Juvenile Recurrent Respiratory Papilloma: Variable Intersurgical Intervals

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Objectives/Hypothesis: To analyze the patterns of surgical frequency in pediatric patients undergoing surgery with CO₂ laser ablation for juvenile onset recurrent respiratory papillomatosis (JORRP). The hypothesis is that over time there is a high variability in surgical frequency independent of the use of an adjuvant therapy.

Study Design: Retrospective case review.

Methods: All pediatric patients treated surgically with the CO₂ laser for JORRP by two senior surgeons at a tertiary pediatric hospital over an 11-year period were evaluated. Regression analysis was performed. An online survey was conducted of the American Academy of Pediatric Otolaryngology membership on their practice patterns regarding JORRP.

Results: Twenty-nine patients were identified, and of those, 20 were included in regression analysis. Several distinct patterns were noted. Only five of the 20 patients (25%) had a constant rate of procedures throughout the observation period. Three (15%) of the patients had continual decrease and one (5%) of the patients had a continual increase in the surgical rate throughout the study period. Eleven (55%) had a fluctuation in the pattern of their recurrences. When queried on how they approach when to repeat intervention for JORRP patients, more than 16 responses were given, and the most common determinants included standard set interval, previous operative findings, and previous interval.

Conclusions: The natural fluctuation in intersurgical intervals without the use of any adjuvant therapy confounds the use of intersurgical interval as an outcome measure for the success of adjuvant therapy. Accelerations and decelerations were noted but cannot be explained.

Key Words: Juvenile onset recurrent respiratory papillomatosis, cidofovir; intersurgical interval, papilloma.

Level of Evidence: 4


INTRODUCTION

Recurrent respiratory papillomatosis is a disorder characterized by wart-like growths in the aerodigestive tract, usually involving the larynx and having a tendency to recur relentlessly after surgical removal or medical treatment.guest. Juvenile onset recurrent respiratory papillomatosis (JORRP) typically becomes manifest before the age of 5 years and is the most common benign tumor of the larynx in children. Incidence of JORRP is estimated to be 4.3 per 100,000 children in the United States,2,3 Typically, the papillomas have unpredictable growth patterns ranging from spontaneous remission to multiple recurrences into adulthood but rarely malignant transformation. The thrust of managing children with JORRP is maintaining patency of the airway while enabling the child to live a life as near to normal as possible.

The link between JORRP and human papillomavirus (HPV) type 6 and 11 was reported in 1982.4–7 Despite decades of attempts to find a cure, methods of management remain much the same as those that were being employed 40 years ago.8 Several staging systems have emerged to quantify the extent of disease.9–11 Surgical methods of maintaining airway patency in children with JORRP include removal of lesions by grasping with cup forceps or ablation with a laser or the microdebrider. In addition to surgical ablation, adjuvant interventions including interferon, intralesional cidofovir, propranolol, and a host of others have been introduced.12–16 In spite of the initial enthusiasm following the introduction of these modalities, most of them have not gained widespread or sustained use.

Because current therapy is not curative, the treatment goals include maintaining a patent airway and an adequate voice with a durable remission. At this time, management still relies on periodic debulking of papilloma. Due to the recurrent nature of the disease, many children have repeated endoscopic removal of the papillomata throughout their lifetime. Larson and Derkay noted that almost 17% of children had more than 40 lifetime procedures.17

This project documented the course of a cohort of pediatric patients who were treated from September 2000 through August 2011 at a tertiary care hospital. None of the patients had any novel treatment modalities during this period. Charts of each patient were reviewed, and the number and date of each procedure...
per patient were recorded. This information documents the course of these patients along with the erratic pattern of recurrence within individual patients and among the entire cohort.

The variations in intraoperative intervals and surgical frequency seen in this cohort highlight the fact that there are naturally occurring variations in the patterns of recurrence, and these may be difficult to distinguish from the effects of new treatments. Increases in intraoperative intervals and decreases in surgical frequency have been used as indicators of successful innovations in papilloma treatment, and this analysis questioned if these outcome measures were valid.

MATERIALS AND METHODS

A retrospective review was performed of pediatric patients treated for JORRP at a tertiary pediatric hospital over an 11-year period from September 2000 through August 2011. The patients were evaluated for demographic information and date of each surgery.

To reduce intrasurgeon variability, the patients of only two surgeons were included for analysis. Neither surgeon used a staging system; however, both scheduled the next surgical procedure based on the current endoscopic findings (burden of disease) and the most recent previous surgical interval. Both utilized only the CO2 laser for treatment of the lesions, with the surgical goal of removing the vast majority of disease in each setting.

We plotted the number of cumulative surgeries versus days since the first surgical intervention in the observation period and then performed regression using least squares. A $P$ value for each quadratic coefficient was calculated. A $P$ value of $<.05$ for each coefficient was used to determine whether the best fit regression was linear or nonlinear (statistical software: Minitab; Minitab Inc., State College, PA). To determine if the pattern of surgery was linear (constant) or nonlinear, analysis was performed on those patients who had undergone four or more procedures.

A questionnaire was sent to the membership of the American Society of Pediatric Otolaryngology (ASPO), Web site (http://www.aspo.us) in 2007. Each ASPO member was invited by email to complete the questionnaire, which surveyed participants on type of practice environment, interventions used, and the clinical determinants for surgical intervention.

RESULTS

Rate of Surgeries

There were a total of 29 JORRP patients identified during the 11-year study period who met inclusion criterion. Four of the patients underwent only one surgical procedure during the review period and were excluded from analysis (resultant $n = 25$) (Table I). These patients

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$SD =$ standard deviation.
were treated solely with CO₂ laser by one of two surgeons. These surgeons consistently scheduled repeat surgery based on the same criteria, and intraoperatively used the same surgical goal of removing the majority of disease. The mean age at the time of the first surgery within the study period was 79 months and the median was 67 months (range, 11–184 months). The mean total number of surgical procedures during the 11-year period per child was 10.8 (range, 1–37). The mean intersurgical interval was 170 days (range, 7–707 days). The mean shortest interval between surgical interventions in a given patient was 90 days (range, 7–326 days), whereas the mean longest interval in a given patient was 328 days (range, 77–707 days). There was a significant variance in the intraoperative intervals within individual patients (range, 64–59,608 intervals) noted. The
intervals between surgical interventions performed on these patients were calculated and the patterns were analyzed (Fig. 1).

The total number of procedures versus days since the first surgery was plotted (Figs. 2–4) and regression analysis was performed for those patients who underwent four or more procedures (n = 20). Five of the 20 patients (25%) had a linear rate of procedures throughout the observation period. Nine (45%) of the patients had an overall decrease in the rate of surgeries throughout the study period; three had a continual decrease and six had an increase followed by a decrease. Six (30%) of the patients had an overall increase in the surgical rate; five had a decrease followed by an increase, and one had a continual increase.

Survey

Eighty-nine of 250 eligible ASPO members participated in the survey, a rate that is on par with other
similar surveys in the literature. Sixty-three percent practiced as part of an academic department, and 49% had <10 JORRP cases per year. Although 83% always or usually use photodocumentation, 56% stated that they rarely or never used a systematic staging system when treating this disease. Of the 30% of the ASPO members who always or usually used a staging system, five different systems were noted, including five physicians who routinely used a staging system that they devised themselves. When queried on how they approach when to repeat intervention for JORRP patients, more than 16 responses were given, with the most common determinants including standard set interval, previous operative findings, and previous interval.

DISCUSSION

Several investigators have documented a variable growth rate and surgery rate of JORRP among patients. Some of these reports include patients who have had adjuvant therapies. Hawkes et al. noted that of their 67 patients, 59% had a decelerating rate of surgeries with time, 37% had a constant surgery rate, and 4.3% had an accelerating surgery rate. In a study of 57 Danish patients, Silverberg et al. noted that 67% of patients had a decelerating surgery rate, and 33% had a constant or accelerating rate. Campisi et al. looked at a cohort of 146 patients and found that 64% had a decreasing rate of surgery over time, 27% had a constant surgery rate (linear time course), and 9% had an increasing rate over time. One possible shortcoming in some of these studies was that a variety of treatments was used. Our review represents a single treatment modality in the hands of two senior surgeons with a similar approach to JORRP management.

Although our cohort of 29 patients demonstrated a general tendency for a decrease in frequency of surgeries over time, this tendency was not consistent. In fact, 25% of the patients had no change in frequency of surgery over time, and by the end of the study period, 45% had an overall decrease and 30% had an overall increase. These changes in frequency occurred spontaneously without the introduction of an adjuvant therapy. Eleven (55%) had a fluctuation in the pattern of their recurrences during this 11-year period, but the accelerations and decelerations that were noted could not be explained.

The highly variable growth pattern within our group is further confirmed by the large range of shortest and longest intervals between surgeries in our patients. The shortest interval between surgical interventions in a given patient ranged from 21 to 326 days, whereas the longest interval in a given patient ranged from 77 to 707 days. The total number of surgical procedures ranged from between 1 and 37. This high degree of currently unpredictable variability would make it difficult to attribute a change in surgery rates to an innovative treatment.

Although a change in intraoperative interval has been used as an outcome measure of efficacy for new treatments or therapies, the intraoperative interval can be affected by many factors. Hawkes et al. eloquently noted that the rate of surgery in his cohort was significantly affected by several factors that were not initially obvious. These investigators noted that the impact of surgeon variability in determining the timing for the next surgical procedure was significant. They also acknowledged a wide variation of criteria used to determine the timing for the return to the operating room among the surgeons in their study. In fact, in our survey of the ASPO membership, there were 16 different responses to the question on how to approach when to repeat intervention for JORRP patients. Beyond the criteria for the timing for the next procedure, surgical frequency could also be affected by several intraoperative issues. These include specific surgical objectives (radical or more conservative ablation) or surgical technique (laser ablation or microdebrider).

In an attempt to address and minimize the variables raised by other reports, we have included the patients from only two physicians who share a uniform approach to the timing of the next surgical procedure, perform the surgery solely with the CO₂ laser, and share the intraoperative philosophy of aggressive removal of the vast majority of disease at each setting.

Rimell et al. noted that additional factors may impact the clinical course for each patient including viral type, host immunocompetence, and environmental factors. Pou et al. identified a more aggressive course in patients who had simultaneous HPV and herpes simplex virus infections. There are likely additional, as yet undiscovered, variables that also affect the clinical course among patients.

This project delineated the clinical course of 29 patients seen over an 11-year period at a single tertiary pediatric hospital. It chronicled the intervals between interventions in a group of patients cared for by two otolaryngologists. Our observation of changing frequency of surgery in frequent yet unpredictable patterns cannot be fully explained. Individual patients were seen to have exacerbations and remissions of disease with no obvious cause. We saw that fluctuations, either accelerations or decelerations of surgical rates, occur independent of any novel treatment. Although the cause of this variability is not yet understood, its impact on research efforts is profound.

Studies devised to assess new treatment modalities will need long-term follow-up and a large population of patients to be able to distinguish a change in clinical course due to an innovative treatment rather than an erratic clinical course in an individual patient. Perhaps our data can be used as historical controls when trying to examine the impact of novel therapies. It appears that one cannot look at the patterns of recurrence to assuredly attribute a change in surgical frequency to the introduction of an innovative therapy.

CONCLUSION

JORRP has an enormous impact on the life of the children it affects. The time course of the disease, including patterns of regression and exacerbations, is
not fully understood. This project demonstrated that the growth pattern within individual patients who have not received any innovative treatments is highly variable. Thus, attributing an increase in the interval between surgical interventions to the introduction of a novel therapy may be erroneous. This review serves to confirm the unpredictable nature of the disease. Our patients seemed to have worsening and improvement of disease at different times, with no clear cause or change in treatment regimen. The mission of this project was to illustrate the difficulties in designing a project for assessing the efficacy of new treatments in this peculiar disease and to recognize that the interval between surgeries may not be a valid outcome measure.

BIBLIOGRAPHY