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## **SAFETY AND EFFICACY OF THERMOTHERAPY IN THE TREATMENT OF BURULI ULCER DISEASE**

Fach: Infektiologie

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### **Background**

Buruli ulcer is an infectious disease of the skin categorized as neglected tropical disease by the WHO. The causative organism, *Mycobacterium ulcerans*, is peculiar in its ability to produce a macrolide exotoxin called mycolactone, its propensity to develop secondary lesions and in its striking sensitivity to heat. Cases have been reported from more than 30 countries over the world with a strong focus on West Africa. In Cameroon several endemic regions including the Nyong river Basin and the surroundings of lake Mapé report more than 100 cases per year, mainly children below the age of 15 years. The mode of transmission is not well understood but there appears to be a link to slow flowing or stagnant water bodies. The clinical picture is characterized by skin lesions ranging from small papules or nodules with intact epidermis to larger and debilitating ulcerations. BU lesions may be single or multiple in close proximity or disseminated across the whole body. Ulcers typically present with undermined edges, a base resembling cotton wool and surrounding induration. Laboratory confirmation rests on detection of acid fast bacilli in Ziehl-Neelsen stained direct smear examinations, detection of IS2404 by PCR, which is specific for *M. ulcerans*, culture and histopathology. Primary treatment for decades was surgical removal, until the WHO recommended a combination of streptomycin and rifampicin in 2004. Local heat application was first explored as treatment option in 1974 and re-established in 2009 using phase change material as heat source. The purpose of this trial was to confirm the results in a larger patient cohort.

## **Methods**

The study was conducted at the district hospital of Ayos located within an endemic region in Cameroon. Patients with lesions clinically diagnosed as BU without co-existing severe communicable or non-communicable diseases willing to participate were eligible for enrolment. Only laboratory confirmed patients entered the final analysis. Heat treatment was applied for up to 56 consecutive days in two daily sessions starting at 4:00 and 10:00 p.m. After regular wound dressings heat packs containing sodium-acetate-trihydrate as phase change material were mounted covering the lesions and a safety margin. The target temperature at the skin surface was 39-42° C. Temperature recordings were performed automatically at ten minute-intervals by dataloggers. The study was conducted under GCP standards and externally monitored by the Coordination Center for Clinical Studies, Heidelberg. Primary outcome measures were the proportion of patients whose lesions healed within six months after completion of heat treatment and the proportion of those healed, who remained free of recurrence until 24 months after completion of heat treatment. The study was approved both by the Cameroonian ethics committee and the Ethics Committee of Heidelberg University.

## **Results**

Following active case finding 65 patients were enrolled into the study. An infection with *M. ulcerans* was laboratory confirmed in 55 patients. One patient was excluded for non-compliance, one died for reasons unrelated to BU and heat treatment. 53 patients entered the final analysis. Within six months after completion of heat treatment 92.5% patients were clinically cured of their *M. ulcerans* infection. 85% of those remained recurrence free until the 24<sup>th</sup> month of follow-up. Adverse events were limited to local skin reactions, which subsided within a few days. The applied quantity of heat  $\geq 40^{\circ}$  C per day ranged from 1.6 hours to 10.9 hours. The cumulative quantity of heat ranged from 74 hours to 558 hours.

## **Conclusion**

The current results demonstrate that local heat application is an effective, safe, well tolerated, cheap and simple therapeutic option for the treatment of Buruli ulcer disease. Retrospective analysis of patients with suspected treatment failure revealed probable other causes such as erysipelas and immune-pathological reaction in a majority of them indicating that the true efficacy may be underestimated by this study. The absence of relevant side effects makes local heat application a very promising community based treatment of early lesions where laboratory confirmation may be unavailable or unaffordable.