

Corticosteroid Therapy in Combination with Antibiotics for Erysipelas

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ABSTRACT: **Background:** Erysipelas, an acute infection of the dermal and subcutaneous tissue, is normally treated with antibiotics. Previous data indicated that treatment with prednisone in combination with antibiotics results in significant acceleration of the healing phase.

Objectives: To investigate the effectiveness of corticosteroids combined with antibiotics for the treatment of erysipelas.

Methods: A retrospective study was conducted on hospitalized patients diagnosed with erysipelas between 2004 and 2011 at the Department of Dermatology at Sheba Medical Center, Israel. Data included epidemiology, medical background, and course of the disease as documented at admission and during hospitalization.

Results: Data were collected on 173 patients (66% males) who were divided into two groups: a control group treated with antibiotics only (97 patients) and a study group treated with antibiotics and prednisone (76 patients). The study group presented with a more severe form of erysipelas (bullous) and those patients were hospitalized for a longer period (8.5 vs. 7 days). Nevertheless, the study group exhibited a 71% clinical improvement shortly after being treated with prednisone, without significant side effects. Short-term follow-up revealed more edema in the study group; however, long-term follow-up revealed a higher incidence of erythema and recurrence of erysipelas in the control group. The return to full function was faster in the study group than in the control group.

Conclusions: Combining prednisone with antibiotics for the treatment of erysipelas should be considered, especially in severe cases. In addition, a prospective double-blind study should be conducted to verify these conclusions.

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KEY WORDS: erysipelas, corticosteroid, antibiotic, treatment, cellulitis

Erysipelas is an acute infection of the dermal and subcutaneous tissue that can also involve the lymphatic capillaries [1,2]. The main causes are Group A β -hemolytic streptococci and *Staphylococcus aureus* [1,3]. Lymphedema is a predispos-

ing factor that also increases the risk of relapse [1]. The onset of skin lesions is often preceded by prodromal symptoms, such as malaise, chills, and high fever, which, if present, usually occur 48 hours prior to cutaneous involvement. The cutaneous complaints include pruritus, burning, tenderness, and swelling [4].

Erysipelas is found in the lower extremities in 70–80% of patients. The face is affected in only 5–20% of cases [5]. There is no known difference in incidence and clinical course between men and women. Studies have indicated that predisposing factors, rather than gender, account for any male/female differences in incidence [6]. Local signs of inflammation, such as warmth, edema, and tenderness, are common. Infections of greater severity may occur in diabetic patients, who may develop numerous vesicles and bullae, along with petechia and even necrosis. Local recurrence has been reported in up to 20% of patients with predisposing conditions, which can lead to mutilating and restricting results such as elephantiasis nostras verrucosa. Other potential rare complications include bacteremia and septic shock. The infection can also spread to the heart valves, joints, and bones [6].

The standard treatment for erysipelas is an antibiotic, specifically penicillin [1-3,7,8] or cephalosporin (first generation), given for approximately 10 days. In severe cases, antibiotics may be given intravenously during hospitalization. Clinicians have generally avoided prescribing corticosteroids for active infection because of their known immunosuppressive effects and due to concerns about long-term complications. However, previous data have shown that corticosteroids are beneficial and safe for treatment of a wide variety of infections, including bacterial meningitis, tuberculous meningitis, tuberculous pericarditis, severe typhoid fever, tetanus, bacterial arthritis, and pneumocystis pneumonia when given in conjunction with antimicrobial agents [9].

A previous Scandinavian prospective study reported that erysipelas healed significantly more rapidly when prednisone was added to the conventional antibiotic therapy [10,11]. Similarly, Ezzine et al. [12] showed that a combined treatment of antibiotics and corticosteroids caused rapid regression of fever, pain, and cutaneous signs. The goal of the present study is to describe our experience regarding the efficacy of a combination of corticosteroids and antibiotics for the treatment of erysipelas.

*The first and second authors contributed equally to this study

PATIENTS AND METHODS

This retrospective study was based on data collected between 2004 and 2011 from patients diagnosed with erysipelas limited to the lower limbs. The patients were all treated at the Department of Dermatology at the Sheba Medical Center, which is the largest tertiary center in Israel. All enrolled patients were 18 years of age or older. In total, 76 patients were treated with a combination of antibiotics and prednisone and 97 patients were treated with antibiotics only.

The patients' files were analyzed and preliminary epidemiological data were retrieved, including age, gender, site of initial infection, co-morbidities at diagnosis, risk factors, and information about previous episodes of erysipelas. Clinical data retrieved included description of the skin lesion (in terms of redness, swelling, and tenderness as described in the medical files), systemic symptoms, laboratory tests, medications administered, duration of hospitalization, and treatment side effects. Follow-up data were collected from out-patient clinic visits.

A telephone survey was also conducted among a small subgroup of the patients treated between the years 2010 and 2012. Patients were questioned about their medical condition after being discharged from the hospital, including persistent skin erythema, edema, pain, recurrent episodes of erysipelas, and the use of prophylactic antibiotic treatment. The subjects were asked only yes or no questions about their current medical status since their hospitalization concerning the erysipelas. Questions related to the presence of edema, redness persistence, pain, and a recurrent episode of infection. If the answer was positive, they were asked to rate the severity of the symptom on a scale of 1–5, where 1 represents the lowest and 5 the highest degree of that symptom. The study was approved by the ethics committee of the hospital.

Our usual treatment protocol for prednisone addition for patients with the severe form of erysipelas includes 0.5 mg/kg prednisone for 2–3 days until improvement and then tapering down by 10 mg prednisone every 2 days until cessation. The treatment is given only after fever declines and WBC count decreases. All patients were given prednisone while still on antibiotics.

Data entry and statistical analysis was performed using Statistical Package for the Social Sciences (SPSS Inc., Chicago, IL, USA) version 15.0 for Windows. Confidence intervals were extended to a level of 95%. A *P* value below 0.05 was accepted as statistically significant. Values are expressed as mean ± standard deviation.

RESULTS

Data were collected on 173 patients. The average age at diagnosis was 55.8 years ± 17.7 years, the female to male ratio was 1:1.98 (58 females, 115 males, 66% male, *P* < 0.001). The patients were

divided into two groups. The study group included 76 patients (31 females and 45 males) who were treated with antibiotics (e.g., procaine penicillin, oxacillin, cefamezin, clindamycin, or ofloxacin) and corticosteroids. The control group included 97 patients (27 females and 70 males) who were treated with antibiotics alone. The groups did not differ statistically in terms of age, gender, or co-morbidities present at the time of erysipelas diagnosis. [Table 1]. These co-morbidities were documented prior to initiation of prednisone therapy, thereby excluding the possibility of adverse effects due to glucocorticosteroids. No statistically significant differences were noted among risk factors, such as tinea pedis, lymphedema, stasis dermatitis, and post-surgery scars.

Overall, 134 patients (77.5%) exhibited co-morbidities at the initial diagnosis; the most common were hypertension (37.6%) and obesity (23.7%), followed by cardiac disease (22%) and diabetes (17.9%).

Table 2 shows the disease severity of the two groups. Statistically significant differences were found between the groups in terms of hospitalization duration and the diagnosis of bullous erysipelas. A significantly higher percentage of patients in the study group (38.2%) presented with the severe form of erysipelas (bullous) when compared with the control group (20.6%) (*P* < 0.05). The patients in the study group had longer hospital stays (8.5 ± 3.7 days) compared to the patients in the control group (7 ± 5 days). No significant differences were noted between the two groups in terms of WBC count, fever, duration of antibiotic treatment, the presence of lymphadenopathy and/or lymphangitis.

The study group was treated with an average dosage of 32.8 mg prednisone per day. The first dose was given on day 5.5 of hospitalization, for an average of 6.4 days. Overall, 71% of these patients exhibited significant clinical improvement after one or two days of treatment. No significant side effects were apparent. The improvement was defined by local improvement in the erythema, pain, size of lesion, and extent of leg edema. Short-term

Table 1. Comparison of demographic data, co-morbidities, and risk factors of erysipelas between the study group and the control group (N= 173), *P* = non-significant

	Study group	Control group
No. of patients	76	97
Men:women	45:31	70:27
Mean age (years)	56.4	55.3
Diabetes mellitus (%)	15.8	19.6
Hypertension (%)	42.1	34
Cardiac disease (%)	22.4	21.6
Obesity (%)	25	22.7
Tinea pedis (%)	67.1	71.1
Lymphedema (%)	13.2	10.3
Stasis dermatitis (%)	7.9	11.3
Scarring (%)	11.3	17.5

follow-up conducted 2 weeks after discharge from the hospital revealed significant differences in edema between the study and control groups (31.6% vs. 15.5%, respectively, $P < 0.05$), as summarized in Table 3. All other follow-up indices, including redness, pain, recurrent episodes, and repeated hospitalization, showed no statistically significant differences between the two groups.

A small subgroup of 45 patients (26%) also participated in the telephone survey. This subgroup included 27 patients from the original control group and 18 from the study group. All patients were asked to rate the erythema, pain, and edema they had experienced since their hospitalization. Significantly more patients from the control group (29.6%) experienced redness when compared to the study group (5.6%), and these patients required treatment for recurring incidents ($P < 0.05$). The study group also reported a more rapid return to full function when compared to the control group (41 vs. 172 days). This difference between the groups neared statistical significance ($P = 0.1$). Pain and edema did not significantly differ between the two groups.

DISCUSSION

Steroids are a non-conventional treatment for skin infections. A previous prospective study, conducted in Scandinavia, randomized 108 hospitalized patients with a diagnosis of erysipelas to 8 days of treatment with antibiotics coupled either with prednisolone or a placebo. The prednisolone-treated patients had a median length of hospital stay of 5 days vs. 6 days for the placebo-treated patients ($P < 0.01$). The patients in the placebo group also underwent significantly longer intravenous treatments compared to the prednisolone group [10,11].

In the present retrospective study, patients presenting with erysipelas in the lower limbs were divided into two treatment groups to permit evaluation of the effect of a treatment that included prednisone in addition to antibiotics. The study and control groups were matched with respect to age, gender, and co-morbidities, but the study group had a more severe form of erysipelas, as reflected by a longer hospitalization (8.5 vs. 7 days) and the clinical appearance of a bullous type of erysipelas. This indication reflects our policy to give steroids in the cases where slow or insufficient resolution is expected. Nevertheless, overall, 71% of the patients in the study group exhibited significant clinical improvement of their situation 1 to 2 days after the launch of prednisolone treatment. Thus, as expected, prednisone seems to be a modifying agent in the disease course. The short-term follow-up of the patient's condition after discharge indicated significantly more edema in the study group than in the control group, which could either reflect the more severe disease in the study group or the temporary effect of steroids in that respect. However, despite being performed on a small group of patients, the long-term telephone survey showed a significantly lower prevalence of recurrence and persistent erythema within the study group. Edema was similar between

Table 2. Disease severity: comparison between the study group and the control group

	No. of hospitalization days	WBC count	Fever	Duration of antibiotic treatment (days)	Bullous disease	Lymphadenopathy	Lymphangitis
Control group	7	13447	37.6	10.9	20.6%*	43.3%*	19.6%
Study group	8.5	14241	37.8	11	38.2%*	43.4%*	22.4%
<i>P</i> value	0.03	NS	NS	NS	0.01*	NS	NS

*Near significant

WBC = white blood cell count, NS = non-significant

Table 3. Short-term follow-up

	Recurrent erysipelas	Edema	Erythema	Pain	Repeated hospitalization	ER visit	Long-term complications
Control group	14.4%	15.5%	14.4%	8.2%	8.1%	8.1%	5.2%
Study group	17.1%	31.6%	22.4%	7.9%	4.9%	7.3%	5.3%
<i>P</i> value	NS	0.01	NS	NS	NS	NS	NS

NS = non-significant, ER = emergency department

Table 4. Telephone survey results

	Recurrent erysipelas	Chronic edema	Persistent erythema	Chronic pain	Recurrent hospitalization	Return to full function
Control group	22.2%	18.5%	29.6%	11.1%	7.4%	88.9%
Study group	16.7%	11.1%	5.6%	5.6%	16.7%	100%
<i>P</i> value	NS	0.04	NS	NS	NS	NS

NS = non-significant

the two groups at this endpoint, suggesting that a further, more significant, improvement in the study group occurred, especially when one considers that at a short-term follow-up it was more severe in this group. Furthermore, the treated group tended to return to full function earlier. These differences were not statistically significant, probably due to the small sample of participants included in the telephone survey (26%). To note, although the survey showed a higher rate of recurrent hospitalization in the treated group, it only reflects the severity of the cases treated with prednisone. The tendency to recur later cannot be prevented by prednisone treatment only, and preventive antibiotic treatment should be considered in those cases. A larger sample may have yielded results of greater accuracy.

Unlike the findings in previous studies [10,11], our study group showed only minor faster healing and shorter hospitalization periods in response to the combination of prednisone and antibiotics. This can be explained by the greater severity of the erysipelas among patients in the present study group, as reflected by the fact that 38.2% of patients in the study group presented with bullous erysipelas. This severe condition requires additional hospitalization time, regardless of treatment. A further difference between the current study and the previous ones is that the patients in the study conducted in

Scandinavia received prednisone treatment from the first day of hospitalization, compared to day 5.5 in our study.

The present study has several limitations. In general, most cases diagnosed with erysipelas tend to be mild and are treated in the community; therefore, the patients in the present study represented those with the more severe forms of the disease that needed hospitalization. In addition, this was a retrospective study based on data collected from patients' files; therefore, the groups were not randomized. Furthermore, it was not a case control study.

Despite these limitations and the greater severity of the erysipelas in the study group, the patients treated with prednisone clearly benefited from this treatment. They showed less redness, a faster return to full function after treatment, and lower recurrence rates than those treated with antibiotics alone. In addition, immediately after steroid initiation, improvement was noted, and this may contribute to the possibility of discharge earlier from the hospital despite their more severe disease. Most importantly, the study group showed no significant side effects due to prednisone.

CONCLUSIONS

This study shows that prednisone, given in conjunction with antibiotics as a treatment for severe cases of erysipelas, can contribute to faster recovery rates and a more rapid return to full function, with less risk of recurrence and persistent local erythema. We therefore recommend to consider administering prednisone as soon as the patient's fever drops, in order to accelerate improvement. A prospective double blind study should be conducted to verify our conclusion.

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Capsule

Loss of muscle strength prior to knee replacement: a question of anatomic cross-sectional area or specific strength?

Culvenor and co-authors determined whether loss in thigh muscle strength prior to knee replacement is caused by reductions of muscle strength in the anatomic cross-sectional area or by reductions of specific strength. The 100 participants in the Osteoarthritis Initiative who underwent knee replacement and whose medical records included data on thigh isometric muscle strength and magnetic resonance imaging (MRI) (58 women, and 42 men, mean age 65 ± 8 years, mean body mass index [BMI] 29 ± 5 kg/m²) were matched with a control (no knee replacement) for age, gender, height, BMI, and radiographic severity. Knee replacement cases had significantly smaller extensor (but not flexor) anatomic cross-sectional areas than controls at time 0 (women, OR_{adj} 1.89, 95% confidence interval [95%CI] 1.05–3.90; men, OR_{adj} 2.22, 95%CI, 1.04–4.76), whereas no significant differences were found at time -2. Women who had knee replacement showed lower levels of extensor

specific strength than controls at time 0 (OR 1.59 [95%CI 1.02–2.50]), although this difference was not observed in men and did not maintain significance after adjustment for pain (OR_{adj} 1.22 [95%CI 0.71–2.08]). Female cases lost significantly more extensor specific strength between time -2 and time 0 than controls (OR_{adj} 3.76 [95%CI 1.04–13.60]), whereas no significant differences were noted at time -2, or in men. The authors concluded that prior to knee replacement, a significant reduction in knee extensor strength appears to occur in women through two mechanisms: one driven by pain (loss of specific strength) and one independent of pain (loss of muscle anatomic cross-sectional area). Men who underwent knee replacement showed significantly reduced levels of extensor anatomic cross-sectional area, but not significantly lower strength or specific strength.

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Eitan Israeli