

Management of Recurrent Respiratory Papillomatosis: Current Status

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ABSTRACT

Recurrent respiratory papillomatosis is benign disorder which affects children and requires long-term multiple surgical extirpations. The authors present their experience of different techniques in 35 patients and the literature is reviewed.

Keywords: Recurrent respiratory papillomatosis, Endoscopic excision, Microdebrider, Laser, Cold knife excision.

INTRODUCTION

Recurrent respiratory papillomatosis (RRP) is a clinically difficult situation to manage with a curative intent. RRP is the most common benign neoplasm of the larynx in children. The course and severity of the disease is variable and untreated, it may lead to life threatening situations with catastrophic consequences. Management of RRP revolves around repeated surgeries to prevent airway obstruction, improve voice, and managing pulmonary dissemination in severe cases. This often leads to progressive deterioration of voice, due to scarring and finally decreases the quality of life.¹ The devastating consequences affect an estimated 80 to 1500 new cases of childhood-onset RRP in the United States each year while the incidence of new cases is given to be around 4.3 per 100,000 children.² The complete cure for RRP in one go is generally difficult and patients need repeat surgeries. The tools are generally being used to include carbon dioxide laser, microdebrider, coblator and cold instrumentation. Recent developments in management of RRP focus on preventing recurrence, decreasing surgical scarring and preventing pulmonary complications. Newer adjuvant antiviral therapy cidofovir and interferons are being tried in this regard. The scope of this article is to discuss and critically analyze the indications and complications of surgical and nonsurgical treatments, and review literature of adjuvant therapies.

BACKGROUND

Epidemiology, Transmission and Virology of RRP

Recurrent respiratory papillomatosis (RRP), which is caused by human papilloma virus types 6 and 11, is the most common benign neoplasm of the larynx among children and the second most frequent cause of childhood hoarseness. Three clinical patterns of RRP are classically described: Juvenile-onset

(JORRP), adult-onset (AORRP) and Juvenile-onset with persistence into adulthood. Juvenile-onset RRP (JORRP) is diagnosed most commonly between 2 and 4 years of age; 75% of diagnoses are made before the fifth birthday.¹⁴ JORRP is generally more aggressive than adult-onset RRP (AORRP) and there is a tendency for the disease to be more aggressive when the onset is earlier. This more aggressive nature of disease is manifested by early recurrence, subglottic and tracheal involvement, unpredictable response to adjuvant antiviral therapy and extralaryngeal involvement. The most common types identified in the airway are HPV 6 and HPV 11, the same types responsible for more than 90% of genital condylomata. Specific viral subtypes may be correlated with disease severity and clinical course. Children infected with HPV 11 appear to be at higher risk of obstructive airway disease and have a greater likelihood for need of tracheotomy to maintain a safe airway.³ In another significant study it was concluded that clinical course was more closely associated with age of the patient (at diagnosis and at the time of the current surgery) than with HPV type, however, HPV 11 is more closely associated with a younger age at diagnosis than it is associated with an aggressive clinical course.⁴ It is clear that factors other than HPV type and age of the patient determine disease course. Some possible role of status of the child's immune system, length of time in the birth canal, volume of virus in the birth canal, GERD and mode of delivery have been postulated by various authors but causative association has not been established. The risk of a child contracting the disease from a mother who has an active genital condylomatous lesion during vaginal delivery is one in between 231 and 400 cases. However, the characteristics that distinguish this child from the other 230 to 399 remain elusive.⁵ It has also been found that in HPV infected mothers cesarean delivery is protective and patients with childhood-onset RRP are more likely to be first-born and vaginally delivered than are control patients of similar age.⁵

Surgical Management of Recurrent Respiratory Papillomatosis

Rationale of surgical ablation should be to reduce tumor burden, decrease disease spread, create a safe and patent airway, improve voice quality, preserve anatomy, and increase time between surgical intervals. HPV is known to exist in normal appearing tissues adjacent to papillomas, hence complete eradication is not always possible and such repeat surgeries may result in progressive scarring and airway stenosis. It is still a matter of debate that which is the best tool to use but most authors and literature supports the CO₂ lasers as one of the standards of care. Our experience of about 35 cases over 17 years also supports the same after having tried almost all the modalities. The CO₂ laser vaporizes the lesions with precision, causing minimal bleeding. When used with a no-touch technique, it minimizes damage to the vocal cords and limits scarring. However, multiple sessions are required to keep the disease under control. Other lasers like KTP pulsed dye laser have also been used by other authors. Zeitels reported on office-based use of the 532 nm pulsed KTP laser for treatment of recurrent glottal papillomatosis and dysplasias, noting at least 75% regression of disease in two-third of patients who could tolerate the procedure. Rees and Koufman also demonstrated tolerance for in-office pulsed dye laser treatments involving 328 procedures in 131 adult patients, with patients overwhelmingly preferring the in-office pulsed dye laser over surgeries under general anesthesia.⁷ There is an increasing popularity to use the microdebrider for surgical removal of RRP (Table 1). The technique is relatively fast, safe, well-tolerated and avoids potential problems associated with the carbon dioxide laser. It has also been shown to cause equivalent immediate postoperative pain, greater improvement in voice

quality and the overall procedure cost is lower in some centers.⁸ A web-based survey of members of the American Society of Pediatric Otolaryngologists (ASPO) found the majority of respondents now favoring the use of “Shaver” technology.⁹ On the contrary, laser remains the most popular technique for surveyed British Association of Paediatric Otolaryngology (BAPO) members.¹⁰ In authors experience, advantages of the microdebrider are faster removal of a significant amount of laryngeal pathology and less expensive than the laser. The disadvantages of microdebrider is bulky powered instrument shaft that sometimes limit visualization, and occasionally microdebrider may be too harsh and injure delicate subepithelial tissues of the vocal fold or other endolaryngeal structures. Because no surgical intervention eradicates papillomas curatively, in situations where papilloma excision is difficult or has potential poor consequences, it is prudent to accept some residual papilloma rather than risk damage to normal tissue and produce excessive scarring. Even with the removal of all clinically evident papillomas, latent virus remains in adjacent tissue. Therefore, the aim of therapy in extensive disease should be to reduce the tumor burden, decrease the spread of disease, create a safe and patent airway, optimize voice quality, and increase the time interval between surgical procedures. Staged papilloma removal for disease in the anterior commissure is appropriate to prevent the apposition of two raw mucosal surfaces. Disease should be sequentially followed up and a staging system, such as Derkay Severity Score, Vocal Handicap Index and patient-reported Quality Metric Short Form 12 should be used to monitor the disease load, voice changes and finally the quality of life. This also goes a long way in effectively documenting the treatment strategies and quantify the benefits of any proposed therapeutic option.

Table 1: Comparison of different surgical techniques of Juvenile papilloma removal

<i>Laser excision</i>	<i>Cold knife technique</i>	<i>Microdebrider</i>
Use a “defocused spot size” 0.5–0.75 mm, with a low power (2–4 W) on intermittent superpulse setting	Inject epinephrine subepithelially throughout the intended RRP excision site	Submucosal injection of epinephrine. Microdebrider starting setting should be 800–1200 and then can be adjusted accordingly
Repeated doses of laser energy are not delivered to the same exact location consecutively	Use sharp and avoid blunt instruments. Blunt instruments avulse more mucosa	Smallest and most conservative microdebrider blade should be used
Stay superficial and avoid penetration to deeper lamina or ligaments	Always raise a microflap on vocal cords and use micro cup forceps for avulsing the papilloma elsewhere	Hold the microdebrider “blade or port” 1-2 mm over the RRP disease and allow the suction from the instrument to draw the RRP tissue and prevent deeper injury
Use a cord retractor when there is a subglottic extension	Direction of pulling should be cephalad or caudal, anterior or posterior pulling causes more stripping of mucosa	Support the vocal cord to prevent sudden debridement of deeper parts of vocal cord
Safety of personal against fumes and laser misfires, tube fire and eye protection are important	Do not create raw area bilaterally in anterior commissure. Stage the procedure and do one side at a time	Use suction trap to collect the biopsy material for histopathological review
Particularly helpful in anterior commissure and subglottis	Most preferred for glottis and vocal cord lesions	Most preferred for supraglottis

Role of Tracheostomy

There is a general consensus that tracheostomy should be avoided at all costs in management of RRP. Only where the facilities for management of RRP do not exist or patient is in severe stridor, tracheostomy can be pursued as a life saving measure. In RRP, tracheostomy may cause seeding and pulmonary dissemination, which is much more a difficult problem to tackle. Sometimes surgeons perform tracheostomy to access subglottic region for RRP removal due to anesthetic considerations, such practices should be condemned and access should be obtained by either spontaneous, jet ventilation or apnea methods. Authors preferred technique is to adequately ventilate the patient, then remove the ET tube, keeping the direct laryngoscope in place and removing the papillomas from posterior glottis and subglottis while the patient is in apnea for few minutes. Patient is reintubated through the direct laryngoscopy if the oxygen saturation falls below 90. This method can be repeated till all the papillomas are satisfactorily removed.

Combining Intralesional Cidofovir with Conventional Surgery

Cidofovir is a cytosine nucleoside analog that is incorporated into the growing DNA chain of both viruses and mammals. It has been shown to inhibit HPV growth both *in vitro* and *in vivo* studies. Pransky et al¹¹ published the first case series of intralesional cidofovir use in pediatric patients with severe RRP, observing a dramatic response though not complete eradication in four out of five patients. The use of cidofovir for RRP ation is considered an 'off-label' use of the medication. Concerns of its potential nephrotoxicity, inducing dysplasia and malignant transformation, high cost and unpredictable response prohibit its liberal use. Although a Cochrane review of antivirals (including cidofovir) as adjuvant therapy for the treatment of RRP was unable to identify any randomized controlled trials and concluded that there was insufficient evidence about the efficacy of their use.¹² This has not stopped most of the pediatric otolaryngologists from using cidofovir in treatment of RRP as subjectively most of the physicians experienced a clinical benefit.⁹ At this point of time, there is no evidence to guide which patients will be more likely to respond to adjuvant treatment with cidofovir, but a consensus recommendation of its use is given by RRP Task Force meeting in Las Vegas, Nevada in May 2005.¹³ Table 2 lists its current recommendation.

It is done by ablation of the papillomas, a Storz needle is used to inject cidofovir at the base of the removed lesion. An alternative disposable needle is a 22 gauge 7.00 in spinal needle. Concern about airway compromise, particularly when injecting at the level of the vocal cords, can be bypassed by temporary intubation with an endotracheal tube for a few minutes. This technique is done to ensure adequate exposure to cidofovir and spread of the depot.¹⁴

Other Adjuvant Antiviral Therapies

Interferon Alpha

The exact mechanism of interferon action is unknown but appears to involve modulation of host immune response by increasing production of a protein kinase and endonuclease, which inhibit viral protein synthesis. They have significant side effects like flu-like symptoms, chills, headache, myalgias, and some times may cause adverse reactions like elevation of liver transaminase levels, leukopenia, spastic diplegia, and febrile seizure. The typical dose of interferon for children with RRP is 5 million units/m² body surface area administered by subcutaneous injection on a daily basis for 28 days, then 3 days per week for atleast a 6 month trial. There is conflicting evidence on its use, which has declined over years.

Other Adjuvant Therapies

Ribavirin, acyclovir, ranitidine, Indole-3-carbinol (I-3-C), mumps vaccine, retinoids, photodynamic therapy (PDT-DHE), photodynamic therapy (PDT-Foscan), Cox-2 inhibitors (celebrex) and gene therapy have been evaluated for treatment of RRP. Not only they have encouraging results but also have opened doors for future research in understanding and treating the RRP.

Prevention of RRP

The most interesting and promising recent development in the prevention of RRP is the quadrivalent HPV vaccine (Gardasil™; Merck and Co. Inc., Whitehouse Station, NJ, USA). This vaccine is currently licensed by the FDA for the prevention of cervical cancer, adenocarcinoma *in situ*, and intraepithelial neoplasia grades 1-3; vulvar and vaginal intraepithelial neoplasia grades 2-3; and genital warts associated with HPV 6, 11, 16, and 18. Currently this appears to be the most promising methodology of preventing RRP. Although studies on its long-term prevention are lacking but there appears to be a definitive protection from juvenile onset respiratory papillomatosis.¹⁵

Table 2: RRP task force meeting in Las Vegas, Nevada in May 2005 recommendations

1. Cidofovir should be routinely presented as a treatment option in moderately to severely afflicted RRP patients; that is, those patients who require frequent surgery, have worsening airway compromise or severely impaired communication or who may otherwise be considered for tracheostomy.
2. Use of cidofovir should be discouraged in patients with more mild disease until long-term results from its use have been established.
3. Informed consent should be obtained prior to use of cidofovir, documenting risks of nephrotoxicity, potential carcinogenicity and other unknown long-term implications.
4. Adverse responses to the use of cidofovir, especially evidence of dysplasia or malignant transformation to squamous cell carcinoma should be reported.

Cesarean section in high-risk carriers of HPV or patients having frank condylomata acuminata lesions in anogenital tract is logically a good option to prevent its occurrence. However, there is no universal recommendation to do so, seeing the morbidity, cost and lack of clear cut evidence of such a practice.

RRP Task Force Meeting in Las Vegas, Nevada in May 2005 Recommendations (Table 2)

Recurrent respiratory papillomatosis cases need to be handled with care in specialized centers with laser and microdebrider facilities. Counseling needs to be done about need for repeat surgeries. Method of doing first surgery is very important as a bad vocal cord scarring caused in the first surgery may stay for life.

The role of adjunct therapies including cidofovir needs to be seen in the correct perspective.

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