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Main Articles

Nonsurgical management of surgical otitis media with effusion

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Abstract

The objective of this paper was to determine the effectiveness of combined steroid–antimicrobial therapy for otitis media with effusion (OME) of sufficient duration to justify tympanostomy tube insertion.

A consecutive sample of 122 children with bilateral OME of at least three months duration, or unilateral OME of at least six months duration, despite treatment with one or more beta-lactamase stable antibiotics was studied. The treatment group received prednisolone plus a beta-lactamase stable antibiotic for 10 days, with responders receiving an additional six weeks of chemoprophylaxis. The control group received no medication. The child's caregiver decided which group the child should be in.

Resolution of effusion in all affected ears occurred in 32 per cent of steroid-treated children and in 2 per cent of controls ($p<0.001$) at three to four weeks post-therapy. Relapse of effusion occurred in over 40 per cent of initial responders within six months, reducing the final resolution rate to 25 per cent (95 per cent CI: 15–36 per cent).

It was concluded that treatment with oral steroids should be considered in selected children with chronic OME prior to surgical intervention. One in every four children whose caregiver consents to this therapy may avoid or postpone surgery for at least six months.

Key words: Otitis media with effusion; Drug therapy; Adrenal cortex hormones; Clinical trials

Introduction

Systemic steroids have shown promising, though inconsistent, results when used to treat otitis media with effusion (OME) in children. Because of this inconsistency, we advised against the routine use of oral steroids for OME in a previously published meta-analysis of randomized clinical trials (Rosenfeld *et al.*, 1991). Conversely, withholding therapy is also not warranted, because strong evidence exists for steroid efficacy – children receiving steroids for seven to 14 days are 3.6 times more likely than placebo-treated controls to have both ears effusion free at the end of therapy (Rosenfeld *et al.*, 1991). Further, antibiotics plus steroids may improve clearance of OME at one month by on average 25 per cent (Stool *et al.*, 1994), however this result just misses statistical significance. A reasonable compromise would be to reserve steroid therapy for children who might otherwise require surgical intervention for refractory OME (Rosenfeld, 1992), but only retrospective data are available in this regard (Perisco *et al.*, 1978).

This clinical trial was undertaken to determine the effectiveness of oral steroids in children with 'surgical' OME – bilateral effusions of at least three months duration, or unilateral effusion of at least six months duration, despite treatment with a beta-lactamase stable antibiotic. No published clinical trials have been limited to children with this degree of refractory disease. A concurrent antimicrobial drug was given because combined steroid–antimicrobial therapy offers lower rates of short-term relapse than steroids alone (Rosenfeld, 1992). To prevent long-term relapse, responders were treated with antimicrobial prophylaxis, based on the ability of such therapy to prevent recurrent acute otitis media (AOM) (Williams *et al.*, 1993). Emphasis was placed on identifying children most likely to respond favourably to steroid therapy by comparing outcome with baseline epidemiological factors.

Proper interpretation of this study requires a

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distinction between efficacy and effectiveness. *Efficacy* describes treatment results in ideal settings, such as a randomized trial with strict inclusion criteria and prospective documentation of disease duration (Last, 1988). Steroid efficacy for OME has already been assessed (Rosenfeld *et al.*, 1991), and the purpose here was not to replicate prior research. In contrast, *effectiveness* describes treatment results in real-world settings, such as an observational trial with broad inclusion criteria and a necessary reliance on historical information and caregiver preference in guiding therapy. Because effectiveness is often less than efficacy, estimates of both are needed if clinical research is to influence clinical practice. The purpose of this observational study is to assist in attaining this goal.

Methods

The study was conducted at a hospital-based paediatric otolaryngology practice in Brooklyn, New York. All children referred by their primary care practitioner (PCP) for evaluation of OME over a 12-month period beginning October 1, 1992, were considered for study entry. OME was defined as the presence of a middle ear effusion (either unilateral or bilateral) without the usual signs and symptoms of AOM (fever, otalgia, irritability). Diagnosis was made by a validated otoscopist (R.M.R.) using pneumatic otoscopy (Kaleida and Stool, 1992), and confirmed by a tympanogram pattern of type B (effusion) or C2 (high negative pressure with a gradual gradient) (Paradise *et al.*, 1976).

Children with bilateral OME of at least three months duration, or unilateral OME of at least six months duration, despite treatment with one or more courses of a beta-lactamase stable antibiotic were included in the study. Upon entry, demographic factors, disease characteristics, and OME risk factors were recorded. OME duration was assessed by the history given by the caregiver, discussion with the child's PCP, and review of prior audiograms and tympanograms. A child was designated as otitis prone if there were three AOM episodes during the past six months, or four in the past year with at least one within six months. Adenoid hyperplasia was diagnosed in light of a positive radiograph or a suggestive clinical history (chronic mouth breathing and hyponasal voice). There were no specific exclusion criteria (e.g. Down syndrome or cleft palate).

Allocation to the treatment group (steroid–antimicrobial therapy) or the control group (no medication) was based on the caregiver's choice following a discussion of the risks and benefits of steroid therapy for OME. Specifically, caregivers were informed that steroids could worsen varicella infection if it occurred during or shortly after treatment, and that OME response rates might be only 15 to 20 per cent. The risk of relapse following treatment was also discussed. If a caregiver declined steroid therapy, the specific reason was recorded. Steroid therapy was not offered when a varicella-susceptible child had known or suspected viral exposure in the prior three weeks.

The treatment group received prednisolone 1.0 mg/kg/d for five days followed by 0.5 mg/kg/d for an additional five days. A concurrent beta-lactamase stable antibiotic was also given for 10 days. Cefpodoxime proxetil was preferred because of its broad antibacterial spectrum, excellent beta-lactamase stability, convenient twice-daily dosing schedule, and low incidence of gastrointestinal side effects (Frampton *et al.*, 1992). If the child had been previously treated with cefpodoxime, an alternative drug (cefixime, cefprozil, or amoxicillin-clavulanate) was selected which would not duplicate prior therapy. When financial constraints were involved, trimethoprim–sulphamethoxazole (TMP–SMX) was prescribed. Caregivers were advised to discontinue the steroid and call immediately if varicella developed during treatment. Management of the control group included observation and/or surgical intervention of each individual.

The first follow-up was scheduled three to four weeks after study entry. Resolution was defined as the absence of OME in both ears, determined by pneumatic otoscopy and a tympanogram pattern of type A or C1; anything less than complete resolution was considered a treatment failure. Patients lost to follow-up were also considered treatment failures. Responders in the treatment group began sulfisoxazole prophylaxis consisting of a single daily dose for a minimum of six weeks or until the end of the viral season (October through to May). A second follow-up was performed six months after study entry for the treatment group only; because most subjects in the control group had surgery, a second follow-up was not performed for them. At follow-up evaluations, caregivers were questioned regarding drug tolerance and potential side effects.

Data were entered into a microcomputer database and a random 10 per cent subset of records checked for entry validity. Descriptive analysis was performed using MINITAB statistical software (Minitab Inc., 1993). Hearing levels (HL) were recorded as the pure tone average (PTA) of 500, 1000 and 2000 Hz of the poorer hearing ear, or of the composite ear if only soundfield audiometry could be performed. Association of dichotomous risk factors with outcome (complete response *versus* treatment failure) was performed using exact conditional inference (Mehta and Patel, 1991) for the odds ratio (OR), 95 per cent confidence interval (CI), and level of statistical significance. Continuous variables (age, effusion duration) were compared with an exact version of the Wilcoxon rank sum test (Mehta and Patel, 1991). A two-sided alpha level of 0.05 was chosen to reflect statistical significance. .

Results

Of 249 children with OME referred over the 12-month recruitment period, 122 met the study inclusion criteria. Seventy-three caregivers (60 per cent) agreed to treatment with a steroid and

TABLE I
CLINICAL CHARACTERISTICS OF 122 CHILDREN WITH CHRONIC OME

Characteristic	Group	
	Control $n = 49$	Treatment $n = 73$
Mean age, years (SD)	4.0 (2.8)	4.4 (2.6)
Male gender, n(%)	34 (69)	44 (60)
Median effusion duration, m(range)	6 (36)	6 (3–24)
Bilateral effusion, n(%)	44 (90)	59 (81)
Retracted and opaque TM, n(%)	11 (22)	29 (40)
Median PTA (range)	28 (10–63)	28 (17–55)
Otitis prone, n(%)	32 (65)	27 (37)
Day-care or school, n(%)	31 (63)	49 (67)
Passive smoke exposure, n(%)	9 (18)	17 (23)
Winter season entry, n(%)	24 (50)	42 (58)
Adenoid hyperplasia, n(%)	17 (35)	25 (34)
Underlying disease, n(%)	3 (6)	3 (4)
Prior otitis media surgery, n(%)	3 (6)	3 (4)

PTA = pure tone average; TM = tympanic membrane.

concurrent antibiotic. Cefpodoxime was used most often (67 per cent), followed by amoxicillin-clavulanate (11 per cent), TMP–SMX (11 per cent), cefixime (7 per cent), and cefprozil (4 per cent). The 49 caregivers in the control group declined steroid therapy because they were against steroids (30 per cent) or they were against additional antibiotics (20 per cent); there was a separate indication for adenoidectomy (16 per cent); they were concerned over the effect of steroids on varicella (12 per cent); their child was enrolled in speech therapy (10 per cent); or there was a baseline sensorineural hearing loss (10 per cent).

Subjects in the control and treatment groups were comparable (Table I) except for a higher prevalence of otitis prone children among controls (65 *versus* 37 per cent; $p = 0.001$). The typical study participant was a male preschooler who had had bilateral OME for six months, though effusions of more than eight months duration occurred in 25 per cent of the sample. Approximately one-third of children also had adenoid hyperplasia based on radiographical or clinical findings (snoring, mouth breathing, and hyponasality). Six children had an underlying disorder, such as Down syndrome (two), a submucous cleft palate (two), Hunter-Hurler syndrome (one), or Spritzen syndrome (one).

At the first follow-up, resolution of OME occurred in 32 per cent of steroid-treated children (95 per cent CI; 21–43 per cent) and 2 per cent of controls (95 per cent CI; 0–11 per cent). One child in the treatment group was lost to follow-up and considered a treatment failure. Odds ratios for resolution in the treatment group were 8.5 times higher ($p = 0.001$) for steroid-treated children with unilateral, instead of bilateral effusions (Table II). Children who were not otitis prone displayed a trend ($p = 0.08$) towards increased resolution. There was no significant association between the treatment group outcome at the first follow-up and age, effusion duration, audiometric PTA, tympanic membrane appearance, season of entry, day-care attendance, adenoid hyperplasia, or passive smoke exposure. Low statistical power may account for some of these findings.

At the second follow-up, resolution of OME had occurred in 25 per cent of steroid-treated children (95 per cent CI; 15–36 per cent); five children were lost to follow-up and considered treatment failures. Resolution rates were unavailable for the control group, because 90 per cent had received myringotomy with tube insertion prior to this time. Odds ratios for resolution in the treatment group were 3.8 times higher ($p = 0.05$) when the child was not otitis prone, and 3.6 times higher ($p = 0.05$) when the PTA

TABLE II
PROGNOSTIC FACTORS FOR RESOLUTION OF OME AT FIRST FOLLOW-UP IN 73 STEROID-TREATED CHILDREN

Prognostic factor	Outcome at 1st Follow-up				
	Factor level	Resolved n (%)	Failed n (%)	Exact OR (95% CI)	Exact p-value
Bilateral effusion	No	10 (71)	4 (29)	8.5 (2.3–36.0)	0.001
	Yes	13 (22)	46 (78)		
Retracted and opaque TM	No	15 (34)	29 (66)	1.4 (0.5–3.9)	0.62
	Yes	8 (29)	21 (72)		
Winter season entry	No	9 (29)	22 (71)	0.8 (0.3–2.3)	0.80
	Yes	14 (33)	28 (67)		
Otitis prone	No	18 (39)	28 (61)	2.8 (0.9–9.6)	0.08
	Yes	5 (19)	22 (81)		
Day-care or school	No	9 (37)	15 (63)	1.5 (0.5–4.3)	0.59
	Yes	14 (29)	35 (71)		
Adenoid hyperplasia	No	18 (37)	30 (63)	2.4 (0.8–8.2)	0.18
	Yes	5 (20)	20 (80)		
Passive smoke exposure	No	16 (29)	40 (71)	0.6 (0.2–1.9)	0.38
	Yes	7 (41)	10 (59)		

CI = confidence interval; OR = odds ratio; TM = tympanic membrane.

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TABLE III
PROGNOSTIC FACTORS FOR RESOLUTION OF OME AT SECOND FOLLOW-UP IN 73 STEROID-TREATED CHILDREN

Prognostic factor		Outcome at second Follow-up			
	Factor level	Resolved n (%)	Failed n (%)	Exact OR (95% CI)	Exact *p*-value
Bilateral effusion	No	6 (43)	8 (57)	2.9 (0.8–10.2)	0.09
	Yes	12 (20)	47 (80)		
Retracted and opaque TM	No	14 (32)	30 (68)	2.9 (0.9–11.3)	0.10
	Yes	4 (14)	25 (86)		
Winter season entry	No	9 (29)	22 (71)	1.5 (0.5– 4.5)	0.58
	Yes	9 (21)	33 (79)		
Otitis prone	No	15 (33)	31 (67)	3.8 (1.0–18.1)	0.05
	Yes	3 (11)	24 (89)		
Day-care or school	No	6 (25)	18 (75)	1.0 (0.3– 3.2)	0.99
	Yes	12 (24)	37 (76)		
Adenoid hyperplasia	No	15 (31)	33 (69)	3.3 (0.9–15.7)	0.09
	Yes	3 (12)	22 (88)		
Passive smoke exposure	No	13 (23)	43 (77)	0.7 (0.2– 2.7)	0.75
	Yes	5 (29)	12 (71)		
PTA > 25 dB HL	No	8 (36)	14 (64)	3.6 (1.0–14.0)	0.05
	Yes	5 (14)	32 (86)		

CI = confidence interval; HL = hearing level; OR = odds ratio; PTA = pure tone average; TM = tympanic membrane.

was less than 25 dB HL (Table III). The median PTAs at study entry for children who resolved and failed were 22 dB HL and 30 dB HL, respectively. Children with unilateral effusions displayed a trend ($p = 0.09$) towards increased resolution, as did those without adenoid hyperplasia ($p = 0.09$) or with normal tympanic membranes ($p = 0.10$). There was no significant association between treatment group outcome and age, effusion duration, season of entry, day-care attendance, or passive smoke exposure. Low statistical power may account for some of these findings.

Relapse of effusion between the first and second follow-up periods occurred in nine out of 23 steroid-treated children who initially had complete resolution, and three out of five steroid-treated children who initially had unilateral resolution of bilateral disease. The overall relapse rate was therefore 43 per cent (12/28), with a 95 per cent CI of 25 to 63 per cent. All children who relapsed had received sulphisoxazole prophylaxis for a minimum of six weeks. None of the caregivers reported any significant complications related to the steroid therapy, though two noted an increase in their child's appetite. No child contracted varicella during, or shortly after, treatment.

Discussion

Treatment with oral steroids should be considered for selected children with chronic OME prior to surgery provided that both the physician and caregiver have realistic expectations concerning therapy. Despite an initial response rate of 71 per cent for unilateral effusions and 22 per cent for bilateral effusions (Table II), only 25 per cent of children remained disease-free at six months post-treatment. Consequently, four children must be treated for a single child to achieve a lasting benefit. We cannot predict with certainty which child will respond, but children who are not otitis prone or have an initial PTA less than 25 dB HL may have a better prognosis (Table III). Unfortunately, children who respond and then relapse may spend more time with OME than if they had initially opted for surgery. The potential for such delay must be considered when prescribing steroid therapy for a child with bilateral OME and an associated speech delay, or a baseline sensorineural hearing loss.

Although no serious side effects have been reported from steroid therapy for OME, several precautions are warranted. Disseminated varicella is primarily a theoretical risk, because it has only been reported when dosages of 2.0 or more mg/kg/d of prednisone were administered during the viral incubation phase (Rosenfeld, 1992). Regardless, children receiving short courses of steroids should be considered for therapy with oral acyclovir if varicella develops during treatment (AAP, 1993). Additional precautions include withholding steroid therapy from children with known or suspected varicella exposure in the past three weeks, and discontinuing the steroid should exposure occur during therapy. Further, steroids should always be administered with a concurrent antibiotic, because children with OME treated with steroids alone may be at increased risk for AOM. Repeated courses of steroid therapy are contraindicated, because most children have a transient depression of adrenal function (serum cortisol less than 10 μg/d) which may last for up to three weeks post-treatment (Rosenfeld, 1992). The clinical significance of this transient depression, if any, is unknown.

Treatment with an antibiotic alone should precede steroids, because antibiotics have a significant effect on resolution of persistent middle ear effusion (Rosenfeld and Post, 1992; Williams *et al.*, 1993). Although increased OME response rates have not been reported with extended spectrum antibiotics (Rosenfeld and Post, 1992), a rising percentage of bacteria are producing beta-lactamase (Bluestone *et al.*, 1992). Given this trend, treatment of amoxicillin failures with a beta-lactamase stable agent appears prudent, and was therefore a part of the inclusion criteria for this study. Steroids may be cost-effective for effusions of lesser duration (Berman *et al*, 1994),

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but the potential risks of therapy argue for a more cautious approach. Such caution underlies the basic philosophy of this clinical trial, which was to reserve steroids for children with 'surgical' OME as previously defined.

Several unique aspects of this study deserve mention. Inclusion criteria were more restrictive than in other published trials, requiring OME persistence for at least three months (six months if unilateral) and failure of a beta-lactamase stable antibiotic to resolve the effusion. This explains the modest initial response rate of 32 per cent in this study, *versus* a mean rate of 60 per cent in other steroid–antimicrobial trials (Schwartz *et al.*, 1980; Puhakka *et al.*, 1985; Lambert, 1986; Berman *et al.*, 1990; Podoshin *et al.*, 1990). In addition, this is the first trial to combine a steroid with an extended spectrum cephalosporin and to use post-treatment antimicrobial prophylaxis. Whereas all children did not receive the same antibiotic, this would not affect outcome because choice of drug does not influence resolution rates of OME (Rosenfeld and Post, 1992; Williams *et al.*, 1993). The relatively long follow-up period of six months permitted identification of factors associated with lasting response, namely absence of hearing loss or the otitis prone condition (Table III). A trend was also observed favouring children with unilateral effusions, normal tympanic membranes, or nonobstructing adenoids. Follow-up periods in most other published studies were between one and three months, which may be too early to identify prognostic factors.

The goal of this investigation was to define resolution rates, relapse rates, and prognostic factors that would apply to steroid–antibiotic therapy for OME in real-world settings. Because this was not an efficacy trial, randomization acquired secondary importance. Randomization reduces bias in treatment allocation, but treatment decisions are rarely unbiased; 40 per cent of caregivers in this study rejected steroids as a management option. Five randomized trials (Schwartz *et al.*, 1980; Puhakka *et al.*, 1985; Lambert, 1986; Berman *et al.*, 1990; Podoshin *et al*, 1990) and a meta-analysis (Rosenfeld *et al*, 1991) have already documented steroid efficacy, and the purpose here was not to duplicate prior research. Thus, emphasis was placed on obtaining generalizable results, a goal which might be compromised by the ethical consequences of randomization on the physician–patient relationship (Hellman and Hellman, 1991). Interestingly, the 30 per cent increase in resolution rates at first follow-up is nearly equivalent to the 31 per cent mean increase observed in randomized trials (Schwartz *et al.*, 1980; Puhakka *et al.*, 1985; Lambert, 1986; Berman *et al.*, 1990; Podoshin *et al.*, 1990), and the 36 per cent increase seen in a non-randomized study (Perisco *et al.*, 1978). This corresponds to findings by Paradise and co-workers (Paradise *et al.*, 1984) who reported comparable results in parallel randomized and non-randomized (caregiver allocation) trials for recurrent tonsillitis. Nonetheless, we cannot exclude completely the possibility of allocation bias if caregivers systemically preferred further medical management (steroid and antibiotic) for milder cases, whilst reserving surgery for more severe cases.

The control group in this trial received no medication, in contrast to most other studies in which an antibiotic without a steroid was administered. However, all children had already failed treatment with at least one 10-day course of a beta-lactamase stable antibiotic; the median number of courses per child was four. Further, all had received their last course within 30 days of study entry, a condition which was cause for exclusion in most published antibiotic trials for OME (Rosenfeld and Post, 1992). Therefore, additional antibiotic would have probably produced no significant benefit. Moreover, most caregivers were already frustrated by the lack of response to numerous antibiotics, and were against additional treatment. The treatment group received a concurrent antibiotic to reduce the chance of AOM relapse secondary to the steroid, not to increase response rates. Finally, even if administering an antibiotic to the controls would have diminished the observed 30 per cent steroid effect at first follow-up, it would not have altered the estimated response and relapse rates for the treatment group.

Potential study shortcomings include historical documentation of effusion duration, verbal compliance check, unblinded outcome assessment, and lack of control group data at the second follow-up. All children in this study were referred by a PCP, and many had their effusions documented by office tympanometry on multiple occasions. When doubt existed regarding effusion duration, the lowest reasonable duration was chosen. Although compliance was assessed verbally, this method is the norm in actual clinical practice. The outcome assessment was unblinded, but objective; tympanometry (performed by an impartial audiologist) was used to confirm pneumatic otoscopy findings. Without control group results at the second follow-up, it cannot be determined whether the 25 per cent resolution rate in the treatment group was caused by therapy or by natural history. Extended observation of chronic OME, however, is rarely of benefit (Maw, 1983), and would generally not be acceptable to caregivers referred to a specialist for evaluation.

Oral steroid therapy should be considered an option prior to surgery for OME. Whether to treat, or not, requires an informed discussion between physician and caregiver regarding the potential risks and benefits of therapy. A resolution rate of only 25 per cent (95 per cent CI; 15–36 per cent) at six months may be unsatisfactory if the child already has speech, hearing, or behavioural sequelae associated with the OME. Further, relapse beyond six months may occur, especially in the otitis prone child. In this situation, any transient benefit of therapy might be offset by the potential risks and side effects of repetitive medical treatment. Children without hearing loss who are not otitis prone appear to benefit most from steroid therapy; unilateral disease, nonobstructing adenoids, and a normal tympanic mem-

brane may also have some prognostic value. When a decision is made in favour of steroid therapy, a concurrent therapeutic antibiotic should be given; treatment with steroid alone is contraindicated (Stool *et al.*, 1994). Antimicrobial prophylaxis for six weeks or longer is recommended for children who show an initial favourable response to therapy.

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