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 0.8 we would need 23 in each group.

RESULTS

Table 1 – Baseline characteristics according to treatment allocation

	Placebo group (n=26)	Ibuprofen group (n=25)
Male	15 (58%)	20 (80%)
Age (mean [sd]), years	40.2 (14.1)	45.6 (12.9)
Diabetes mellitus	2 (8%)	2 (8%)
Peripheral vascular disease	1 (4%)	1 (4%)
Obesity (BMI>30)	3 (12%)	7 (30%)
Lymphoedema	1 (4%)	1 (4%)
Previous cellulitis	3 (12%)	6 (25%)
Sepsis (≥2 SIRS criteria)	4 (15%)	0
Use of NSAIDS[a] between symptom onset and randomisation	14 (54%)	12 (48%)
Use of paracetamol between symptom onset and randomisation	17 (68%)	16 (67%)
Received antibiotics for this episode prior to randomisation	20 (77%)	16 (64%)
Presentation >48h after symptom onset	16 (62%)	10 (40%)
Lower limb cellulitis	21 (81%)	17 (68%)
Upper limb cellulitis	5 (19%)	8 (32%)
Grew GAS[b] from skin swabs	5 (19%)	3 (12%)
Grew MSSA[c] from skin swabs	6 (24%)	3 (12%)
Grew MRSA[d] from skin swabs	2 (8%)	2 (8%)

a. Non steroidal anti-inflammatory drugs
b. Group A Streptococcus
c. Methicillin Susceptible *Staphylococcus aureus*
d. Methicillin Resistant *Staphylococcus aureus*

- 51 patients were enrolled, of whom 48 had sufficient data for the primary endpoint
- Inflammation 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 -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

Table 2a – Primary outcome measure, intention to treat population

	Placebo (n=23)	Ibuprofen (n=25)
Regressed within 48hours	15 (65%)	20 (80%)

p=0.25

Table 2b- Primary outcome measure, per protocol population

	Placebo (n=18)	Ibuprofen (n=20)
Regressed within 48hours	11 (61%)	15 (75%)

p=0.36

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 chance or not.

Table 3 – Secondary outcome measures

	Placebo	Ibuprofen	p
Duration of intravenous antibiotics[a]	3 (3-4)	3 (2-4)	0.43
Time to return to normal leg function[a,b]	7 (4-10)	7.5 (6-9)	0.52
Return to usual activities at day 14	10/14 (71%)	19/20 (95%)	0.06
Cellulitis completely resolved at day 6	7/20 (35%)	5/19 (26%)	0.56
Cellulitis completely resolved at day 14	10/14 (71%)	13/20 (65%)	0.69
Median leg pain score on day 6	0 (0-1)	0 (0-1)	0.94
Median leg tightness score on day 6	0 (0-2)	1 (0-2)	0.63
Safety endpoints			
Need for hospital admission in first 14 days	1 (4%)	1 (4%)	0.73
Mean (sd) serum creatinine at day 6 (μM/L)	71 (11.8)	75 (12)	0.25
Proportion creatinine >120 at day 6	0	0	N/A
Proportion with ≥ moderate epigastric pain or heartburn at any time days 1-6	0	2 (8%)	0.16

a. (Median[IQR]), days
b. Limited to those with lower limb cellulitis.

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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]).

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