

Hepatitis B Vaccination and Associated Oral Manifestations: A Non-Systematic Review of Literature and Case Reports

Tarakji B, Ashok N, Alakeel R¹, Azzeghaibi SN, Umair A, Darwish S, Mahmoud RS², Elkhatat E²

Departments of Oral Maxillofacial Sciences and ²Restorative Dentistry Sciences, Alfarabi College of Dentistry and Nursing, ¹Department of Clinical Laboratory Sciences, King Saud University, Alfarabi College of Medicine, Riyadh, Saudi Arabia

Address for correspondence:

Dr. Bassel Tarakji
Department of Oral and
Maxillofacial Sciences, Alfarabi
College of Dentistry, King Abdullah
Road, Riyadh, Saudi Arabia.
E-mail: denpol@yahoo.co.uk

Abstract

Hepatitis B vaccine has been administered in children and adults routinely to reduce the incidence of the disease. Even though, hepatitis B vaccine is considered as highly safe, some adverse reactions have been reported. A literature search was carried out in PubMed, accessed via the National Library of Medicine PubMed interface, searching used the following keywords: Hepatitis B vaccine and complications from 1980 to 2014. A total of 1147 articles were obtained out of which articles, which discuss the complications occurring orally or occurring elsewhere in the body, which have the potential to manifest orally after hepatitis B vaccination were selected. A total of 82 articles were identified which included 58 case series or case reports, 15 review articles, 4 cross sectional studies, 3 prospective cohort studies, one retrospective cohort study and a case control study. After reviewing the literature, we observed that complications seen after Hepatitis B vaccination are sudden infant death syndrome, multiple sclerosis, chronic fatigue syndrome, idiopathic thrombocytopenic purpura, vasculitis optic neuritis, anaphylaxis, systemic lupus erythematosus, lichen planus and neuro-muscular disorder. Of these complications, some are manifested orally or have the potential to manifest orally. Although, most of the complications are self-limiting, some are very serious conditions, which require hospitalization with immediate medical attention.

Keywords: Complications, Hepatitis B vaccine, Oral, Vaccination

Introduction

According to World Health Organization (WHO) estimate, two billion people (one-third of the world population) have serologic evidence of past or present hepatitis B virus (HBV) infection and 360 million are chronic carriers and at risk of liver disease.^[1,2] Approximately, 620,000 deaths occur every year from acute and chronic squalae secondary to hepatitis B and 4.5 million new cases of hepatitis B are reported each year worldwide.^[3] Chronic hepatitis B has been identified as one of the most common causes of liver failure and hepatocellular carcinoma.^[4]

Hepatitis B virus is spread by blood-to-blood contact, unprotected sexual contact with multiple partners, viral exposure during medical procedures such as dialysis and surgeries, accidental exposure such as needle stick injuries and vertical transmission from mother to child are the common routes of infection with both HBV. HBV is carried in the blood, and various body fluids, such as saliva, menstrual and vaginal discharges, seminal fluid, serous exudates, and various body fluids contaminated with blood.

Previous studies had evaluated the presence and transmission of HBV through saliva and gingival crevicular fluid, which emphasizes the risk of transmission of these viruses to dentists and dental health care workers.^[5,6] Vice versa, dentists can infect their patients by HBV if adequate infection control policies are not applied.^[7] As evidence, there are 9 reports of infected dentists and oral surgeons who transmitted the virus to their patients during dental procedures during 1974 and 1982.^[8] It has also been seen that HBV virus can persist in the environment and last for 1 day.^[9]

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Method of Collection of Data

A literature search was done in PubMed, accessed via the National Library of Medicine PubMed interface (<http://www.ncbi.nlm.nih.gov/pubmed>), using the following keywords: Hepatitis B vaccine and complications from 1980 to 2014. A total of 1147 articles were obtained. These articles were obtained, and from their bibliographies, pertinent secondary references were also identified and acquired. We also used the “Related Articles” feature of PubMed to identify further references of interest within the primary search. Articles that discuss the complications occurring orally or occurring elsewhere in the body that have the potential to manifest orally after hepatitis B vaccination were selected. Based on these criteria, 82 articles were identified and included in this review. These articles included 58 case series or case reports, 15 review articles, 4 cross-sectional studies, 3 prospective cohort studies, one retrospective cohort study and case-control study.

Hepatitis B vaccine

Development of hepatitis B vaccine in 1982 has been a landmark progress in the prevention of this dreadful disease. Vaccination is the most effective measure to reduce the incidence of hepatitis B. In 1991, the WHO recommended the integration of universal hepatitis B vaccination by 1997 to prevent and control on a global scale HBV infection and its long-term, serious sequel.^[10] Hepatitis B vaccine is administered in children in around 150 countries and has been routinely included in infant or adolescent immunization.

Several hundred million doses of hepatitis B vaccine have been administered worldwide with an excellent record of safety and efficacy. The site of injection and mode of administration are critical factors in achieving an optimal response. The vaccine should be given intramuscularly into the deltoid region in children (≥ 1 year of age) and adults or into the anterolateral thigh in newborns and infants (< 1 year of age).^[3] The result of effective implementation of hepatitis B vaccination has resulted in the reduced incidence of acute hepatitis infection, carrier state and also hepatitis related mortality.^[3,11] A significant reduction of the incidence was reported after vaccination in highly endemic areas such as Taiwan, Hawaii, etc.^[12,13]

Even though hepatitis B vaccine is considered highly safe, rarely there have been contradicting case reports highlighting the adverse effect of this vaccine on certain individuals. Although, most of the dental practitioners are aware of the risks posed by hepatitis B in dental practice, not many are aware of the complications following hepatitis B vaccination. The aim of this paper is to discuss the possible complications associated with hepatitis B vaccinations with a special emphasis on the complications that is seen or has the potential to manifest orally.

Complications seen after hepatitis B vaccination

Serious disorders, which are alleged to be resulted or associated with hepatitis B vaccination are:

Sudden infant death syndrome

This allegation was made by Margolis *et al.* in 1999, though this doesn't have much credibility.^[14]

Chronic fatigue syndrome

Chronic fatigue syndrome (CFS) is described as a prolonged persistent or relapsing fatigue. The etiologies of CFS are similar to infection.^[15] A retrospective Canadian study found many patients who reported with CFS had undergone a hepatitis B vaccination.^[16]

Multiple sclerosis

Multiple sclerosis is a chronic inflammatory demyelinating disorder of the central nervous system. Between 1996 and 1997 concerns were raised that hepatitis B immunization may be linked to new cases or flare-ups of multiple sclerosis or other demyelinating diseases, following a report of primary demyelinating events within 8–10 weeks of immunization against hepatitis B using a recombinant vaccine at a hospital in Paris.^[16]

Thrombocytopenic purpura

Thrombocytopenic purpura occurring after hepatitis B vaccination was first reported in 1994 by Poullin and Gabriel.^[17]

Vasculitis

Vasculitis is a disorder that destroys blood vessels by inflammation where both arteries and veins are affected. Some patients have developed vasculitis after hepatitis B vaccination. Vasculitis after hepatitis B vaccination was first reported by Allen *et al.* in 1993.^[18] Clinical manifestations, include polyarthritis, pain in the cervical column, maculopapular rash, Raynauds phenomenon and fever.^[19] In another case report, two women developed large artery vasculitis shortly after receiving hepatitis B vaccine, which resulted in renal failure.^[20]

Rheumatic arthritis

Rheumatic arthritis is a chronic inflammatory disease that principally affects the joints. Rheumatic arthritis, followed by hepatitis B vaccination was first reported by Vautier and Carty^[21] Maillefert *et al.* have reported of six women who developed rheumatic arthritis following hepatitis B vaccination. They also reported the occurrence of arthritis, arthralgia and myalgia after the vaccination.^[19]

Optic neuritis

Optic neuritis is a multi-etiological condition consisting of the inflammation of the optic nerve that may cause a complete or partial loss of vision. A case of optic neuritis after hepatitis B vaccination was reported by Albitar *et al.*^[22]

Vaccine related anaphylaxis

Anaphylaxis after hepatitis B vaccination was first reported by Lear *et al.* in 1995.^[23]

Minor adverse reactions seen after hepatitis B vaccination include minor symptoms at the site of injection, malaise, headache, nausea, rash, influenza such as symptoms, dizziness, arthralgia, lichen planus (LP), lupus erythematosus, urticaria, parasthesia and drowsiness and neuromuscular disorders.^[24,25]

Oral manifestations of hepatitis B vaccination

The complications after hepatitis B vaccination, which may be observed intra-orally are discussed below.

Lichen planus

Lichen planus is a chronic inflammatory mucocutaneous disease, which affects the stratified squamous epithelium exclusively and frequently involves the oral and genital mucosa, skin, nails and scalp. The etiology of LP is unknown. Predisposing factors for this condition are anxiety, diabetes, autoimmune diseases, intestinal diseases, drugs, stress, hypertension, infection dental materials, neoplasms, and genetic predisposition.

Incidence of LP after hepatitis B vaccination was first reported by Ciaccio *et al.* in 1990.^[26] Fifty cases of LP have been reported after hepatitis B vaccination. Some cases are seen as early as 3 days after vaccination, and some are seen as late as 120 days after vaccination. Although, most of the LP cases had presented with skin involvement, some cases had mucosal involvement, including the oral mucosa.^[27-29] The clinical signs and symptoms and management of LP manifested in the oral cavity are mentioned in Table 1.

In a multicenter case study done by gruppo italiano studi epidemiologici in dermatologia on 577 newly diagnosed LP cases, it was seen that hepatitis B surface antigen (HBsAg) patients of any age and sex had double the risk of developing LP compared with HBsAg negative patients.^[30] Al-Khenaizan *et al.* made three conclusions regarding the appearance of LP after hepatitis B vaccination.^[31]

- Association is a rare event
- Lichen planus can occur irrespective of the type of vaccine

Table 1: Clinical features and management of lichen planus after hepatitis B vaccination

Oral signs and symptoms
Oral lesions most commonly involve lips, followed by buccal mucosa and dorsum of the tongue
Most common pattern seen orally is white reticular linear streaks
Other patterns seen orally are multiple violaceous papules and pigmentation
Most of the patients reported with itching and some reported with pain in the lesion
Management
Most of the oral lesions are accompanied by cutaneous lesions.
Oral corticosteroids are prescribed until the disappearance of the last lesion
Dapsone (1.5 mg/kg) can be given after the initial disease activity is controlled with corticosteroids

- Latent period for the appearance of eruption ranges from a few days to 3 months after any of the three doses recommended.

Lichen planus is probably caused by a T-cell mediated immunological reaction to an induced antigenic change in the skin or mucosa in predisposed patients. A key early event in LP is the genetically induced increased production of TH1 cytokines.^[32] HBsAg plays a central role in LP secondary to hepatitis B vaccination. It is assumed that LP is caused by a sensitizing protein S, which has epitopes common to keratinocytes and to the protein component of different vaccines. Hence, it is likely that the immune system recognizes an epitope on keratinocytes that is similar or identical to protein S of the virus and thus stimulates cytotoxic T lymphocytes to induce apoptosis of disturbed keratinocytes.^[33] LP after hepatitis B vaccination was managed with oral steroids and oral histamines.^[29]

Lichenoid reaction

Saywell *et al.* reported a case where a 16-year-old Caucasian male developed pruritic eruption 8 weeks after vaccination.^[34] Macules were seen over limbs and trunk with no mucosal involvement. Skin biopsy confirmed it to be a lichenoid reaction. Lichenoid like reaction was also reported by Lefort *et al.*^[35] Protein S fraction of HBsAg is believed to play a role in the pathogenesis of lichenoid reaction. Cases reported with either LP or lichenoid reaction after hepatitis B vaccinations are given in Table 2.^[26-29,31,35-55]

Idiopathic thrombocytopenic purpura

Incidence of idiopathic thrombocytopenic purpura after hepatitis B vaccination was first reported by Poullin and Gabriel in 1994 and then by Meyboom *et al.* in 1999.^[17,56] Forty eight cases of thrombocytopenic purpura after hepatitis B vaccination were published in the literature; all have been cured with some cases showing signs of recurrence. Thrombocytopenia was seen after every dosage of vaccination and it seems to start after 11 days to 3 months of vaccination.

Patients may present with petechiae, ecchymosis and splenomegaly. Intraorally, some patients manifested with wet petechiae.^[57,58] Hepatitis B vaccine contains yeast, aluminum, thimerosal and HBsAg epitopes, which may trigger an autoimmune reaction resulting in idiopathic thrombocytopenic purpura.^[59] Most of the cases do not require any treatment, while some patients responded with corticosteroid therapy. The complete reversibility of these cases reveals the benign nature of this complication.^[58] Cases of idiopathic thrombocytopenic purpura reported after hepatitis B vaccination have been listed in Table 3.^[17,56-58,60-65]

Systemic lupus erythematosus

Systemic lupus erythematosus is an autoimmune disease of unknown etiology. The administration of hepatitis B vaccine has been found to be associated with the onset of systemic lupus erythematosus.^[66]

Table 2: LP or lichenoid reaction following hepatitis B vaccination

Author (years)	Number of cases	Presentation	Article type	Article title
Ciaccio and Rebora ^[26]	1	LP	Case report	LP following HBV vaccination: A coincidence?
Trevisan and Stinco ^[36]	1	LP	Case report	Lichen ruber planus following HBV vaccination
Pusel <i>et al.</i> ^[37]	1	LP	Case report	Lichen planus and vaccination against hepatitis B
Halevy and Shai ^[38]	1	Lichenoid reaction	Case report	Lichenoid drug eruptions
Aubin <i>et al.</i> ^[39]	1	LP	Case report	LP following HBV vaccination: A coincidence?
Lefort <i>et al.</i> ^[35]	1	LP	Case report	Lichen plan et vaccination anti hepatite B
Grezard ^[40]	2	LP	Case series	Lichen plan et vaccination contre l'hepatite B. Deux observations
Leport ^[41]	1	LP	Case report	Lichen plan et vaccin contre l'hepatite B
Zabarino ^[42]	1	LP	Case report	Lichen plan secondaire a une vaccination par Engerix B registered chez une fillette de 4 ans
Morallion <i>et al.</i> ^[27]	3	LP	Case series	Lichen plan de l'enfant après vaccination anti hepatite B 3 cases
Gisserot <i>et al.</i> ^[28]	3	LP	Case series	LP after hepatitis B vaccination, 3 new cases
Saywell <i>et al.</i> ^[34]	1	Lichenoid reaction	Case report	Lichenoid reaction to hepatitis B vaccination
Mérigou <i>et al.</i> ^[43]	4	LP	Case series	Lichen planus in children: Role of the campaign for hepatitis B vaccination
Ferrando <i>et al.</i> ^[44]	1	LP	Case report	LP following hepatitis B vaccination
Rebora <i>et al.</i> ^[45]	2	LP	Case series	LP as a side effect of HBV vaccination
Schupp and Vente ^[46]	1	LP	Case report	LP following hepatitis B vaccination
Bardazzi <i>et al.</i> ^[47]	1	LP	Case report	Graham Little- Piccardi-Lasseur syndrome following HBV vaccination
Pemberton <i>et al.</i> ^[48]	1	Lichenoid reaction	Case report	Oral lichenoid lesions after hepatitis B vaccination
Agrawal <i>et al.</i> ^[29]	1	LP	Case report	LP after HBV vaccination in a child: a case report from Nepal
Usman <i>et al.</i> ^[49]	1	Lichenoid reaction	Case report	Lichenoid eruption following hepatitis B vaccination: First North American case report
Al-Khenaizan ^[31]	1	LP	Case report	LP occurring after hepatitis B vaccination: a new case
Limas and Limas ^[50]	5	LP	Case series	LP in children: A possible complication of hepatitis B vaccination
Daramola <i>et al.</i> ^[51]	1	LP	Case report	LP following hepatitis B vaccination in an African girl
Calista and Morri ^[52]	1	LP	Case report	LP induced by hepatitis vaccination: A new case and review of literature
Criado <i>et al.</i> ^[53]	1	LP	Case report	Two case reports of cutaneous adverse reactions following hepatitis B vaccine: LP and granuloma annulare
Agrawal and Shenoj ^[54]	1	Lichenoid reaction	Case report	LP secondary to hepatitis B vaccination
Kanwar ^[55]	16	LP	Case report	LP in childhood: Report of hundred cases

HBV: Hepatitis B virus, LP: Lichen planus

Table 3: Idiopathic thrombocytopenic purpura after hepatitis B vaccination

Author (years)	Number of cases	Article type	Article title
Poullin and Gabriel ^[17]	2	Case report	Thrombocytopenic purpura after recombinant hepatitis B vaccine
Meyboom <i>et al.</i> ^[56]	28	Case report	Thrombocytopenia reported in association with hepatitis B and A vaccines
Ronchi <i>et al.</i> ^[57]	3	Case series	Thrombocytopenic purpura as adverse reaction to recombinant hepatitis B vaccine
Neau <i>et al.</i> ^[60]	7	Retrospective cohort study	Immune thrombocytopenic purpura after recombinant hepatitis B vaccine: Retrospective study of seven cases
Llimiñana <i>et al.</i> ^[61]	1	Case report	Immune hemolytic anemia and thrombocytopenic purpura after recombinant hepatitis B vaccine administration
Maezono and Escobar ^[62]	1	Case report	Thrombocytopenic purpura after hepatitis B vaccine
Conesa <i>et al.</i> ^[63]	1	Case report	Thrombocytopenic purpura after recombinant hepatitis B vaccine. A rare association
Ferreira <i>et al.</i> ^[64]	1	Case report	Trombocitopenia autoimmune apos vacinac, ao contra hepatite B
Jadavji <i>et al.</i> ^[65]	3	Case series	Thrombocytopenia after immunization of Canadian children, 1992-2001
Polat <i>et al.</i> ^[58]	1	Case report	Severe thrombocytopenia after hepatitis B vaccine in an infant from Turkey

Tudela *et al.* reported a 43-year-old woman with a manifestation of systemic lupus erythematosus, 2 weeks after administration of hepatitis B vaccine.^[67] The anti-nuclear antibodies and anti DNA antibodies were positive. No oral manifestation

was reported in this case. In another case report by Guiserix *et al.*, a 26 year old female was reported with systemic lupus eythematosus 1 week after receiving hepatitis B vaccination.^[68] Although the patient manifested with

cutaneous and mucocutaneous eruptions, no intra oral change was reported. Another case of systemic lupus erythematosus was reported by Maillefert *et al.* in 1999.^[19]

It is believed that, thimerosal or aluminum hydroxide or Hb surface protein present in the vaccine may induce an immune reaction, which leads to systemic lupus erythematosus.^[68] Tudela *et al.*,^[67] recommended treatment of lupus erythematosus with prednisone and cyclophosphamide.

Neuromuscular disorders

Certain neuromuscular disorders have been reported after hepatitis B vaccination. Case reports include sensory nerve neuropathy, vestibulocochlear neuropathy, and precipitation of hereditary motor sensor neuropathy.^[69] Maillefert *et al.* reported a case where a patient manifested with mental nerve neuropathy following hepatitis B vaccination. This patient also manifested with pain in the cervical column and arthralgia.^[70]

Guillain-Barre syndrome is an acute polyneuropathy affecting the peripheral nervous system which is possibly caused by an auto immune response to foreign agents. The disorder is characterized by a symmetrical weakness that affects the lower limbs first and progresses in an ascending fashion. Lower cranial nerves may be affected leading to oropharyngeal dysphagia and respiratory difficulties. Patient may also have pain, trouble speaking and bilateral weakness of facial muscles.^[71] Some cases of Bell's palsy have also been reported after hepatitis B vaccination.^[72] Twenty cases of polyradiculo-neuropathy and Guillain-Barre syndrome have been reported in literature after hepatitis B vaccination. These are listed in Table 4.^[72-81] Apart from these disorders, hepatitis B vaccination has also been associated with myasthenia gravis, polyarteritis nodosa and myopathy.^[69] Patients with Guillain-Barre syndrome most often require hospitalization.

Incidence of Bell's palsy has been reported after hepatitis B vaccination.^[72,82,83] Bell's palsy is a sudden onset of unilateral temporary paralysis of facial muscles, resulting from seventh cranial nerve dysfunction. The etiology and pathogenesis of Bell's palsy remains unclear. There is a concern that reactivation of latent herpes simplex virus-associated infections of the geniculate ganglia of facial nerves may be one of the causes of Bell's palsy. Auto-immune mechanism has also been proposed for the cause of Bell's palsy. It has been hypothesized that an immunomediated segmental demyelination may be involved.^[82]

Conclusion

Hepatitis B vaccination has reduced the incidence of hepatitis B. Over a thousand million doses of hepatitis B vaccine have been administered already and rarely a few adverse effects were reported after vaccination. But we have to remember that all medical procedures including vaccination have a risk of side effects.

As some complications after hepatitis B vaccinations are manifested intra orally, it is necessary for dentists to know about these adverse reactions. According to our knowledge, this is the first attempt ever made to review the complications appearing orally after hepatitis B vaccination. Dentists need to keep in mind the possibility of hepatitis B vaccination as a possible etiology if a patient presents with LP, systemic lupus erythematosus, idiopathic thrombocytopenic purpura and neuro muscular disorders. A randomized control clinical trial with a large sample size should be undertaken in the future to substantiate the findings in these case reports.

Doctors should be careful in advising hepatitis B vaccination for a patient who is already manifesting an autoimmune disease. Informed consent should be obtained from the patient

Table 4: Guillain-Barre syndrome reported after hepatitis B vaccination

Author (years)	Number of cases	Article type	Article title
Centers for disease control and prevention ^[73]	2	Case series	The safety of HBV vaccine
Shaw <i>et al.</i> ^[72]	9	Case series	Postmarketing surveillance for neurologic adverse events reported after hepatitis B vaccination. Experience of the first three years
Tuohy ^[74]	1	Case report	Guillain-Barré syndrome following immunization with synthetic hepatitis B vaccine
McMahon <i>et al.</i> ^[75]	2	Prospective cohort study	Frequency of adverse reactions to hepatitis B vaccine in 43, 618 persons
Kakar and Sethi ^[76]	1	Case report	Guillain-Barré syndrome associated with hepatitis B vaccination
Créange <i>et al.</i> ^[77]	1	Case report	Lumbosacral acute demyelinating polyneuropathy following hepatitis B vaccination
Sinsawaiwong and Thampanitchawong ^[78]	1	Case report	Guillain-Barré following recombinant hepatitis B vaccine and literature review
Sindern <i>et al.</i> ^[79]	1	Case report	Inflammatory polyradiculoneuropathy and spinal cord involvement and lethal outcome after hepatitis B vaccine
Seti <i>et al.</i> ^[80]	1	Case report	Guillain-Barré syndrome following vaccination with hepatitis B vaccine
Khamaisi <i>et al.</i> ^[81]	1	Case report	Guillain-Barré syndrome following hepatitis B vaccination

HBV: Hepatitis B virus

before hepatitis B vaccination. Most of the dental practitioners and assistants who themselves undergo hepatitis B vaccination should also be aware of these complications. Although, most of the complications are self-limiting, some are very serious conditions, which require hospitalization with immediate medical attention. Benefits provided by the hepatitis B vaccination far outweigh its adverse reactions because hepatitis B is a serious disease, which can even lead to chronic liver failure and hepatocellular carcinoma.

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