Evidence summary: Wound management: doxycycline for chronic wounds

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QUESTION

What is the best available evidence regarding the effectiveness of doxycycline for healing chronic wounds?

CLINICAL BOTTOM LINE

There is some limited evidence to support the use of doxycycline when administered systemically or locally to promote healing of chronic wounds in humans[1-3]. However, given the international effort to reduce the use of antibiotics wherever possible, its use should only be considered when other treatments to assist healing have not been successful[4].

Chronic wounds are characterised by increased levels of pro-inflammatory cytokines and proteases that inhibit the healing process by disrupting essential mitogenic activity[3]. Doxycycline, which belongs to the tetracycline group of antibiotics, promotes healing of the chronic wound by inhibiting matrix metalloproteinase (MMP) production and action[1,5,6]. (Level IV)

There has been a considerable amount of research into the effectiveness of doxycycline and other tetracyclines in both animal[e.g.7-9] and *in vitro* studies[e.g.5,10]. (Level IV). These studies have focused on a wide range of conditions, including healing responses in intestinal anastomosis in rats, corneal damage in rabbits from chemical warfare agents, extensive myocardial infarction in rats, impact on healing after rotator cuff repair in rats, and damage to human corneal epithelial cells.

There have also been studies in humans on a range of conditions; for example, osteoarthritis[11], rheumatoid arthritis[12], and the use of doxycycline-releasing sinus stents to prevent restenosis postoperatively[13]. (Level III) However, the research on the effectiveness of doxycycline in improving healing in chronic wounds is still very limited[6].

The following three studies have examined the impact of doxycycline on chronic wounds in humans:

- A small pilot randomised, controlled trial[1] assessed the efficacy of topical doxycycline (1%) compared to hydrogel (placebo) in treating diabetic, full-thickness, chronic lower-extremity ulcers in seven patients. All wounds treated with doxycycline (n=4) healed at individual healing rates of 4, 7, 24 and 30 weeks. Only one in three wounds healed in the control group (at four weeks). Subsequent treatment with doxycycline was offered to the two remaining control participants; a 60% reduction of wound size over 12 weeks was noted for the one participant who accepted the offer. Granulating tissue and epithelialisation was evidenced at 30 weeks for all ulcers treated with topical doxycycline. Analysis at 34 weeks of the healing outcomes in the seven patients indicated that topical doxycycline significantly increased the healing rate of these ulcers (p=0.05) compared to hydrogel. In respect to the safety of the treatment, no adverse effects were noted from either the topical doxycycline or the hydrogel. (Level II)
- Another pilot study[2] (n=20) investigated the effectiveness of oral doxycycline as an adjunct to compression therapy for non-healing venous leg ulcers. Ten patients received doxycycline 20mg twice daily while the remaining 10 were given 100mg twice daily. After four weeks of treatment the reduction in the median ulcer area in the high dose group was 48% (p=0.1) and there was a significant reduction (p=0.2) in the wound fluid total MMP. These effects were not evident in the low dose group. (Level III)
- The third study[3] compared the clinical effects of systemic and local doxycycyline in a group of 45 patients with chronic periodontitis. The participants were randomised into three groups of 15 with 5 treatments: systemic doxycycline (SD) only, local doxycycline (LD) only, SD + scaling and root planing (SD + SRP), LD + SRP, and SRP only as the control. Among the measures were probing depth and clinical attachment level. All clinical parameters were significantly reduced by all treatments ($p \leq 0.05$) although only the LD and SD treatments provided significant clinical healing. The LD treatment achieved significantly higher probing depth reduction than the PD treatment ($p \leq 0.05$). The authors suggested that, given these results and as locally applied doxycycline did not have the side effects of systemic doxycycline, that it might be preferable to use the topical version as an adjunct to mechanical treatment. (Level III)

RISK FACTORS

- Common allergic reactions to oral doxycycline include hives, shortness of breath, and swelling of the face, lip, tongue, or throat[6]. (Level IV)
- While skin reactions to oral doxycycline treatment are not common, they include redness, swelling, and blistering rash[6]. (Level IV)

- Systemic reactions to oral doxycycline have been reported and include headache, dizziness, fever, chills, rash, nausea, vomiting, diarrhoea, thrush, or vaginitis[6]. (Level IV)
- Oral doxycycline can also cause photosensitivity[6]. (Level IV)
- Reactions to topical doxycycline have not been reported[1] (Level II), [6] (Level IV).
- Contributing to the development of microbial resistance to the antibiotic is a potential risk. However, topical doxycycline 1% is at a substantially higher level (that is, 10,000mg/mL) than the minimal inhibitor concentration required for 50% pathogenic growth reduction, thereby minimising the likelihood of doxycycline-resistant bacteria developing[1]. (Level IV)

PAEDIATRIC CONSIDERATIONS

Repeated administration of tetracycline to neonates and young children is associated with staining of developing teeth and should not be prescribed for children under eight years of age (some policies indicate not below 11 years)[14]. More recent studies conducted specifically on doxycycline have reported no or negligible tooth staining from the use of this antibiotic[15-18]. (Level III) This outcome may be at least partly explained by doxycycline's much lower binding affinity with calcium[15]. (Level IV)

CHARACTERISTICS OF THE EVIDENCE

This evidence summary is based on a structured search of the literature and selected evidence-based health care databases. The evidence in this summary is from:

- A pilot RCT human study[2]. (Level II)
- A study which included both a pilot RCT in humans (Level II) and an *in vitro* component (Level IV)[1].
- A cohort study[3]. (Level III)
- Three studies examining the effectiveness of doxycycline in human conditions other than chronic wounds[11] (Level 1), [12] (Level II), [13] (Level III).

- Experimental research papers involving *in vitro* and *in vivo* protocols[5,7-10]. (Level IV)
- Research papers presenting evidence on the mechanisms of doxycycline action[1,6]. (Level IV)
- A review of agents that cause discolouration of teeth[14]. (Level IV)
- Reports of four cohort and observational studies that examine the effect of doxycycline on children's teeth[15-18]. (Level III)

Note: the findings from the three doxycycline studies involving humans[1-3] should be interpreted with caution given the very small sample sizes.

BEST PRACTICE RECOMMENDATIONS

- The use of topical or oral doxycycline could be considered to treat chronic, non-healing wounds (Grade B)
- In keeping with the WHO policy on the use of antibiotics, doxycycline should only be considered when a chronic wound has not responded to other methods of treatment. (Grade A)
- Clinicians need to be observant for signs of allergic response to oral doxycycline. (Grade A)
- The healing progress of the wound should be regularly reviewed and management strategies changed when indications suggest that healing has stalled. (Grade A)

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KEYWORDS

Doxycycline, chronic wound healing.