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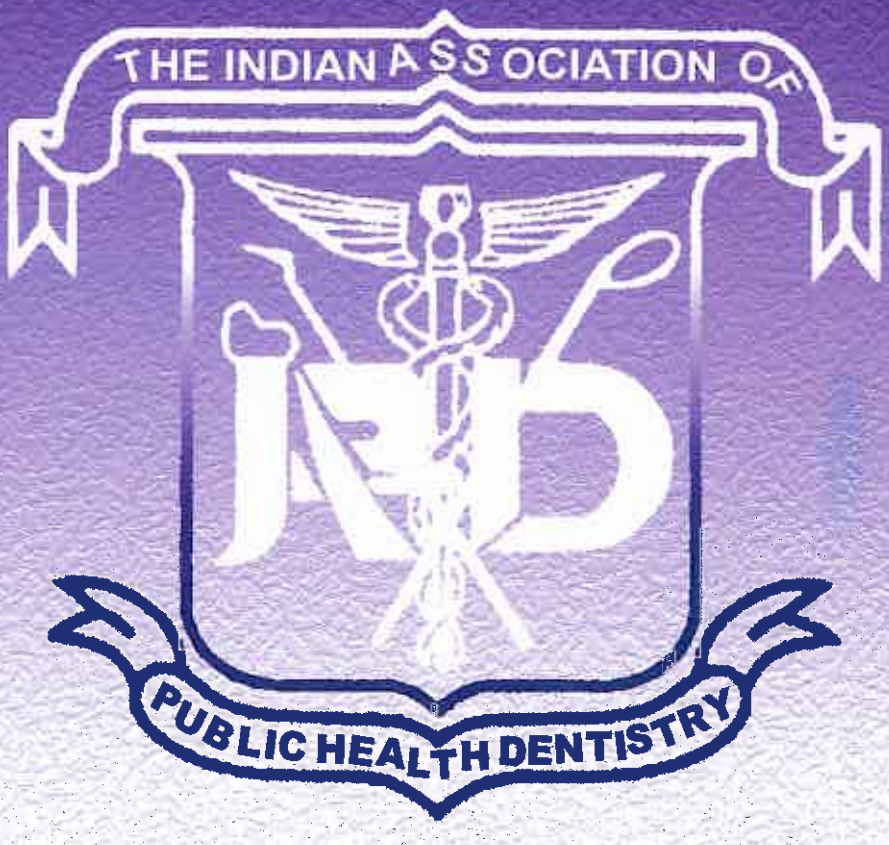

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Caries Vaccine - I. Today's Myth !

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ABSTRACT

Dental caries is a microbial disease of the teeth. Traditional way of managing this disease is by surgical intervention. But the current trend is to prevent the occurrence of the lesion. Caries vaccine is one of the methods of preventing and eradicating dental caries. Contemporary research is aimed at evolving a potent and effective caries vaccine. The present review gives an overview of the current developments, drawbacks and potential of this avenue of revolutionary caries management.

INTRODUCTION

Dental caries is a microbial disease of the teeth, characterized by demineralization of the inorganic portion and dissolution of the organic substance of the tooth. [1] It is a multifactorial disease with interplay of principle factors like host, micro flora, substrate and time. Skulls of Cro-Magnon people, who inhabited the earth 25,000 years ago, show evidence of tooth decay. The earliest recorded reference to oral disease is from an ancient Sumerian text (5000 BC)[2] that describes "tooth worms" as a cause of dental decay. The Chinese subscribed to the 'tooth worm' theory of dental caries and used acupuncture around 2700 BC to treat pain associated with tooth decay. This has evidence from the oracle bone inscription excavated from the ruins of the Ying Dynasty.

Though the evidence of presence of the disease has been found since prehistoric days, management of these carious lesions have been popularized and emphasized in the recent 100 years. The problem faced in managing these cases is mainly because of its high prevalence rate worldwide. Results of a survey done in Indian population of school going age showed a caries prevalence of about 58.1% [3]. Survey among U.S. population showed an incidence of 45.3% in children and 93.8 % in adults with either past or present coronal caries [4].

Huge amounts of money and time are spent in treating dental caries. A dental expenditure of 56.6 billion dollars has been accounted in 1999, with an average expected increase of 2.3% per annum [5].

The influence of socioeconomic status of an individual on susceptibility to caries has been a matter of much debate. Socioeconomic status[6] is a very broad and often very vaguely defined measure of an individual's characteristics in terms of income, education, job and attitudes. In general individuals who belong to low socio-economic groups are experiencing more disease problems of various kinds- and dental caries is no exception. Indian children classified as being of 'low' level social class were those experiencing the highest caries increment. However, the effect of socioeconomic variables on caries experience is certainly not similar in all populations. Thus, it is commonly believed that if a rural population migrates towards major cities (urbanization), this may in and of itself lead to increased caries experience because of easier access to modern commodities like refined food. Refined diet or 'Junk foods' are soft, sticky and they do not have cleansing action on tooth. Further refined diets lack starch and are rich in sucrose, which makes them cariogenic. However, in the high socioeconomic strata there is an improved awareness to the importance of oral hygiene and there is increased utilization of dental services. Thus paradoxically higher socio-economic status is often accompanied by a lower caries attack rate.

This widespread dental caries can potentially be prevented perhaps eradicated by interfering with the transmission, colonization and acid production of the micro – organisms. This present review is an overview on the current challenges posed in developing an effective caries vaccine.

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DENTAL CARIES PATHOGENS

A wide group of microorganisms are identified from carious lesions. Of them, the main pathogenic species involved in the initiation and development of the dental caries are Streptococcus mutans, Lactobacillus acidophilus, Actinomyces viscosus[7].

MANAGEMENT

The traditional way of managing this disease was by a surgical approach of *"drill and fill"*. However this has slowly evolved into a more conservative mode, the medical model[8] of management which includes

1. Limiting Substrate-	Diet Modification
2. Modifying Micro Flora-	Mouth Rinse And Topical Fluoride Application
3. Disrupting Plaque-	Brushing
4. Modifying Tooth Surface-	Systemic And Topical Fluoride Application.
5. Stimulating Saliva Flow-	Sugarless Chewing Gums
6. Restoring Tooth Surface-	Pit And Fissure Sealants

Prevention is better than cure – when this thought was seeded in the minds of medical practitioners, various methods of preventing life threatening infectious diseases with high mortality and morbidity were introduced. One of the ways of preventing the disease is by immunizing the population against the disease.

Vaccines[9] are preparations of live or killed microorganisms, or their products used for immunization. They induce artificial active immunity.

History of Vaccines:

Edward Jenner was the pioneer in the field of immunization. Small pox was one of the most fatal epidemics of 18th century. He noticed that the cowboys were immune to smallpox epidemic. He reasoned out the cause as the active acquired immunity in the cowboys against small pox due to their constant exposure to cowpox antigen (1796). He implicated the same concept to protect his 18-month-old child by inoculating the cowpox antigen and succeeded in developing vaccine against small pox. According to WHO reports, small pox is completely eradicated now. Similarly, Louis Pasteur succeeded in developing vaccine against anthrax and hydrophobia (Rabies).

Thus, *"Eradication is better than prevention and cure"* is the logical rationale behind managing infectious conditions. The ultimate goal in caries therapy was also to identify a foolproof, economical and effective model of caries eradication. This can be achieved by interfering with the colonization and acid production of microorganisms by vaccines.

History of Caries Vaccine:

Based on the above concept, vaccine for dental caries was also tried out. When the first caries immunization experiments were performed in the 1930s, Lactobacillus was used as an antigen. Immunization against lactobacillus was only partially successful and could not provide adequate protection against caries. This is because lactobacilli is more a consequence than a cause of caries initiation (Fitzgerald) and was present only in the deep carious lesions[10].studies by Houte et al showed that lactobacilli has low affinity to tooth structure[11].

Streptococcus mutans became the target in virtually all immunization experiments after their redetection in 1960. It was recognized as the major pathogen because of its initial colonizing ability in early dental plaque.

What went wrong in caries vaccine?

When an antigen is introduced into the host, antibodies are produced to the antigen by the host defense system. Thus the antigen is neutralized and destroyed. The surface antigens are the most important antigens to initiate a disease in the host. Some microorganisms like Influenza and Mutans Streptococci (MS) can change their antigens.

Changing antigenecity of MS makes the production of a specific vaccine against it difficult[12]. By this way, bacteria can avoid forces of the immune response. Thus when a vaccine is produced against the organism, the bacteria can change its antigenic structure and make the total vaccine useless.

Pathogenic bacteria can change surface proteins that are the targets of antibodies. Some bacteria avoid the host antibody response by changing from one type of fimbriae to another, by switching fimbrial tips. Antigens may vary or change within the host during the course of an infection, or alternatively antigens may vary among multiple strains (antigenic types) of a parasite in the population. Antigenic variation usually results from site-specific inversions or gene

conversions or gene rearrangements in the DNA of the microorganisms. But the exact mechanism of antigenic variation in MS is still not known.

Antigenic Components Of MS

The components of bacteria that can be used as antigens for vaccine production are

1. Glucan binding protein B (GBP)[13]

The molecular pathogenesis of dental caries involves the binding of the insoluble glucan to the bacterial cell surface. Glucan binding proteins (GBP) produced by MS are the proteins which aid in this binding.

2. Dextranases:

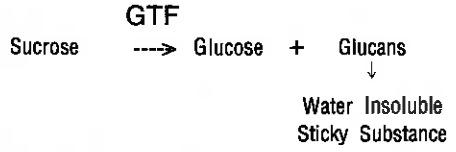
Dextran is the important constituent of early dental plaque. Dextranase is an enzyme produced by MS. They destroy dextran and thus the bacterium can invade dextran rich early dental plaque. Dextranase when used as an antigen can prevent colonization of the organism in early dental plaque[14].

3. Cell wall antigens AG I / II:

Several cell wall proteins of MS have been identified. The largest among these proteins are the antigens I & II. They have a high molecular weight. This protein has a fibrillar structure and constitutes the fuzzy coat of the organism when viewed in electron microscope. These antigens function as an *adhesin* that enables adherence of bacteria to salivary pellicle coated tooth surface and aggregation of streptococcus mutans by salivary components [15].These are the main antigenic components that were used in the beginning of the caries vaccine research.

2- Glucosyl transferase GTF:

GTF of bacteria convert sucrose into water soluble and water insoluble glucans(fig 1). Glucans bind together food debris, epithelial cells ,mucous and bacteria. which aid in attachment of bacteria on to the tooth surface[16]. Glycosyl transferase is the most potent among the antigenic components and is the one used with proven effectiveness in the current research.



Mechanism of action of caries vaccine:

Vaccines prepared from Cell wall antigen, Glucan binding protein and Dextranase are targeted to inhibit colonization of bacteria and those against glycosyl transferase inhibit the acid production.

As with any other immunization mechanism, caries immunization can be active or passive.

Active Immunization / Vaccination:

Vaccination involves administration of antigen into the host, stimulating host immune response to produce antibodies against the antigen. Either whole antigen or sub unit vaccines can be administered. Attenuated whole streptococcus mutans can be administered as antigen. The disadvantage of this is that the antigen may contain the fimbrial M protein, which cross –reacts with heart tissue.

MS possess antigenic components that elicit antibodies that cross react with human heart muscle (sarcolemmal sheaths). As yet, no postmortem examinations of monkeys immunized with S mutans have revealed any indications for heart damage[17]. Since dental caries is not a life threatening disease, advocates of caries vaccine must show its *safety* and efficiency. Thus any caries vaccine intended for parenteral administration must be free of antigen that may cross-react with heart muscle.

Active immunization with caries Vaccines can be administered either to stimulate systemic antibody production or mucosal antibody production.

In systemic route[18] after subcutaneous immunization, with streptococcus mutans, it is possible to detect rise in the specific antibody titer. When the antigen reaches blood circulation, it stimulates T cells, which in turn stimulates B lymphocytes to transform into plasma cells and produce Immunoglobulin G (IgG) into the circulation. Antibody produced neutralizes the antigen. Antibody produced reaches the tooth surface through gingival crevicular fluid or through inflammatory fluid. (. Lehner T, Challacombe Sj, Caldwell J.1978)

Ig G is mainly a serum immunoglobulin. Higher IgG levels can be obtained in the oral cavity when there is a mild inflammation, like during tooth eruption The efficacy of serum IgG protection is questionable since dental caries occurs in areas inaccessible to blood components.

On administering the antigen via mucosal routes[6,19,20] , the antigens come in contact with Mucosa Associated Lymphoid Tissue (MALT), either Gut Associated Lymphoid Tissue (GALT) or Nasal Mucosa Associated Lymphoid Tissue (NALT). When the ingested antigens come in contact with GALT, i.e., payer's patches of small intestine, lymphoblasts are triggered, taken up by mesenteric lymph nodes and thoracic duct to systemic circulation. Lymphoblasts are seeded in the lamina propria of mucosal tissues throughout the body including salivary glands. They induce local clonal expansion of cells and maturation into plasma cells to secrete IgA. S- IgA antibodies can also be detected in external secretions like saliva, tears, milk .Thus ingested antigens induce secretory Immunoglobulin A, (S-IgA) response at distant mucosal surfaces including those in the oral cavity via saliva, by common mucosal immune system.

Earlier studies of mucosal immunization were done by injecting MS cells or purified GTF into salivary gland region to induce IgA secretion. This had the disadvantage of altering the function of the gland. Later studies are using done using oral, intra nasal , intratonsilar routes of administration. Childer's studies indicated that nasal immunization was more effective in inducing mucosal responses in adults[21].

Salivary agglutinin titer[22] levels on immunization of rats near salivary glands with S.mutans vaccine are shown in Table 1.Higher antibody titer in the infected and immunized rats provide effective protection against caries. Advantage of active immunization is that it results in enhanced immune responses with possibilities of longer periods of protection. Thus mucosal immunization is advantageous over systemic immunization. Disadvantage is that they cannot be used in immune compromised individuals. Other systemic pathologies that can be produced by the natural antigen are yet to be studied.

Passive Immunization:

In this route, readymade antibodies against streptococcus mutans antigens are isolated and administered to provide immediate protection against caries.

Passive immunization can be achieved in the following ways.

1. Local route

Topical application of mouse monoclonal antibodies to Ag I/II to cleaned tooth surfaces of human volunteers inhibits subsequent implantation of MS or recolonization by indigenous MS for up to 2 years after 2-week treatment.

2. Systemic route

Significant reduction in caries can be achieved by administering milk containing IgG antibodies from cows and egg-yolk antibodies IgY[23].

Advantages of passive immunization are that immediate protection can be achieved. This can be employed in immune compromised patients also. Antibody structure can be manipulated by genetic engineering so that specificity of anti body variable region can be maintained while modifying constant region to humanize the antibody. Disadvantages include transient protection. Repeated administration is needed for effective vaccination.

CONCLUSION

Caries can potentially be reduced by interfering with the transmission of MS, eliminating the established populations from oral cavity, increasing the acid resistance of the tooth and control of carbohydrate composition of the diet. The first two factors can be controlled by caries vaccine. Thus knowing the basis of vaccine and reasons for failure will be the first step in the evolution of a successful caries vaccine production.

Table 1: Salivary agglutinin titer levels on immunization of rats near salivary glands with S.mutans vaccine

RATS	ANTIBODY TITER
Non infected	0.0 µg/dl
Infected	5.0 µg/dl
Infected And Immunized	40.0 µg/dl

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