Comparative Efficacy of Three Surgical Modalities for Recurrent Respiratory Papillomatosis

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Abstract

Abstract Background:Recurrent respiratory papillomatosis (RRP) is recurring benign papillomatous lesions which still relies on repeated surgical treatment. However, there is no guidelines of surgical technique nowadays. Objectives: This retrospective cohort study aims to obtain a better understanding of RRP, and select the best surgical modality for RRP among microdebrider, CO2 laser and KTP laser. Study design: Retrospective cohort study. Methods: Medical records of 112 RRP patients treated at EYE&ENT Hospital of Fudan University from 2018 to 2021 were reviewed, with at least 6-month follow-up. Three treatment subgroups(microdebrider, CO2 laser and KTP laser) were analyzed within AO-RRP and JO-RRP populations respectively. Results: 112 patients (39 JO-RRP and 72 AO-RRP) and a total of 353 surgical procedures were included. Jo-RRP group had higher Derkay anatomical score($p<0.05$), lower percentage of dysplasia and an earlier trend in recurrence($p<0.05$) than Ao-RRP group. There were no significant differences among three surgical modalities on median treatment intervals(MTI) or survival curves($p>0.05$), with the Jo-RRP MTI of the microdebrider(92.5[47.3˜200]), CO2 laser(140[70˜255]), KTP laser(90[62.3˜221.3]), and Ao-RRP microdebrider(267.50[152.5,449.5]), CO2 laser(247.5[145.5,474.7]), KTP laser(107.5[68.3,330.5]). Conclusion and Significance: The Jo-RRP patients have more concomitant invasiveness, but less dysplasia than AO-RRP patients. Three surgical modalities appear to be equally effective in management of Jo-RRP or AO-RRP. Key Words: Papillomatosis, surgery, treatment, recurrence, efficacy.

Introduction

Recurrent respiratory papillomatosis (RRP) is characterized by recurring benign papillomatous lesions in the respiratory tract, particularly the larynx, causing dysphonia, airway obstruction, and dysphagia occasionally. Existing evidence about disease risk factors is limited but includes both maternal HPV infection and patient smoking and sexual behaviors[1]. The age is an independent factor affecting disease aggressiveness of RRP, due to which RRP is usually categorized into juvenile onset and adult onset depending on presentation before or after the age of 12 years, respectively[2]. Generally, Jo-onset RRP is the most common benign tumors in the larynx of children, shows a high recurrence rate and diffuse involvement in the respiratory tract, which are prone to recurrence, and require multiple surgeries, causing heavy psychological pressure and financial burden on families. On the contrary, Adult-onset RRP is more localized and appears more frequently as a solitary lesion[3]. Malignant transformation of adult-onset RRP to squamous cell carcinoma has been reported to occur in 3-7% of cases[4].

RRP is a rare disease. Treatment requires experience and may be very difficult. Surgical debulking with or without adjuvant treatment remains the mainstay of treatment, which mainly aims to reduce the number and frequency of recurrences since no definitive curative therapy is known so far.[5] However, there is no standard guidelines for the choice of surgical technique nowadays. Commonly used surgical modalities include traditional cold instruments, microdebriders, 10,600nm carbon dioxide(CO2) laser, 532-nm pulsed potassium-titanyl-phosphate(KTP) laser[6]. Factors that can influence decision-making are the effectiveness

and safety of surgical techniques, patient factors, surgeon preferences, and the availability of laser equipment in medical institutions.

In the few studies that compare the efficacy of different surgical modalities, the researchers did not found the optimal surgical modality to treat RRP. Papaspyrou presented the experience in treating laryngeal papillomatosis in three institutions over a period of 10 years wihiout distinction between children and adults. In the experience, CO2 laser therapy was the most common modality applied alone or combined with other treatment modalities and no major complication was observed. They also presented that there was no significant difference in repeat operation rate between the two larger patient groups, the one treated with CO2 alone and the other treated with cold instruments alone. El-Bitar[7] conducted a retrospective study of seventy-three operations, the microdebrider was proved to be less time-consuming than the carbon dioxide laser when used in patients with juvenile-onset recurrent respiratory papillomatosis, whit soft tissue complications were nonexistent. In 2015, Murono published a questionnaire to the department of otolaryngology at all 80 Chuo University hospitals in Japan with regard to the use of surgical instruments. A trend was observed towards lasers (50 hospitals) rather than micro devices (16 hospitals) or cold instruments (20 hospitals). Among the 50 hospitals that regularly undergo laser surgery, the most commonly used carbon dioxide (CO2) laser is followed by titanium-based potassium phosphate laser[8]. In 2016, a Germany multicenter cohort study reported that CO2 laser remained the most common surgical modality used alone or in combination with other treatment modalities[5]. Papaioannou[9] reported that the treatment of choice is surgical excision with the CO2 laser combined with the quadrivalent or polyvalent vaccine. According to the consensus of the International Pediatric Otolaryngology Group(IPOG) regarding operative considerations, the surgical modality with the greatest support is laryngeal microdebrider (65% "almost always" and 3% "almost never"), while the consensus on the use of CO2 laser is 0% "almost always" and 68% "almost never", and the use of KTP lasers is 10% "almost always" and 71% "almost never"[10].

Herein, we conducted a retrospective cohort study to obtain a better understanding of RRP, and select the best surgical modality for RRP among microdebrider, CO2 laser and KTP laser.

Materials and methods

For both pediatric and adult populations, medical records were reviewed retrospectively of patients who had been treated for RRP with operating room procedures,in the period from January 2018 to April 2021. The inclusion criteria included patients with a diagnosis of RRP and at least 6 months of follow-up. Each patient signed an informed consent form before surgery. Patients were excluded if they did not fulfill these requirements, or if they had received tracheostomy.

The following patient demographic data were collected and analyzed: age, gender, smoking status, symptoms at the first procedure, length of follow-up time, localization of the papillomas, histological findings(evidence of dysplasia), number of surgical procedures, the type and date of the surgical treatment(Microdebrider, or CO2 laser or KTP laser), recurrence rate. The treatment intervals were calculated based upon these dates. Anatomical Derkay severity scores were captured for all patients preoperatively. The survival curves were plotted based on the recurrence events and follow-up time, through which we could compare the recurrence trends of patients used three different surgical modalities. According to Derkay et al, the aerodigestive tract is divided into 25 subsites with each given a score if disease is present (0 is no lesion, 1 is surface lesion, 2 is raised lesion, and 3 is bulk lesion).[11]

Treatment groups were stratified as microdebrider, CO2 laser and KTP laser. We analyzed AO-RRP and JO-RRP populations respectively, and we also combined the pediatric and adult data for comparison among three treatment modality groups.

The calculation of the interval of treatment is started at 00:00 on the first day after surgery, and ended at the time when the patient undergoes surgery again because of a recurrence of the lesion. How to determine whether a patient is the recurrent case or not? The surgeons recorded photographs or videos of hard laryngoscopy or electronic fiber laryngoscopy to compare preoperative and postoperative lesions. Criteria for judging recurrence: papillary lesion reappear in the same or adjacent parts of the previous operation, which

is pathologically confirmed as papillomas after surgery. When the interval between surgeries is recorded, this case will be treated as a new case for re-entry follow-up after surgery. Those who had not relapsed at the end of the follow-up date were also counted separately as truncated data.

Statistics were performed using SPSS (IBM SPSS Statistics 26). Continuous variables with a normal distribution were compared using a 2-tailed t-test and/or analysis of variance. Continuous variables without a normal distribution were compared with Mann–Whitney test or Kruskal–Wallis test. Categorical variables were compared with either chi-squared test or Fisher's exact. The survival curve were plotted in GraphPad Prism based on the recurrence events and follow-up time. A value of $P<0.05$ was considered statistically significant.

Results

There were 112 patients (39 JO-RRP patients and 72 AO-RRP patients) met inclusion criteria, and a total of 353 surgical procedures were included. The average age was 7.4(JO-RRP patients) and 46(Ao-RRP patients), respectively. The female–male ratio is 16:23 in Jo-RRP patients, and 19:54 in Ao-RRP patients. There were 181 procedures performed in Jo-RRP group, with either the microdebrider(n=152), CO2 laser(n=18), or KTP laser(n=11), and 172 procedures were performed in Ao-RRP, with either the microdebrider (n=46), CO2 laser(n=102), or KTP laser(n=24). It can be seen that surgeons prefer to use microdebrider in Jo-RRP treatment and CO2 laser in adult patients.

The treatment intervals(days) in the JO-RRP population(median[P_{25}-P_{75}], 99[50,205]) was shorter compared to AO-RRP population(median[P_{25}-P_{75}], 230.0[132.0,455.0])($p<0.05$)(Fig.1A). Besides, the JO-RRP patients had higher Derkay anatomical score(mean [SD], 13.0[6.2]) than AO-RRP patients(mean [SD], 6.95[4.90]) ($p<0.05$)(Fig.1B), and it is conceivable that there were more Jo-RRP patients with dyspnea symptom at the first visit(17/39, 43.6%) compared to AO-RRP patients(8/72, 11.1%). JO-RRP patients had significantly worse disease burden at initial procedure compared to AO-RRP patients. These findings corroborate previous studies suggesting a more aggressive disease course in children, which necessitates more regimented intervals until the child's airway has grown. The most susceptible anatomical site of lesions is the glottis in both of these two groups, followed by the supraglottic and subglottic. However, postoperative pathological result of each procedure showed that the proportion of histopathology containing dysplasia in JO-RRP group(7/181, 3.9%) was smaller than that in AO-RRP group(105/172, 61.0%) (Table I.).

We also performed subgroup analyses according to the surgical modalities(Table II). In addition to age of onset, disease regression measured by the Derkay scoring system was comparable among the treatment groups. For the pediatric patients, the treatment intervals(Days) in the microdebrider group (median[P_{25}-P_{75}], 92.5[47.3˜200]), CO2 group (median[P_{25}-P_{75}], 140[70˜255]), KTP group (median[P_{25}-P_{75}], 90[62.3˜221.3]). For the adult patients, the treatment intervals(Days) in the microdebrider group (median[P_{25}-P_{75}], 267.50[152.5,449.5]), CO2 group (median[P_{25}-P_{75}], 247.5[145.5,474.7]), KTP group (median[P_{25}-P_{75}], 107.5[68.3,330.5]). CO2 laser surgery represented the longest treatment interval both in Jo-RRP and Ao-RRP patients, but no significant differences were found among three subgroups($p>0.05$)(Fig.2).

The recurrence trends of patients used three different surgical modalities were no significant difference($p>0.05$), but Jo-RRP group has a clearly earlier trend in recurrence than Ao-RRP group($p<0.05$)(Fig.3). That is to say, three surgical modalities appeare to be equally effective in management of Jo-RRP or AO-RRP, which is encouraging for institutions that do not have laser modalities readily available. Other factors of decision-making on surgical modalities need to be focused in future studies.

Discussion

Although various medicine and even HPV vaccines have been tried to be applied to adjuvant therapy for RRP, mainstay of treatment has largely been surgical, which has evolved from microdebrider and other cold instruments to include certain types of laser instruments over the past few decades.

Microdebrider is a dynamic rotational dissection device with suction assist, which has become the preferred treatment for handling JO-RRP in recent years. Microdebrider can easily push the mass away from the

base and suck up, remove the mass accurately, cause it can easily reach the throat and trachea under the laryngoscope. Patel[12] noted in a retrospective study that the operation time was significantly shortened since the CO2 laser switched to microdebrider, with the advantages of saving surgical costs, avoiding the risk of airway burns that may occur during laser surgery and the possibility of vaporization of virus particles. Microdebrider may replace CO2 lasers, the preferred method of airway clearance in these patients, and become the surgical modality of choice for RRP in some institutions. In addition, microdebriders may be a more cost-effective tool for removing bulky diseases than lasers alone, that's why it has become the main surgical modality to treat Jo-RRP. Go a step further, Huang[13] notes that the surgeons prefer to use microdebrider for bulky tumors and use KTP laser peeling technique for near-normal structure. This mixing mode can help surgeons shorten surgery time and make it easier to control bleeding, and it may avoid injury to the stratified structure of the vocal cords. Actually, microdebrider has some drawbacks. Hemostasis is an issue with cold techniques, but the surgical field of microdebrider could remains clear most of the time due to the suction of the connection[14].

CO2 laser was applied to the treatment of RRP as early as the early 1970s, which replaced the traditional cold instrument, and gradually become a recognized treatment method for laryngeal diseases. The wavelength of the CO2 laser (10 600 nm) is absorbed by water, allowing the lesion to evaporate with a high percentage of intracellular water[15]. However, CO2 laser operation is time-consuming, expensive, and potentially dangerous of airway burning. One of the most serious risk factors is airway combustion, normal tissue burns and medical staff damaged If the intraoperative procedure is improper.

Unlike the CO2 laser, the angiolytic laser uses the peak in the absorption spectrum of the oxygen hemoglobin rather than water, which helps to selectively ablate the vascularized lesion without excessive thermal damage. As a kind of the angiolytic laser, KTP laser seems has great advantages in RRP resection, due to the blood-rich nature of RRP[16]. In other words, the KTP laser can better preserve the surrounding tissue and hemostasis control. Huang[13] revealed that serial KTP laser procedures can effectively control RRP while preserving phonatory function and maintaining adequate voice quality through a longitudinal follow-up study. Burns[17] also demonstrated that diseases in the anterior commissure of glottis can be treated with minimal risk of scarring or adhesions, whether using KTP lasers alone or as a complement to other surgical modalities, with minimal preservation of the potential superficial intrinsic layer.

There have been few studies that directly compare the effects of different surgical modalities on RRP recurrence rates. The results of our study are consistent with these studies. Hock[16] analyzed the Derkay score improved between first and last procedure in group of three surgical modalities(KTP, CO2, and microdebrider), and found no significant difference among the three treatment groups. Preuss[18] suggested no correlation between the recurrence rate and surgical modalities. However, these studies lacked a unified indicator of effectiveness, and did not compare the three surgical modalities in Jo-RRP and Ao-RRP separately.

Patients with RRP often need to undergo repeated surgeries, which is a heavy financial burden. Medical institutions have started transferring the performance of some procedures from the operating room to the office, which would theoretically result in substantial savings. The flexible CO2 wave-guide laser has been developed and commercially available for several years, which can transfer surgery in the operating room to the office under local anesthesia[19]. A study of Ao-RRP case series concluded that office procedures are significantly more cost-effective than operating room procedures, but their use may be limited by patient tolerance and the increased frequency of the procedure[20].

In our study, treatment intervals and recurrence trends did not differ across three subgroups in both Jo-RRP and Ao-RRP patients, that is to say, three surgical modalities appeared to be equally effective in terms of controlling the recurrence of RRP. Therefore, the same recurrence rate control effect can be achieved using microdebrider for medical institutions without laser equipment. More attention should be paid to other factors such as the economic cost, availability and complications of surgery in decision-making of the surgical modality, which should be further investigated. In addition, Derkay score was used to grade the lesion anatomy to ensure the comparability between different groups, which was rarely used in previous

reports. Studies in the future would require detailed reporting of disease burden, so that patients could be risk stratified by group. Pre-op and post-op Derkay scores or other consisten quantitative metrics are necessary, to accurately stage the bulk and severity of disease to allow for more standardized reporting of disease.

There are several limitations to this study. First, this is a retrospective cohort study, we couldn't collect detailed case information in a completely random manner. Secondly, we did not investigate the outcome of complications because most patients may have undergone multiple surgeries. Future studies should conduct more randomized controlled tests and include postoperative complications in statistics to determine the best surgical modalities.

Conclusions

The Jo-RRP patients have more concomitant invasiveness, but less dysplasia than AO-RRP patients. Three surgical modalities appeare to be equally effective in management of Jo-RRP or AO-RRP.

Disclosure statement

No potential conflict of interest was reported by the author(s).

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