A double-blind randomised controlled trial of ibuprofen compared with placebo for uncomplicated cellulitis

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BACKGROUND

• Cellulitis is a common, painful and disabling condition, with an estimated 14.5 million cases annually and $3.7 billion of ambulatory care costs annually in the USA alone [1].
• Intravenous antibiotics usually result in rapid bacterial killing, and ongoing signs of inflammation are likely to be due to the patient’s inflammatory response to bacterial exotoxins rather than the infection itself [2, 3].
• A single, unblinded, small, pseudo-randomised trial has previously shown that patients receiving ibuprofen had more rapid regression of cellulitis than those receiving antibiotics alone [4]. Despite the dramatic results of this study, it has never been reproduced, and this treatment has not become standard of care.

We conducted a double blind, placebo controlled, parallel group, 1:1, two arm, investigator-initiated randomised trial at two public hospitals in Australia.

METHODS

• Patients were recruited from the outpatient parenteral antibiotic therapy services of the two hospitals.
• Inclusion criteria were: 1) Cellulitis or erysipelas of the upper or lower limb (defined as diagnosed by an Infectious Diseases specialist or fellow); 2) Age 18-80 years; 3) Receiving intravenous cefazolin; 4) Commenced effective parenteral antibiotics <24 hours prior to randomisation.
• Exclusion criteria were: 1) Complicated cellulitis (any of: abscess; post-operative wound infection; deep venous thrombosis; necrotising fasciitis); 2) Allergy to NSAIDS 3) Acute or chronic renal impairment; 4) Peptic ulcer disease; 5) Pregnancy; 6) Chicken pox or shingles; 7) Taking regular NSAIDS or corticosteroids; 8) Taking anticoagulants.
• The intervention was ibuprofen 400mg TDS orally for five days, or identical placebo. Both groups received IV Cefazolin 2g q12h for a clinician-determined duration.
• The primary outcome was the proportion of patients with regression of inflammation within 48 hours of the first effective dose of parenteral antibiotics.
• “Regression of inflammation” was assessed twice daily by a nurse and was defined as the superior edge of inflammation having moved inferiorly rather than continuing to expand or not changing.
• The sample size was based on Dall et al [4], where the primary outcome was met in 80% of the ibuprofen group and 10% of the control group. We assumed a drop from 60% to 40% was more plausible; with alpha 0.05 and beta 0.2 we would need 23 in each group.

RESULTS

• 51 patients were enrolled, of whom 48 had sufficient data for the primary endpoint.
• Infarction had begun to regress at 48 hours in 20 participants (80%) in the ibuprofen group compared with 15 (65%) in the placebo group (Absolute risk difference +15% [95% CI 1.0 - 10% to +40%]), p>0.05.
• There was no significant difference in any secondary outcome.
• Ibuprofen appeared safe, with no patient developing renal impairment or necrotising fasciitis.

None of the authors have any relevant conflicts of interest to declare. This study was supported by a grant from the Northern Territory Government Research Innovation Board. Salary support was provided by Australia’s National Health and Medical Research Council (Career Development Fellowships to JSD [#1083105] and SYCT [#1065736]).

CONCLUSIONS

• This trial demonstrated no significant benefit of adjunctive ibuprofen in adults with uncomplicated cellulitis.

The trial was powered to detect a large effect, and hence it is unclear if the 15% absolute improvement in the primary endpoint in the ibuprofen group was attributable to dose of parenteral antibiotics.

REFERENCES