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Review Article

Public Health Section

Current Status of Intranasal COVID-19 Vaccine, its Usage and Efficacy: A Narrative Review

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ABSTRACT

The creation of a vaccine against Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2) has received top focus worldwide. The majority of the COVID-19 vaccine candidates are administered Intramuscularly (IM). Intranasal (IN) vaccines offer a great benefit due to the first involvement of mucosa of the nasal cavity in the due course of disease, also SARS-CoV-2 is spread through respiratory secretions which are infectious, and mucosal immunity due to IN vaccination could contribute significantly to controlling this disease. IN vaccination has been shown in preclinical and clinical investigations to produce significant levels of neutralising antibodies, mucosal IgA, and T-cell responses that protect against SARS-CoV-2 infection in the respiratory pathway. Blocking Coronavirus Disease-2019 (COVID-19) infection and transmission requires the immune system response at the initial infection site of the virus. Many IN vaccines are currently under trial for their safety and efficacy, while some are recently approved for use in specific conditions in India and are proven to be protective against the virus and also safe. In this context, this review will provide knowledge of the IN vaccines for their effectiveness and application.

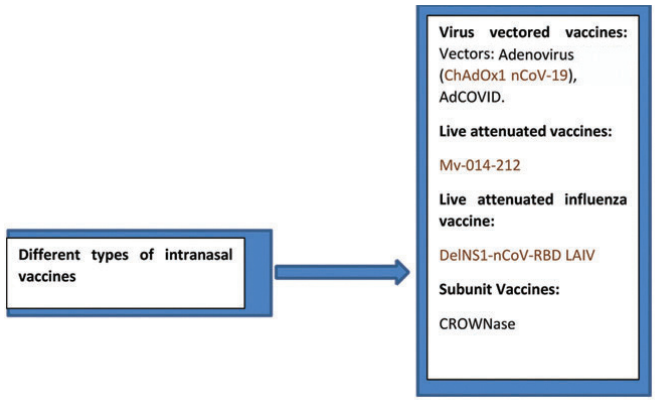
Keywords: Infection, Mucosal vaccines, Oral vaccines, Vaccination

INTRODUCTION

COVID-19 is caused due to SARS-CoV-2. Through interaction with another individual who has the virus, one can contract COVID-19. The virus can affect any organ system, but majorly it affects the respiratory system. People who have COVID-19 may experience a number of symptoms, ranging in severity from moderate to severe. Symptoms could start to show up after 2-14 days, on an average of 5-6 days of exposure to the virus. Besides from a high temperature or chills, symptoms may also include cough, dyspnoea, exhaustion, body ache, headache, anosmia, sore throat, congestion, rhinorrhoea, nausea, vomiting, and diarrhoea [1]. The amazing ability of our immune system to react and remember harmful material it encounters, is used by vaccines. A perfect vaccination should offer immediate, comprehensive, long-lasting protection by preventing the illness from leading to serious outcome, hospitalisation, and death. Following vaccination, B-cells that create antibodies mediate the adaptive immune response [2].

Vaccination through the mucosal route can provide an effective and safe method for achieving robust immune responses (systemic, humoural) in addition to mucosal immunity (IgA) in humans because the principal entry portal for coronavirus in the body is mainly made up of mucosal surfaces (Oral, Nasal). The first-line barrier to coronavirus is our nasal compartment before the virus spreads to the pulmonary system [3-6]. The infection caused by SARS-CoV-2 will show no symptoms or as a moderate upper respiratory illness, but will nonetheless cause the oral and nasal mucosa to shed the virus. According to the study, shedding in silent infections was of shorter length but frequently to comparable virus levels initially. Transmission of the coronavirus has been linked to asymptomatic and presymptomatic shedding [7]. There are several COVID-19 vaccines, the bulk of which are IM injections that induce protective immunity. IN vaccines are being developed for COVID-19 [Table/Fig-1]. They have demonstrated the potential to elicit an immune response that is antibody-mediated and robust cell-mediated immunity, protective mucosal immunity with ease to administer.

Intranasal vaccine can also reduce the infection caused by COVID-19 virus, shedding and replication as well as the progression of the disease and by generating IgA antibody responses in the mucosa of cavity of nose, which limits the transmission of virus [8].



[Table/Fig-1]: Different types of Intranasal (IN) vaccines.

REVIEW

A vast network of non lymphoid cells, chemicals, lymphocytes, makes up mucosal immunity (e.g., cytokines, chemokines, and antibodies). Injectable vaccinations typically do a poor job of inducing mucosal immunity, however IN immunisation can strongly induce mucosal immunity. This helps to restrict the growth of mucosal infections. The respiratory epithelial layer, which is the first line of defence is activated when a virus enters into the cavity of the nose [9,10]. Upper respiratory tract is poorly controlled by IM vaccinations, which results in silent or milder clinical infections that can still spread the virus to others. IN vaccinations, additionally, may promote sterile immunity against mucosal infections [10]. Wu S et al., originally showed that an Ad5-vectored vaccine that was replication-defective, evoked both immune responses that are systemic and mucosal against SARS-CoV-2 when administered IN [11]. Single mucosal (simultaneous oral and IN delivery), or Ad5-nCoV IM produced increased levels of serum neutralising Ig in ferrets. The development of IgA antibodies in trachea-lung washes which are S-specific, according to mouse research, can only be increased by immunisation with IN. Ferrets were resistant

to infection caused by viruses in respiratory tracts after mucosal vaccination after SARS-CoV-2 challenge; whereas, IM immunisation failed to decrease the virus in the respiratory tract significantly. IN immunisation with Ad5-S-nb2 induces immunity (mucosal, systemic) in rhesus macaques and mice, as shown by Feng L et al., [12].

BBV154

An IN SARS-CoV-2 vectored chimpanzee adenovirus vaccination called BBV154 has poor replication. It consists of a ChAd vector with a replication defect that expresses stable spike SARS-CoV-2. In a study, it has been observed that BBV154 administration IN had great safety profiles and evoked strong immune response (mucosal and humoral) and the one which is mediated by Th1. Heterologous vaccination of COVAXIN-prime (IM) and BBV154 (IN) boosters has induced cross-variant protective immune responses [13]. For emergency usage (in individuals over 18-year-old) in India, a nasal COVID-19 vaccination based on Washington University is approved as a booster dose for those who have received the other two doses of vaccines [13]. The clearance comes after the Government of India granted emergency use permission for the IN vaccine as a primary series of two doses in September. This makes the IN vaccine the world's first to be approved as both a primary vaccination for COVID-19 and a booster.

3100 participants participated in Phase-3 studies across 14 trial. sites in India for immunogenicity and safety. Third dose (Booster) of the BBV154 IN vaccine was given to research participants who had already received approved COVID-19 vaccines and Heterologous booster dose studies for safety and immunogenicity were performed. Nine trials locations were used for the clinical trials in India [14]. This vaccine offers the dual advantages of facilitating the rapid creation of variant-specific vaccinations and facilitating simple nasal administration that permits bulk immunisation to guard against new Variants Of Concern (VOC). It has the potential to be a crucial tool for mass immunisation campaigns during pandemics and endemics [15]. Almost any adult in India can receive the vaccination, which is given as drops in the nose. Both those who have never gotten a COVID-19 vaccination and those who have previously received COVID-19 shots are eligible.

In India, two doses of the COVID-19 vaccination have now been administered to an estimated 900 million people. In addition to not requiring a needle, the key benefit of the nasal vaccine is that it stimulates an immune response in the nose and upper airway, the place where the virus takes entry into the body. By doing this, it may be able to stop an infection and end the transmission cycle. This nasal vaccine's technology is also flexible, enabling quick and simple adjustments to accommodate newly emerging VOC [16]. A recent study compared the effectiveness of vaccines given by IN and IM route delivery of a chimpanzee adenovirus-vectored vaccine (ChAd-SARS-CoV-2-S) expressing a stabilised S protein. Contrary to hamsters receiving IM vaccine, those getting vaccination through the IN route had a stronger immune response, which is mediated by antibodies, that was able to neutralise the SARS-CoV-2 infection. Additionally, the inoculated hamsters were shielded against SARS-CoV-2 exposure and were not affected by a viral infection, which would have caused weight loss in the hamsters. Also, a decrease in inflammatory genes transcript levels and better clinical conditions were seen, as well as lower viral loads in pulmonary and IN swabs. By providing IN vaccination, the vaccine increases protection from SARS-CoV-2 infection and decreases viral particle spread [17].

COVI-VAC

The Serum Institute of India has begun producing COVI-VAC, a live-attenuated IN vaccine for COVID-19, in conjunction with Codagenix (United States), which is currently conducting a Phase-3 clinical research (NCT04619628) to evaluate its safety and immunogenicity against SARS-CoV-2. An IN vaccine, live attenuated called CoviLiv™ expresses all proteins of SARS-CoV-2, not just spike, allowing for the generation of broad immunity against a variety of viral antigens and possibly boosting effectiveness against variations. The vaccine was created with the use of the Codagenix platform technology, which re-codes a virus' genetic code to transform it from a pathogen that causes disease into a stable and secure live-attenuated vaccine. CoviLiv will be tested against circulating SARS-CoV-2 strains in healthy adults in nations with poor vaccination rates like Africa, perhaps South America, and Asia in the worldwide Phase-3 trial to look for its safety, effectiveness, and immunogenicity to placebo. CoviLiv's preliminary clinical data show that the dose chosen for the IN vaccine had a seroresponse rate of 100% and established mucosal immunity, efficient to block nasal replication. CoviLiv also stimulates widespread cellular immune responses against a number of SARS-CoV-2-proteins, including those seen in Omicron BA.2. Serum Institute of India is also examining the possibility of CoviLiv as a booster shot IN along with Codagenix, in Phase-1 clinical investigation (UK based), along with efficacy trial (Phase-3). In this ongoing investigation, healthy adults who have previously received COVID-19 vaccinations with mRNA or adenovirus vectors will have their booster response assessed [18].

AdCOVID

AdCOVID, developed by US-based Alt Immune, Adenovirus-vectored vaccine for IN administration that expresses the Receptor Binding Domain (RBD) of the SARS-CoV-2 spike protein healthy adult volunteers in the age group of 18 to 55 years, participated in a clinical trial Phase-1 for the AdCOVID vaccine to assess its immunogenicity and safety. AdCOVID was administered to the subjects as a nasal spray in either 1 or 2 doses at three dosage levels. The immunogenicity assessment of AdCOVID included serum binding and neutralising antibody titre mucosal IgA antibody from nasopharyngeal swabs post-vaccination, in addition to the primary research outcome of safety and tolerability. AdCOVID seems to be well tolerated. The immunogenicity results showed that none of the investigated immunological parameters produced immune responses that were as strong as anticipated. The response and the percentage of people responding to AdCOVID were significantly less than what had been shown for other vaccines previously approved for use in emergency, despite antibodies being found that bound the SARS-CoV-2 Spike protein and neutralised the virus. After this Phase-1 trial is over, Alt Immune will stop working on developing AdCOVID [19].

NasoVAX was also examined by Alt Immune in clinical trials Phase II (NCT04442230). It is a recombinant monovalent influenza vaccine that is delivered intravenously. The antigen of influenza is expressed in the target cell via an adenovector. Compared to conventional influenza vaccines, this results in a wider and quicker immunological response [20]. With elevated IgG antibody levels and a sizable quantity of mucosal immunological response, the IN vaccination induced a potent antibody-mediated immune response. These results indicate that non invasive IN vaccines should be taken into consideration for the development of vaccine in future [21].

ChAdOx1 nCoV-19 Vaccine

In conjunction with AstraZeneca, Oxford University is creating the vaccine ChAdOx1 nCoV-19. The ChAdOx1 vector used for the vaccine is an adenovirus that causes the common cold but has been genetically altered such that it cannot multiply in people. An initial dose of vaccine was administered to 30 previously unvaccinated study participants IN. Additionally, 12 participants who had previously received a typical two-dose COVID-19 immunisation schedule by injection were given the IN vaccine as part of a study to examine the viability of the IN vaccine as a booster. In a Phase-1 experiment, their nasal vaccine candidate fell short, failing to elicit

a robust immune response in the nasal mucosa of the majority of patients. In comparison to IM immunisations, the spray also induced lesser systemic immune responses. They speculated that a significant portion of the spray might be ingested and incinerated in the stomach. The vaccination should ideally be injected right into the lungs [22-24].Their vaccine did not perform well.

Ad5-nCoV

Chongqing Zhifei Biological Products and CanSino Biologics Inc. researchers performed a placebo-controlled, randomised double-blind research to find out the safety and immunogenicity of the Ad5-nCoV inhalation vaccination in individuals aged above 18 years (NCT04840992). They developed an inhaled version of the vaccine that had been approved for use at the time of emergency as a booster dose by the country's drug regulator. With the brand name, Convidecia Air™ is a non invasive alternative that employs a nebuliser to turn liquid into an aerosol for inhalation through the mouth. It uses the same viral vector technical platform as the IM version Convidecia™. With just one breath, Convidecia Air™, a needle-free medication, can successfully stimulate an all-encompassing immune response against the SARS-CoV-2 virus [25,26]. The vaccine is approved in 2 countries, China and Morocco.

MV-014-212

A chimeric SARS-CoV-2 spike is a viral protein, enveloped, present in the live, attenuated, human respiratory syncytial virus, recombinant, known as MV-014-212. An attenuated, immunogenic version of MV-014-212 was found in African Green Monkeys (AGMs). MV-014-212 one mucosal dose protected against SARS in AGMs. In a clinical trial Phase-1, MV-014-212 is now being assessed as an IN vaccination (NCT04798001) [27].

CROWNase

CROWNase, an inhalation treatment being tested as a novel COVID-19 vaccination at the Illinois Institute of Technology in Chicago, has the capability to reduce infection caused by SARS-CoV-2. S-protein provides SARS-CoV-2 which appears like a crown, allowing the virus to spread infection by adhering to hACE2. Human-derived compounds that coat the S-protein aid the virus in evading our immune system and infecting the host cells. By dissolving the S-covering, the protein's CROWNase activates the immune system by revealing the protein component. This hinders the virus's ability to infect human cells even more. The receptor Angiotensin Converting Enzyme 2 (ACE2) is a component of CROWNase, which enhances the effectiveness of its viral binding. CROWNase inhalation treatment is intended to be used in an outpatient situation. According to the researchers, CROWNase may also be used orally, as a pill, injectable, solution, eye drops or ointment, or as a nasal spray in addition to being inhaled [28].

DelNS1-2019-nCoV-RBD-OPT

DelNS1-2019-nCoV-RBD-OPT1, IN spray, influenza vectored, live attenuated vaccine pointing (RBD) of viral S protein, has successfully completed its Phase-1 and 2 clinical studies indicating that the vaccine is well tolerated and induces mucosal as well as systemic immunity. Currently, the vaccine is undergoing a Phase-3 trial [29].

Safety and Efficacy

Given the advantages of nasal vaccine over traditional vaccines, which improve patient compliance and reduce the need for specialist healthcare workers to administer the vaccine, vaccine delivery via the nasal route seems to be a viable option. At the pulmonary pathogen's entrance point, IN vaccination has the ability to produce a prolonged and cross-protective immune system response.

Clinical trials are increasing, indicating the widely recognised requirement for IN vaccinations that can be administered easily and provide greater benefits over other vaccine delivery systems in terms of formulation costs. Other than those for influenza, which show the efficiency of this method, the benefits of directly boosting the mucosal immune response via IN route are apparent, albeit they have not yet been fully appreciated. These studies must be conducted for both efficacy and safety [30].

CONCLUSION(S)

The global catastrophe of COVID-19 has accelerated the momentum of the vaccination market like never before. Clinical studies in rhesus macaques and mouse models have led to the development of a variety of IN vaccines. Studies have shown that these vaccines can suppress viral replication and transmission/spread by activating mucosal immunity (secretory) (sIgA) in the upper respiratory tracts. The mucosa of the nasal cavity serves as the initial line of defense against SARS-CoV-2 entry before dissemination into the lungs, making the IN vaccine an ideal strategy for avoiding COVID-19. Without a question, IN vaccines have a potential benefit over IM vaccines. The vaccination method selected, functional vaccine components like adjuvants and vaccine carriers all affect a vaccine's overall immunostimulatory efficiency. The safety and efficacy profiles of the majority of the SARS-CoV-2 IN vaccines have not yet been proven in people because they are still in early-stage clinical trials.

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