International Journal of Otorhinolaryngology and Head and Neck Surgery
Aslam MA et al. Int J Otorhinolaryngol Head Neck Surg. 2022 Sep;8(9):783-786
http://www.ijorl.com
pISSN 2454-5929 | eISSN 2454-5937

DOI: https://dx.doi.org/10.18203/issn.2454-5929.ijohns20222088

Review Article

Impact of HPV vaccination on number of surgical procedures required in recurrent respiratory papillomatosis and its potential use as an adjuvant

Mohammed Afeef Aslam[1]*, Yusuf Maududi[2]

[1]Department of ENT, SPR Royal Hallamshire Hospital, UK
[2]Imperial College School of Medicine, London, UK

Received: 27 July 2022
Accepted: 12 August 2022

***Correspondence:**
Mohammed Afeef Aslam,
E-mail: afeef93@hotmail.co.uk

ABSTRACT

People who suffer from recurrent respiratory papillomatosis have to undergo multiple surgical procedures for debulking resulting in complications such as reduced quality of voice. Data source was Pubmed articles. The objective of this study was to review the current literature on HPV vaccination and its impact on RRP and whether it may help reduce the number of surgical procedures required. Articles from year 2000 onwards were searched for on PubMed. Overall articles show significant increase in surgical intervals post HPV vaccination. HPV vaccination appears to be a safe adjuvant therapy in the management of recurrent respiratory papillomatosis.

Keywords: Recurrent respiratory papilloma, Human papilloma vaccine, Surgery

INTRODUCTION

Overview of recurrent respiratory papilloma

Recurrent respiratory papillomatosis (RRP) is a condition characterized by benign papillomatous (wart-like) growths in the airway which can lead to hoarse voice and airway obstruction. 90% of RRP is from two subtypes of human papilloma virus (HPV) those being types 6 and 11. HPV 11 being the more virulent strain associated with earlier presentation, longer duration of disease, more surgical procedures and more frequent malignant transformation.[1]

HPV infections are amongst the most prevalent sexually transmitted diseases with up to 75% of people in the United States acquiring genital HPV in their life time.[2] Most HPV infections in children are due to vertical transmission when passing through the birth canal of infected mothers, leading to juvenile onset RRP. Approximately 0.7% of infants exposed to maternal anogenital warts develop RRP.[3] In 12% of cases transmission is via the placenta and therefore caesarean section may not be completely preventative.[3] RRP incidence has been estimated as 4.3 per 100,000 in children and 1.8 per 100,000 in adults.[4] RRP is the most common benign laryngeal neoplasm in children and remains the second most common cause of childhood hoarseness.[5] Other manifestations of the disease include wheeze, stridor, dyspnoea and chronic cough.[5]

The main form of treatment of RRP is through surgical debulking. Aim of surgery is to remove as much papilloma as possible in order to improve airway patency whilst preservation of normal vocal cord and surrounding laryngeal structures. Surgery can be in the form microdebriders, CO_2 laser, or cold steel dissection. HPV may be present in mucosa that appears outwardly to be macroscopically unaffected and therefore distinguishing normal cells from infected cells is currently not possible and this residual disease contributes to rapid recurrence of papillomatous lesion post micro-debridement. Complications mainly due to multiple procedures being

required include hoarse voice, webbing, and glottic stenosis. In extreme circumstance tracheostomy may be needed for more extensive disease with risk of airway obstruction. Unfortunately, half of patients with tracheostomy develop tracheal papillomas due to seeding of the disease.[3] Studies suggests adults with RRP have higher voice handicap scores, worse acoustic and worse perceptual voice outcomes the more surgeries they have.[6,7]

By reducing the frequency of surgical procedures patients may experience less unwanted side effects from operations and subsequently better voice outcomes. The aim of the study was to explore the current literature in the effectiveness of HPV vaccination in reducing the frequency of required operation in patients with RRP.

Overview of HPV vaccine

The first HPV vaccine targeted two oncogenic HPV subtypes 16 and 18 (Cervarix, GlaxoSmithKline) and was introduced in 2004 to primarily prevent cervical cancer. In 2006 Gardasil by Merck Sharp Dohme, was introduced targeting HPV subtype 6, 11, 16 and 18. Thus preventing genital warts, cervix, vaginal, anal, cervical cancers as well as RRP. A 9-valent HPV vaccine Gardasil et al has recently been released targeting an additional five oncogenic subtypes (31, 33, 45, 52 and 58).[9]

The HPV vaccine contains virus like particles (VLPs) in a similar concept to the hepatitis B vaccine. VLP vaccines comprise of a high density of HPV surface proteins which subsequently elicit a strong T cell and B cell immune response.[5]

The national NHS HPV vaccination programme uses the 4-valent Gardasil et al.[8] The vaccine works best if girls and boys get it before they come into contact with HPV. In England, girls and boys aged 12 to 13 years are offered the 1st HPV vaccination in year 8 of school.[8] The second dose is offered 6 to 24 months after the first dose. People who have the 1st dose of HPV vaccine at 15 years of age or above will need to have 3 doses of the vaccine in order to have the same level of protection. Current trends indicate that vaccination of pre-adolescent females will further decrease the prevalence of genital warts and in turn hopefully reduce the vertical transmission in newborns.[9] For countries using Gardasil in girls aged 15-19 ano-genital warts decreased significantly by 31% [RR 0.69 (CI 0.6-0.79)].[9]

HPV vaccination impact on number of surgical procedures required to tackle rrp and use as a potential adjuvant

Emerging data suggests strong role for vaccination as adjuvant treatment for people with RRP in order to help reduce the frequency of debulking surgical procedures required.

A 2014 study by Hočevar-Boltežar et al consisting consisting of 11 adults with RRP found an increase in the mean time between surgical intervention from 271 to 537 days (p=0.03) after Gardasil et al.[10] Similarly Goon et al in 2017, reported a cohort of 12 adults RRP patients aged 27-78 years who experienced a more than seven fold decrease in their incidence rates of papillomatosis requiring surgical intervention after receiving Gardasil.[11]

A 2016 systematic review by Dion et al found 9 out of 12 studies to show a decrease in disease recurrence and increase in the time period between patients requiring further surgical intervention.[12]

A 2019 meta-analysis by Rosenberg et al studied the effects of the HPV vaccine on RRP in 63 patients.[13] Analysis showed a significant reduction in the number of surgeries per year. Prior to vaccination on average each patient underwent four surgeries in a year. After vaccination on average patients would undergo one surgery every one and half years.[13]

More recently a 2022 non placebo controlled intervention study by Smahelova et al compared recurrencies in pre-vaccination and postvaccination period of 42 patients.[14] In this non randomised trial, the frequency of recurrences requiring surgical treatment was significantly lower after vaccination (from 0.85 to 0.36 recurrences yearly). No difference in postvaccination recurrences was found between patients with newly diagnosed and recurrent RRP. Therefore, these findings suggest that the earlier the patient receives HPV vaccine the sooner the burden of disease may be reduced.

DISCUSSION

A 5-year report in Australia following implementation of HPV vaccination program has been published in 2018.[13] Quadrivalent vaccine had been introduced in 2007, to Australia, with more than 80% uptake in girls and 75% uptake in boys. The report showed a decline in RRP annual incidence from 0.16 to 0.02 per 100,000 children in 2016 (p=0.034). This study offers promise that HPV vaccine may help to eradicate RRP.[15] Similarly, Marowitz et al noted greater than expected reduction in HPV related disease in the United States 10 years from the introduction of the quadrivalent vaccine.[16] 2004 versus 2013 data from Boston, Massachusetts showed a decrease of genital warts from 3.5% to 1.5% among females and 3.6% to 2.9% among males respectively.[17]

Two additional strategies to help reduce juvenile RRP have been proposed including vaccination of neonates born to women with clinically diagnosed genital warts.[18] Secondly vaccination of pregnant women screened and infected with HPV 6/11 may boost maternal titres of antibodies and increase transference of those antibodies to the new born.[19] The vaccine does not contain live virus so with respect to immunization of pregnant women there is no risk of infecting the foetus. During a phase 3 trials of

the quadrivalent vaccine 20,551 women aged 15-45 years received quadrivalent HPV vaccine or placebo at day 1 and months 2 and 6.[20] Urine pregnancy tests were performed immediately before each injection; participants testing positive were not vaccinated. Women who became pregnant after enrolment were discontinued from further vaccination until resolution of pregnancy. All pregnancies were followed for outcomes.[20] 1796 women became pregnant. However no negative pregnancy related outcomes were attributed to the vaccine.[20] Immunization of pregnant women with tetanus toxoid and inactivated influenza has already been shown to dramatically reduce the risks of both maternal and new borns from these diseases and thus this principle could be applied to the use of HPV vaccination.[21]

About 20% of RRP patients require adjuvant medical treatment in addition to surgery. Current criteria for adjuvant therapy includes four or more surgical procedures annually, rapid recurrence of papilloma with airway compromise and multisite spread of the disease.[3] Treatments can be broadly divided into those which inhibit HPV replication and proliferation such as cidofovir and bevacizumab and immunomodulators such as programmed death ligand 1 pathway inhibitors.

CONCLUSION

In this literature review HPV vaccination post diagnosis of RRP has shown some promise in helping to limit the degree of recurrence of RRP and increasing the interval time between operations. We feel therefore that there is enough evidence to support the use of HPV vaccination, safely as an adjuvant therapy for RRP.

Funding: No funding sources
Conflict of interest: None declared
Ethical approval: Not required

REFERENCES

1. Rabah R, Lancaster WD, Thomas R, Gregoire L. Human papillomavirus-11-associated recurrent respiratory papillomatosis is more aggressive than human papillomavirus-6-associated disease. Pediatr Dev Pathol. 2001;4(1):68-72.
2. Kimberlin DW. Current status of antiviral therapy for juvenile-onset recurrent respiratory papillomatosis. Antiviral Res. 2004;63(3):141-51.
3. Fortes HR, Ranke FM, Escuissato DL, Neto CA, Zanetti G, Hochhegger B, et al. Recurrent respiratory papillomatosis: A state-of-the-art review. Respir Med. 2017;126:116-21.
4. Chadha NK, James A. Adjuvant antiviral therapy for recurrent respiratory papillomatosis. Cochrane Database Syst Rev. 2012;12(12):CD005053.
5. Derkay CS, Bluher AE. Update on Recurrent Respiratory Papillomatosis. Otolaryngol Clin North Am. 2019;52(4):669-79.
6. Lehto L, Aaltonen LM, Rihkanen H. Longstanding recurrent laryngeal papillomatosis: impact on voice quality. Eur Arch Otorhinolaryngol. 2007;264(7):777-82.
7. Ilmarinen T, Nissilä H, Rihkanen H, Roine RP, Pietarinen-Runtti P, Pitkäranta A, et al. Clinical features, health-related quality of life, and adult voice in juvenile-onset recurrent respiratory papillomatosis. Laryngoscope. 2011;121(4):846-51.
8. NHS. HPV vaccine overview, 2022. Available at: https://www.nhs.uk/conditions/vaccinations/hpvhuman-papillomavirus-vaccine/. Accessed on 20 July 2022.
9. Wangu Z, Hsu KK. Impact of HPV vaccination on anogenital warts and respiratory papillomatosis. Hum Vaccin Immunother. 2016;12(6):1357-62.
10. Boltežar I, Matičič M, Sereg-Bahar M, Gale N, Poljak M, Kocjan B, et al. Human papilloma virus vaccination in patients with an aggressive course of recurrent respiratory papillomatosis. Eur Arch Otorhinolaryngol. 2014;271(12):3255-62.
11. Goon P, Scholtz LU, Sudhoff H. Recurrent respiratory papillomatosis (RRP)-time for a reckoning? Laryngoscope Investig Otolaryngol. 2017;2(4):184-6.
12. Dion GR, Teng S, Boyd LR, Northam A, Mason-Apps C, Vieira D, et al. Adjuvant Human Papillomavirus Vaccination for Secondary Prevention: A Systematic Review. JAMA Otolaryngol Head Neck Surg. 2017;143(6):614-22.
13. Rosenberg T, Philipsen BB, Mehlum CS, Dyrvig AK, Wehberg S, Chirilă M, et al. Therapeutic Use of the Human Papillomavirus Vaccine on Recurrent Respiratory Papillomatosis: A Systematic Review and Meta-Analysis. J Infect Dis. 2019;219(7):1016-25.
14. Smahelova J, Hamsikova E, Ludvikova V, Vydrova J, Traboulsi J, Vencalek O, et al. Outcomes After Human Papillomavirus Vaccination in Patients With Recurrent Respiratory Papillomatosis: A Nonrandomized Clinical Trial. JAMA Otolaryngol Head Neck Surg. 2022;148(7):654-61.
15. Novakovic D, Cheng ATL, Zurynski Y, Booy R, Walker PJ, Berkowitz R, et al. A Prospective Study of the Incidence of Juvenile-Onset Recurrent Respiratory Papillomatosis After Implementation of a National HPV Vaccination Program. J Infect Dis. 2018;217(2):208-12.
16. Markowitz LE, Gee J, Chesson H, Stokley S. Ten Years of Human Papillomavirus Vaccination in the United States. Acad Pediatr. 2018;18(2S):3-10.
17. Perkins RB, Legler A, Hanchate A. Trends in Male and Female Genital Warts Among Adolescents in a Safety-Net Health Care System 2004-2013: Correlation With Introduction of Female and Male Human Papillomavirus Vaccination. Sex Transm Dis. 2015;42(12):665-8.
18. Schaffer A, Brotherton J, Booy R. Do human papillomavirus vaccines have any role in newborns and the prevention of recurrent respiratory

papillomatosis in children? J Paediatr Child Health. 2007;43(9):579-80.
19. Shah KV. A case for immunization of human papillomavirus (HPV) 6/11-infected pregnant women with the quadrivalent HPV vaccine to prevent juvenile-onset laryngeal papilloma. J Infect Dis. 2014;209(9):1307-9.
20. Garland SM, Ault KA, Gall SA, Paavonen J, Sings HL, Ciprero KL, et al. Pregnancy and infant outcomes in the clinical trials of a human papillomavirus type 6/11/16/18 vaccine: a combined analysis of five randomized controlled trials. Obstet Gynecol. 2009;114(6):1179-88.
21. Healy CM. Vaccines in pregnant women and research initiatives. Clin Obstet Gynecol. 2012;55(2):474-86.

Cite this article as: Aslam MA, Maududi Y. Impact of HPV vaccination on number of surgical procedures required in recurrent respiratory papillomatosis and its potential use as an adjuvant. Int J Otorhinolaryngol Head Neck Surg 2022;8:783-6.