Impact of medications and lifestyle factors on wound healing: A pilot study

KEY WORDS
- Chronic wound
- Drug therapy
- Lifestyle factor
- Wound healing

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Background: Wound chronicity can be due to a range of intrinsic and extrinsic factors, some of which can be controlled. **Aim:** The main aim of this pilot study was to explore how medications, smoking, and alcohol affect healing rates in a sample of patients at three tertiary wound care clinics. **Methods:** Seventy-three patients, each with an open wound, were included in the study. Medical history, concomitant medications, smoking status, and alcohol consumption were recorded. Patients' wounds were classified as healing or nonhealing based on the comparisons of wound size change since previous visits. Logistic regression with groups of medications known to affect wound healing was undertaken to investigate their ability to independently predict outcome. **Results:** Groups were well matched for comorbidities, and amount of concomitant medications taken. Logistical regression identified antibiotics as being associated with healing, although this did not reach statistical significance (P=0.07). Alcohol consumption over the recommended allowance was associated with nonhealing (P=0.043). **Conclusion:** The results suggest that excess alcohol consumption may delay wound healing. A larger study is needed to further the questions.

Wound healing is a complex phenomenon conducted by various types of tissues, cell lineages, and hormones, all functioning in collaboration (Martin, 1997). Chronic wounds fail to progress through the wound healing cycle, and typically become suspended in one phase. Numerous aetiological factors have been identified as promoting chronicity in wounds, including venous and arterial insufficiency, diabetes, and autoimmune diseases (Schreml et al, 2010). Other factors that can negatively affect wound healing include some pharmacotherapies, surgical intervention, infection, trauma, psychological stress, and smoking (Silverstein, 1992; Kiecolt-Glaser et al, 1995; Karukonda et al, 2000a; Edwards and Harding, 2004).

Patients with chronic wounds typically have several comorbidities (Stadelmann, 1997) and polypharmacy is also common (Sussman, 2007). Medications can either assist or inhibit specific phases of wound healing (Karukonda et al, 2000b; Sussman, 2007). Some examples of drugs, with a summary of their individual impact on wound healing, are provided in *Appendix 1*.

Despite known detrimental effects on wound healing, the majority of these medications are clinically important, and cessation is not always feasible when a patient develops a wound.

For example, Warfarin is essential in reducing thromboembolism in patients with a metallic heart valve, yet impacts negatively on wound healing (Douketis et al, 2008). Aspirin is another example of a potentially essential medication that hinders wound healing (Raghavan et al, 2006).

Lifestyle factors can also impact wound healing. For example, alcohol consumption can impede wound healing and increase the incidence of infection. Regardless of the level of alcohol consumption (i.e. acute or chronic), it has been demonstrated to disturb re-epitheliasation, angiogenesis, collagen production, wound closure, and increases susceptibility to infection (Guo and Dipietro, 2010).

AIM

In the present study, the authors sought to evaluate clinically relevant pharmacological agents and

lifestyle factors to determine whether they could provide information, which could determine whether they were positive or negative predictors of wound healing within a diverse population of patients with a variety of wound types.

METHOD

Sample

Patients were recruited from three tertiary wound care clinics in South Wales. These clinics carry out approximately 100 consultations per week, with an average 3,000 patients seen annually. Inclusion criteria were consecutive attendees with an open wound. There were no exclusion criteria.

Data collection

A database was designed and the collection of data piloted at a clinic prior to commencing the study. No changes were made to the database or collection technique following the pilot.

The data were collected prospectively from medical and nursing case notes and entered directly into the database over a 2-week period in 2011. Data were collected as an audit, thus ethical approval was not required, and all data were anonymised at the point of entry into the database.

Basic demographic data, wound characteristics and size, past medical history, and concurrent drug use (i.e. medications, alcohol, smoking) were collected (*Box 1*). Excessive alcohol consumption was defined as consumption of >14 units per week for women, and >21 units per week for men (Prior, 2009).

Wound size was compared to the previous visit and classified as either healing (reduction in size) or nonhealing (size static or enlarging). For patients with multiple wounds, the largest wound at the point of enrolment was selected as the target wound and was investigated for change in size.

Data queries were discussed with the clinician at the time of the clinic and either resolved by reference to the medical notes or by their clinical judgment.

ANALYSIS

Data were analysed using Microsoft Access® and SPSS v16. Normality of distribution of numerical values was assessed using the Kolmogrov–Smirnov test. Continuous variables are expressed as mean and standard deviation. Differences between groups were investigated using Student's t-test. To investigate factors independently/predicting healing status, logistic regression was undertaken. $P<0.05$ was considered significant.

RESULTS

Demographic data

Data were collected from 73 patients (age, 65.9 years ± 17.9 years; range 16–98 years). Just over half of the participants were women (37/73; 51%), which reflects the average population of Cardiff (Cardiff Research Centre, 2011). The majority of participants had leg ulcers (52/73; 71%). *Table 1* shows the range of wound types in the study population and their healing status. The average healing rate was 49% (36/73).

The majority of patients (62/73; 85%) had a concurrent medical condition known to have an adverse effect on wound healing (*Table 2*). However, a concurrent medical condition did not predict a nonhealing wound.

Where there were more than five patients all taking the same class of medication, logistic regression was undertaken to determine the statistical significance. No specific class of medication was found to be an independent predictor of wound healing (*Table 3*), although taking antibiotics approached significance in relation to wound healing ($P=0.07$), and vasodilators with nonhealing ($P=0.087$).

Box 1. Data collected

Demographic information
- Age
- Sex

Wound characteristics
- Wound type
- Wound duration
- Wound size
- Wound description
- Wound outcome

Past medical history
- Cardiovascular disease
- Diabetes
- Connective tissue disease
- Autoimmune disease
- Malignancy
- Recent surgery

Medications
- Antiplatelets
- Antibiotics
- Anticancer drugs
- Anticoagulants
- Antihistamines
- Colchicine
- Corticosteroids
- Non-steroidal anti inflammatory drugs
- Phenytoin
- Vasodilators
- Vasoconstrictors

Lifestyle factors
- Cigarette smoking
- Alcohol consumption

Table 1. Wound aetiology in relation to outcome

Wound aetiology	Healing, n (%)	Nonhealing, n (%)	Total
Leg ulcer	26 (52)	24 (48)	50
Venous	17 (53)	15 (47)	32
Traumatic	4 (40)	6 (60)	10
Arterial	1 (25)	3 (75)	4
Other*	5 (100)	0 (0)	5
Surgical	8 (47)	9 (53)	17
Pressure	1 (20)	4 (80)	5
Total	**36 (49)****	**37 (51)**	**73**

*Diabetic foot ulcer ($n=1$), foot ulcer not specified (n=1), neuropathic ($n=1$), vasculitis/rheumatic ulcer ($n=1$), laceration ($n=1$).
**Taken as the average healing rate.

Table 2. Concurrent medical conditions in relation to outcome

Comorbidity	Healing, n (%)	Nonhealing, n (%)	Total	*P*-value
Cardiovascular	21 (49)	22 (51)	43 (34)	0.63*
Malignancy	4 (31)	9 (69)	13 (10)	0.77*
CTD	6 (55)	5 (45)	11 (9)	0.73*
Diabetes	9 (64)	5 (36)	14 (11)	1.00*
Autoimmune	5 (42)	7 (58)	12 (9)	1.00*
Recent surgery	9 (39)	14 (61)	23 (18)	0.80*
Obese	4 (50)	4 (50)	8 (6)	1.00*

*Not statistically significant ($P>0.05$). CTD, connective tissue disease.

Table 3. Medication in relation to wound healing

Medication	Healing, n (%)	Nonhealing, n (%)	Total	*P*-value
NRM	17 (57)	13 (43)	30	0.300*
Antiplatelets	5 (26)	14 (74)	19	0.184*
Antibiotics	9 (64)	5 (36)	14	0.071*
NSAIDs	3 (30)	7 (70)	10	0.091*
Vasodilators	2 (29)	5 (71)	7	0.087*
Anticancer drugs	2 (33)	4 (67)	6	0.514*
Antihistamines	1 (20)	4 (80)	5	0.915*
Corticosteroids	4 (80)	1 (20)	5	0.254*
Anticoagulants	3 (75)	1 (25)	4	–
Quinine	0 (0)	2 (100)	2	–
Other**	1 (40)	3 (60)	4	–
Total	43 (44)	55 (56)	102	–

*Not statistically significant (*P*>0.05). **Phenytoin (*n*=2), colchicine (*n*=1), vasoconstrictors (*n*=1). NMR, no relevant medications; NSAIDs, nonsteroidal anti-inflammatory drugs.

Excess alcohol consumption predicted nonhealing (*Table 4*), while smoking did not predict nonhealing. Polypharmacy did not predict wound healing (*Table 5*), although there was a general trend towards polypharmacy and nonhealing. *Figure 1* shows the relationships between healing and the 10 most common factors investigated in this study.

DISCUSSION

The aim of this pilot study was to investigate the effect of medications and lifestyle factors on wound healing. Data from 73 patients were analysed, but this represents only a small population from which conclusions cannot be drawn with certainty. However, a number of interesting findings warrant discussion and further research.

Alcohol was significantly associated with nonhealing (*P*=0.043), a finding supported by research that suggests excess alcohol consumption has an inhibitory effect on the inflammatory response during wound healing (Radek et al, 2009). Furthermore, during the proliferative phase alcohol delays epithelial coverage, blood vessel growth and collagen synthesis (Radek et al, 2009). The importance of limiting alcohol intake during wound healing is justified by these findings.

Patients with nonhealing wounds were taking a higher percentage of some drugs than patients with healing wounds. Those drugs most associated with delayed wound healing were antiplatelet, vasodilators, anticancer agents, and antihistamines. Therefore, whether the benefits outweigh the risk of these drugs is debatable, and individual patients should be carefully reviewed.

Antibiotics came close to association with wound healing, although this failed to reach statistical significance (P=0.071). Antibiotics are often utilised in patients with chronic wounds to manage infection (Stadelmann, 1997). However, these agents should only be used in clinically infected wounds (Karukonda et al, 2000b). While antibiotics may eliminate infection, and thus promote wound healing (Penhallow, 2005), they may also reduce the tensile strength of wounds (Diehr et al, 2007).

This study highlighted antihistamines as the drug with arguably the worst effect on wound rates. Histamine causes vasodilatation, thus facilitating the entry of healing mediators to the wound site (Stead, 1990). However, due to the small sample size and the non-significant difference of wound healing, more research is required.

Our study also highlighted that vasodilators were somewhat associated with nonhealing. Vasoconstriction is required early in the wound healing process to control haemorrhage (Diehr et al, 2007). Vasodilatation follows to allow healing factors into the wound space. Selective adenosine A2A receptor agonists have been found to reduce inflammation, increase extracellular matrix deposition and increases vascularisation in wounds (Valls et al, 2009).

However, long-term use of vasodilators in the treatment of leg ulcers is not recommended (Ongenae and Phillips, 1996). In the present study, patients taking these drugs typically had reduced healing rates. This suggests that long-term vasodilators may have a negative impact on wound healing.

Table 4. Lifestyle factors in relation to wound healing

Lifestyle factor	Healing, n (%)	Nonhealing, n (%)	Total	*P*-value
Alcohol†	0 (0)	4 (100)	4	0.043*
Smoking	5 (45)	6 (55)	11	0.960

†Excess alcohol consumption. *Statistically significant (P<0.05)

Table 5. Polypharmacy in relation to wound outcome

Number of medications	Healing, n (%)	Nonhealing, n (%)	Total	*P*-value
None	4 (57)	3 (43)	7	0.30*
1	7 (64)	4 (36)	11	0.82*
2–3	9 (56)	7 (44)	16	0.82*
4–6	8 (47)	9 (53)	17	0.82*
≥7	8 (36)	14 (64)	22	0.82*
Total	**36 (49)**	**37 (51)**	**73**	**0.82***

*Not statistically significant (*P*>0.05).

"Smokers experience a higher incidence of dehiscence and infection in postoperative wounds, and slower healing of chronic wounds."

A greater number of patients taking antiplatelets or anticancer drugs had nonhealing wounds. Acetylsalicyclic acid is an antiplatelet drug that has been found to hinder wound healing by reducing the activation and aggregation of platelets, preventing thrombus formation (Karukonda et al, 2000a). As a result, clinicians should refrain from using antiplatelet therapies in patients with wounds, unless there is an urgent requirement. Thus, individual assessment is paramount prior to prescription.

Anticancer drugs have been found to have a negative effect on the healing of surgical wounds (Valls et al, 2009). For example, nitrogen mustards (Farhat et al, 1958; Hardesty, 1958; Kaiser et al, 1961) and methotrexate (Calnan and Davies, 1965) have a negative effect on wound healing. Despite this, simple cessation is unlikely to be adequate among cancer patients, meaning that wounds in this population should be carefully monitored, and adjuvant wound healing modalities considered.

Though it did not reach statistical significance in the present study, elsewhere, smoking has also been found to delay wound healing, primarily due to immunosuppressive action (Sorensen et al, 2004; 2009) and reduction of collagen synthesis and deposition (Sorensen et al, 2009). Smokers experience a higher incidence of dehiscence and infection in postoperative wounds, and slower healing of chronic wounds (Model, 1985; Sorensen et al, 2005). Clinicians should strongly advise patients to cease smoking.

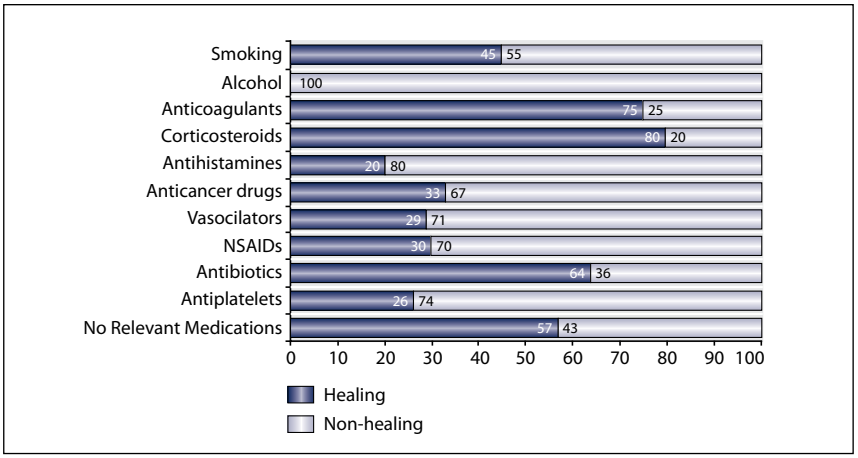

Figure 1. Medication and lifestyle factors, and wound outcome.

CONCLUSION

This pilot study has highlighted some interesting avenues for further research. While excess alcohol consumption may be a useful discriminating factor in identifying wounds prone to nonhealing, a larger study is needed to explore the impact of medications on healing. Further research is required to develop easy, yet sensitive, methods of rapidly detecting those patients at risk of developing chronic wounds. WUK

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Appendix 1. Drug classes and their impact on wound healing

Drug	Effects on wound healing
Alcohol	Increases risk of infection; inhibit wound closure; reduction in re-epithelialisation, angiogenesis and collagen synthesis; can lead to nutrient deficiency.
Antibiotics	Anti-inflammatory effects; affects collagen cross-linking, leading to interference with the tensile strength of wounds.
Anticancer drugs	Inhibits healing of surgical wounds; impair collagen synthesis and wound strength. Methotrexate is a folic acid inhibitor and cytotoxic agent and has been found to have a detrimental effect on wound healing as it inhibits the reduction of folic acid needed for the synthesis of RNA and DNA.
Anticoagulants	Increase risk of haematoma and seroma formation; possible thrombus and/or emboli formation, may lead to haemorrhage and tissue necrosis.
Antihistamines	Affects platelets, mast cells and basophils thus preventing vasodilation. Reduces tensile strength of wound and granulation tissue.
Antiplatelets	Irreversibly inhibits the enzyme cyclo-oxygenase, which suppresses thromboxane and prostaglandin production. Inhibits platelet aggregation; inhibits inflammatory mediators by arachidonic acid metabolites, increases risk of wound haematoma.
Cigarettes	Releases reactive oxygen species, preventing phagocytosis and bactericidal actions of inflammatory cells. Affects most phases in wound healing; reduction in red blood cells, fibroblasts and macrophage; increase platelet adhesion; severe reduction in peripheral blood flow and oxygen tension.
Colchicine	Affects inflammatory phase; affects tissue formation phase by reducing fibroblast proliferation; affects tissue remodeling phase by degradation of newly formed extracellular matrix; inhibits wound contraction.
Corticosteroids	Inhibits fibroplasia and granulation tissue formation; decrease platelet adhesion.
Nonsteriodal	Affects inflammatory phase; inhibits cyclooxygenases; reduction in tensile strength of wound.
Phenytoin	Affects inflammatory phase; inhibit wound contraction; decreases collagen remodeling; increases collagen synthesis and blood vessel formation.
Vasoconstrictors	Affects microcirculation and tissue remodeling phase, leading to tissue hypoxia.
Vasodilators	Enhances tissue perfusion, thus enhancing wound healing in ischaemic ulcers and Raynaud's disease. Reduces inflammation, increase extracellular matrix deposition and increases vascularization. Not recommended for long-term use in leg ulcers.

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