Impact of a nitric oxide-generating wound dressing in diabetic foot ulcers in patients receiving antibiotics: post-hoc analysis

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Introduction

- Hard-to-heal wounds, such as diabetic foot ulcers (DFUs), are often compromised by microorganisms that contribute to chronicity and infection risk, particularly in high-risk patients such as those with diabetes[1]
- Nitric oxide (NO) is a potent antimicrobial[2] and antibiofilm[3] molecule produced by the mammalian innate immune response to microorganisms, with as-yet unrealized potential in wound care[4]
- A novel wound dressing technology that generates NO, via acidification of nitrite within a superabsorbent dressing, has demonstrated antibiofilm activity *in vitro*[5]
- In a randomized controlled trial (RCT) in DFUs, the population treated with a NO-generating dressing (NOGD) showed statistically significant superiority in percentage area reduction (PAR) and complete healing, over a standard of care (SoC) control population[6]
- 30% and 34% of DFUs were judged to be infected at baseline in the SoC and NOGD populations, respectively[6], and over half were recorded as receiving antibiotics at some point during the RCT

Objective

To evaluate the impact of a novel prototype NO-generating wound dressing, compared with standard of care (SoC), on DFU wound healing in patients that were receiving antibiotics

Methods

- A post-hoc analysis of the ProNOx 1 randomized controlled trial of a NO-generating wound dressing[6] compared to SoC was performed.
- This aimed to determine the impact of NO-generating wound dressing on DFU healing outcomes in patients receiving antibiotics at commencement and/or during the study (i.e., at baseline, or as recorded at dressing change visits).
- The study was conducted in 10 UK wound care centres, and primary endpoint analysis has been reported (Edmonds *et al*, 2018)[6].
- Endpoints were:
  i. Percentage area reduction (PAR) of DFUs at week 12
  ii. Healed status of DFUs at week 12
- Only patients who received antibiotics and whose DFUs were treated per protocol[1] were included in this analysis

Results

- 63 of 124 patients with DFUs (51%) were recorded as receiving antibiotics at the start and/or at some point during the RCT[6]:
  - 33/63 (52%) in the SoC population
  - 30/61 (49%) in the NOGD population
- 30 different antibiotics were prescribed across both patient populations (Table 1)

Table 1. Antibiotics received by patients in the SoC and NOGD populations in the RCT[1]

Antibiotics				(* antifungal)
Amoxicillin	Clarithromycin	Erythromycin	Penicillin	Tetracycline
Augmentin	Clindamycin	Flucloxicillin	Rifampicin	Trimethoprim
Cefalexin	Co-Amoxiclav	Gentamycin	Sofradex	Vancomycin
Ceftriaxone	Co-Trimoxazole	Gentisone HC	Toucan	Augmentin
Chloramiphemid	Doxycycline	Metronidazole	Teicoplanin	Piperacillin
Ciprofloxacin	Ertapenam	Nitro Furantoin	Terbinafin*	Tazobactam

Results

- Mean percentage area reduction (PAR) was 4.5-times greater in this NOGD population (■) than the SoC population (■) (Fig 1)
- Median PAR was 97% greater in NOGD population than SoC
- IQR was 31% smaller in NOGD population than SoC population

	SoC (n=33)	NOGD (n=30)
Mean PAR	13.6%	61.5%
Median PAR	44.3%	87.1%
IQR (Q1, Q3)	97.7% (-4.5%, 93.2%)	67.4% (32.6%, 100%)

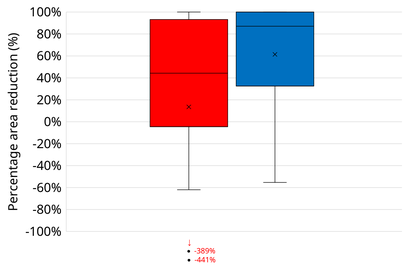

Figure 1. Boxplots of DFU PAR at week 12 in the SoC (■) and NOGD populations (■) receiving antibiotics

- Full (100%) PAR was 61% (19/31) in this NOGD population compared to 43% (13/30) in this SoC population (Fig 2-3)
- 9 DFUs (27%) increased in area in this SoC population (■), while 4 DFUs (13%) increased in area in this NOGD population (Fig 2-3)
- Two outlier DFUs had large area increases in the SoC population (Fig 2)

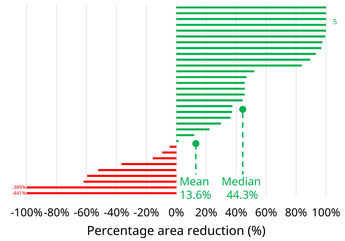

Figure 2. Waterfall plots of each DFU PAR at week 12 in SoC population. (■) PAR increase, (■) PAR reduction

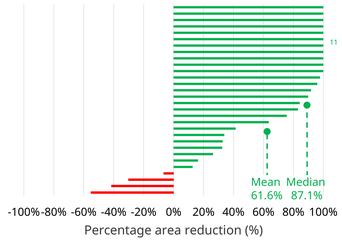

Figure 3. Waterfall plots of each DFU PAR at week 12 in NOGD population. (■) PAR increase, (■) PAR reduction

- Kaplan Meier plots show progression to complete DFU healing over 12 weeks (Fig 4)
- NOGD population (●) saw more healed DFUs at each week compared to SoC (●) (Fig 4)

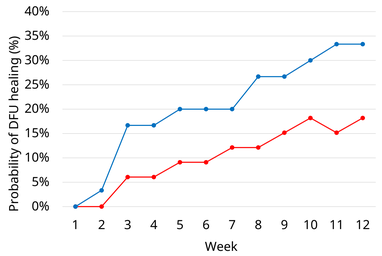

Figure 4. Kaplan-Meier plots showing the progression of healed DFUs over 12 weeks. (●) SoC, (●) NOGD

Discussion

- The majority of antibiotics prescribed were for confirmed or suspected DFU infection
- In this high risk DFU group, the differences in outcomes between SoC and NOGD populations that received antibiotics at some point during the RCT[6] were notable in every metric
- DFUs in the NOGD population were:
  - ✓ Reduced in area faster (per mean and median PAR)
  - ✓ Less likely to enlarge in area
  - ✓ More likely to close (full PAR)
- The superabsorbent NOGD, which generates antimicrobial NO within, appears to be effective compared to SoC in challenging DFUs that are likely to be locally infected or at risk of infection
- Future studies could explore these initial observations by standardizing SoC, utilizing infection/colonization measurement techniques, or expanding clinical settings and geographies

Conclusion

A novel prototype NO-generating wound dressing appears to support healing of DFUs more effectively than SoC in patients requiring antibiotics at some point during an RCT

1. Armstrong et al. Diabetic foot ulcers and their recurrence. N Engl J Med 2017; 376: 2367-237.
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