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Short-Course, Low-Dose Oral Betamethasone as an Adjunct in the Treatment of Acute Infective Sinusitis

A Comparative Study with Placebo

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Abstract

Objective: To assess the effect of a short course of low-dose oral corticosteroid used as an adjunct to antimicrobials in patients with acute infective sinusitis.

Study design and patients: Double-blind, randomised, placebo-controlled study including 42 patients with a clinical diagnosis of acute infective sinusitis. The study was performed at three primary healthcare sites in South Africa during the period January–November 2003.

Intervention: Two equal groups received either betamethasone 1mg orally ($n = 21$; the treatment group) or placebo tablets ($n = 21$; the placebo group) once a day in the morning for five consecutive days. All patients received amoxicillin-clavulanic acid 625mg orally, three times daily for 5 days.

Main outcome measure: Patients rated symptoms on a daily symptom score card for 5 days and were examined by the investigator at diagnosis (day 0) and on the second visit (day 6).

Results: Headache, facial pain, nasal congestion and dizziness improved significantly from baseline in the treatment group compared with the placebo group over 5 days of treatment ($p = 0.028$, $p \leq 0.047$, $p \leq 0.04$ and $p \leq 0.051$, respectively). Percussion tenderness improved significantly ($p = 0.049$) and clearance of purulent secretions almost reached significance ($p = 0.058$) in the treatment group compared with the placebo group.

Conclusion: This study suggests a benefit of oral corticosteroid added to antimicrobial treatment of acute sinusitis and documents the first successful use of a short course of low-dose oral corticosteroid in patients with acute infective sinusitis.

The use of topical intranasal corticosteroid therapy as an adjunct to antibiotics has been shown to be effective in improving symptoms in the treatment of acute infective sinusitis.[1-3] Acute infective sinusitis usually follows viral upper respiratory tract infection.[4] The mucosa in the sinuses becomes inflamed and oedematous; this obstructs the sinus drainage at the osteomeatal complex. Bacteria that colonise the nasal passages and nasopharynx multiply in the blocked or partially obstructed sinuses and secretions are retained. Inflammatory episodes in allergy impair sinus ventilation and mucociliary clearance, which may lead to acute sinusitis.[4] Other predisposing factors are nasal anatomical variants and

non-allergic rhinitis, which cause ostial obstruction, hypoxia and retention in the sinuses.[4] Topical intranasal corticosteroids reduce inflammation and oedema in acute sinusitis.[1-3]

Micro-organisms usually found in acute infective sinusitis are *Streptococcus pneumoniae*, *Haemophilus influenzae* and *Moraxella catarrhalis*.[4] A meta-analysis of antibiotics used in sinusitis confirmed that penicillin or amoxicillin 500mg three times daily for 10 days is effective in the treatment of acute, uncomplicated sinusitis.[5] However, owing to the increased prevalence of β-lactamase-producing organisms, amoxicillin-clavulanic acid and other drugs are becoming more relevant and are often drugs of choice in primary healthcare facilities.[6]

Low-dose oral corticosteroids have been shown to have marginal and transient hypothalamic-pituitary-adrenal axis suppression if used for a short period (i.e. <7 days).[7]

Intranasal corticosteroids are costly compared with oral corticosteroids. The former are available in the form of metered nasal sprays that are troublesome to administer for most first-time users. Young et al.[8] showed that a history of purulent nasal discharge, and signs of pus in the nasal cavity and the throat, is a better criterion than radiography or C-reactive protein for selecting patients who will benefit from antibiotic treatment.

In this study we aimed to investigate the efficacy of oral betamethasone in the management of clinically diagnosed acute infective sinusitis.

Patients and Methods

Study Participants

Forty-two patients with clinically diagnosed acute infective sinusitis (16 male and 26 female, mean age 29 years) were randomised into two groups after providing signed informed consent. Computer-generated random numbers were used with no stratification. Patients were enrolled between January and November 2003 from three primary healthcare sites (two primary healthcare clinics and one private primary healthcare practice).

The investigators clinically diagnosed and examined the patients. Patients had to have six or more of the following symptoms for <12 weeks: headache, cough, facial pain, nasal congestion or stuffy nose, purulent rhinorrhoea or postnasal drip, and dizziness. The presence or absence of purulent secretions in the nose and pharynx and percussion tenderness over the maxillary and frontal sinuses was also evaluated. Patients were eligible for inclusion if the total symptom score was ≥6 (maximum possible 21 points); at least one nasal symptom had to be moderate or severe (score ≥2 points) and purulent rhinorrhoea or postnasal drip had to be present (score ≥1 point).[1]

Patients with the following conditions were excluded from the study: nasal polyps, anatomical abnormalities of the nose (anterior rhinoscopy was used), glaucoma, cataracts, dyslipidaemia, myopathies, tuberculosis, diabetes mellitus, hypertension, disseminated fungal infection, peptic ulcer diseases, bleeding tendencies, liver cirrhosis, psychiatric conditions and active wounds. Patients receiving antimicrobial therapy or anti-inflammatory agents, oral corticosteroids in the past 4 weeks or intranasal corticosteroids in the past 2 weeks, pregnant and nursing women, patients allergic to penicillin, and immunocompromised patients were also excluded.

The faculty of Health Sciences Research Ethics Committee of the University of Pretoria approved the study protocol.

Study Design and Treatment

This was a randomised, double-blind study. Betamethasone 1mg tablets (the treatment group) or placebo tablets (the placebo group) were randomly assigned to patients for 5 days, taken orally in the morning (between 7 and 9am) to mimic the normal circadian variation. Patients and investigators were blinded to treatment. All patients received amoxicillin-clavulanic acid 625mg tablets three times daily for an empiric 5 days' treatment. Symptoms were evaluated retrospectively in the evening for the day. Instructions were clearly given to the patients on how to take daily treatment. All tablets were taken after meals. Other medication such as oral decon-

gestants, antihistamines and mucolytics were not permitted. The permitted analgesic was paracetamol 1000mg for pain; patients took this as needed on a 6-hourly basis with a maximum of 4000 mg/day. The use of this pain medication was scored in the patient diary.

Assessments and Measurements

Demographic variables collected at baseline were age, sex, history of upper respiratory tract infection, and history of allergic rhinitis.

Patients were given a symptom score diary in which to score the symptoms daily in the evening for 5 days. Concomitant medications and adverse events were also entered on the diary card. Each symptom was scored separately using a 0–3 severity scale: 0 = none, 1 = mild, 2 = moderate, 3 = severe.[1]

The investigator scored the symptoms and signs on the day of diagnosis (day 0) and again on the second visit (day 6) after treatment.

Data Analysis

Two-way frequency tables were constructed separately for each symptom and day on which the symptoms were observed. Symptom categories were grouped in two different ways, each grouping providing a different two-way table. In the first grouping the categories none/mild and moderate/severe were grouped yielding two new categories. For the second grouping categories mild/moderate/severe were grouped with the category 'none' as the second grouping (table I).

Two-way frequency tables were used, from which the percentage of none/mild and moderate/severe or none and mild/moderate/severe symptom severity combinations experienced per day were obtained. These four row proportions were plotted separately against day for treatment and placebo. Weighted linear regression equations were fitted to graphs with row percentages none/mild and moderate/severe or none and mild/moderate/severe symptom severity combinations as dependent variables and day as predictor. The differences in the rate of increase or decrease of the dependent variable against day of treatment and placebo for each symptom were then compared statistically using t-tests, by comparing the relevant slopes (table II). One-sided t-tests were used because it was expected that the treatment should have a steeper slope than placebo.

Similar two-way frequency tables were constructed for treatment and placebo separately with

Table I. Frequency tables of percentages of symptoms between the severity categories on day 0 and day 6 in patients with acute infective sinusitis in the betamethasone and placebo groups

Symptom	Day	Moderate/severe		None/mild		Mild/moderate/severe		None	
		B	P	B	P	B	P	B	P
Headache	0	85.71	61.9	14.29	38.1	100	100	0	0
	6	9.52	33.33	90.48	66.67	38.1	57.14	61.9	42.86
Cough	0	23.81	23.81	76.19	76.19	52.38	47.62	47.62	52.38
	6	0	0	100	100	9.52	19.05	90.48	80.95
Facial pain	0	80.95	71.43	19.05	28.57	100	100	0	0
	6	4.76	23.81	95.24	76.19	14.29	38.1	85.71	61.9
Nasal congestion	0	95.24	90.48	4.76	9.52	100	100	0	0
	6	9.52	23.81	90.48	76.19	28.57	71.43	71.43	23.57
Postnasal drip	0	76.19	71.43	23.81	28.57	100	100	0	0
	6	4.76	9.52	95.24	90.48	28.57	71.43	71.43	28.57
Fever	0	76.19	71.43	23.81	28.57	100	95.24	0	4.76
	6	0	0	100	100	9.52	14.29	90.48	85.71
Dizziness	0	57.14	47.62	42.86	52.38	80.95	71.43	19.05	28.57
	6	0	19.05	100	80.95	9.52	23.81	90.48	76.19

B = betamethasone 1 mg/day + amoxicillin-clavulanic acid 625mg three times daily; **P** = placebo + amoxicillin-clavulanic acid 625mg three times daily.

Table II. Change in treatment effects for the duration of therapy expressed as slope values (the increase or decrease of symptoms over treatment period) in patients with acute infective sinusitis in the betamethasone and placebo groups

Symptom	Treatment	None/mild	Moderate/severe	None	Mild/moderate/severe
Headache	B	0.153	−0.153	0.113	−0.107
	P	0.078	−0.078	0.091	−0.083
	p-Value	0.028[a]	0.028[a]	0.17	0.1
Facial pain	B	0.126	−0.126	0.154	−0.147
	P	0.085	−0.085	0.113	−0.112
	p-Value	0.12	0.12	0.047[a]	0.025[a]
Nasal congestion	B	0.155	−0.155	0.134	−0.112
	P	0.117	−0.117	0.067	−0.054
	p-Value	0.064	0.064	0.04[a]	0.034[a]
Dizziness	B	0.09	−0.09	0.137	−0.137
	P	0.046	−0.046	0.097	−0.097
	p-Value	0.05[a]	0.05[a]	0.051[a]	0.051[a]

a Significant p-value favours betamethasone therapy; p-value is calculated for the difference in the slopes between the treatment and placebo groups (i.e. change due to therapy over time as a dependent factor).

B = betamethasone 1 mg/day + amoxicillin-clavulanic acid 625mg three times daily; **P** = placebo + amoxicillin-clavulanic acid 625mg three times daily.

one variable being day (only day 0 and day 6) and the second variable having presence and absence of the sign as categories. Row percentages were used and differences between the percentages for the absent and the present categories of a sign were compared using one-way t-tests for treatment and placebo. These comparisons were made for both day 0 and day 6 (table III).

Results

The percentages in each category of severity (none/mild and moderate/severe or none and mild/moderate/severe) were regressed per day, providing two slopes, one for placebo and one for treatment (table II). Good fits of regression lines were obtained with R^2 values ranging from 0.6071 to 0.9882.

All symptoms improved in both groups as shown by the difference in row percentages between the severity categories on day 0 and day 6 (table I).

Headache, facial pain, nasal congestion and dizziness improved significantly in the treatment group compared with the placebo group according to severity categories as shown by the p-values comparing the two slopes (table II).

Clinical signs improved significantly according to the row percentages of absent and present signs on day 0 and day 6 in both treatment and placebo groups ($p < 0.0001$ and $p \leq 0.0049$, respectively, according to Fisher's Exact Test; table III).

Table III. Percentage of patients with signs present or absent on day 0 and day 6 in patients with acute infective sinusitis in the betamethasone and placebo groups

Sign	Day	B		P	
		present	absent	present	absent
Purulent secretions[a]	0	100	0	100	0
	6	18.2	81.8	40	60
Percussion tenderness[a]	0	95.5	4.5	84.2	15.8
	6	22.7	77.3	40	60

a Significant difference in favour of betamethasone therapy ($p \leq 0.0575$).

B = betamethasone 1 mg/day + amoxicillin-clavulanic acid 625mg three times daily; **P** = placebo + amoxicillin-clavulanic acid 625mg three times daily.

The signs in the treatment group improved significantly as shown by low row percentages of present signs and high row percentages of absent signs on day 6 compared with row percentages in the placebo group, with percussion tenderness $p = 0.049$ and purulent secretions $p = 0.058$ on day 6 (table III).

The mean of the sum of the number of times (maximum three times per day) paracetamol tablets were taken decreased significantly in both treatment ($p = 0.003$; 95% CI 2.09, 3.4) and placebo groups ($p = 0.0001$; 95% CI 2.25, 2.7). There was no significant difference between the two groups in the mean of the sum of the number of times paracetamol tablets were taken (figure 1).

Treatment with betamethasone 1mg was well tolerated. No adverse effects or eruptions of new diseases associated with the use of betamethasone were reported. Two cases of adverse reaction were reported with amoxicillin-clavulanic acid alone, namely, cough and maculopapular rash.

The presence or absence of a recent history of viral upper respiratory infection was used as a variable in the study to determine whether there is a difference in response of the symptoms to oral betamethasone. There was no significant difference in response to treatment, possibly because of the small sample size.

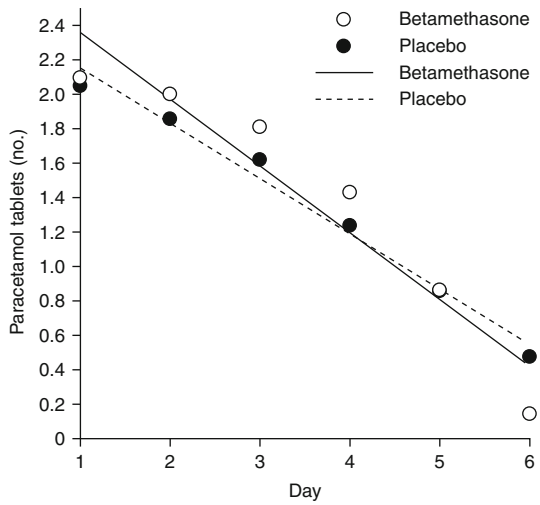

Fig. 1. Mean number of times paracetamol tablets were consumed according to day (from day 1 to day 6) and treatment groups. Treatment in the betamethasone group consisted of betamethasone 1 mg/day + amoxicillin-clavulanic acid 625mg three times daily; treatment in the placebo group consisted of placebo + amoxicillin-clavulanate potassium 625mg three times daily. No significant difference between treatment groups was demonstrated.

Discussion

The main findings of the study were that betamethasone 1mg added to amoxicillin potassium clavulanate significantly improved headache, facial pain, nasal congestion and dizziness from baseline compared with placebo in patients with acute infective sinusitis. Percussion tenderness and purulent secretions improved significantly in both treatment groups from baseline. However, both signs improved significantly more in the betamethasone group than in the placebo group.

These findings confirm those of other authors who have also demonstrated the beneficial effects of topical corticosteroids in the treatment of acute infective sinusitis. Most of these trials were driven by the pharmaceutical industry. This is, however, the first report on the use of oral corticosteroids rather than topical nasal application.

Meltzer et al.[2] suggested that the addition of flunisolide topical nasal spray as an adjunct to antibiotics for the treatment of sinusitis was judged the most effective treatment in a global evaluation and tended to improve symptoms, to decrease inflammatory cells in nasal cytograms, to normalise ultrasound scans, and to aid regression of radiographic abnormalities compared with placebo spray. Recurrence of rhinosinusitis was more likely in the placebo group and tended to occur earlier and be more severe after discontinuing antibiotic than in the flunisolide group. Meltzer et al.[1] compared the treatment of patients randomised to amoxicillin clavulanate potassium alone with those concomitantly receiving mometasone nasal spray 400μg twice daily. Total and individual scores of inflammatory symptoms associated with the obstruction process (headache, congestion and facial pain) decreased significantly compared with placebo, whereas symptoms associated with the secretory process (cough and postnasal drip) improved to a lesser degree.

Yilmaz et al.[3] showed that the recovery rate from acute sinusitis is significantly higher in children receiving intranasal budesonide and cefaclor treatment than those receiving pseudoephedrine and cefaclor. Furthermore, Dolor et al.[9] supported the findings of Meltzer et al.[1,2] and Yilmaz et al.[3]; he reported a significantly higher clinical success rate as well as a more rapid improvement in patients treated with fluticasone propionate versus placebo in addition to cefuroxime for an acute episode of rhinosinusitis.

Topical intranasal corticosteroids have been shown to safely improve symptoms when given as adjuncts to antimicrobials in the treatment of acute bacterial sinusitis.[1-3] Topical intranasal corticosteroids are, however, expensive and troublesome to administer for first-time users. This perhaps justifies the use of short courses of systemic corticosteroids in this clinical setting.

Low-dose oral corticosteroids have been shown to have marginal and transient hypothalamic-pituitary-adrenal axis suppression if used for a short period.[7] Prednisolone l0mg or its equivalent betamethasone 1mg given over 5 days showed mild, transient adrenal suppression with a quick recovery within 3 days after termination of therapy.[7]

Conclusion

Betamethasone taken orally over 5 days improved the symptoms and signs of acute bacterial sinusitis when used as an adjunct to amoxicillin-clavulanic acid. There were no reported adverse events associated with betamethasone administration.

Further prospective studies are needed to investigate oral corticosteroids in acute infective sinusitis in large sample sizes. The effects of the presence or absence of a recent history of upper respiratory tract infection on outcome of symptoms compared with a history of chronic allergic rhinitis also need further evaluation to establish the effect of aetiology on outcome.

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