

Fusidic acid cream in the treatment of impetigo in general practice: double blind randomised placebo controlled trial

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Abstract

Objective To test the hypothesis that fusidic acid would not increase the treatment effect of disinfecting with povidone-iodine alone in children with impetigo.

Design Randomised placebo controlled trial.

Setting General practices in Greater Rotterdam.

Participants 184 children aged 0-12 years with impetigo.

Main outcome measures Clinical cure and bacterial cure after one week.

Results After one week of treatment 55% of the patients in the fusidic acid group were clinically cured compared with 13% in the placebo group (odds ratio 12.6, 95% confidence interval 5.0 to 31.5, number needed to treat 2.3). After two weeks and four weeks the differences in cure rates between the two groups had become smaller. More children in the placebo group were non-compliant (12 v 5) and received extra antibiotic treatment (11 v 3), and more children in the placebo group reported adverse effects (19 v 7).

Staphylococcus aureus was found in 96% of the positive cultures; no strains were resistant to fusidic acid.

Conclusions Fusidic acid is much more effective than placebo (when both are given in combination with povidone-iodine shampoo) in the treatment of impetigo. Because of the low rate of cure and high rate of adverse events in the placebo group, the value of povidone-iodine in impetigo can be questioned.

Introduction

Impetigo is the most common skin infection in children; it is caused mainly by *Staphylococcus aureus* and sometimes by *Streptococcus pyogenes* (group A).^{1 2} Some authors suggest that an expectant attitude with disinfection but no antibiotic treatment would suffice in mild cases.³⁻⁵ Immediate antibiotic treatment is advised for most cases of impetigo, to achieve a quick cure and prevent spread of the infection to other children.⁴⁻⁶ Oral antibiotic treatment has long been the first choice.⁷ In recent years, however, the resistance of staphylococci to oral antibiotics has increased dramatically.^{1 8-11} Topical antibiotic treatment with mupirocin has been shown to give results equal to or even better than oral treatment.^{1 9 12 13} In general, children comply better with topically administered

treatment than with oral treatment,¹³ and fewer systemic side effects occur.⁸

Fusidic acid is recommended as the first choice topical antibiotic in the Dutch College of General Practitioners' guidelines on the treatment of impetigo.³ Some authors discourage the topical use of fusidic acid because of its value in systemic treatment,^{5 14} although other authors recommend that mupirocin should be reserved for treatment of nasal carriage of *S aureus* in specific groups of patients.^{3 15} A recent meta-analysis of three randomised trials found the overall clinical effect of fusidic acid cream in patients with impetigo to be equal to that of mupirocin,¹⁶ but the effectiveness of fusidic acid has never been assessed in comparison with placebo. The cost of fusidic acid compares favourably with that of mupirocin.

We compared the effectiveness of fusidic acid cream and placebo cream, both added to a disinfecting treatment with povidone-iodine, in the treatment of impetigo in children.

Methods

Participants

We asked general practitioners in the Greater Rotterdam area to report patients aged 0-12 years with non-bullous impetigo presenting at their surgery. We excluded patients who were immunocompromised; patients with extensive lesions (estimated area more than 5% of the total skin surface), infections of deeper skin structure, temperature >38.5°C, hypersensitivity to povidone-iodine, or hyperthyroidism; patients who had used topical or systemic antibiotics in the previous 48 hours; and patients for whom informed consent was not obtained. The medical ethics committee of Erasmus University and University Hospital Rotterdam approved the trial protocol.

A research nurse visited the children at home, usually the same day. The nurse recorded the duration of impetigo, nature of the lesions (redness, crusts, pustules, and painfulness), number of lesions, localisation and estimated area of lesions, body temperature, presence of regional lymphadenopathy, recent use of antibiotics, demographic data, and pre-existence of eczema and took a swab of the lesions.

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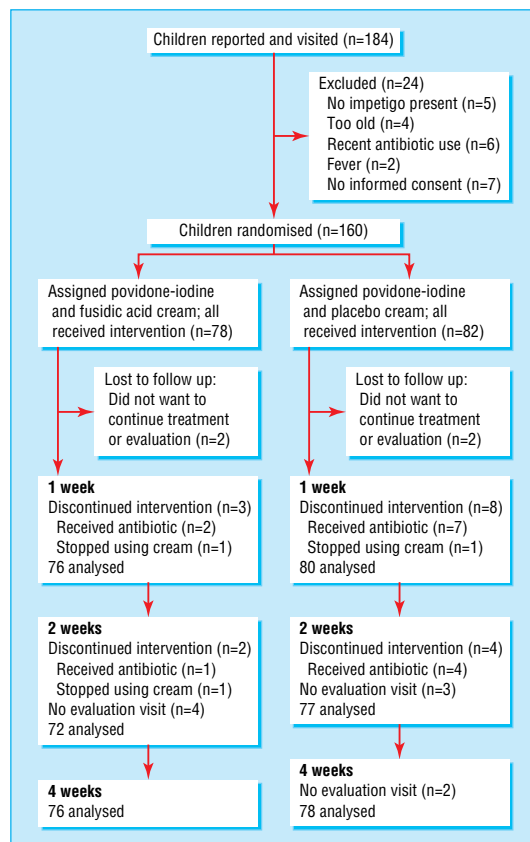
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Flow and follow up of participants

Interventions

The lesions were washed gently with povidone-iodine shampoo (Betadine shampoo; ASTA, Diemen, Netherlands), 75 mg/ml twice daily. The study cream was applied three times a day. The study cream was either 2% fusidic acid cream (Fucidin; Leo Pharmaceutical Products BV, Weesp, Netherlands) or placebo cream. Patients were advised to use the study cream for a maximum of 14 days or until the lesions had disappeared and to use common hygienic measures (cutting nails short, use of personal towels).

The research nurse visited participants at home for evaluation at 7, 14, and 28 days after the start of treatment, recorded data on clinical cure, compliance, use of other drugs, violation of the protocol, and side effects, and took a swab of the lesions if they were still present. General practitioners were free to prescribe other treatment such as oral antibiotics if the impetigo worsened or did not improve, but they were encouraged to comply with the study protocol for at least the first week.

Assignment and masking

The placebo cream, prepared by the pharmacist, did not differ in colour, smell, or consistency from the fusidic acid cream. An independent statistician provided a computer generated list of random set numbers. The research nurse was unaware of the treatment allocation.

Outcomes

Primary outcome measures were clinical cure, improvement, and size of affected area, as assessed by the research nurse, and bacterial cure after 7, 14, and

28 days. We defined clinical cure as the complete absence of lesions or the lesions having become dry and without crusts; remaining local redness of intact skin was acceptable. Adverse effects were secondary outcome measures. We considered baseline characteristics, causative pathogen, and resistance of the pathogen to fusidic acid at baseline as possible confounding factors.

Statistical analysis

We analysed the results both by intention to treat and per protocol; results of the per protocol analyses are presented in the full version on bmj.com. We used logistic regression analysis to calculate crude and adjusted odds ratios for dichotomous outcome measures. Baseline characteristics that had at least a weak relation ($P < 0.25$) with the outcome variable in univariate logistic regression analyses were considered to be potentially adjusting variables. With a postulated spontaneous cure of 50% at one week and a detectable absolute difference of 25% in the treatment group, with $\alpha = 0.05$ and $\beta = 0.10$, the planned study population was 85 children in each group.

Results

From February 1999 to November 2000, 58 general practitioners reported 184 children with impetigo. After the inclusion visit of the research nurse, 160 children were included and randomised (fig). The groups were comparable with respect to baseline characteristics (table 1). We decided to exclude children with missing evaluation visits from the analysis.

The proportion of children cured clinically at one week was 55% in the fusidic acid cream group and 13% in the placebo group, resulting in a number needed to treat of 2.3. At two weeks and four weeks the results

Table 1 Baseline characteristics of study population (n=160). Values are numbers (percentages) unless stated otherwise

	Fusidic acid cream (n=78)	Placebo cream (n=82)
Mean (SD) age (years)	4.8 (2.9)	5.1 (2.7)
Boys	47 (60)	51 (62)
Dutch origin	47 (60)	48 (59)
Attending day care or school	59 (76)	66 (80)
Mean (SD) No of lesions	11.4 (13.3)	13.2 (14.5)
Mean (SD) affected area (cm ²)	5.6 (7.3)	7.3 (11.4)
Mean (SD) body temperature (°C)	36.5 (0.7)	36.6 (0.7)
Lymphadenopathy	32 (41)	25 (30)
Mean (SD) duration of impetigo (days)	9.6 (8.0)	9.2 (10.2)
Localisation:		
Head	61 (78)	61 (74)
Trunk	22 (28)	29 (35)
Limbs	36 (46)	33 (40)
Pre-existing eczema	10 (13)	12 (15)
Pathogen isolated:		
<i>Staphylococcus aureus</i>	66 (85)	61 (74)
<i>Streptococcus pyogenes</i> (A)	1 (1)	4 (5)
Both	1 (1)	7 (9)
None	10 (13)	10 (12)
Fusidic acid resistance (<i>S aureus</i>):		
Resistant	0/67 (0)	0/68 (0)
Intermediately sensitive	3/67 (4)	7/68 (10)
Sensitive	64/67 (96)	61/68 (90)
Mupirocin resistance (<i>S aureus</i>)	1/67 (1)	0/68 (0)
Erythromycin resistance (<i>S aureus</i>)	6/67 (9)	8/68 (12)

were still in favour of fusidic acid, but the differences were smaller and the results were no longer significant (tables 2 and 3). After adjustment for confounding baseline variables the association between fusidic acid and cure after one week was increased (table 3). Clinical improvement and cure combined was hardly confounded by baseline imbalances.

Side effects

Side effects were experienced in 26 cases—seven occurred in the fusidic acid group and 19 in the placebo group. The most frequent side effects were pain (two in the fusidic acid group *v* six in the placebo group) and burning (one *v* four) during administration of the povidone-iodine shampoo. Other side effects were redness (two in each group), burning from the study cream (one in placebo group), itching from both applications (two in placebo group), and pain and irritation from both applications (one in each group).

Bacteriological results

For all the baseline visits and 431 (94%) of the 459 follow up visits, swabs were available or lesions were cured. *S aureus* was found in 135 (96%) of the 140 positive cultures at baseline (table 1); *S pyogenes* and mixed infections were found in a minority of cases. The proportion of children with bacterial cure at one week was 91% in the fusidic acid group compared with 32% in the placebo group (table 2).

Table 2 Clinical effect and bacterial cure (intention to treat analysis). Values are numbers (percentages)

	Fusidic acid cream (n=76)	Placebo cream (n=80)
One week		
Clinical effect:		
Cure	42/76 (55)	10/80 (13)
Improvement	25/76 (32)	37/80 (46)
Failure	9/76 (11)	33/80 (41)
Bacterial cure	63/69 (91)	23/72 (32)
Two weeks		
Clinical effect:		
Cure	53/72 (73)	46/77 (60)
Improvement	17/72 (23)	20/77 (26)
Failure	2/72 (3)	11/77 (14)
Bacterial cure	62/70 (89)	52/70 (74)
Four weeks		
Clinical effect:		
Cure	70/76 (92)	69/78 (88)
Improvement	5/76 (7)	7/78 (9)
Failure	1/76 (1)	2/78 (3)
Bacterial cure	71/75 (95)	70/75 (93)

Table 3 Clinical cure: results of logistic regression analysis. Odds ratios (95% CI) fusidic acid cream (F) versus placebo (P)

	Cured	Cured or improved
One week: (F, n=76; P, n=80)		
Crude	8.7 (3.9 to 19.3)	5.2 (2.3 to 11.9)
Adjusted	12.6 (5.0 to 31.5)	5.5 (2.3 to 13.4)
Two weeks: (F, n=72; P, n=77)		
Crude	1.9 (0.9 to 3.8)	5.8 (1.2 to 27.3)
Adjusted	1.9 (0.8 to 4.1)	5.2 (1.1 to 24.9)
Four weeks: (F, n=76; P, n=78)		
Crude	1.5 (0.5 to 4.5)	2.0 (0.2 to 22.2)
Adjusted	1.8 (0.5 to 5.9)	2.3 (0.1 to 50.5)

What is already known on this topic

Impetigo is the most common skin infection in children

Fusidic acid, which is advocated as topical treatment in several countries, has never been investigated in a placebo controlled study

What this study adds

In combination with povidone-iodine, treatment with fusidic acid is much more effective than placebo

None of the strains of *Staphylococcus aureus* isolated at baseline showed resistance to fusidic acid

The value of treatment with povidone-iodine alone can be questioned

Discussion

The results do not support conservative treatment with disinfecting measures alone. Treatment with povidone-iodine combined with placebo cream had a very disappointing cure rate of 13% at one week. After two and four weeks the differences between the two treatments were smaller and no longer significant. If it was not due to the possibly benign spontaneous course of impetigo, this finding was probably caused by the fact that more patients in the placebo group had “crossover treatment” with antibiotics. Fourteen per cent of the patients in the placebo group compared with 4% in the fusidic acid group returned to their general practitioner because of failure of treatment and received an extra, usually oral, antibiotic treatment.

A small number of swab results (12.5%) were negative at baseline—because we were studying patients with a clinical diagnosis of impetigo we had no reason to exclude these patients. *S aureus* was the pathogen most often found, which accords with other investigations showing that the predominant organism in impetigo has changed from *S pyogenes* to *S aureus* in recent years.¹¹ We did not find resistance to fusidic acid in our study population, indicating that many years of use of topical fusidic acid has not resulted in appreciable resistance in staphylococci in the general population. The resistance to erythromycin in staphylococci was higher, in accordance with the international trend. Although oral antibiotics are used for impetigo in many countries, this finding provides an extra argument for topical treatment with fusidic acid cream.

Our recent meta-analysis showed that fusidic acid and mupirocin were equally effective in treating impetigo,¹⁶ but fusidic acid costs less. We conclude that topical fusidic acid cream is an effective treatment for impetigo, with very few side effects, and can be considered a first choice in the treatment of impetigo in general practice. The value of sole or adjunctive treatment with povidone-iodine can be questioned.

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A memorable study day Rehumanise yourself

"You can never go back," I was always being told by colleagues who had regretted not gathering more training experience before taking up their consultant posts. This was therefore my motto as I attempted to accumulate diverse training experiences.

I had been working on a research oriented forensic unit treating people with personality disorder, a new venture in uncertain times for these services in Britain. Most patients were offenders with severe problems, and I spent my time categorising and classifying their problems, formulating any possible link between their offending and their disorders, and thus directing the treatment approaches and interventions. Assessment had become my forte, and I breathed diagnostic systems and psychological ratings. With an eye on outcome, we probably overmeasured, with little evidence available to identify which variables might be the most important in the future. Patients' ratings had become as important to me as their stories and how they came to be.

I decided to take a study day and was accepted as a visitor to a therapeutic community, a psychotherapeutically oriented NHS residential group of men and women also with personality disorder. After my early coffee and staff introductions, I waited with interest to see how the psychological assessments contrasted with those in my own unit. To my surprise I was shepherded through the residents' door while the staff disappeared upstairs to do their evaluations on new referrals. Somewhat disorientated, I sat through the first residents' group where the weekend's problems were discussed. People introduced themselves, but I felt a bit disarmed. What were the diagnoses? How long had they had their problems? How bad were things? Next followed the chores, and,

luckily, I'm not bad at cleaning. I could guess from the healed (and not so healed) lacerations peeping out from sleeves as to some of the residents' psychopathology, but gradually my usual frames of reference were replaced by my interest in their coping with adversity as much as any possible disorder. As we ate lunch, I detected tensions among the group, but, as the outsider with no role, I felt focused on the people rather than the causes or their management.

I felt both sad and elated as the day ended, with the sense that, for once, I had actually learnt something on a study day in psychiatry. I've always been a bit cynical about experiential training, but being unprepared and having no preconceptions had somehow liberated my ability to empathise. Maybe I had re-experienced the process of active rather than critical listening.

Now, some time on, I still look for the diagnosis, for ratings of severity and suchlike, but I try to suspend my judgment just that little bit longer to get a sense of the person behind the scores. As Patrick McGoohan famously said in *The Prisoner*, "I am not [just] a number."

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We welcome articles up to 600 words on topics such as *A memorable patient, A paper that changed my practice, My most unfortunate mistake*, or any other piece conveying instruction, pathos, or humour. If possible the article should be supplied on a disk. Permission is needed from the patient or a relative if an identifiable patient is referred to. We also welcome contributions for "Endpieces," consisting of quotations of up to 80 words (but most are considerably shorter) from any source, ancient or modern, which have appealed to the reader.