

# The Application of 0.75% Metronidazole Gel for the Treatment of Chronic Wounds: Two Case Reports and Literature Review

**Ruijuan Si**

Qingdao University

**Jing Han**

Qingdao University

**Xue Zhang**

The People's Hospital Of Shinan District, Qingdao.

**Fang Ji**

The People's Hospital Of Shinan District, Qingdao.

**Xu Yang**

Qingdao University

**Ju Zhang** (✉ [zhangju111@qdu.edu.cn](mailto:zhangju111@qdu.edu.cn))

Qingdao University <https://orcid.org/0000-0002-0441-2905>

---

## Case Report

**Keywords:** deep wounds, metronidazole, diabetic foot ulcer, nursing

**Posted Date:** June 18th, 2020

**DOI:** <https://doi.org/10.21203/rs.3.rs-35421/v1>

**License:** © ⓘ This work is licensed under a Creative Commons Attribution 4.0 International License.

[Read Full License](#)

---

# Abstract

**Objective:** To explore the application of metronidazole gel in the healing of chronic foot wounds.

**Methods:** On the basis of reviewing the previous literature, routine debridement care and local application of metronidazole gel were applied to two patients with foot wounds and observations of wound healing were made. The wound of patient A was a deep wound, and the wound of patient B was a diabetic foot ulcer complicated by gangrene.

**Results:** The bleeding and exudate of the patient with a deep wound gradually disappeared, and the wound healed. In the patient with the diabetic foot ulcer, the bleeding and exudate decreased. This was followed by the gradual size reduction of the wound and the formation of a scab over the large wound size.

**Conclusion:** Metronidazole gel was effective in wound resolution of anaerobic bacteria infected wounds. It can serve as a way to relieve patients' pain with a promising therapeutic effect. The effectiveness of metronidazole in the treatment of deep wounds and diabetic foot patients requires further and larger-scale research studies to confirm the findings shown here.

## Background

Deep wounds refer to wounds that progress deep enough to reach or extend below the muscularis. These wounds have an anoxic environment conducive to the growth of anaerobic bacteria. Anaerobic bacteria infection of skin and soft tissue often results in rancid secretion, gas production, extensive tissue necrosis, and tends to extend into the subcutaneous tissue and the fascia surface, which forms the sinus tract [1]. The diabetic foot is a general term for full-thickness wounds below the ankle of diabetic patients, which can be infected wounds, ulcerations and/or destruction of deep tissues associated with neurological abnormalities and varying degrees of peripheral vascular disease [4]. The main adverse consequences of diabetic foot disease are foot ulcers and amputation, which can also lead to increased morbidity and mortality[2]. Globally, the prevalence of foot ulcers in patients diagnosed with diabetes is between 4% and 10% and these diabetic patients have a 12%-25% risk of developing foot ulcers during their lifetime [5]. Infection of diabetic feet can lead to neuropathy, ischemia which is the most common cause of hospitalization for diabetic patients [3].

Metronidazole (MTZ) is a first generation 5-nitroimidazole antibiotic [6]. Its active antibacterial mechanism is through affecting the synthesis of bacterial DNA processing, transcription, and translation; broadly acting on anaerobic bacteria [7]. Thus, MTZ affects the replication and growth of bacteria to achieve its antibacterial effects. Therefore, MTZ has been widely used in the treatment of bacterial vaginitis, periodontitis, and pelvic inflammatory diseases for many years [8]. Moreover, due to the systemic adverse reactions caused by long-term oral administration of MTZ, local external treatment is favored by doctors and patients [9, 10]. Considering the effective anti-anaerobic effect of MTZ gel and its ease of use. MTZ gel was applied to treat a patient with a deep foot wound and a patient with diabetic

foot gangrene. Overall, we report that the wound condition in both circumstances was significantly improved.

## Case Report

### Case A

A 77-year old male patient was admitted to hospital on 20th August 2019 due to 8 years of right limb dysfunction, accompanied by a cough and expectoration for 2 days prior to admission. Previous medical history of the patient was: osteoporosis, ischemic heart disease, Parkinson's disease, hypertension. In addition, the patient was diagnosed with cerebral infarction sequelae upon admission. Physical examination after admission showed that the patient's right limb muscle strength was grade 0 and the muscle tension was low, while his left limb muscle strength was grade 3 and the muscle tension was normal. The big toe of the right foot had a  $0.5 \times 0.8$  cm skin lesion with a ruddy base and swollen red surrounding skin. A small amount of exudate was present, suggestive of wound infection. Facial expression scoring method showed that the pain score was at 3 points, which was determined to be mild pain.

After the patient was admitted to the hospital, the wound was washed with hydrogen peroxide and then washed with normal saline to keep the local skin clean before drying. On 11th September, the wound surface area had marginally reduced to  $0.5 \times 0.6$  cm. There was still a small amount of exudate in the wound and the pain score remained at 3 points, revealing that the situation was persisting and had not been alleviated. Following further consultation, 0.75% MTZ gel (Jiangsu Zhiyuan Pharmaceutical Co., Ltd., Chinese medicine standard H10980213, Specification: 20 g/ Branch) was applied to the wound (Fig. 1), and the wound surface state was closely observed on a daily basis (Fig. 2). On 15th September, it was observed that the wound exudate, redness and swelling had all decreased, and the area of the wound had decreased to  $0.3 \times 0.2$  cm (Fig. 2A-2B). On 19th September (8th day of medication), the wound area had further reduced to  $0.2 \times 0.1$  cm (Fig. 2C). The wound had completely healed by the 22nd September (day 11); bleeding and exudate were absent and redness had subsided (Fig. 2D).

### Case B

A 87-year old female patient was admitted to hospital on 27th November 2019 due to 3 years of inability to move both lower limbs, accompanied by a cough and expectoration for 5 days prior to admission. Previous medical history of the patient was: Type II diabetes mellitus, ischemic heart disease, hypertension, brain atrophy. The admission diagnosis of this patient was sequelae of cerebral infarction. Physical examination after admission showed that the limb muscle strength of the patient was grade 2 and the muscle tension was low. The patient had black gangrenous lesion on the left foot with an area of  $3 \times 5.5$  cm, which was accompanied with a small amount of exudate (Fig. 3A). The plantar dorsal artery pulse of patient was weakened and the facial expression scoring method showed a pain score of 2 points, which was determined to be mild pain.

After the patient was admitted to the hospital, the wound was cleaned with hydrogen peroxide before MTZ gel was applied to the wound surface and bandaged with sterile gauze. The condition of the affected limb was closely observed to keep the affected foot clean, and the dressing was changed when exudate was observed. The wound area and healing status were recorded by camera. In addition, basic care and psychological care were strengthened throughout. The patient was instructed to rest in bed, elevate the affected limb and perform functional exercises to promote blood circulation and prevent disuse syndrome. The blood circulation of the affected limb was observed through the swelling degree, skin temperature, and coloration. Moreover, the blood glucose of the patient was maintained at approximately 10 mmol/L by injecting short-term insulin. On 6th December, the patient's necrotic detached without intervention, and some small wounds had scabbed over (Fig. 3B). In addition, the amount of exudate was reduced, and the odor had improved. MTZ gel was then used daily and necrotic tissue was debrided. On 12th December, the entire wound on the patient's foot had scabbed and some began to detach to reveal healed skin beneath (Fig. 3C). In addition, exudate and odor had ceased. On 19th December, more scabs detached, revealing healed skin, and the overall scab area was significantly reduced (Fig. 3D). On 25th December, the patient was discharged as instructed. The patient was instructed to continue the use of MTZ gel and the healing status was also observed.

## Discussion And Conclusion

In clinical practice, in addition to the treatment of the primary disease, it is particularly important to ensure the patient's comfort. The skin is the largest tissue and organ of the human body and is easily damaged by external and/or internal factors, resulting in skin wounds. Elderly patients are particularly susceptible to skin damage due to insufficient nutrition and reduced skin elasticity [11]. The presence of skin wounds can cause pain and anxiety in patients, increasing the risk of infection, and even affecting the treatment of the primary disease [12]. Therefore, timely and effective treatment of patients' skin wounds should be prioritised by the healthcare provider.

In this article, the deep foot wound of one patient was caused by an ingrown nail, which damaged the nail groove and adjacent tissues. Crushing injury caused by ingrown toe or fingernails often lead to secondary infection of the subdural hematoma, subsequently evolving into subdural abscesses. Whereas Patient B's wound was due to long-term diabetic hyperglycaemia, aging and other factors that caused the progressive deterioration resulting in a substantial non-healing diabetic foot ulcer with gangrene. The main pathogen of these wounds is typically *Staphylococcus aureus* [13]. In the case of these patients and for others with infections, antibiotics such as cephalosporin should be considered for use to control the infection while keeping the wound surface clean and dry. In addition, wounds infected by anaerobic bacteria do not need to be bandaged. In typical wound healing of anaerobic bacteria infected wounds, it is necessary to ensure a good external environment interface for the promotion of self-healing and to allow the affected wound to breathe (exposed to oxygen). Purulent wounds will eventually cease to produce discharge and scab over by themselves, forming a natural protective layer without external treatment. However, in the cases reported here, after the application of conventional nursing methods failed to show significant improvement, and based on the pharmacological effect of MTZ against

anaerobic bacteria, 0.75% MTZ gel was continuously applied to the wound surface. MTZ gel has the advantages of being affordable and readily accessible to healthcare providers. The simple and convenient local application of MTZ gel can increase the compliance of patients with routine medication use. Patient A's deep foot wound healed completely after 11 days of applying MTZ gel, and patient B's diabetic foot gangrene wound also improved significantly. Taken together these cases supported the effectiveness of MTZ in wound healing, particularly in chronic non-healing and infected wounds.

MTZ gel contains nitroimidazole substances, which are reduced to amino groups in oxygen-free environments [6]. Nitroimidazole groups can also combine with glucuronic acid within the human body to promote metabolism, as well as having a broad-spectrum effect on antibiotic resistant strains of anaerobes and parasitic worms [14]. In clinical practice, MTZ gel is shown to be effective in treating and preventing infections caused by anaerobic bacteria. For example, patients with abdominal respiratory tract or pelvic infections were shown to be treated effectively with MTZ gel [15]. MTZ gel can also play a role in preventing and treating oral anaerobic bacteria infection [8, 17]. The absorption properties of MTZ gel means that the drug can be broadly used throughout the human body; it can directly enter saliva, liver abscesses, or be used to enter cerebrospinal fluid [16]. However, MTZ gel was shown to have no effect on facultative aerobic bacteria growth or aerobic bacterial infections, thus correct diagnosis of infection symptoms should be made prior to the choice of using MTZ gel treatment.

Although our study was limited by the number of patients, it still demonstrated promising results. Simple application of a topical ointment helped to improve the patient's compliance and treatment enthusiasm. In addition to the application of drugs in the treatment process, it is also necessary to keep the wound clean and dry. Due to various factors such as trauma and poor life habits, deep wounds have a relatively high incidence rate, and anaerobic infection caused by deep wounds will seriously affect the prognosis of patients [18]. Diabetic foot, as the main complication of diabetes, is the main reason for the amputation of patients. In addition, diabetic ulcers also cause a huge economic burden on patients, their families and society [19]. If local application of MTZ can cure a considerable proportion of patients, the wound care management process and treatment time may be significantly reduced, without the need for further surgical intervention. In view of the anti-anaerobic effect of MTZ, and its successful application in the cases of foot wounds shown here, MTZ gel may also provide beneficial effects for the enhanced healing of surgical wound infections and anaerobic infections caused by trauma. Therefore, the authors believe that MTZ gel can be extended to the treatment of deep wounds of the feet and the treatment of widespread anaerobic infections, as was the case in the diabetic foot reported here. Although MTZ gel in wound healing was shown to be promising, to form solid conclusions, further research and validation is required. Furthermore, previous literature has reported that a compound MTZ gel containing silver ions or a mixture of metronidazole and iodine was superior to MTZ gel use alone in some respects [20], which also implicated the use of MTZ and provides new ideas for our future research.

## **Declarations**

## **Acknowledgements**

Not applicable.

## Authors' contributions

Study design: JZ, RJS, XY.

Study implementation: FJ, XZ.

Manuscript writing: RJS, XY.

Revisions for important intellectual content: JH, JZ.

## Funding

Youth Program of National Natural Science Foundation of China (No. 81701838).

## Availability of data and materials

Not applicable.

## Ethics approval and consent to participate

The protocol for the research project was approved by the Ethics Committee of Affiliated Hospital of Qingdao University and the research approval number is QYFYWZLL25773.

## Consent for publication

All participants gave informed consent for the research, and that their anonymity was preserved.

## Competing interests

The authors declare no conflict of interest.

## References

1. Shimura S, Watari H, Komatsu M, Kuchibiro T, Fukuda S, Nishio H, et al. Antimicrobial susceptibility surveillance of obligate anaerobic bacteria in the Kinki area. *J Infect Chemother.* 2019; 25(11); 837-44.

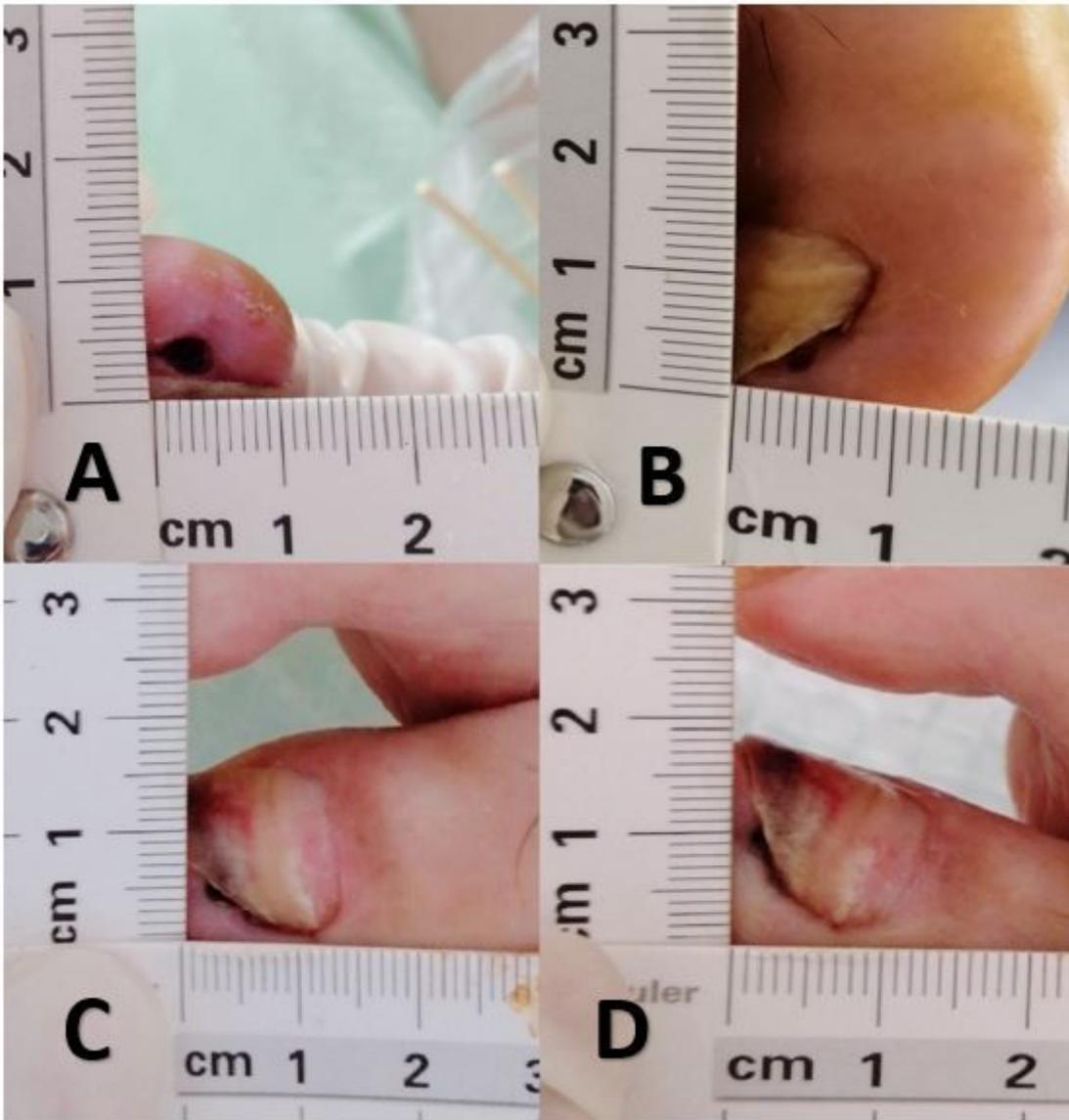
2. Jones NJ, Harding K. 2015 International Working Group on the Diabetic Foot Guidance on the prevention and management of foot problems in diabetes. *International Wound Journal*. 2015; 12(4); 373-4.
3. Boulton AJ, Vileikyte L, Ragnarson-Tennvall G, Apelqvist The global burden of diabetic foot disease. *The Lancet*. 2005; 366(9498); 1719-24.
4. Prompers L, Huijberts M, Apelqvist J, Jude E, Piaggese A, Bakker K, et al. High prevalence of ischaemia, infection, and serious comorbidity in patients with diabetic foot disease in Europe. Baseline results from the Eurodiale study. *Diabetologia*. 2007; 50(1); 18-25.
5. Kurup R, Ansari AA, Singh (2019) A review on diabetic foot challenges in Guyanese perspective. *Diabetes & Metabolic Syndrome: Clinical Research & Reviews*. 2019; 13(2); 905-12.
6. Ypsilantis E, Carapeti E, Chan The use of topical 10% metronidazole in the treatment of non-healing pilonidal sinus wounds after surgery. *International journal of colorectal disease*. 2016; 31(3); 765-67.
7. Moody M. Metrotop: a topical antimicrobial agent for malodorous wounds. *British journal of nursing*. 1998; 7(5); 286-9.
8. Bottino MC, Arthur RA, Waeiss RA, Kamocki K, Gregson KS, Gregory Biodegradable nanofibrous drug delivery systems: effects of metronidazole and ciprofloxacin on periodontopathogens and commensal oral bacteria. *Clinical oral investigations*. 2014;18(9); 2151-8.
9. Mitchell CM, Hitti JE, Agnew KJ, Fredricks Comparison of oral and vaginal metronidazole for treatment of bacterial vaginosis in pregnancy: impact on fastidious bacteria. *BMC Infectious Diseases*, 2009; 9(1); 1-6.
10. Wang AP, Zhu XJ, Zhu TJ, Zhang JZ, Wang JB, Liu Clinical Efficacy and Safety Evaluation of 0.75% Metronidazole Gel versus Vehicle in the Treatment of Rosacea. *The Chinese Journal of Clinical Pharmacology*. 2002; 18(03); 163-6.
11. Yang Y, Hao DF, Chu WL, Feng G, Zhang Retrospective analysis of hospitalized cases in wound repair center from a tertiary hospital at Beijing in 2017. *Chinese Journal of Injury Repair and Wound Healing*. 2019; 14(5); 344-9.
12. Vardhan M, Flaminio Z, Sapru S, Tilley CP, Fu MR, Comfort C, Li X, Saxena The Microbiome, Malignant Fungating Wounds, and Palliative Care. *Frontiers in cellular and infection microbiology*. 2019; 3(9); 1-7.
13. Sollid JU, Furberg AS, Hanssen AM, Johannessen Staphylococcus aureus: determinants of human carriage. *Infection, Genetics and Evolution*. 2014; 21(1); 531-41.
14. Somayaji , Jariwala U, Jayachandran P, Vidyalakshmi K, Dudhani RV. Evaluation of antimicrobial efficacy and release pattern of tetracycline and metronidazole using a local delivery system. *Journal of periodontology*. 1998; 69(4); 409-13.
15. Li BL, He SX, Li Comparison of efficacy of standard triple and quadruple regimens in eradication of Helicobacter pylori in patients with peptic ulcer and chronic gastritis. *Western medicine*. 2019; 31(7); 1053-6.

16. Yan M, Dou RM, Wang Evaluation of the clinical efficacy and safety of minocycline hydrochloride ointment combined with metronidazole in the treatment of chronic periodontitis. *Chinese Journal of Clinicians*. 2016; 10(8); 1124-7.
17. Mahesh L, Kumar VR, Jain A, Shukla S, Aragoneses JM, Martínez GJM, et al. Bacterial Adherence Around Sutures of Different Material at Grafted Site: A Microbiological *Materials(Basel)*, 2019; 12(18).
18. Wang YX, Li HH, Chang J, Wang GR, Zhang H, He Influencing factors of hospital stay in department of general surgery in a Shanxi provincial 3A-grade hospital. *Chinese Remedies & Clinics*. 2016; 16(12); 1714-7.
19. Tan TW, Shih CD, Concha-Moore KC, Diri MM, Hu B, Marrero D, Zhou W, Armstrong Correction: Disparities in outcomes of patients admitted with diabetic foot infections. *PLoS ONE*. 2019 ;14(2).
20. Brako F, Luo CJ, Matharu RK, Ciric L, Harker A, Edirisinghe M. et al. A Portable Device for the Generation of Drug-Loaded Three-Compartmental Fibers Containing Metronidazole and Iodine for Topical Application. *Pharmaceutics*. 2020; 12(4).

## Figures



Figure 1



**Figure 2**

A: Before MTX application, the wound surface of the patient was red and swollen with exudate, wound area was 0.5 x 0.6 cm. B: On 15th September, the condition of the wound improved and the area decreased to 0.3 x 0.2 cm. C: On the 8th day of medication, the wound area was reduced to 0.2 x 0.1 cm. D: On 22nd September , the wound was completely healed.



**Figure 3**

A: Before MTZ application, the foot of the patient was partly necrosed with a wound of 3.5 x 5.5 cm. B: On 6th December, the patient's necrotic tissue fell off and some small wounds scabbed. C: On 12th December, all of the wound on the patient's foot had scabbed over and areas of scabs that fell off revealed healed skin beneath. D: On 19th December, most of the scabs gradually fell off, remaining scabbed over area was significantly reduced.