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ORIGINAL ARTICLE

Medications affecting healing: an evidence-based analysis

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Abstract

The purpose of this arm of the study was to investigate the impact of medication on healing times of the various wound types, including acute wounds and leg ulcers. A prospective longitudinal study design was used, with de-identified data collected using an electronic mobile wound care database system. Three main categories of data were collected, including patients' demographics, wounds types and treatment characteristics. For acute wounds, there was a total of 1732 patients with 2089 acute wounds. The average healing time was about 35 days. The only significant association was with chemotherapy, which increased healing time by 21 days ($P = 0{\cdot}048$). There were non-significant trends towards reduced healing times with antibiotics (0·5 days; $P = 0{\cdot}853$), anticoagulants (1·7 days, $P = 0{\cdot}673$) and corticosteroids (4·98 days, $P = 0{\cdot}303$). Non-steroidal anti-inflammatory drugs (NSAIDs) were associated with a non-significant increase in healing time (2·17 days, $P = 0{\cdot}707$). For leg ulcers, there was a total of 264 patients with 370 leg ulcers. We only examined the impact of antibiotics, anticoagulants, corticosteroids and NSAIDs on healing times as they had an adequate number of wounds to analyse. The average healing times of leg ulcers were found to be 73 days. None of the classes of medications had any significant impact on healing time. Both anticoagulants and NSAIDs increased healing time by (22·5 days, $P = 0{\cdot}08$) and (12·5 days, $P = 0{\cdot}03$), respectively. On the other hand, antibiotics and corticosteroids decreased healing times non-significantly by (9·1 days, $P = 0{\cdot}33$) and (21·6 days, $P = 0{\cdot}84$), respectively.

Introduction

The cost of managing wounds globally is estimated to reach $22 USD billion by 2020 (1). This cost is only associated with wound dressings and supplies and does not include costs associated with loss of work productivity or cost of the total health care systems, including hospitalisations (2).

Wound-healing processes have been extensively studied and reported in the literature using both laboratory and clinical studies. Four stages of wound healing have been described, and these include haemostasis, inflammation, proliferation and tissue remodelling (3–5). Many factors have been identified as contributing to wound healing, and these include age, comorbidities, infections, non-adherence to treatment plan, nutrition, smoking and alcoholism and medications (6–8).

Several classes of medications were reported to affect the healing of wounds in the literature. These classes include corticosteroids, high doses of non-steroidal anti-inflammatory drugs (NSAIDs), antiplatelets, vasoconstrictors and antineoplastics (8). Each of these classes interfere with one or more of the four

Key Messages

- several classes of medications were reported in the literature to affect healing of wounds; these classes include corticosteroids, high doses of non-steroidal anti-inflammatory drugs (NSAIDs), antiplatelets, vasoconstrictors and antineoplastics
- the purpose of this arm of the study is to investigate the impact of medication on healing times of the various wound types, including acute wounds and leg ulcers
- For acute wounds, chemotherapeutic medications significantly increased healing time by 21 days; there were non-significant trends towards reduced healing times with antibiotics (0·5 days; $P = 0{\cdot}853$), anticoagulants (1·7 days, $P = 0{\cdot}673$) and corticosteroids (4·98 days, $P = 0{\cdot}303$), and NSAIDs were associated with a non-significant increase in healing time (2·17 days, $P = 0{\cdot}707$)

- For leg ulcers, anticoagulants and NSAIDs increased healing time non-significantly by (22·5 days, $P = 0{\cdot}08$) and (12·5 days, $P = 0{\cdot}3$), respectively; on the other hand, antibiotics and corticosteroids decreased healing times non-significantly by (9·1 days, $P = 0{\cdot}33$) and (21·6 days, $P = 0{\cdot}84$), respectively
- Other factors, including advanced age >65 years, diabetes mellitus, infection and non-adherence to treatment, were consistently significantly associated with the healing times of acute wounds and leg ulcers irrespective of the class of medications patients were taking

stages of the wound-healing processes. Corticosteroids inhibit epithelial proliferation and thus cause impairment of inflammatory response. This, in turn, results in incomplete granulation, reduced wound contraction and possibly increased risk of wound infection (9,10). High doses of NSAIDs decrease the tensile strength of wounds, thereby reducing wound contraction and delaying the epithelialisation process (11,12). Antiplatelets, on the other hand, decrease platelet adhesion and activation. This then inhibits epithelial proliferation of keratinocytes (11,13). Anticoagulants can inhibit coagulation factor production. Vasoconstrictors contribute to tissue hypoxia by restricting microcirculation (14). Antineoplastic drugs lower collagen production, impair proliferation of fibroblasts and inhibit contraction of wounds. They also have been shown to increase the risk of wound infection (15).

To date, very few studies have reported associations between medications and healing. Most of the published literature comes from small retrospective studies (8,9,12,13,15). To our knowledge, this is the first large study to report prospectively on the impact of medications on healing time. The study presented here is part of a broader programme of work that aimed to implement a web-based electronic wound care system in rural Australia to benchmark wounds aetiologies, healing and costs across a wide geographical area (6,7,16). The specific aims of the current study are to investigate the impact of medication on healing times of the various wound types, including acute wounds and leg ulcers.

Method

The study methods have been reported extensively in previous publications (6,7,16). Briefly, a prospective longitudinal study design was used, with de-identified data collected using an electronic mobile wound care database system. Three main categories of data were collected, including patients' demographics, wounds types and treatment characteristics. Data on comorbidities and factors affecting healing, including hypertension, diabetes, osteoarthritis, advanced age, mobility and obesity, were collected. Only de-identified data were used for this analysis. The data were obtained only from organisations that used an electronic wound care system to enter the data and manage wound healing. Ethics approval was obtained from the Monash University Human and Ethics Committee (CF10/0326 : 2010000129).

Data analysis

Statistical analysis was undertaken to identify whether medications were associated with reduced wound-healing time and which classes of medications were most strongly associated with healing time. Because of the large positive skew of healing times, bootstrapped confidence intervals were used for the analysis. This method provides more robust results than alternative methods and enables statistical comparisons between different subgroups (e.g. wound types, demographics). This approach has been extensively explained in full in previous publications (6,7).

The first stage of the analysis was to undertake univariate analyses to identify key 'predictor variables' that were significantly associated with healing time. The Independent Samples t-test was used to assess whether two groups defined by the presence of different elements of interest (e.g. presence of a comorbidity, factors affecting healing or medication affecting healing) were statistically different in terms of mean healing time. Elements that were statistically significant were selected for the second stage of the analysis. A significance level of 5% ($P < 0{\cdot}05$) was used, with calculations performed using the IBM SPSS statistics package.

Multiple linear regression was used in the second stage of the analysis. All significant predictor variables found in the first stage were entered into the regression model simultaneously to determine whether each variable continued to be significantly associated with the outcome of interest (i.e. healing time) over and above the influence of the other included predictor variables.

These analyses were performed for each wound type, including acute wounds and leg ulcers. The impact of each medication class (antibiotics, anticoagulants, chemotherapy, corticosteroids and NSAIDs) on healing times was examined.

Results

The results of this longitudinal study on wound healing addressed only the commonly used medications that have a significant impact on healing, including antibiotics, anticoagulants, NSAIDs, corticosteroids and chemotherapeutic drugs. There were 3726 wounds documented from 2350 patients, resulting in average of 1·6 wounds per patient. This study only reports on patients with acute wounds and leg ulcers.

All patients had more than one comorbidity, as listed before in previous publication (6). Examples of comorbidities include hypertension (31·7%), diabetes mellitus (21%), long-term infections (17·7%), osteoarthritis (14·7%), coronary artery disease (14·4%), cancer (10·9%), hyperlipidaemia (7·9%) and asthma (7·1%).

We classified acute wounds as wounds that would progress through the normal stages of wound healing and show definite signs of healing within 4 weeks. Acute wounds are associated with surgery, crush or trauma. Chronic wounds, such as leg ulcers, do not progress through the stages of healing and take longer than 4 weeks to resolve (17,18). Leg ulcers affect the lower limbs and usually take a long period of time to heal, which can be up to 12 months or longer. Possible causes of leg ulcers include vascular, neuropathic, metabolic,

haematological, trauma, tumours, infection, panniculitis and pyoderma (18).

Acute wounds

In this study, we included acute wounds that were associated with surgery, crush or trauma. For acute wounds, there was a total of 1732 patients with 2089 acute wounds. The average healing time was about 35 days. The only significant association was with chemotherapy, which significantly increased healing time by 21 days ($P = 0{\cdot}048$). There were non-significant trends towards reduced healing times with antibiotics (0·5 days; $P = 0{\cdot}853$), anticoagulants (1·7 days, $P = 0{\cdot}673$) and corticosteroids (4·98 days, $P = 0{\cdot}303$). NSAIDs were associated with a non-significant increase in healing time (2·17 days, $P = 0{\cdot}707$).

Other factors, including advanced age >65 years, diabetes mellitus, infection and non-adherence to treatment, were consistently significantly associated with the increased healing times of acute wounds irrespective of the class of medications patients were taking (Table 1 a–e).

Leg ulcers

For leg ulcers, we included the following types: neuropathic/diabetic, venous and undefined leg ulcers. There was a total of 264 patients with 370 leg ulcers. We excluded arterial leg ulcers and mixed ulcers due to their small numbers. We only examined the impact of antibiotics, anticoagulants, corticosteroids and NSAIDs on healing times as they had adequate numbers of wounds to analyse. The average healing time of all leg ulcers was found to be 73 days. None of the classes of medications had any significant impact on healing time. Both anticoagulants and NSAIDs increased healing time by (22·5 days, $P = 0{\cdot}08$) and (12·5 days, $P = 0{\cdot}3$), respectively. On the other hand, antibiotics and corticosteroids decreased healing times non-significantly by (9·1 days, $P = 0{\cdot}33$) and (21·6 days, $P = 0{\cdot}84$), respectively. The impacts of medication were largely non-significant: other factors, such as pressure/friction/shear, diabetes, cancer and peripheral vascular disease, were found to have a significant effect on increased healing times of leg ulcers, as shown in Table 2 (a–d).

Discussion

Wound healing is a complex biological process that consists of haemostasis, inflammation, proliferation and remodelling. To our knowledge, this is the first longitudinal study examining the impact of medications on specific types of wounds and healing times in patients over a 3-year period. Most studies reporting on medications and wound healing are derived from animal studies or in vitro studies.

In our study, for acute wounds, we found that the only two classes of medication that increase healing times were chemotherapeutic agents and NSAIDs. However, the delay in healing was statistically significant for chemotherapeutic drugs but not for NSAIDs.

A review by Guo and DiPietro, 2010, reported on the effect of chemotherapeutic drugs, non-steroidal anti-inflammatory drugs and glucocorticoid steroids on wound healing (10). Our results were consistent with their proposal. The authors have explained that chemotherapeutic drugs impede the inflammation phase of the healing process and therefore increase the risk of wound infection, which result in increased healing time. For NSAIDs, the authors proposed that they interfere with wounds by stopping the proliferation process of cells, resulting in a decrease in the number of fibroblasts and thereby weakening the epithelisation process and the process of wound healing. On the other hand, our findings were inconsistent with what the authors proposed regarding the impact of steroids on healing time. Our study showed a non-significant reduction of wound healing with corticosteroids. The authors, however, found that topical low-dose corticosteroids accelerated wound healing, which is again consistent with our findings.

For leg ulcers, none of the medications caused a significant increase in healing time. However, other factors, such as pressure/friction/shear, diabetes and cancer, had a significant impact on healing times. Wilson and Clark highlighted that other factors that compromise the immune response, such as obesity, stress, anxiety and depression, are also important in impaired wound healing and increase wound complications (17).

Wound healing is quite varied due to wound type. The majority of wounds in this study were acute and healed in a normal linear healing process. The chronic wounds, however, by definition do not have a normal linear progression and are often complicated by multiple systemic factors. The prolonged inflammatory stage of healing in chronic wounds affects the body's ability to repair itself, leading to an increase in tissue damage and an associated increase in wound colonisation and infection. Without further intervention, the healing times are negatively impacted, or these wounds do not heal (19,20). The study found that other factors, such as friction, pressure, the presence of comorbidities and ageing, were more significant in reducing healing time than medications.

In our study, we found that medications did not delay healing significantly as reported in the literature. A proposed explanation would be that most of the medications examined were only used on a short-term basis, such as analgesics and antibiotics, and their full effect in impeding medications are not significantly manifested. Another explanation could be that comorbidities and delayed age are more significant in delaying the healing of wounds than the medications patients are taking.

The current study has a few limitations. Firstly, the original study had a total of 3726 wounds documented from 2350 patients. The number of wounds that were able to be included in the final analysis is relatively small due to their sub-classification into acute and chronic wounds and various other reasons, such as the patients who were taking specific medications of interest. Secondly, we were unable to ascertain the length of time the patients were on the included medications. The length of exposure to the various medications may have affected healing times of certain wounds.

Conclusion

For the patients with acute wounds, chemotherapy drugs significantly delayed wound healing, whereas corticosteroids, anticoagulants and antibiotics did not. For leg ulcers, none of the medications studied significantly affected healing; however,

Table 1 Acute wounds.

Model	B	Sig. (two-tailed)	95% confidence interval	
			Lower	Upper
(a) Antibiotics				
(Constant)	35·587	0·001	32·309	39·134
Antibiotics	−0·545	0·853	−6·021	4·572
Advanced age >65 years	12·272	0·001	6·539	17·656
Diabetes mellitus	9·217	0·022	1·568	17·074
Infection (confirmed)	13·765	0·005	5·425	22·970
Non-adherence to treatment plan	28·847	0·013	7·481	54·085
PVD	28·817	0·002	13·485	45·089

Model	B	Sig. (two-tailed)	95% confidence interval	
			Lower	Upper
(b) Anticoagulants				
(Constant)	35·530	0·001	32·516	38·804
Anticoagulants	−1·744	0·673	−10·156	6·434
Advanced age >65 years	12·545	0·001	6·929	18·436
Diabetes mellitus	9·229	0·019	1·762	17·052
Infection (confirmed)	13·570	0·002	4·626	22·848
Non-adherence to treatment plan	28·781	0·013	6·111	50·905
PVD	28·968	0·001	13·966	45·485

Model	B	Sig. (two-tailed)	95% confidence interval	
			Lower	Upper
(c) Chemotherapy				
(Constant)	34·741	0·001	31·811	37·841
Chemotherapy	20·983	0·048	1·593	43·342
Advanced age >65 years	11·980	0·001	6·223	17·520
Diabetes mellitus	9·329	0·013	1·332	17·109
Infection (confirmed)	13·695	0·003	5·132	22·946
Non-adherence to treatment plan	29·366	0·012	5·619	51·425
PVD	29·379	0·001	14·210	47·278

Model	B	Sig. (two-tailed)	95% confidence interval	
			Lower	Upper
(d) Corticosteroids				
(Constant)	35·578	0·001	32·404	38·329
Corticosteroids	−4·986	0·303	−13·862	5·299
Advanced age >65 years	12·719	0·001	7·212	18·837
Diabetes mellitus	9·342	0·019	1·929	16·894
Infection (confirmed)	13·465	0·003	4·984	23·400
Non-adherence to treatment plan	28·706	0·021	6·322	54·237
PVD	29·224	0·002	12·830	46·592

Model	B	Sig. (two-tailed)	95% confidence interval	
			Lower	Upper
(e) Non-steroidal anti-inflammatory drugs				
(Constant)	35·289	0·001	32·400	38·576
NSAIDs	2·172	0·707	−8·710	13·164
Advanced age >65 years	12·212	0·001	6·668	17·434
Diabetes mellitus	9·203	0·023	1·580	17·368
Infection (confirmed)	13·475	0·006	4·982	22·585
Non-adherence to treatment plan	28·766	0·026	4·037	53·074
PVD	28·586	0·001	13·083	45·253

PVD, peripheral vascular diseases.

Table 2 Leg ulcers.

Model	B	Sig. (two-tailed)	95% confidence interval	
			Lower	Upper
(a) Antibiotics				
(Constant)	76·475	0·001	40·450	113·500
Antibiotics	−9·008	0·333	−26·137	12·177
Advanced age >65 years	20·746	0·065	−1·262	42·794
Cancer	−40·610	0·007	−69·378	−7·429
Diabetes mellitus	−21·515	0·021	−40·951	−3·932
Pressure/friction/shear	45·078	0·006	18·510	76·496
PVD	23·778	0·061	0·763	50·395

Model	B	Sig. (two-tailed)	95% confidence interval	
			Lower	Upper
(b) Anticoagulants				
(Constant)	66·921	0·001	31·196	102·468
Anticoagulants	22·511	0·081	−3·371	46·982
Advanced age >65 years	18·527	0·094	−5·356	38·778
Cancer	−38·431	0·018	−70·414	−6·968
Diabetes mellitus	−22·783	0·020	−40·588	−3·749
Pressure/friction/shear	42·216	0·004	13·576	72·161
PVD	22·527	0·079	−2·752	47·615

Model	B	Sig. (two-tailed)	95% confidence interval	
			Lower	Upper
(c) Corticosteroids				
(Constant)	72·339	0·001	39·831	105·905
Corticosteroids	−21·592	0·084	−46·685	2·180
Advanced age >65 years	21·256	0·043	0·703	42·282
Cancer	−34·908	0·021	−63·968	−4·606
Diabetes mellitus	−21·504	0·023	−40·722	−3·238
Pressure/friction/shear	44·626	0·005	16·879	73·937
PVD	24·114	0·054	−0·752	47·995

Model	B	Sig. (two-tailed)	95% confidence interval	
			Lower	Upper
(d) Non-steroidal anti-inflammatory drugs				
(Constant)	73·287	0·001	39·394	107·000
NSAIDs	12·484	0·344	−14·858	39·975
Advanced age >65 years	20·780	0·081	−2·233	43·902
Cancer	−42·388	0·008	−72·483	−10·612
Diabetes mellitus	−22·766	0·020	−41·003	−3·941
Pressure/friction/shear	42·790	0·008	14·365	73·516
PVD	24·495	0·050	0·443	48·790

NSAIDs, non-steroidal anti-inflammatory drugs.

although not statistically significant, both antibiotics and corticosteroids decreased healing times, and both anticoagulants and NSAIDs increased healing time. Other factors, such as being older than 65 years, pressure/friction/shear, non-adherence to treatment and infection, were found to significantly impact healing times for both acute wounds and leg ulcers.

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