EFFICACY OF TONSILLECTOMY FOR RECURRENT THROAT INFECTION IN SEVERELY AFFECTED CHILDREN

Results of Parallel Randomized and Nonrandomized Clinical Trials

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Abstract We studied the efficacy of tonsillectomy, or tonsillectomy with adenoidectomy, in 187 children severely affected with recurrent throat infection. Ninety-one of the children were assigned randomly to either surgical or nonsurgical treatment groups, and 96 were assigned according to parental preference.

In both the randomized and nonrandomized trials, the effects of tonsillectomy and of tonsillectomy with adenoidectomy were similar. By various measures, the incidence of throat infection during the first two years of follow-up was significantly lower ($P \leq 0.05$) in the surgical groups than in the corresponding nonsurgical groups. Third-year differences, although in most cases not significant, also consistently favored the surgical groups. On the other hand, in each follow-up year many subjects in the nonsurgical groups had fewer than three episodes of infection, and most episodes among subjects in the nonsurgical groups were mild.

Of the 95 subjects treated with surgery, 13 (14 per cent) had surgery-related complications, all of which were readily managed or self-limited.

These results warrant the election of tonsillectomy for children meeting the trials' stringent eligibility criteria, but also provide support for nonsurgical management. Treatment for such children must therefore be individualized. (N Engl J Med 1984; 310:674-83.)

TONSILLECTOMY has long been the most common major operation performed on children in the United States,[1,2] yet indications remain uncertain and controversial,[3-5] and regional tonsillectomy rates vary widely.[6] Among currently sanctioned indications for tonsillectomy,[7-10] recurrent throat infection is at once the most frequently invoked[11,12] and the most problematic. Not only do opinions differ over how many episodes, of what character, and over what period constitute grounds for tonsillectomy,[5,11,13] but one standard pediatric textbook rejects recurrent throat infection altogether as a valid indication.[14] To some extent, these differences of opinion reflect differences in physicians' training, experience, and personal attitudes and values,[4,5] but more fundamentally, they reflect the fact that the degree of benefit conferred by tonsillectomy in reducing the occurrence of throat infection has not been established.[3,4,15,16]

In the few controlled trials that have been reported, each of which involved tonsillectomy combined with adenoidectomy, children who received surgery indeed had lower rates of throat infection during the succeeding two years than did control children, but even the control children's rates were not impressively high; moreover, they declined from the first follow-up year to the second.[17-20] On their face, therefore, these results suggest that the benefits of tonsillectomy may not be of sufficient magnitude to justify the operation's cost and risks.[21] Viewed more closely, however, both the conclusiveness and the generalizability of the trials' results appear doubtful for the following reasons: seriously affected children were excluded, many of the subjects appeared not to have had unduly frequent or clinically important previous episodes of throat infection and therefore not to have been at appropriately high risk for such trials, and it is not clear that monitoring and documentation of illness during the trials were adequate.[3,4,15]

We report here the results of two parallel clinical trials of tonsillectomy, under certain circumstances combined with adenoidectomy, in a group of children whose histories of recurrent throat infection met stringent criteria for frequency, clinical features, treatment, and documentation and whose courses after enrollment in the trials were carefully monitored and documented. Assignment to either surgical or nonsurgical treatment groups was made randomly in one of the trials and according to parental preference in the other.

METHODS

Recruitment of Subjects, Evaluation, and Eligibility

The trials were conducted at the Children's Hospital of Pittsburgh between August 1971 and June 1982, as part of a comprehensive study of indications for tonsillectomy and adenoidectomy.[4,22,23] Subjects were recruited from among hospital outpatients (whose evaluation by the study team was made a prerequisite for tonsil or adenoid surgery at the hospital) and from among children referred by community practitioners or directly by parents. During the first five years of the study each referred child received a standardized, multiphasic evaluation.[4] Thereafter, such evaluations were performed only in children who, on initial screening, were found to be eligible or potentially eligible for one or more of the study's trials of tonsillectomy and adenoidectomy. Excluded from consideration for any trial were two classes of children: those judged to require prompt removal of large tonsils or adenoids because of proved or suspected alveolar hypoventilation, sustained difficulty in swallowing, or marked discomfort in breathing, and those disqualified because of prior tonsil or adenoid surgery, major physical or emotional disease, structural middle-ear damage or sensorineural hearing loss, hypogammaglobulinemia (IgG, IgA, or IgM level >2 S.D. below the mean value for the child's age), simultaneous enrollment of a

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sibling in the study, or inability to meet the projected schedule of follow-up visits.

Eligibility for the tonsillectomy trials hinged on a history of recurrent episodes of throat infection (i.e., tonsillitis, pharyngitis, or tonsillopharyngitis). For a child to be eligible, his or her episodes had to meet defined standards in each of four categories: frequency of occurrence, seven or more episodes in the preceding year, five or more in each of the two preceding years, or three or more in each of the three preceding years; clinical features, each episode characterized by one or more of the following: oral temperature of at least 38.3°C, cervical lymphadenopathy (enlarged [>2 cm] or tender cervical lymph nodes), tonsillar or pharyngeal exudate, or positive culture for group A beta-hemolytic streptococcus; treatment, antibiotics administered in conventional dosage for proved or suspected streptococcal episodes; and documentation, each episode and its qualifying features substantiated by concurrent notation in a clinical record.

Children with histories that met all standards except documentation were followed prospectively. Those who had two or more observed episodes of throat infection, with patterns of frequency and clinical features consistent with the initial history, were considered eligible for the trials.[13] Each determination of eligibility was based on independent assessments by a pediatrician and an otolaryngologist on the study team.

Some of the children who were eligible for the tonsillectomy trials were also eligible for concurrent trials of adenoidectomy, mainly because of recurrent otitis media or nasal obstruction or both.[4] These children were considered candidates for tonsillectomy combined with adenoidectomy rather than for tonsillectomy alone.

Consent, Randomization, and Assignment to Treatment

One or both parents of each eligible child (and the child, if he or she seemed able to comprehend) were informed in detail about the potential benefits and risks of surgery and about the trials' rationale and methods. Consent was then obtained to assign the child randomly to either surgical or nonsurgical treatment. Parents were advised that children initially assigned to nonsurgical treatment could subsequently receive surgery at the parents' request provided that the eligibility criteria continued to be met. Children whose parents gave verbal and written consent for random assignment were stratified into three age categories — 3 through 4 years, 5 through 6 years, and 7 through 15 years — and assigned randomly, within categories and balanced within each block of four subjects, to either a surgical (tonsillectomy or tonsillectomy with adenoidectomy, depending on eligibility) or corresponding nonsurgical control group. Children whose parents withheld consent were assigned according to parental preference; this assignment was termed "nonrandom."

Surgery and Related Management

Operations were performed as soon after assignment as practicable. Subjects were given advance explanation and preparation and were admitted to the hospital on the day before surgery. Parents were urged to room-in. Surgery was performed by or under the supervision of a study-team otolaryngologist, with the patient under general endotracheal anesthesia. A dissection-and-snare technique was used for tonsillectomy; reverse adenotomes and curettes, under both direct and mirror vision, were used for adenoidectomy.

Follow-up Procedures

Randomized and nonrandomized subjects were followed systematically in the same manner: a standardized telephone or in-person inquiry was made biweekly concerning the day-by-day occurrence of specified symptoms and events, including sore throat and absence from school, and standardized clinical examinations were performed at six-week intervals and at the time of respiratory illnesses. Prompt reporting of symptoms and examinations for minor illnesses other than uncomplicated common colds were encouraged. During after-clinic hours and on weekends and holidays a study-team member was on call. No fees were charged, and reimbursement was offered for visit-related expenses. Data concerning symptoms and events were recorded only if reported within 18 days after occurrence. A "sore-throat day" was defined as one on which a sore throat, even if mild or intermittent, reportedly lasted a total of one hour or longer.

Virtually all data were obtained and all examinations were carried out by study personnel, who used standardized methods and forms for quantifying, rating, and recording observations and whose interobserver reliability was assessed and maintained by means of comparisons made systematically when practicable. (For example, in 100 consecutive, paired, independent observations of tonsillar size and erythema, respectively [five-point scales], and in 200 such observations of lymph-node size [four-point scale], there was interobserver agreement in 83, 72, and 80 per cent, respectively, and disagreement by one point in the rest.) Occasional observations by other health professionals were incorporated in the data set if they were well documented. Visits for routine examination and for minor illness were conducted by pediatric nurse practitioners using standardized procedures and algorithms. For other illnesses, and at routine visits every six months, each subject was examined by a pediatrician. Data forms for each visit were verified independently to ensure accuracy of recording and conformance to diagnostic definitions.

Definition and Classification of Episodes of Throat Infection

Definition of a throat-infection episode was based on specified criteria that are not presented in full in this report because of their considerable detail (but are available from the authors). For example, when sore throat was present, diagnosis of an episode required a clinical observation of redness of the tonsils or pharynx, or new findings of cervical lymphadenopathy and a positive throat culture for group A beta-hemolytic streptococcus; additional findings were required when sore throat was not present. Symptoms or signs occurring within a 30-day period were considered components of a single episode provided that no interruption in their occurrence exceeded 9 days. However, once standard antibiotic treatment had been administered for an episode for 10 consecutive days, the further persistence of symptoms or signs, or their recurrence after any interval, was considered part of a new episode. Each diagnosed episode was rated "mild," "moderate," or "severe" on the basis of a scoring system (available from the authors) that involved both local and systemic symptoms and signs. Cervical lymphadenopathy, when not associated with an episode of throat infection, was termed "isolated."

Management of Episodes of Throat Infection

A throat culture was obtained whenever throat infection was diagnosed or suspected. Cultures were processed and evaluated for the presence of group A streptococci by the hospital microbiology laboratory, using standard methods. Cultures showing growth of any degree were considered positive. Penicillin V (250 mg) — or in the case of presumed allergy to penicillin, erythromycin (10 mg per kilogram of body weight) — was prescribed four times daily for 10 days for all subjects with positive cultures and also for those whose cultures were negative but who had been treated presumptively from the outset and had improved markedly within 48 hours. When throat infection or lymphadenopathy of recent onset persisted after treatment, when culture-positive episodes recurred repeatedly, or when compliance seemed doubtful, penicillin was prescribed in larger doses or for longer periods or was administered intramuscularly.

Data Analysis

Except where otherwise indicated, outcome data were derived from subjects' experiences in whole-year blocks in originally assigned treatment groups. The experiences of nonsurgical subjects were counted from the day after assignment unless throat infection was present at that time, in which case experience was counted from the day after termination of the episode. The experiences of surgical subjects were counted from the day after surgery.

Data from the randomized and nonrandomized trials were analyzed separately. Within each trial, data concerning the outcomes of tonsillectomy and of tonsillectomy with adenoidectomy were also analyzed separately; however, since none of the differences in outcome between the two surgical groups (tonsillectomy alone and tonsillectomy with adenoidectomy) and between the two corre-

sponding nonsurgical groups were large or statistically significant, the respective within-trial data sets were pooled. Accordingly, the terms "surgery" and "surgical" hereafter refer to all subjects who underwent either tonsillectomy alone or in combination with adenoidectomy.

All statistical tests were two-tailed. Chi-square tests incorporated the Yates correction.[24] Log-linear models[25] were used to test for interactions between treatment status (i.e., surgical or nonsurgical), outcome, and selected characteristics of subjects. Chi-square tests were used to test for significant associations between selected characteristics of controls and their outcomes. Log-linear models and life-table analyses[26,27] were computed using the BMDP3F[28] and BMDP1L[29] statistical programs, respectively. Each life-table analysis involved both Wilcoxon[27] and Savage[30] test statistics; when the resulting P values differed, the larger of the two was used.

Results

Selection of Trial Subjects and Comparability of Treatment Groups

The disposition of the 2043 children referred for evaluation during the study period is shown in Figure 1. A total of 187 children satisfied the eligibility criteria for the trials either initially or after variable periods of observation. Figure 2 summarizes the initial assignments to treatment groups and subsequent tenure within or migration from these groups. Selected demographic and clinical characteristics of the subjects are shown in Table 1.

Interval from Assignment to Surgery and Starting Points in the Trials

Among subjects treated with surgery, the median interval from assignment to surgery was 44.0 days (range, 8 to 307) for those assigned randomly and 46.5 (range, 7 to 276) for those assigned nonrandomly. Operations were performed within 90 days after assignment in 81 per cent of subjects assigned randomly and in 83 per cent of those assigned nonrandomly. Most delays were due to intercurrent illness or postponement of operation until the winter, spring, or summer recess from school. In neither the randomized nor the nonrandomized trial were there significant differences between surgical and nonsurgical groups in the distribution of trial starting points by quartile of the year (January through March, April through June, and so forth).

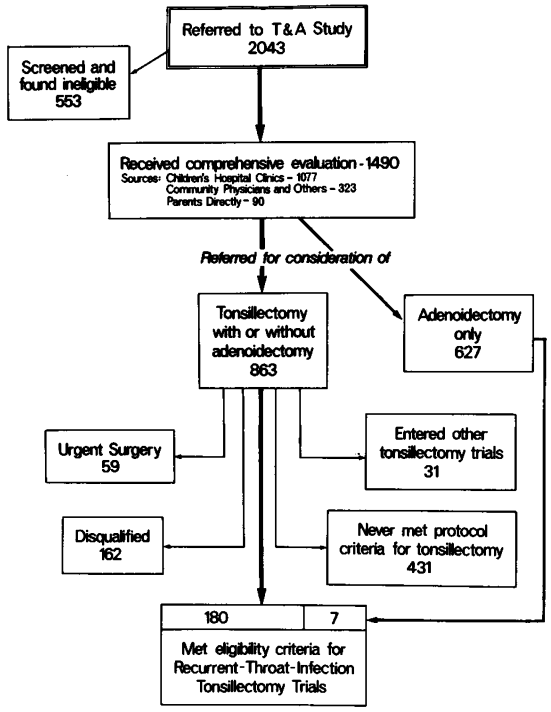

Figure 1. Trial Subjects in Relation to Other Children Referred for Study.
T & A denotes tonsillectomy and adenoidectomy.

Comprehensiveness of Surveillance

One measure of the comprehensiveness of surveillance for throat-related illness was the degree of adherence to the trials' schedule of appraisals. During the first, second, and third follow-up years for subjects randomly assigned to surgery, the mean numbers of days for which specified follow-up information was recorded were 332, 346, and 349, respectively, and the mean numbers of examinations performed were 7.3, 8.1, and 7.9, respectively. For control subjects the corresponding values were 346, 349, and 350 days and 9.8, 9.1, and 8.8 examinations. Corresponding data for nonrandomly assigned subjects were similar.

A second measure consisted of the proportions of sore-throat days that were associated with concurrent clinical examinations at which a diagnosis of throat infection was either confirmed or ruled out. ("Concurrent" was defined as occurring within seven days of a single sore-throat day or of the most proximate of a series of sore-throat days, if evidence of infection was found, and within one day, if evidence of infection was not found.) During the first, second, and third follow-up years the proportions of examination-associated sore-throat days, excluding those occurring immediately after surgery, were 73.9, 66.1, and 68.1 per cent, respectively, for the randomly assigned surgical group and 82.2, 83.5, and 85.6 per cent, respectively, for controls. Most of the remaining sore-throat days seemed to represent symptoms that were of minor importance (i.e., lasting one day or less) or attributable to common colds (i.e., accompanied by coryza or cough) or to other causes (e.g., varicella). The residual proportions that were not accounted for were 1.5, 9.2, and 3.1 per cent, respectively, for the randomly assigned surgical group and 4.5, 3.5, and 2.3 per cent, respectively, for controls. Corresponding data for subjects assigned nonrandomly were similar.

A third, indirect measure of surveillance was the frequency with which evidence of throat infection was found during examinations of children who did not contemporaneously (from seven days before to seven days after examination) report a sore throat. Such evidence was found in only 13 (1.2 per cent) of 1101 examinations of randomly assigned subjects and in only 7 (0.6 per cent) of 1100 examinations of nonrandomly assigned subjects.

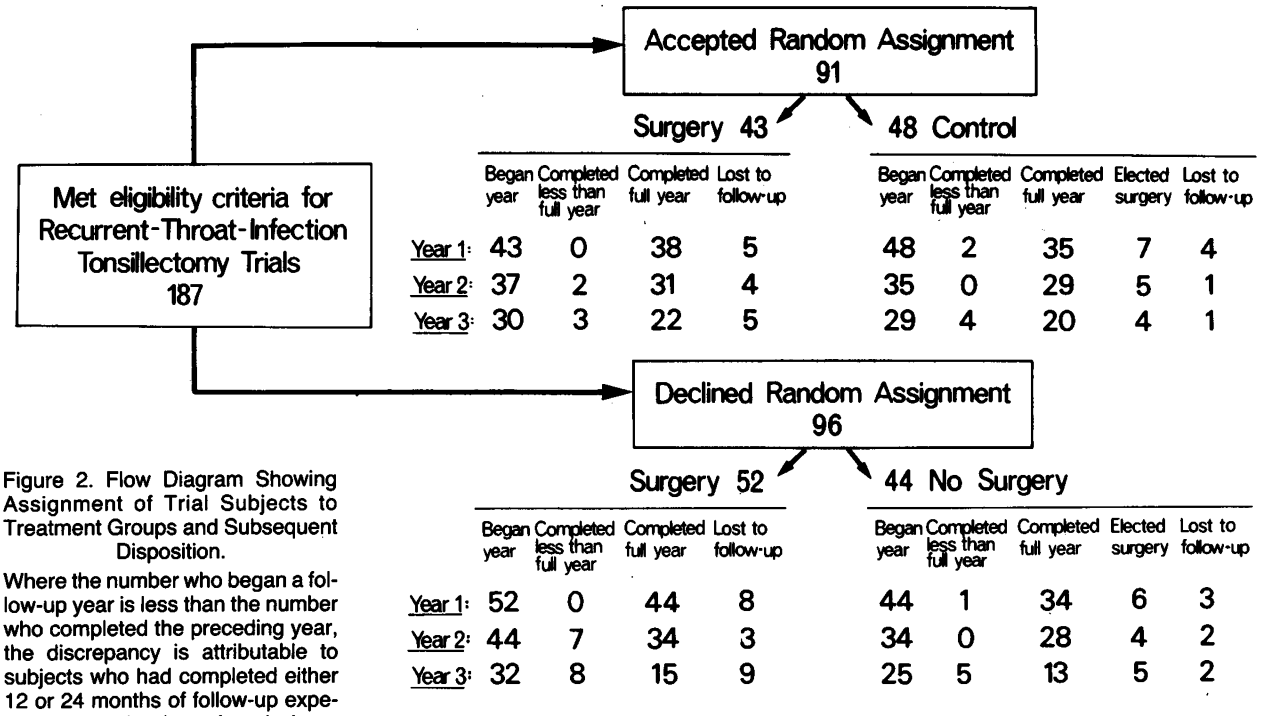

Figure 2. Flow Diagram Showing Assignment of Trial Subjects to Treatment Groups and Subsequent Disposition.

Where the number who began a follow-up year is less than the number who completed the preceding year, the discrepancy is attributable to subjects who had completed either 12 or 24 months of follow-up experience at the time of analysis.

Occurrence of Observed Episodes of Throat Infection

Although a minimum of three years of follow-up had originally been contemplated for all subjects, at the time that these analyses were performed some subjects had been followed for shorter periods, about one quarter had been lost to follow-up, and about one third of the subjects initially assigned to a nonsurgical treatment group had been withdrawn from the group, at their parents' request, for treatment with surgery (Fig. 2). In part to take these circumstances into account, the data were analyzed from various standpoints.

Whole-Year Experiences

Table 2 shows data on the occurrence of observed throat-infection episodes in randomly assigned subjects during the first, second, and third whole years of follow-up. The data are presented in four clinical categories of episodes: all combined, moderate or severe, streptococcal, and "counting" (i.e., characterized by one or more of the four qualifying clinical features of episodes used in determining trial eligibility). Not included in the table, by definition, are data derived from experiences of less than a full year's duration — i.e., resulting from either limited follow-up or withdrawal of a child from the control group, for surgical treatment. This limitation notwithstanding, Table 2 shows that the surgical group had consistently lower throat-infection rates than the control group, particularly in regard to episodes rated moderate or severe. On the other hand, the illness rates among subjects who remained in the control group were not consistently high — for example, during the first, second, and third follow-up years the proportions of such subjects who experienced more than one moderate or severe episode were only 26, 24, and 5 per cent, respectively. Table 3 shows that the results were similar in subjects assigned nonrandomly. Fourth-year throat-infection rates in both the randomized and nonrandomized trials remained consistently lower in the surgical groups, but the numbers of subjects were smaller than in the third year, and the differences, as in most of the third-year analyses, were not significant.

Life-Table Analysis

In both the randomized and nonrandomized trials, comparisons of subjects with the four categories of throat-infection episodes were carried out by means of life-table analyses, using as end points the time of occurrence of the first, second, and third episodes, respectively, during each of five follow-up periods: first year, first two years, first three years, second year, and third year. Unlike the analyses summarized in Tables 2 and 3, these analyses incorporated data from fractional-year experiences. Examples of the 120 comparisons are shown in Figure 3. Without exception, the comparisons favored surgical over nonsurgical treatment. Of the 60 comparisons involving randomly assigned subjects, 48 showed significant differences ($P<0.01$ in 41; $0.01<P\leq0.05$ in 7); the 12 third-year analyses accounted for 10 of the 12 nonsignificant differences. In the nonrandomized trial, 46 of the 60 comparisons showed significant differences ($P\leq0.01$ in 37; $0.01<P<0.05$ in 9), and the 12 third-

year analyses accounted for 8 of the 14 nonsignificant differences.

Effects of Status Change and Loss to Follow-up

Table 4 shows that for each follow-up year of the randomized trial, among both surgical and control subjects who became lost to follow-up, the throat-infection rates before their loss had generally been lower than the corresponding rates among subjects who remained in their originally assigned groups for the full year. In contrast, the rates for control subjects withdrawn by their parents from the control group to receive surgery had been consistently higher before withdrawal than the rates for subjects who remained in the control group throughout the year. Corresponding data for subjects assigned nonrandomly were similar and showed identical trends. Thus, on the basis of the numbers of subjects in each category and the respective rates involved, if all subjects had retained their original assignments and remained under surveillance, the throat-infection rates would probably have been higher for the nonsurgical groups and lower for the surgical groups — and thus the measured efficacy of surgery would have been greater — than the data in Tables 2 and 3 and in the life-table analyses indicate[31]; moreover, these differentials would probably have been additive as the follow-up period became longer.

Table 1. Distribution of Selected Demographic and Clinical Characteristics of 187 Subjects, According to Treatment Group.

Characteristic	Randomly Assigned Groups		Nonrandomly Assigned Groups	
	Surgical (N = 43)	Control (N = 48)	Surgical (N = 52)	Nonsurgical (N = 44)
	no. of patients (%)			
Age (yr)				
3–4	5 (12)	7 (15)	6 (12)	5 (11)
5–6	11 (26)	10 (21)	16 (31)	16 (36)
7–15	27 (63)	31 (65)	30 (58)	23 (52)
Sex				
Male	21 (49)	19 (40)	19 (37)	29 (66)
Female	22 (51)	29 (60)	33 (63)	15 (34)
Race				
Black	5 (12)	5 (10)	3 (6)	2 (5)
White	38 (88)	43 (90)	49 (94)	42 (95)
History of episodes of throat infection before entry *				
≥7 in 1 yr	20 (47)	11 (23)	18 (35)	13 (30)
≥5/yr for 2 yr	5 (12)	5 (10)	11 (21)	6 (14)
≥3/yr for 3 yr	18 (42)	32 (67)	23 (44)	25 (57)
Infection-free size of tonsils[15] at entry				
1+	3 (7)	5 (10)	6 (12)	4 (9)
2+	15 (35)	17 (35)	14 (27)	17 (39)
3+	19 (44)	23 (48)	23 (44)	22 (50)
4+	6 (14)	3 (6)	9 (17)	1 (2)
Surgical trial				
Tonsillectomy only	27 (63)	29 (60)	27 (52)	32 (73)
Tonsillectomy with adenoidectomy	16 (37)	19 (40)	25 (48)	12 (27)
Upper respiratory allergy according to specified algorithm †				
Definite or probable	10 (23)	16 (33)	13 (25)	13 (30)
Possible or unlikely	33 (77)	32 (67)	39 (75)	31 (70)
Siblings ‡				
None	7 (16)	5 (10)	14 (27)	11 (25)
Younger only	9 (21)	17 (35)	26 (50)	10 (23)
Older only	22 (51)	18 (38)	10 (19)	17 (39)
Older and younger	5 (12)	8 (17)	2 (4)	6 (14)
Parents' socioeconomic status *				
Executive or professional	4 (9)	12 (25)	14 (27)	10 (23)
Commercial, clerical, or skilled workers	11 (26)	19 (40)	21 (40)	23 (52)
Semiskilled or unskilled workers	9 (21)	3 (6)	6 (12)	6 (14)
Disabled, public assistance, or unemployed	19 (44)	13 (27)	10 (19)	5 (11)
Other	0 (0)	1 (2)	1 (2)	0 (0)
History of tonsil or adenoid surgery in parents				
Neither parent	11 (26)	7 (15)	8 (15)	10 (23)
One parent	14 (33)	19 (40)	29 (56)	20 (45)
Both parents	17 (40)	20 (42)	14 (27)	13 (30)
Unknown	1 (2)	2 (4)	1 (2)	1 (2)
Referral source				
Children's Hospital clinics	24 (56)	19 (40)	29 (56)	17 (39)
Community physicians, others	13 (30)	24 (50)	19 (37)	21 (48)
Parents directly	6 (14)	5 (10)	4 (8)	6 (14)

*The distributions of randomly assigned surgical and control subjects with respect to this characteristic differed significantly ($P \leq 0.05$).

†Available from the authors.

‡The distributions of nonrandomly assigned surgical and nonsurgical subjects with respect to this characteristic differed significantly ($P \leq 0.05$).

Characteristics of Subjects in Relation to Outcome

In the randomized trial no significant interactions were found between treatment status (i.e., surgical or nonsurgical), outcome, and any of the following characteristics of subjects: age, sex, frequency of episodes according to history (seven or more the preceding year, five or more in each of the two preceding years, or three or more in each of the three preceding years), tonsillar size on entry, specific trial eligibility (tonsillectomy alone or with adenoidectomy), probable presence or absence of respiratory allergy, number of siblings, and socioeconomic status. Similarly, no significant associations were found between any of these characteristics and the outcome in control subjects. However, because the numbers of subjects in the respective subgroups were small, the power of these analyses to detect differences was limited. Within each of the subgroups, throat-infection rates were invariably lower for subjects treated surgically than for controls, but not all the differences were significant. For example, in the randomized trial the differences within the 3- to 6-year age subgroup (3 to 4 years and 5 to 6 years combined) were significant for all combined episodes, those that were moderate or severe, and "counting" episodes but not for streptococcal episodes during the first year, whereas the differences within the 7- to 15-year subgroup were significant for each of the four categories of episodes during both the first and second years.

Secondary Outcome Measures

Table 5 summarizes data from the first three whole years of follow-up for three secondary outcome measures of throat-related illness: the cumulative proportions of visits at which "isolated" cervical lymphadenopathy was found, the numbers of parent-reported

Table 2. Distribution of Randomly Assigned Subjects, According to Number of Observed Episodes of Throat Infection, Whole Follow-up Year, Type of Episode, and Treatment Group.

Type of Episode *	Treatment Group (No. of Subjects)	No. of Episodes					Total No. of Episodes	Episodes per Subject		P Value †
		0	1	2	3	≥4		range	mean	
		number of subjects								
Follow-up Yr 1										
All combined	Surgical (38)	16	9	8	2	3	47	0–8	1.24	0.001
	Control (35)	4	6	6	7	12	108	0–10	3.09	
Moderate or severe	Surgical (38)	35	3	0	0	0	3	0–1	0.08	0.001
	Control (35)	12	14	5	2	2	41	0–7	1.17	
Group A β-strep	Surgical (38)	27	6	5	0	0	16	0–2	0.42	0.007
	Control (35)	13	13	6	2	1	35	0–4	1.00	
Counting	Surgical (38)	22	8	4	3	1	29	0–4	0.76	0.001
	Control (35)	6	6	7	8	8	93	0–10	2.66	
Follow-up Yr 2										
All combined	Surgical (31)	15	7	2	1	6	50	0–10	1.61	0.001
	Control (29)	4	5	5	7	8	77	0–7	2.66	
Moderate or severe	Surgical (31)	26	5	0	0	0	5	0–1	0.16	0.002
	Control (29)	12	10	2	4	1	30	0–4	1.03	
Group A β-strep	Surgical (31)	27	2	2	0	0	6	0–2	0.19	0.001
	Control (29)	11	12	3	3	0	27	0–3	0.93	
Counting	Surgical (31)	20	7	0	1	3	23	0–5	0.74	0.001
	Control (29)	4	8	4	6	7	65	0–7	2.24	
Follow-up Yr 3										
All combined	Surgical (22)	6	6	4	3	3	39	0–6	1.77	NS
	Control (20)	6	4	2	3	5	44	0–6	2.20	
Moderate or severe	Surgical (22)	16	6	0	0	0	6	0–1	0.27	NS
	Control (20)	13	6	0	1	0	9	0–3	0.45	
Group A β-strep	Surgical (22)	16	5	0	1	0	8	0–3	0.36	NS
	Control (20)	12	4	2	1	1	15	0–4	0.75	
Counting	Surgical (22)	10	5	5	2	0	21	0–3	0.95	NS
	Control (20)	7	3	6	1	3	33	0–6	1.65	

*β-strep denotes beta-hemolytic streptococcus. See text for definition of "counting" episode.

†The three classes used were 0, 1–2, and ≥3 episodes, respectively; P values determined by the chi-square test with 2 degrees of freedom. NS denotes not significant (P>0.05).

sore-throat days, and the reported amount of school missed at least in part because of sore throat. In most instances the results appeared to be more favorable in surgical than in nonsurgical groups, but differences of notable magnitude were found mainly in regard to isolated cervical lymphadenopathy. As in the whole-year outcomes regarding observed episodes of throat infection (Tables 2 and 3), these results incorporate the influence of subject migration and therefore probably understate differences attributable to surgery.

Untoward Reactions

In the 95 subjects treated with surgery the mean reported duration of postoperative sore throat was 4.9 days. Thirteen children had surgery-related complications, and six of them required one or more extra days in the hospital. Four of the children had hemorrhage: two before and two after hospital discharge. Bleeding was easily controlled in all four, and none required transfusion. Two children given succinylcholine to prepare them for intubation had prolonged muscular paralysis attributed to previously unrecognized cholinesterase deficiency; both required assisted ventilation. One of the two also had pharyngitis, as did three additional children, one of whom had pharyngitis in conjunction with otitis media and bronchitis. One child had severe nausea for two days, and one had severe dysphagia for one week. Two children reportedly had fever intermittently for two weeks but were not examined.

One child treated surgically and four treated nonsurgically had erythematous rashes while receiving penicillin prescribed for throat infection. No subject was known to have rheumatic fever, glomerulonephritis, or bronchial asthma.

Discussion

In these parallel clinical trials designed to avoid, insofar as possible, the limitations of earlier trials, tonsillectomy with or without adenoidectomy was unequivocally effective for two years, and was probably effective for at least one additional year, in reducing the frequency and severity of episodes of throat infection. On the other hand, a substantial proportion of the subjects who did not undergo tonsillectomy had relatively little throat infection.

Differences between the treatment groups in regard to secondary outcome measures were less clear-cut and of uncertain clinical importance. "Isolated" cervi-

Table 3. Distribution of Nonrandomly Assigned Subjects, According to Number of Observed Episodes of Throat Infection, Whole Follow-up Year, Type of Episode, and Treatment Group.

Type of Episode *	Treatment Group (No. of Subjects)	No. of Episodes					Total No. of Episodes	No. of Episodes per Subject		P Value †
		0	1	2	3	≥4		range	mean	
		number of subjects								
Follow-up Yr 1										
All combined	Surgical (44)	14	10	8	5	7	78	0–8	1.77	0.04
	Nonsurgical (34)	6	4	5	3	16	105	0–12	3.09	
Moderate or severe	Surgical (44)	33	10	0	1	0	13	0–3	0.30	NS
	Nonsurgical (34)	21	8	3	1	1	23	0–6	0.68	
Group A β-strep	Surgical (44)	34	7	2	1	0	14	0–3	0.32	0.02
	Nonsurgical (34)	18	11	2	2	1	26	0–4	0.76	
Counting ‡	Surgical (44)	17	18	2	5	2	46	0–5	1.05	0.02
	Nonsurgical (34)	7	9	3	5	10	82	0–10	2.41	
Follow-up Yr 2										
All combined	Surgical (34)	12	9	9	3	1	40	0–4	1.18	0.001
	Nonsurgical (28)	5	5	5	5	8	70	0–8	2.50	
Moderate or severe	Surgical (34)	31	2	1	0	0	4	0–2	0.12	0.02 ‡
	Nonsurgical (28)	18	9	1	0	0	11	0–2	0.39	
Group A β-strep	Surgical (34)	31	3	0	0	0	3	0–1	0.09	0.001
	Nonsurgical (28)	15	7	2	3	1	24	0–4	0.86	
Counting	Surgical (34)	18	10	6	0	0	22	0–2	0.65	0.001
	Nonsurgical (28)	6	8	6	5	3	48	0–5	1.71	
Follow-up Yr 3										
All combined	Surgical (15)	3	7	2	1	2	22	0–4	1.47	0.04
	Nonsurgical (13)	0	2	3	3	5	41	1–6	3.15	
Moderate or severe	Surgical (15)	10	5	0	0	0	5	0–1	0.33	NS
	Nonsurgical (13)	7	3	1	2	0	11	0–3	0.85	
Group A β-strep	Surgical (15)	11	2	1	1	0	7	0–3	0.47	NS
	Nonsurgical (13)	4	6	1	1	1	15	0–4	1.15	
Counting	Surgical (15)	7	5	1	2	0	13	0–3	0.87	NS
	Nonsurgical (13)	2	2	4	3	2	29	0–5	2.23	

*β-strep denotes beta-hemolytic streptococcus. See text for definition of "counting" episode.

†The three classes used were 0, 1–2, and ≥3 episodes, respectively; P values, determined by the chi-square test with 2 degrees of freedom. NS denotes not significant (P>0.05).

‡One degree of freedom; the two classes used were 0 and ≥1 episode, respectively.

cal lymphadenopathy, which was more prevalent in the nonsurgical groups, presumably entailed minor discomfort and may have been indicative of otherwise inapparent tonsillar inflammation. Sore-throat days and sore-throat–associated school absence — measures used in earlier studies[17,18,20] — were reported more often for subjects treated nonsurgically, but the underlying events were variable and of limited specificity, and most of the differences found between surgical and nonsurgical groups were not significant.

Inherent in these trials were certain sources of potential bias. One source was the fact that for subjects treated surgically but not for those treated without surgery, a period routinely intervened between assignment and the starting point in a trial. This raised the possibility that seasonally related risks of illness in surgical and nonsurgical groups may have differed, or that a decline in the occurrence of throat infection with increasing age may have accounted, at least in part, for the better outcomes observed in the surgical groups. However, as noted above, an analysis showed that the seasonal distributions of starting points for surgical and nonsurgical groups were similar, and the data in Tables 2 and 3 show relatively little change in the infection rates for nonsurgical groups from the first follow-up year to the second.

Bias may also have resulted from the trials' necessarily nonblind circumstances. Subjects who underwent surgery, their parents, and study personnel may have assumed that tonsillectomy was efficacious, and this in turn may have led to reduced awareness or reduced detection of illness in surgical groups — a possibility underscored by the somewhat lower level of surveillance in these groups. The result would have been to overstate the efficacy of surgery. On the other hand, as noted above, the tendency of more frequently ill control subjects to be withdrawn by their parents to receive surgery and of less ill subjects treated surgically to become lost to follow-up probably resulted in an understatement of the efficacy of surgery, the magnitude of which was probably increased for each succeeding year of follow-up. Although the extent to which these various potential biases operated cannot be determined, it seems likely that their net effect was an understatement of efficacy.

To what extent are the findings of these trials generalizable to other children who would meet the stringent eligibility criteria? First of all, our subjects appear to have constituted a cross-section of children in the affected age groups. Secondly, if the trials' unusually close monitoring and prompt application of treatment were in themselves beneficial, subjects treated without

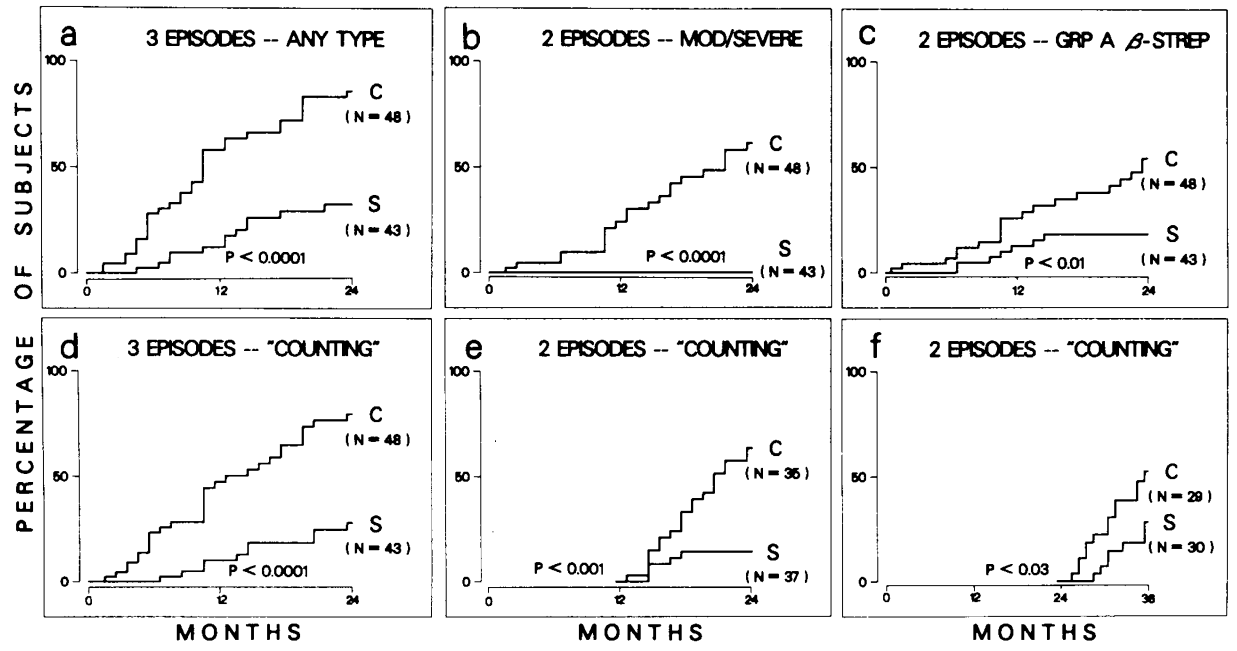

Figure 3. Life-Table Analysis of Cumulative Proportions of Randomly Assigned Surgical (S) and Control (C) Subjects Who Had Three or More Observed Episodes of Throat Infection of Any Type within Two Years (a), Two or More Moderate or Severe Episodes within Two Years (b), Two or More Group A Beta-Hemolytic Streptococcal Episodes within Two Years (c), Three or More "Counting" Episodes within Two Years (d), Two or More "Counting" Episodes within the Second Year (e), and Two or More "Counting" Episodes within the Third Year (f).

surgery may have benefited disproportionately, since those treated surgically had less illness and therefore less need for care. Thus, in comparable children not being studied, the relative effectiveness of surgery may be greater. Finally, the similarity between the outcomes in the randomized and nonrandomized trials suggests that the stringent eligibility criteria resulted in a study population that was reasonably homogeneous in regard to risk. (Random assignment as an issue in the design of clinical trials has been discussed extensively by other authors.[32,33]) It thus seems reasonable to assume that in other groups of children meeting the same stringent criteria, tonsillectomy will produce effects comparable to those reported here.

Caution is needed in applying these findings and assumptions to clinical decision making. The almost uniformly favorable outcome in subjects who underwent surgery, combined with the variable outcome in those who did not, appears to justify but by no means to mandate the performance of tonsillectomy in children with comparable throat-infection experiences. Decisions for or against tonsillectomy in such children should take into account the potential adverse consequences of surgery, including rare catastrophic or severe events not encountered in these trials,[10,34] as well as individual circumstances in relation to various quality-of-life considerations.[35] Thus, decisions may reasonably be influenced by parents' and children's respective preferences, anxieties, and tolerance of illness; school performance in relation to illness-related absence; the accessibility of health-care services; out-of-pocket costs; and the nature of available anesthetic and surgical services and facilities.

Not addressed in these trials were two relatively small but clinically important classes of children: those who require tonsillectomy because of large tonsils causing severe obstructive symptoms, and those with other tonsil-related problems, such as peritonsillar abscess, presumed chronic tonsillitis, chronic cervical lymphadenopathy, and "hot potato" voice, for

Table 4. Rates of Occurrence of Observed Episodes of Throat Infection in Randomly Assigned Subjects, According to Their Retention in or Withdrawal from the Originally Assigned Treatment Group.*

Follow-up Year	Treatment Group Originally Assigned	Subjects Remaining in Original Treatment Group throughout Year	Subjects Withdrawn from Original Treatment Group during Year: lost to follow-up	Subjects Withdrawn from Original Treatment Group during Year: changed to surgical status
		mean no. of episodes of throat infection per subject-month of follow-up †		
First	Surgical (43) *	0.10 (38)	0.06 (5)	NA
	Control (46)	0.26 (35)	0.07 (4)	0.61 (7)
Second	Surgical (35)	0.13 (31)	0.0 (4)	NA
	Control (35)	0.22 (29)	0.0 (1)	0.45 (5)
Third	Surgical (27)	0.15 (22)	0.0 (5)	NA
	Control (25)	0.18 (20)	0.20 (1)	0.28 (4)

*Excludes subjects remaining in originally assigned treatment groups, who were followed for less than a full year. Numbers in parentheses refer to numbers of subjects. NA denotes not applicable.

†During whole year for subjects remaining in original treatment group, and during segment of year before withdrawal for those withdrawn.

Table 5. Isolated Cervical Lymphadenopathy, Sore-Throat Days, and Sore-Throat–Associated School Absence, According to Follow-up Year and Treatment Group.*

Follow-up Year	Treatment Group	Cervical Lymphadenopathy Found at Non–Throat-Infection Visit		Sore-Throat Days †		Sore-Throat-Associated School Absence ‡	
		Randomized Trial	Nonrandomized Trial	Randomized Trial	Nonrandomized Trial	Randomized Trial	Nonrandomized Trial
		% of visits		*no. of days per year*		*no. of days per year*	
First	Surgical	3.0 (38)	4.6 (44)	16.3±14.3 (31)	28.0±23.9 (42)	3.5±4.2 (29)	6.3±6.7 (41)
	Nonsurgical	12.2 (35)	14.2 (34)	18.9±14.6 (33)	20.8±20.2 (34)	6.7±6.9 (30)	7.4±8.6 (31)
Second	Surgical	3.1 (31)	5.6 (34)	10.8±13.4 (29)	13.4±13.7 (37)	4.5±4.5 (28)	4.4±5.6 (25)
	Nonsurgical	14.6 (29)	13.6 (28)	15.1±12.5 (27)	14.5±11.7 (28)	5.9±4.2 (26)	4.3±3.9 (25)
Third	Surgical	0.7 (22)	1.3 (15)	10.7±11.1 (22)	8.8± 7.0 (16)	5.1±5.7 (21)	4.0±5.9 (10)
	Nonsurgical	12.5 (20)	4.6 (13)	19.0±20.2 (21)	16.1±11.5 (13)	5.9±6.2 (21)	7.2±7.8 (13)

*Values are presented as means ±1 S.D. Numbers in parentheses denote numbers of subjects. For bracketed pairs of values, $P \leq 0.05$ by a chi-square analysis of distributions of subjects.

†Limited to subjects with at least 270 days of reportage in a follow-up year. Includes sore-throat days immediately after surgery. Number of days for each subject for each follow-up year was standardized on the basis of 365 days.

‡Limited to subjects 5 years of age or older with at least 130 days of reported school attendance or absence in a follow-up year. School absence immediately after surgery was excluded. Number of days for each subject for each follow-up year was standardized on the basis of a 180-day school year.

which the advisability of performing tonsillectomy remains uncertain.

It must be emphasized that the findings in our subjects cannot properly be extrapolated to children with throat-infection experiences that are less extreme or less well documented. Considering our difficulties in finding sufficient numbers of eligible subjects for study despite intensive efforts over an 11-year period, the results of our systematic reviews of collaborating pediatricians' practice records, and our observations in clinical practice outside the study, we are confident that children with experiences as extreme as those of our trial subjects are exceptional. Accordingly, it seems likely that many of the children who currently undergo tonsillectomy have throat-infection experiences that are less severe, at most conforming to the more permissive guidelines of a number of current quality-of-care standards.[7-10] To assess the reasonableness of these or similar standards, we have recently undertaken a clinical trial of the efficacy of tonsillectomy in such less severely affected children.

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PREVENTION OF ACUTE MOUNTAIN SICKNESS BY DEXAMETHASONE

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Abstract Acute mountain sickness is a syndrome that occurs when unacclimatized persons ascend rapidly to high altitudes. It is postulated that cerebral edema causes its symptoms. Since dexamethasone is useful in treating some forms of cerebral edema, we investigated its role in the prevention of acute mountain sickness. Using a double-blind crossover design, we exposed eight young men to a simulated altitude of 4570 m (15,000 ft) on two occasions. By random assignment, each subject received dexamethasone (4 mg every 6 hours) or placebo for 48 hours before and throughout the 42-hour exposure. The presence of symptoms of acute mountain sickness was established by two methods: a questionnaire and an interview by a physician. Dexamethasone significantly reduced the symptoms of acute mountain sickness. During dexamethasone treatment, the cerebral-symptom score (mean ±S.E.) decreased from 1.09±0.18 to 0.26±0.08, and the respiratory-symptom score decreased from 0.64±0.09 to 0.31±0.06 (both, $P<0.05$). As judged by the interviewing physician, the symptom score decreased from 1.10±0.11 to 0.28±0.07 ($P = 0.01$). We conclude that dexamethasone may be effective in preventing the symptoms of acute mountain sickness. (N Engl J Med 1984; 310:683-6.)

ACUTE mountain sickness is a syndrome characterized by headache, nausea, vomiting, insomnia, and lassitude. These symptoms occur over a period of one to five days when lowlanders ascend to high altitudes.[1-3] The use of acetazolamide[4] and staging (spending time at an intermediate altitude)[5] have been recommended for the prevention of acute mountain sickness, but are only partly effective. With an increasing number of persons visiting areas of high altitude for recreation and other pursuits, a reliable, completely effective prophylactic therapy for acute mountain sickness would be of great value.

The precise pathophysiology of acute mountain sickness is unknown. The most widely accepted theory holds that the symptom complex is due to the development of cerebral edema that is probably vasogenic in origin.[1,6,7] Acute mountain sickness is seen as part of the spectrum of altitude-induced illness that ranges from mild headache to life-threatening cerebral edema.[8]

Dexamethasone, a potent synthetic glucocorticoid with negligible mineralocorticoid activity, is effective in the management of cerebral edema of diverse causes.[9] We hypothesized that, if mild cerebral edema arising from altitude exposure were responsible for the symptoms of acute mountain sickness, then dexamethasone might be an effective prophylactic treatment for this illness. To test this hypothesis, we administered dexamethasone or placebo to eight volunteers and then exposed them to a simulated altitude of 4570 m (15,000 ft) on two occasions. The results of this trial indicate that dexamethasone prevented the occurrence of acute mountain sickness.

Methods

Subjects

The subjects were healthy men, 20 to 26 years of age, residing at sea level. Potential subjects were excluded if they had been exposed to high altitudes within the preceding six months or if they had any physical illness or medical contraindication to altitude exposure or to taking dexamethasone. All gave informed consent.

Twelve subjects completed the first, altitude-exposure, part of the study, but four did not participate in the crossover phase. Three

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