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The Effects of General Anesthesia on Upper Respiratory Tract Infections in Children

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A prospective cohort study of 489 pediatric patients was performed to investigate the prevalence of perioperative respiratory complications and symptomology in children presenting for myringotomy with upper respiratory tract infections (URIs). All children undergoing myringotomy received halothane N_2O/O_2 anesthesia administered *via* face mask. Information on complications and respiratory symptoms was obtained from the anesthesia and recovery room records, and by standardized questionnaire. There were no significant differences in perioperative complications between asymptomatic children (1.23%), symptomatic children fulfilling predetermined URI criteria (1.28%), and symptomatic children that did not fulfill the URI criteria (2.38%). In addition, the prevalence and duration of respiratory symptoms was significantly less in children having received anesthesia and surgery than in a matched group of non-anesthetized controls who did not have surgery. Results from this study suggest that there is no increased morbidity for children presenting at minor surgery with acute uncomplicated URIs and who did not require tracheal intubation. In addition, the administration of general anesthesia and surgery to this group of patients was followed by a decrease in both the appearance and duration of a number of respiratory symptoms. (Key words: Anesthetics, volatile: halothane. Complications: apnea; dysrhythmias; laryngospasm. Infection: pulmonary; upper respiratory; viral.)

DESPITE THE FREQUENT clinical practice of cancelling surgery for patients with respiratory tract infections, support for this practice is somewhat tenous. For example, clinical studies investigating the effect of anesthesia on patients harboring viral infections have, for the most part, been anecdotal in nature or have not directly addressed the problem,[1–4] whereas many animal studies involving a number of different viruses have used anesthetics which are obsolete in today's practice.[5–7] Indeed, Caldwell states, "There is still no published data proving any effect of anesthetic drugs on the incidence of postoperative infections in man."[8]

To this end, a prospective cohort study was designed to investigate the prevalence of perioperative complications in children with infections of the upper respiratory tract who underwent anesthesia and surgery. In addition, an attempt was made to evaluate the effect of anesthesia on the course of such infections.

Methods

Since the literature, albeit sparse, suggested a potential for increased morbidity in infected patients undergoing surgery and anesthesia,[1,3] the study population was carefully chosen to minimize any possible risks, and to meet the University of Michigan's guidelines for studies involving human subjects. For this study, therefore, a procedure of short duration with minimal surgical insult, and where the patient did not require endotracheal intubation, seemed most appropriate. Surgery for myringotomy and tympanostomy tube placement in children with chronic otitis media met these requirements. Halothane, an agent with minimal laryngeal stimulation, was selected as the anesthetic. The prevalence of otitis media and the high incidence of URIs associated with this disease in children were also strong inducements for selecting this population.

The study population (with informed consent and approval from our institutional review committee) consisted of 489 children between the ages of 1 and 12 yr with a history of chronic otitis media who were scheduled for elective myringotomy and tympanostomy tube placement. These children were evaluated at the Otolaryngology Clinic at the University of Michigan Medical Center, and were randomly allocated into a control and surgery group. Both groups were evaluated over a 3-week period. The control group (n = 245) was evaluated at the time of the clinic visit and for a period of 3 weeks thereafter (prior to their surgery). The surgery group (n = 244) was evaluated at the time of their surgery and for a period of 3 weeks postoperatively. Children were classified as having an URI if any two of the following symptoms were manifest: 1) sore or scratchy throat, 2) sneezing, 3) rhinorrhea, 4) congestion, 5) malaise, 6) nonproductive cough, 7) fever less than 101° F, or 8) laryngitis. Combinations of 1) and 5), 2) and 3), 3) and 6), or 4) and 6) required one additional symptom. It was hoped that these criteria would differentiate the child with an URI from one with an allergic or vasomotor rhinitis. In addition, information obtained from the respective parents was used in evaluating the etiology of presenting symptoms. In this way, it was possible to de-

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termine whether the symptoms represented an acute event or simply reflected a chronic or seasonal condition.

Based on these respiratory criteria, the control and surgery groups were subdivided into three groups, respectively. Group I consisted of symptomatic children who fulfilled the criteria for an URI. Group II consisted of symptomatic children who did not fulfill the criteria for an URI. In addition, this group included asymptomatic children who had a history of an URI in the two weeks prior to their clinic visit (control group) or their surgery (surgery group). Group III were asymptomatic children with no recent history of respiratory illness.

Prior to surgery, those children in the surgery group were examined by an anesthesiologist to evaluate their fitness to undergo the procedure. All children received a standard anesthetic of halothane/O_2/N_2O administered *via* face mask. Surgery was performed in a standard manner for placement of the tympanostomy tubes, and each received standard antibiotic otic drops following the procedure (vasocidin). After surgery, children were transferred to the Post-Anesthetic Recovery Room before returning home.

Evaluation of the children in the 3-week follow-up period was by questionnaire, and, if necessary, telephone interview. The questionnaire was standardized in accordance with the National Heart, Blood and Lung Institute's recommendations for respiratory disease questionnaires involving children (ATS-DLD-78-C).[9] All other information, particularly with respect to intra- and immediate postoperative complications was obtained from the anesthesia and recovery room records. All observers were blinded with respect to the outcome variables.

To verify the presence of virus, nasopharyngeal swabs were taken at random from 151 control and surgery group children. Identification of specific viruses followed standard techniques for culture and isolation.[10] Isolation of viruses was by positive cytopathic effect (CPE) using five different cell lines. Cell lines were obtained as cells or primary cultures. Cells used were: 1) Hep-2 cells (obtained from cells of laryngeal carcinoma, 2) HL (a HeLa derivative, University of Michigan), 3) WI-38 (human fetal lung fibroblasts, 4) primary cynomologous monkey kidney cells, and 5) primary human embryonic kidney cells. Typing of the viruses was determined by observations on the type and speed of CPE and the cell lines in which the CPE occurred. The paramyxoviruses were identified by hemadsorption using 0.4% guinea pig red blood cells.

Comparison of the prevalence rates for respiratory complications and symptoms was by chi square analysis. Analytical variables, such as duration of anesthesia and surgery, was by analysis of variance.

TABLE 1. Intraoperative Complications in Surgery Group

Group	Complications		
	Laryngospasm (%)	Dysrhythmias (%)	Apnea (%)
I n = 78	1.28	2.56	0.00
II n = 84	2.38	3.57	0.00
III n = 81	1.23	3.70	2.47
Total n = 243	(1.65)	(3.30)	(0.82)

Results

Completed questionnaires were obtained for a total of 489 children. Sixty-four percent were male, and the mean age was 4.1 yr (range 1–12 yr). This sex ratio and age distribution was consistent for both control and surgery groups and their subgroups. Ninety-two percent of the total population were caucasian. Examination of socioeconomic status (SES) by father's occupation demonstrated a consistent distribution across the SES levels, and SES as determined by level of education suggested that most (59%) had completed high school.

Complications

The overall prevalence of intraoperative complications in the surgery group was less than 3%. Table 1 describes the appearance of respiratory complications in each subgroup. There were no significant differences in prevalence rates for laryngospasm, dysrhythmias, or apnea in each group. Bronchospasm was not observed in any of the groups. The surgical and anesthetic protocols were similar for each group. The mean duration of anesthesia was 19.5 min, and the mean time of surgery was 12.6 min. These times were similar for each group. Similarly, there was no significant difference in the prevalence of complications (laryngospasm, hyperactivity, and emesis) in the immediate postoperative period.

Acute Respiratory Symptoms

The prevalence of presenting symptoms is described in table 2. The most prevalent symptoms were sneezing, rhinorrhea, congestion, and unproductive cough.

The duration of these presenting symptoms was also examined. In group I, the mean duration of sore throat was significantly longer ($P < 0.05$) for control children (4.4 days ± 0.85 SEM) than for surgery children (3.3 days ± 0.86 SEM). Similarly, the duration of malaise was significantly longer in the control group (5.07 ± 0.92) than the surgery group (2.09 ± 0.55). In group II children, the mean duration of rhinorrhea was significantly ($P < 0.05$) longer for control children (7.24 ± 1.31) than surgery children (3.33 ± 0.87). Also, the mean duration of congestion was significantly longer

TABLE 2. Prevalence (per 100) of Presenting Symptoms in the Control and Surgery Groups

Symptoms	Group I		Group II	
	Control (n = 76)	Surgery (n = 78)	Control (n = 74)	Surgery (n = 84)
Sore throat	26.3	18.3	0.0	3.6
Sneezing	38.9	24.4*	6.7	0.0†
Malaise	25.9	25.4	12.0	10.7
Fever	9.5	6.4	4.0	4.8
Rhinorrhea	78.9	78.2	42.9	50.0
Congestion	70.1	53.8*	24.7	16.7
Productive cough	0.0	0.0	0.0	0.0
Unproductive cough	63.2	76.9*	22.9	22.6
Hoarseness	12.0	5.1	3.9	1.2
Headache	4.2	2.6	0.0	1.2

* $P < 0.05$ *vs.* group I control.
† $P < 0.05$ *vs.* group II control.

for the control group (7.13 ± 1.74) than for those receiving anesthesia (2.00 ± 0.41).

Comparison between control and surgery groups for the appearance of new symptoms in the 3-week follow-up period is described in table 3. Group I control children demonstrated significantly ($P < 0.05$) more sore throats, sneezing, malaise, fever, and productive cough than the corresponding surgery groups, whereas group II surgery children showed a higher prevalence of rhinorrhea than group II control children. The appearance of these symptoms was independent of sex, age, and SES.

The duration of these new symptoms was also investigated. In group I, the control group children had significantly ($P < 0.05$) longer duration of sore throat (4.22 days ± 0.80 SEM *vs.* 3.20 ± 1.24), sneezing (4.55 ± 0.72 *vs.* 3.00 ± 0.89), and fever (3.34 ± 0.57 *vs.* 1.92 ± 0.45) than the corresponding surgery group. Conversely, in group II children, the control group had significantly ($P < 0.05$) less sneezing (5.33 ± 1.67 *vs.* 7.50 ± 1.63) and malaise (3.88 ± 1.09 *vs.* 8.57 ± 2.01) than the surgery group. Group III showed no differences in new symptom duration between the control and surgery groups.

To evaluate the degree of disability in the follow-up period, the duration of activity restriction and confinement to bed was examined. No differences were noted within each group and between groups for these variables.

VIRAL ASSAYS

A total of 151 nasopharyngeal swabs were obtained from patients in both control and surgery groups. Positive isolation of virus was obtained for 24.5% of the samples, and these were specifically identified where possible. A description of the viral isolates is shown in table 4. Five virus types were isolated, and these included rhinovirus, respiratory syncytial virus (RSV), parainfluenza virus, enterovirus, and herpesvirus. There were no statistical differences between groups for isolation rates and typing of specific viruses.

NONRESPONSE

The potential for bias in this study was manifest in five areas: 1) exclusion criteria, 2) group selection, 3) questionnaire nonresponse, 4) person completing the questionnaire, and 5) selection of children from whom viral cultures were taken. Exclusion criteria based on age and the need for surgery in addition to myringotomy was applied to all groups equally. Exclusion based on the use of different anesthetic agents was independent of the presence of respiratory symptoms, and thus was not a source of bias. Exclusion of patients due to severe respiratory symptoms was similar for both control and surgery groups. Selection of patients for control and surgery groups was by simple random sampling, and, as such, provided two very homogenous groups in terms of demographic characteristics. This homogeneity was further reflected in the subgroupings, and thus greatly reduced any chance of confounding due to group differences.

The overall response rate to the questionnaire was 74%. The potential bias due to nonresponse to the

TABLE 3. Prevalence (per 100) of New Symptoms Appearing in the Postclinic (Control) or Postsurgical (Surgery) Periods

Symptoms	Group I		Group II		Group III	
	Control (n = 72)	Surgery (n = 63)	Control (n = 62)	Surgery (n = 65)	Control (n = 68)	Surgery (n = 64)
Sore throat	12.9	1.6*	12.9	17.8	8.8	15.9
Sneezing	30.6	11.1*	16.1	23.9	14.7	15.9
Malaise	21.4	9.7*	14.3	21.7	13.2	18.2
Fever	23.9	9.5*	24.2	23.9	19.1	11.4
Rhinorrhea	38.0	25.4	32.3	50.0†	23.5	34.1
Productive cough	33.3	17.5*	14.5	15.2	14.7	11.4
Pneumonia	0.0	0.0	1.5	0.0	0.0	1.4

* $P < 0.05$ group I surgery *vs.* group I control.
† $P < 0.05$ group II surgery *vs.* group II control.

questionnaire was evaluated, and was considered to be negligible, since both respondent and nonrespondent groups were well matched for age, sex, race, and SES. In addition, both groups were well matched for respiratory criteria and outcome. Bias due to the person completing the questionnaire was also evaluated. Since 94% of the questionnaires were completed by the mother, any bias introduced by completion by other parties could be considered negligible. In addition, since the maternal contribution for completion was so high, it would be expected that any reporting bias would affect each group in a similar manner.

Finally, the potential bias due to the selection of children from whom viral cultures were taken was evaluated both in terms of demographic homogeneity and outcome. The average age of the children from whom cultures were taken was 3.9 yr, compared to 3.8 yr for those from whom cultures were not taken. Sixty-eight percent of those cultured were male, compared to 54.3% of those who were not. This was consistent for both surgery and control groups.

The persistence of respiratory symptoms observed in group I patients who had a positive viral culture compared to those who did not have a culture was similar. The trend of longer symptom persistence observed in the control group compared to the surgery group was thus maintained, and was, therefore, independent of whether or not the child had a positive viral culture.

Discussion

The population studied in this study contribute to a well-defined clinical syndrome. Random assignment of control and surgery groups from this population resulted in two very homogenous groups. If we consider the demographic information of the study population, it can be seen that control and surgery groups and their subgroups are well matched for age, sex, race, and socioeconomic status. This information correlates well with the literature regarding children with otitis media.[11–14] The seasonal pattern of infection of otitis media in the study population closely paralleled that of upper respiratory tract infections, in that the preponderance of cases occurred in the winter and spring. The demographic homogeneity between study groups and their subgroups was deemed important, since the chance of confounding is greatly reduced. In addition, this demographic homogeneity was also consistent for the nonresponse groups.

The lack of a significant difference between prevalence rates of laryngospasm for healthy and infected children raises the question of whether or not group I children were indeed sicker than group III asymptomatic children. Attempts have been made to establish the presence of viral infection in symptomatic children by nasopharyngeal culture. Although this information helps correlate symptoms with the presence of virus, it was not possible to culture all children. In addition, even if all children were cultured, the positive isolation of virus under the best of circumstances is never 100%, and varies considerably with the time of culture, the collection of culture, and the analysis. Selection of children for group I was, thus, based primarily on clinical signs and symptoms which were consistent with those attributed to an acute upper respiratory tract infection.[15] Indeed, these are the very criteria that the physician would employ to assess the need for postponement of surgery, and, although a positive isolation of virus would be useful to the physician to confirm the presence of virus, it would be neither a practical nor economical consideration. It is conceivable, therefore, that not all children had viral infections in group I, yet there can be no doubt in terms of their combined signs and symptoms that they posed, by all previously defined criteria, an increased risk of intraoperative complications.[1,3,16] Although this study failed to detect a difference in prevalence rates for complications between the groups receiving anesthesia, the finding is believed to be a true reflection of occurrence for this population of children, and has, therefore, important clinical implications.

TABLE 4. Virus Isolation (Overall Positive Isolation = 24.5%)

	Control Group Isolation 27% (n = 65)	Surgery Group Isolation 22% (n = 86)
	Isolation by Virus Type (%)	
Virus	Control Group	Surgery Group
Rhinovirus	44.4	41.7
R.S.V.	33.3	25.0
Parainfluenza	11.1	25.0
Enterovirus	0.0	8.3
Herpesvirus	11.1	0.0

The second focus of this study was to investigate the effect of halothane on the course of respiratory infection. In the follow-up period, the prevalence of sore throat, sneezing, malaise, fever, and productive cough was significantly lower for those children receiving anesthesia and surgery than for the children that did not. However, since there was more preoperative sneezing in the group I control children than the corresponding surgery group, and the observation that sneezing was also more prominent in the group postoperatively, raised the question of bias due to a skewed distribution. To evaluate this, a Mantel-Haenzsel chi-square analysis was performed, and demonstrated that the increased prevalence of sneezing in the group I control children

postoperatively was indeed valid. In addition to these differences in symptom prevalence, the duration of sore throat, sneezing, and fever was longer for control group I children than for surgery group I children. These data suggest that anesthesia and surgery may have the effect of ameliorating certain symptoms and, indeed, may beneficially alter the natural history of the respiratory infection. Indeed, this appears even more convincing, since the symptoms that show differences between the two groups in the postoperative and postclinic period are those that would naturally occur later in the continuum of a respiratory tract infection. These findings are of special interest, as they add a clinical perspective to a phenomenon that, to date, has only been demonstrated in tissue culture and in animal models.

Unfortunately, a true cause-and-effect relationship between anesthesia and reduced symptoms cannot be established in this model, due to the potential confounding of the myringotomy. Ideally, anesthetic causality can only be established if surgery is performed without anesthesia, or vice versa, neither of which is ethical. Although the control group in this study was not optimal, we feel that it was, nevertheless, appropriate given that: 1) myringotomy and tympanostomy tube placement represent procedures with minimal surgical insult and short duration, and 2) that an understanding of the pathophysiology of chronic otitis media suggests that the potential confounding effect of the myringotomy was minimal.

The study population consisted of children with a history of chronic otitis media which had been refractory to conventional antibiotic therapy. These children had been followed previously by pediatricians who referred them to the Otolaryngology clinic for evaluation for surgery. The etiology of otitis media is primarily attributed to Eustachion tube dysfunction, which may be due to either a functional or mechanical obstruction, abnormal patency, or both.[17-19] Bluestone demonstrated persistent functional obstruction in a series of children with chronic otitis media.[17] In addition, Eustachion tube obstruction may be exacerbated during periods of upper respiratory tract infection.[17,20] The persistent dysfunction of Eustachion tube ventilation produces a negative pressure environment in the middle ear, which favors the accumulation of fluid and mucus. The myringotomy and tube placement, therefore, serves as a palliative measure to maintain positive pressure within the middle ear and provide a means of ventilation in the face of inadequate Eustachion tube function. Since persistent tubal dysfunction effectively isolates the middle ear from the upper respiratory tract, it is difficult to attribute the observed improvement in URI symptoms postoperatively to that of the myringotomy. Conceivably, the only way that myringotomy might influence concurrent URI symptoms is if it was performed on a febrile child with an acute otitis media with purulent effusion. In this case, drainage of an "abscess" may reduce fever and, possibly, influence other symptoms. However, since myringotomy and tube placement is not generally indicated for acute otitis media,[21,22] these children did not serve as a source for our study.

Although one cannot ignore the possible confounding effect of the surgery, the anesthetic contribution to these findings is suggested by results from a number of *in vitro* and animal studies. For example, earlier work using a number of viruses exposed to halothane has demonstrated a dose-dependent inhibition of virus replication, ranging from a slight decrease in virus titer to complete inhibition of progeny virus production. This effect is thought to be due in part to a decrease in the synthesis of nonspecific or specific viral proteins.[23-26] One should bear in mind, however, that, since these *in vitro* experiments required an exposure time equal to the replicative cycle of the virus, their anesthetic exposure was longer than in our clinical study. Nevertheless, the *in vitro* studies demonstrate a strong sensitivity of certain viruses to anesthesia which potentially could be reflected in the clinical situation. While these observations are not considered dogma, they do present an interesting hypothesis to the clinical findings. Also, although respiratory viruses have not been tested in tissue culture, the fact that some are similar in make-up (*i.e.*, enveloped RNA viruses) to those that demonstrate inhibition with halothane suggests that extrapolation of these findings to respiratory viruses may be appropriate. In addition, animal models have demonstrated the ability of some anesthetic agents to ameliorate certain symptoms of respiratory viruses.[5,27] The appearance of specific viral isolates correlated well with the seasonal appearance of viruses in the community, and, although the number of positive isolates was fairly low, this was comparable with many studies.[28-29]

This study has demonstrated that there is no increase in intraoperative and postoperative complications for children presenting at surgery for myringotomy and tube placement with acute uncomplicated upper respiratory tract infections. Indeed, these results suggest that, for this population, postponement of surgery due to the presence of an upper respiratory tract infection is unnecessary. The implications of these findings, therefore, are important to the patient, whose surgery would be performed in a timely manner, and to the hospital, whose efficiency in terms of scheduling, operating room utilization, and cost containment would be improved.

In addition, this study has demonstrated an amelioration of respiratory symptoms following myringotomy and halothane anesthesia. Although the relative contri-

bution of anesthesia and surgery to these findings cannot be quantified within the framework of this study, we feel that it presents a basis for further studies in this area. Although our control groups were not optimal, we believe, given the present state of knowledge regarding perioperative morbidity in the infected patient and the ethical restrictions imposed by this type of study, that our groups were appropriate. In any case, these findings are important to the physician who may now be able to predict with greater certainty the outcome of the interactions between anesthesia, surgery, and the infectious process.

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