclusively oestrogen-regulated. Oestrogen affects wound healing by regulating a variety of genes associated with regeneration, matrix production, protease inhibition, epidermal function, and the genes primarily associated with inflammation(Hardman and Ashcroft, 2008).

Diabetes

Diabetic individuals exhibit a documented impairment in the healing of acute wounds. Moreover, this population is prone to develop chronic non-healing diabetic foot ulcers (DFUs), which are estimated to occur in 15% of all patients with diabetes. DFUs are a serious complication of diabetes, and precede 84% of all diabetes-related lower leg amputations(Brem and Tomic-Canic, 2007). The impaired healing of both DFUs and acute cutaneous wounds in diabetic patients involves multiple pathophysiological mechanisms. DFUs, like venous stasis disease and pressure related chronic non-healing wounds, are always accompanied by hypoxia(Tandara and Mustoe, 2004). Hypoxia which may be derived from both insufficient perfusion and insufficient angiogenesis, is detrimental for wound healing. Hypoxia can amplify the early inflammatory response, thereby prolonging injury by increasing the levels of oxygen radicals (Mathieu et al., 2006; Woo et al., 2007). Diabetic wounds exhibit inadequate angiogenesis. Several studies that have investigated the mechanisms behind the decreased restoration of vasculature in diabetic wounds have implied that EPC mobilization and homing are

impaired, and that the level of VEGF, the primary proangiogenic factor in wounds, is decreased in the diabetic state

(Brem and Tomic-Canic, 2007; Gallagher et al., 2007; Quattrini et al., 2008). The neuropathy that occurs in diabetic individuals probably also contributes to impaired wound healing. Neuropeptides such as nerve growth factor, substance P, and calcitonin gene-related peptide are relevant to wound healing, because they promote cell chemotaxis, induce growth factor production, and stimulate the proliferation of cells. In addition, sensory nerves play a role in modulating immune defence mechanisms, with denervated skin exhibiting reduced leukocyte infiltration (Galkowska et al., 2006; Sibbald and Woo, 2008)

Stress

Studies in both humans and animals have demonstrated that psychological stress causes a substantial delay in wound healing. The hypothalamic-pituitary-adrenal and the sympathetic-adrenal medullary axes regulate the release of pituitary and adrenal hormones. These hormones include the adrenocorticotrophic hormones, cortisol and prolactin, and catecholamines (epinephrine and norepinephrine). Stress also reduces the expression of IL-1α and IL-8 at wound sites—both chemo attractants that are necessary for the initial inflammatory phase of wound healing (Godbout and Glaser, 2006; Boyapati and Wang, 2007).

Medications

Medications which interfere with clot formation or platelet function, or inflammatory responses and cell proliferation have the capacity to affect wound healing.

Systemic glucocorticoids (GC), which are frequently used as anti-inflammatory agents, are well-known to inhibit wound repair via global anti-inflammatory effects and

suppression of cellular wound responses, including fibroblast proliferation and collagen synthesis. Systemic steroids cause wounds to heal with incomplete granulation tissue and reduced wound contraction (Franz et al., 2007). Glucocorticoids also inhibit production of hypoxia-inducible factor-1 (HIF-1), a key transcriptional factor in healing wounds (Wagner et al., 2008). It also may increase risk of wound infection.

Non-steroidal anti-inflammatory drugs (NSAIDs) such as ibuprofen are widely used for the treatment of inflammation and rheumatoid arthritis and for pain management. Low-dosage aspirin, due to its anti-platelet function, is commonly used as a preventive therapeutic for cardiovascular disease, but not as an anti-inflammatory drug (Pieringer et al., 2007). Systemic use of NSAIDS has demonstrated an anti-proliferative effect on wound healing, resulting in decreased numbers of fibroblasts, weakened breaking strength, reduced wound contraction, delayed epithelialization (Dong et al., 1993; Dvivedi et al., 1997; Krischak et al., 2007), and impaired angiogenesis (Jones et al., 1999).

Chemotherapeutic drugs are designed to inhibit cellular metabolism, rapid cell division, and angiogenesis and thus inhibit many of the pathways that are critical to appropriate wound repair. These medications inhibit DNA, RNA, or protein synthesis, resulting in decreased fibroplasia and neovascularization of wounds (Waldron and Zimmerman-Pope, 2003; Franz et al., 2007). Chemotherapeutic

drugs delay cell migration into the wound, decrease early wound matrix formation, lower collagen production, impair proliferation of fibroblasts, and

inhibit contraction of wounds (Franz et al., 2007).

Obesity

Obesity is well-known to increase the risk of many diseases and health conditions, which include coronary heart disease, type 2 diabetes, cancer, hypertension, dyslipidemia, stroke, sleep apnea, respiratory problems, and impaired wound healing. Obese individuals frequently face wound complications, including skin wound infection, dehiscence, hematoma and seroma formation, pressure ulcers, and venous ulcers (Wilson and Clark, 2004). In surgical wounds, the increased tension on the wound edges that is frequently seen in obese patients also contributes to wound dehiscence. Wound tension increases tissue pressure, reducing micro perfusion and the availability of oxygen to the wound (Wilson and Clark,2004; Anaya and Dellinger, 2006). Obesity can be connected to stress, anxiety, and depression, all situations which can cause an impaired immune response (Wilson and Clark, 2004).

Alcohol Consumption

Alcohol impairs wound healing and increases the incidence of infection (Gentilello et al., 1993; Szabo and Mandrekar, 2009). Alcohol exposure diminishes host resistance, and ethanol intoxication at the time of injury is a risk factor for increased susceptibility to infection in the wound (Choudhry and Chaudry, 2006). The higher rate of post-injury infection correlates with decreased neutrophil

recruitment and phagocytic function in acute alcohol exposure (Greiffenstein and Molina, 2008).

Smoking

Smoking increases the risk of heart and vascular disease, stroke, chronic lung disease, and many kinds of cancers. Patients who smoke show a delay in wound healing and an increase in a variety of complications such as infection, wound rupture, anastomotic leakage, wound and flap necrosis, epidermolysis, and a decrease in the tensile strength of wounds (Chan et al., 2006; Ahn et al., 2008). Studies have focused on the effects of nicotine, carbon monoxide, and hydrogen cyanide from smoke that impairs wound healing. Nicotine stimulates sympathetic nervous activity, resulting in the release of epinephrine, which causes peripheral vasoconstriction and decreased tissue blood perfusion to the wound bed. Carbon monoxide aggressively binds to haemoglobin with an affinity 200 times greater

than that of oxygen, resulting in a decreased fraction of oxygenated haemoglobin in the bloodstream. This will impair the oxygen delivery to wound thus impair the healing process. Several cell types and processes that are important to healing have been shown to be adversely affected by tobacco smoke. In the inflammatory phase, smoking causes impaired white blood cell migration resulting in lower numbers of monocytes and macrophages in the wound site and reduces neutrophil bactericidal activity. Lymphocyte function, cytotoxicity of natural killer cells, and production of IL-1 are all depressed, and macrophage sensing of gram-negative bacteria is inhibited(Ahn *et al.*, 2008).These effects result in poor wound healing and an increased risk of opportunistic wound infection. During the proliferative phase of wound healing, exposure to smoke yields decreased fibroblast migration and proliferation, reduced wound contraction, hindered epithelial regeneration, decreased extracellular matrix production, and upset in the balance of proteases. (Ahn et al., 2008).

Surgical Wound

A wound is defined as a disruption in the continuity of the epithelial lining of the skin or mucosa resulting from physical or thermal damage. According to the duration and nature of healing process, the wound is categorized as acute and chronic. Surgical wound is a cut or incision in the skin that is usually made by a scalpel or any surgical instrument during surgery(Robson *et al.,* 2001).

An acute wound is an injury to the skin that occurs suddenly due to accident or surgical injury. It heals at a predictable and expected time frame usually within 8-12 weeks depending on the size, depth and the extent of damage in the epidermis and dermis layer of the skin(Schreml *et al.*, 2010).

There are two main types of acute wounds: surgical and traumatic

a) Surgical-Surgical wounds are incisions made purposefully by a health care professional and are cut precisely, creating clean edges around the wound. Surgical wounds may be closed (with stitches, staples or adhesive) or left open to heal. The healing process for surgical wounds is classified by their potential for infection. Wound Classification System Using the ACS-NSQIPI(American College of Surgeons National Surgical Quality Improvement Program) divided into(Ortega *et al.*, 2012)

1)Clean – A clean surgical wound considered uncontaminated, likely made in an operating room or in a sterile environment procedure.

2)Clean contaminated- A surgical wound that enters the respiratory, GI, genital, or urinary tract in a controlled manner.

3)Contaminated – A surgical wound that was possibly contaminated with bacteria but is not yet infected.

4)Dirty – A surgical wound with a bacterial infection

Chronic wounds or non healing wound on the other hand fail to progress through the normal stages of healing and cannot be repaired in an orderly and timely manner to produce anatomic and functional integrity within a period of 3 months or that has proceeded through the repair process without establishing a sustained, anatomic and functional result. Example of chronic wounds are pressure ulcers, leg ulcers (diabetic/arterial/venous) and burns.

In general, managing wound requires meticulous approach especially in treating the surgical wound. In the beginning the wound should be identified either acute or chronic. Based on that systematic approach needed in addressing the wound. In all surgical wounds there is factors that determine and affect the wound healing. Those factors can be systemic or local. Systemic factors like patient age, co morbidity, smoking habit as well as immunocompromised state will compromise the patients healing ability. Local factors like hypothermia, pain, infection, radiation and tissue oxygen tension directly influence the characteristics of the wound.

1.2 RATIONALE FOR THE STUDY

This study is conducted to evaluate the factors that contribute chronic wound from the routine surgical wound at the wound clinic at HUSM. Chronic wound causes prolong treatment with dressing, antibiotics or surgical intervention which may burden the patients in psychological, emotional and financial aspect. Factors that contribute wound healing in general divided into local and systemic. By identifying the factors that contribute directly on the wound healing, would help to optimize it and improve the healing process.

CHAPTER 3: STUDY PROTOCOL

RESEARCH PROPOSAL FOR MASTER OF MEDICINE

PARTIAL REQUIREMENT FOR MASTER OF MEDICINE (SURGERY) PROGRAMME

UNIVERSITI SAINS MALAYSIA

Research title: Factors associated with chronic wounds among surgical wounds in wound clinic from 2016 till 2019 at Hospital University Sains Malaysia

Protocol number:

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Multiple factors can lead to impaired wound healing. In general terms, the factors that influence repair can be categorized into local and systemic. Local factors are those that directly influence the characteristics of the wound itself, while systemic factors are the overall health or disease state of the patient that affect their ability to heal (Table 1). Many of these factors are related, and the systemic factors act through the local effects affecting wound healing.(Guo and Dipietro, 2010b)

Local factors	Systemic factors
Oxygenation	Age and gender
Infections	Sex hormones
Foreign body	Foreign body

Venous sufficiency	Ischemia Diseases:diabetes,keloids, fibrosis, hereditary healing disorders, jaundice, uremia Obesity Medications: glucocorticoid steroids, non- steroidal anti-inflammatory drugs, chemotherapy Alcoholism and smoking Immunocompromised conditions: cancer, radiation therapy, AIDS Nutrition

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macrophage function, decreased secretion of growth factors, delayed re-epithelialization, delayed angiogenesis and collagen deposition, reduced collagen turnover and remodeling, and decreased wound strength(Gosain and DiPietro, 2004). Several treatments to reduce the age-related impairment of healing have been studied. Interestingly, exercise has been reported to improve cutaneous wound healing in older adults and is associated with decreased levels of pro-inflammatory cytokines in the wound tissue. The improved healing response may be due to an exercise-induced anti-inflammatory response in the wound(Emery *et al.*, 2005).

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