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Review Article

A Review on Modern Use of Intranasal Vaccination in the Treatment of SARS-COV-2

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Abstract

The coronavirus disease 2019 (COVID-19) pandemic has highlighted the urgent need for efficient SARS coronavirus 2 (SARS-CoV-2) preventative vaccines to limit the burden and spread of SARS-CoV-2 in humans. Intranasal immunization is a promising technique for preventing COVID-19 because the nasal mucosa acts as a first line of defense against SARS-CoV-2 entrance before the virus spreads to the lungs. Nasal vaccination has many advantages over traditional vaccine administration methods. These include the simplicity of administration without the use of needles, which decreases the risks of needle stick injuries and disposal. This channel also provides simple access to a crucial portion of the immune system that can stimulate other mucosal sites throughout the body. By targeting immunoglobulin A (IgA), antibodies found only in the mucosa, an intranasal vaccination would elicit immunological responses in the nose, throat, and lungs. Potential pathogens are trapped by the mucosa, which acts as a physical barrier to prevent them from entering the body. Given this, the intranasal vaccine would prevent virus transmission via exhaled droplets or aerosols because there would be no virus in the body to expel .There are several intranasal vaccines for protection against sars-cov2 are under preclinical and clinical trials .The key challenge is in Designing delivery strategies that take into account the wide range of diseases, populations, and healthcare delivery settings that stand to benefit from this unique mucosal route should be prioritized.

Keywords: COVID-19, Intranasal vaccine, Immunoglobulin A, Permeation

Introduction

Coronavirus disease-2019 (COVID 19) caused by novel corona virus, which is officially named severe acute respiratory syndrome coronavirus 2 (SARS – COV-2) has emerged in Wuhan, China in December 2019 and spread around entire globe [2,3,4,5]. Since the recognition of COVID-19, there has been an exponential rise in the number of cases worldwide. As of 1 April 2020, the World Health Organization reported more than 926 000 cases in more than 195 countries, areas, or territories [1,2,6,7].

This virus belongs to group of enveloped RNA beta-coronaviruses and coronaviridae family. The genome of corona virus encodes four predominant proteins, which are the Envelope (E), Membrane (M), Nucleocapsid(N), Spike(S). The S protein is responsible for viral access into respiratory tissue through the Angiotensin-converting enzyme 2 (ACE-2) expressing in epithelial cells [2,8,9].

Reasons for the rapid spread include high transmissibility of the virus [1,10,11], especially among asymptomatic or minimally symptomatic carriers [1,12,13]; the apparent absence of any cross-protective immunity from related viral infections; and delayed public health response measures [1,14-16].

The clinical features of COVID-19 are varied, ranging from asymptomatic state to acute respiratory distress syndrome and multi organ dysfunction. There are three main clinical stages of COVID-19. Stage one is viral response phase, which is period of early infection. It last for about four days and it is typically characterized by symptoms such as fever, cough, sore throat and diarrhoea [2,9]. Stage two is pulmonary phase which usually last between days 5 to 13 [2,9]. At this stage, pulmonary symptoms are first without hypoxia and later hypoxia develops. Stage three is systemic hyperinflammation phase, which is usually from day 14 [2,17].

Age and the presence of comorbid illnesses increase the risk for death among persons with COVID-19 [1,18,19]. COVID-19 infection triggers cytokine storm characterised by hyperinflammation, septic shock complications, coagulation dysfunction and impairment of several vital organs [2,20-23].

The inhalation route of drugs is highly recommended for patients suffering from lung disorders than other administration routes. Drug delivery to the lungs offers several advantages regarding both local and systemic delivery [24].

Certain FDA approved vaccines used in the treatment of COVID 19 are:

1. COVISHEILD
2. COVAXIN
3. PFIZER
4. JOHNSON & JOHNSON
5. SPUTNIK V

COVID-19 Vaccines authorized for emergency use:

1. Pfizer-BioNTech COVID-19 Vaccine
2. Moderna COVID-19 Vaccine
3. Janssen COVID-19 vaccine

Intranasal vaccination has become promising approach in offering immune protection against various pathogens that affects respiratory system including tuberculosis, influenza, coronavirus, respiratory syncytial virus (RSV) [25]. Nasal delivery system offers many benefits over traditional approach to vaccine administration, like it is needle free, non-invasive route of administration with possibility of self-administration [26].

Intranasal vaccination is an attractive strategy to prevent COVID-19 as the nasal mucosa represents 1st line barrier to COVID-19 or SARS-COV-2 entry before viral spread to lungs. It would trigger immune response in the nose, throat and lung mucosa by stimulating a broad immune response – neutralizing IgG, mucosal IgA, and T cell responses. Immune responses at the site of infection – essential for blocking both infection and transmission of COVID-19. So the mucosa acts as physical barrier to potential pathogens [26].

Mechanism and route of intranasal vaccine

Nasal route for drug delivery:

Nasal delivery of vaccines acts as a "first entry block," that is, blocks the infectious agent entry, while invading to the mucosal surface by causing native microbial-specific immune responses, therefore increasing the the overall effectiveness of the vaccine. Additionally, vaccine uptake into the blood circulatory system by absorption through mucosa is often comparatively quick [27]. It is the most appropriate method of immunization because it is rich in T cells, B cells, and plasma cells and stimulates each antigen-specific systemic and mucosal adaptive immune responses. It provides higher patient compliance because of the needle-free delivery.

Antigen uptake in the nose is usually by two mechanisms: paracellular (aqueous pathway) and transcellular (lipoidal) processes. The foremost economical house for drug absorption is that the terribly vascularized lateral wall of the nasal cavity: the tissue layer lined over the turbinates or conchae.

1. In the paracellular mechanism, the antigen uptake nasally is through the aqueous route of transport, and this route is slow and passive. The method chiefly depends on associate inverse log-log correlation between intranasal absorption and therefore the relative molecular mass of water-soluble compounds/antigens [28].

2. In the transcellular mechanism, the antigen uptake nasally is through a lipoidal route and is responsible for the transport of lipotropic antigen supported lipophilicity. Aside from transcellular and paracellular processes, antigens could cross cell membranes by an energetic transport route via passive diffusion (depends on hydrogen ion concentration of atmosphere and pKa of the drug), carrier-mediated suggest that, or transport through the gap of tight junctions in mucosa (i.e., through organic cation or amino acid transport), and endocytic method [uptake of antigen mediate by microfold (M) cells] [29].

There are completely different physiological factors that regulate the absorption of antigen.

- The permeability of a nasal vaccine depends on the type of cells and style of cells in the nasal cavity [30].
- Secretions of nasal mucous membrane enzymes like lactate dehydrogenase [31], oxidative, conjugative enzymes, peptidases, and proteases also act as a barrier and degrade the nasal immunizing agent.
- Stimulation of nasal mucous membrane plays a role in membrane absorption. Parasympathetic stimulates increase permeability of a nasal vaccine [30].
- Viscous nasal mucus secretion may retard the uptake of antigen [30].
- Permeation of antigen is altered in the night (chronokinetics) because of clearance rates and mucosal secretions [34].
- pH of the nasal cavity for adults is 5.5–6.5 and for infants is 5.0–7.0; for higher antigenic absorption, the developed nasal formulation pH scale should be within 4.5–6.5 [32].
- Mucociliary clearance (MCC) takes about 21 min in the nasal cavity, and increased MCC decreases antigen uptake [30,33].

Device use in delivery:

Nasal spray

Unitdose liquid

- Drug delivery devices which deliver a particular, single dose quickly, merely and faithfully [34].
- Hermetically sealed primary glass instrumentation
- Dose volume: 100 µl

Bidose liquid

- Bidose liquid system could be a strong, primeless, intuitive and easy-to-use device with 360° practicality and precise spray characteristics and provides correct two-shot nasal drug delivery [35].
- Hermetically sealed primary glass instrumentality
- Dose volume: 2 × 100 µl

Multi-dose liquid device

- VP3 technology could be a gold ancient for multi-dose nasal sprays [36].
- The VP7 platform was specifically designed to power multi-dose medication product that unit administered nasally or sublingually [37].
- Multi-dose pump with tip-seal technology prevents contamination of bottle content
- snapped on ancient glass bottles 5-20 ml
- 70-100-140 µl per exploit
- single use sleeve/protection cap for every patient prevents malady transmission

Unitdose powder

- No have to be compelled to coordinate feat with inhalation
- Max filling volume: 140 mm^3 (20-50 mg)
- Conventional filling technology (capsule-type)
- In combination with a spacer suited to inhaled vaccines [36].

Bidose powder

- Passive technology
- Best protection of the powder formulation because of special blister laminate (foil)
- Max filling volume: 190 mm^3 (50-100 mg) per chamber
- Intranasal vaccines could save prices for massvaccinations, as a result of a lot of less antigen is required and it is a save and simple administration route [36].

❖ **Advantages**

- It may be administered by an individual [37].
- Better patient compliance [38].
- Small antigenic dose [38].
- Numerous microvilli present in the nasal epithelium offer a far better absorption surface
- Intranasal vaccination could confer protection against infections at alternative mucosal sites, such as the lungs, intestines and veneral tract, and supply cross-protection against variant strains through mucosal antibody secretion [39].
- Mucosal and systemic immune response can be induced [40].
- It is appropriate and safe for children, aged patient, HIV-infected patient and multi-morbid patient and eliminates the risk of needle-related infections and pain [41].
- The intranasal vaccine is not at all invasive, it doesn't have to be injected. So, Nasal protection doesn't need needles and syringes [42].
- Intranasal vaccines may be created in larger batches than other varieties of COVID vaccines [38].

❖ **How it works**

Most viral and bacterial infections begin on the mucosal surfaces; thus, the development of a mucosal immune response may be necessary for protection against infectious agents. As a result, the mucosal route is the most appropriate way of vaccination for specific pathogenic agents because it has been shown to generate both mucosal and systemic immune responses [43,44,45]. Intranasal immunization is able to elicit a protective immune response in the lungs and upper respiratory tract because the highest immune response is usually elicited at the vaccination site and nearby mucosal sites [46,47]. Nasal mucosa appears to be an appropriate site for administering vaccines against respiratory infectious diseases, not only because the nasal cavity is the first site of contact with inhaled macromolecules and a common site of infection by respiratory pathogens, but also because it can stimulate respiratory mucosal immunity by interacting with the NALT [47].

Mucosal vaccination has been shown to generate humoral and cell-mediated immune responses both systemically and at mucosal sites. The immune response elicited by mucosal vaccination is primarily initiated at specific mucosa-associated lymphoid tissue (MALT) [47,48,49]. The MALT lining the nasal cavity is also known as the nasopharyngeal-associated lymphatic tissue, that involves the Waldeyer's ring of tonsils, adenoids and a set of isolated subepithelial lymphoid follicles [47,50].

The NALT is enriched with immunocompetent cells, together with B cells, T cells and phagocytic APCs like macrophages and DCs.

Additionally,
the superimposed epithelium of mucosal follicles forms a specialized cell layer. These cells have microfolds on their top surface and referred to as microfold cells (M cells). M cells play an important role within the initial part of induction of mucosal immune responses. Therefore, M cell targeting is a very important strategy to attain mucosal immunity [48,51,52]. M cells within the NALT are the sites of antigen uptake or induction of mucosal immunity [43,53]. Antigen is actively transported by M cells, to reach dendritic cells, macrophages and B cells, for presentation and processing [43,54]. Consequently activation of antigen-specific CD4+ T helper cells (Th cells) interact with B cells that change into IgA committed (IgA+). IgA+ B cells move to effector sites such as the nasal passage where they differentiate into IgA-producing plasma cells and secrete IgA in dimers. By binding to the polymeric Ig receptor, dimeric IgA transforms into S-IgA, which delivers IgA to effector locations [43,55]. S-IgA is a vital part within the mucosal system [47,56].

S-IgA is able to bind toxins, bacteria, or viruses and neutralize their activity, so preventing entry into the body or reaching the internal organs, and forms a primary barrier of defense against invading antigens [46,57,58]. Local immunoglobulin G (IgG) production is also identified following mucosal immunization, and contributes in pathogen neutralization [47,59]. Due to its sensitivity to protease degradation, IgG concentration is 30–100 times lower than that of S-IgA [47,48]. Furthermore, nasal immunization can result in the production of serum IgA and serum IgG, which can potentially neutralize pathogens that enter the mucosa and prevent systemic spread. When DCs at the mucosa are exposed to antigens, the activated cells may migrate to the proximal draining lymph node and disseminate immune responses to other parts of the body. Apart from the humoral immune reaction, cell-mediated immune reaction is also induced after mucosal vaccination [47,48].

Overall, cells of NALT are contributing in regulation of both humoral and cell-mediated immune responses locally and systemically, giving a broad immune reaction. Since the nasal mucosa is a very important portal of entry for respiratory pathogens, the nasal route has become enticing for the administration of vaccines by reinforcing the nasal mucosal immune response [47].

Current scenario and work on intranasal vaccine:

➢ **BBV154**

BBV 154 is intranasal vaccine encourages a broad immune response like mucosal IgA, neutralizing IgG, and T cell responses. Washington University of school of medicine in St. louis, US is developed this vaccine with the collaboration of Bharat Biotech and Precision Virologics. Transmission and

infection of COVID-19 can be avoided by generating immune responses at the site of infection (in the nasal mucosa). This route has the specified immune systems of the nasal mucosa that's why it has excellent ability for vaccination. This vaccine does not require trained workers. It is Non-invasive and Needle-free dosage form [26].

Formulation and Development

It is an adenovirus vector vaccine, which made from a weakened version of the common cold virus that was originally sourced from chimpanzees. It has been changed to create and target the coronavirus [60].

Pre-clinical trial

Macaques, Hamsters and Mice, were immunized with a single dose of ChAd-SARS-CoV-2-S conferred superior protection against SARS-CoV-2. They got immune response in the nose that is the point of entry for the virus. Hence, it will be effective against transmission, disease and infection [60].

Clinical trial

The study is designed to evaluate the safety, and immunogenicity of three different groups of healthy volunteers who receive either intranasal single dose (vaccine at Day 0, and placebo at Day 28) or two-dose (vaccine at Day 0 and 28) of BBV154 vaccine or Placebo (on Day 0 and day 28). A total of 175 subjects will be enrolled in 2:2:1 ratio and will be conducted in a double-blinded manner. Each subject will record symptoms in a card for seven days after each single dose, to monitor the safety of the vaccine [61].

- **AdCOVID:**

Single dose vaccine that stimulate a broad immune response – neutralizing IgG, mucosal IgA and T cells in the respiratory tract and nasal cavity. AdCOVID is expected to have stability at room temperature for months and for years when refrigerated. That would allow vaccine to distribute without cool-chain requirements. Vaccine does not required needles and its very well tolerated [62].

Altimmune (Gaithersburg, MD) has collaborated with the university of Alabama—Birmingham to develop and test its intranasal AdCOVID vaccine [63].

Formulation and development

The vaccine is a single dose, intranasal adenovirus type-5 vectored vaccine encoding the receptor binding domain (RBD) of the SARS-CoV-2 spike protein, elicits a strong and focused immune response against RBD through the induction of mucosal IgA, serum neutralizing antibodies and $CD4^+$ and $CD8^+$ T cells with a Th1-like cytokine expression profile [64].

Pre-clinical trial

Results of preclinical immunogenicity testing of AdCOVID, following a single administration in two strains of mice by measuring the induction of spike specific antibody levels in sera and bronchoalveolar lavage (BAL) fluids. AdCOVID provided 100% protection against lethal SARS-CoV-2 challenge [64].

Clinical trial

Estimated enrollments of participants are 180. Dose administered as one or two doses conducted in double blinded manner. It is randomized, placebo-controlled study. Volunteers who receive either single dose of AdCOVID, two doses of AdCOVID, single dose of placebo or two doses of placebo administered intranasally. Each subject will record symptoms for 7 days of vaccination [65].

- **COVI-VAC**

Codagenix (Farmingdale, NY) in partnership with Codagenix and Serum Institute of India has developed a single dose, intranasal COVID-19 vaccine candidate that is currently in phase 1 clinical trials in the UK. Vaccine demonstrated a broad immune response, including mucosal IgA, humoral IgG and T cell response [63].

Formulation and development

COVI-VAC will not require a needle and syringe, nor ultra-low temperature freezers as a single-dose, intranasally-delivered vaccine. COVI-VAC can be manufactured at large scale and supports ease of administration in a mass vaccination campaign. COVI-VAC is designed to deliver a safe, live attenuated version of SARS-CoV-2 that may induce a more robust immune response and long-lasting cellular immunity against SARS-CoV-2 compared to other vaccines against the virus [66].

Pre-clinical studies

COVI-VAC is a single dose, intranasal live attenuated vaccine, shown to be safe and efficacious in preclinical animal studies [66].

Clinical trial

Approximately 48 participants are going to be registered into 1 of 3 dose teams (low, medium, high). Among every of those dose teams, participant are going to be appointed randomly to receive either 2 doses of COVI-VAC 28 days apart, 2 doses of placebo (saline), or 1 dose of COVI-VAC and 1 dose of placebo. Neither the participants nor the researchers will know whether COVI-VAC or placebo has been received. To assess the protection of the vaccine, every participant will record symptoms and oral temperature after each dose daily for 14 days [67].

- **Intravacc**

The Netherlands based university, Wageningen bioveterinary university (WBVR) used the viral vector technology and animal technology, and the Dutch Utrecht university's coronavirus expertise will develop a vaccine through vaccine development technology from Intravacc [68].

Formulation and development

The antigen will carries with it a animal disease virus (NDV) vector that expresses the immunogenic spike(S) organic compound of SARS-CoV-2, that's an important target for neutralizing antibodies. NDV has been shown to be safe for intranasal/intratracheal delivery in mammals, also as non-human primates [68].

Preclinical trial

For the pre-clinical study four groups of mice and four groups of hamsters received a pair of intranasal immunizations on day one and day twenty one. One cluster of mice and hamsters received a antigen supported OMV's mixed with rSp (CovOMV) and conjointly the choice a antigen supported OMV's coupled to rSp supported Intravacc's proprietary OMV click technology (CovOMVclick) [69,70].

In the mice, respectively 30 minutes and ninetieth virus neutralizing antibodies were detected. in all the hamsters every candidate vaccines elicited neutralizing antibodies, but the number of antibodies in hamsters that received CovOMVclick was slightly higher compared to the other cluster [69,70].

❖ **Others**

Current research ongoing on other vaccines as follows:-

- **Beijing Wantai Biological Pharmacy Enterprise** Co Ltd will start a mid-stage clinical trial of a nasal spray coronavirus vaccine in china, clinical trial registry data showed [71].

A study involving 720 participants in Phase 2 clinical trial, run by a city-level disease control and prevention center in the eastern province of Jiangsu, will take place from Nov. 17 showed a record in the Chinese Clinical Trail Registry dated Friday. The vaccine will be given at two- or three-week intervals, and can take a look at its safety and skill to elicit immune responses, showed the registry record [72].

The Phase 2 study will also evaluate how pre-existing antibodies against a particular type of flu virus in healthy folks have an effect on the vaccine [71].

- **Eureka therapeutics** has announced successful pre-clinical results from the **InvisiMask** human antibody nasal spray in mice, which offered protection against SARS-CoV-2 pseudo typed virus infection for up to 10 hours [73,74].

Eureka's InvisiMask human antibody nasal spray is meant to neutralize SARS-CoV-2 from airborne droplets and particles within the nasal cavity, the first entry point of SARS-CoV-2 infection [74].

The mAbs are built with a proprietary adhesion technology that will increase their retention on metabolism tissue layer surfaces, extending the period of protection from infection. The researchers found that the mAbs will bind and inhibit quit twenty SARS-CoV-2 variants, together with the extremely infectious D614G mutation. No adverse effects were discovered within the preclinical studies [73].

Storage at room temperature with long shelf life in comparison to vaccines (sub-zero storage) will simplify distribution and expand access.[75]

- Developed by **SaNOtize Research** and Development primarily based in Vancouver, Canada, the treatment was effective in killing SARS-CoV-2 in freelance research lab tests. Further studies in rodents with COVID-19 infection showed over ninety five percent reductions among the primary day after infection. The SaNOtize nasal spray provides a barrier. It contains gas (nitric oxide), that prevents and treats early infection by destroying the virus and preventative infectious agent replication within the cells in the nose. Additionally, nitric oxide has been shown to block the ACE2 receptor essential for the virus to infect our cells [73].

- Zeteo Biomedical has joined forces with Iowa State University's (ISU) Nano vaccine Institute to analysis a nasal COVID-19 vaccine [76].

Zeteo can give nasal delivery device technology and unit dose packaging utilizing its ZEOx2™ Delivery Platform, along with technical services to support the evaluation of a room temperature stable SARS-CoV-2 vaccine underneath development by ISU's Nano vaccine Institute. Zeteo's ZEOx2 Delivery Platform includes nasal delivery devices to support powder and reconstituted powder to liquid vaccine formulations which will be either caregiver- or self-administered. extra collaboration partners involved in the project include the Southwest Research Institute (San Antonio, TX), Skroot Laboratory, Inc. (Ames, IA), and also the University of Iowa (Iowa City, IA). This can be fast track project and is anticipated to be completed by the tip of the year [77].

- An intranasal vaccine against COVID-19 utilizing specialized gene transfer technology is developing by **Rokote Laboratories** Finland. The company, which joined forces with **University of Eastern Finland** (UEF) and **University of Helsinki** (UHEL).

The vaccine developed at the University of Eastern Finland uses gene transfer technology by Academy academician **Seppo Ylä-Herttuala's** research group. The vaccine uses a secure adenovirus carrier that contains a cloned polymer strand that causes nasopharyngeal cells to produce the virus protein that, in turn, produces a response to the vaccine. There's no actual SARS-CoV-2 virus in the vaccine. Preliminary results show that the vaccine has performed well in animal studies, and clinical testing in humans can begin among a number of months [78,79,80,81].

Future challenges

It can only be given by trained person due to complicated administered.

- Special devices required for the delivery of vaccine.
- The price of vaccine may rise.

Conclusion

Corona virus is a major threat all over the world. Specialists are working to develop and implement vaccination and other preventive measures. Antibodies against covid-19 are safe and effective in order to protect general health. Intranasal administration of vaccine represents an ideal strategy against many pathogens that infect via mucosal surface. The intranasal vaccine delivery technique triggers both mucosal and systemic immune responses, preventing pathogen entrance through all mucosal pathways. The non-invasive, needle-free nasal route is helpful for immunization programmes because it improves patient compliance and reduces the requirement for specialized healthcare staff to give the vaccine. BBV154, AdCOVID and COVI-VAC are the vaccines in clinical trials whereas INTRAVACC completed its preclinical trials. Hence, the nasal delivery of vaccine is an attractive option.

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