Letter to the Editor

Intranasal immunization as a preventive measure against SARS-CoV-2

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Dear Editor,

It is known that the development of intramuscular RNA vaccination has been an effective preventive measure against SARS-CoV-2 infection by producing humoral and cellular immune responses that prevent viremia and systemic manifestations caused by COVID-19. However, Tiboni *et al.* report that the intramuscular route does not provide complete protection against viral replication due to the absence of activation of the mucosal immunity of the upper airways, preserving the risk of transmission[1].

Intranasal vaccination is a novel immunization approach that uses the respiratory lining as an entry point for developing antibodies. Intranasal immunization is a promising option to combat COVID-19 since by using the same route of infection as the virus, it sterilizes the respiratory tract and prevents transmission of the virus; moreover, its administration is easy and convenient for people with trypanophobia[2].

The first nasal vaccine, FluMist, was approved in 2003. It has been effective in reducing the incidence and complications of influenza. At the time being, intranasal vaccines against COVID-19 are under investigation as preclinical and clinical phase I and II clinical trials. Only in China and India intranasal vaccines have been approved, differing in their presentation, since in China, they are used in spray form, while in India, they are as drops[3].

Chavda *et al.* observed how intranasal vaccines have an effect at the mucosal and serum levels, and produce systemic immune responses, as do intramuscular vaccines, which could prevent more severe forms of the disease, and also prevent the virus to reach the lower respiratory tract, which reduces the spread of the virus[2].

Aqu Alu *et al.* explain that inhaled vaccines are attractive as they require no injection needles and no qualified personnel and describe the existence of significant advances in subunit protein vaccines and virus vector vaccines in intranasal SARS-CoV-2 vaccines in preclinical and clinical setting studies[3].

Lei *et al.* used the receptor binding domain to develop an intranasal vaccine, in which they observed superior immunogenicity to intramuscular immunogenicity that maintained long-term for wild-type and novel variables. The use of three doses produced and maintained high levels of neutralizing IgG antibodies in serum for at least one year, which also elicited strong immunity in mucosal IgA antibodies and lung T-cell memory, thus evidencing that this process was due to local lung T-cell proliferation, rather than migration of these cells from lymph nodes, resulting in a promising vaccine due to good local and systemic immunogenicity in mice[4].

Cohen *et al.* determined that anti-S antibodies derive primarily from blood transudation rather than local production in sick and vaccinated persons. Although the intramuscularly administered SARS-CoV-2 vaccine boosted mucosal immune responses in infected persons, the increase in antibody titers was higher in plasma than in mucosa, suggesting the need to develop mucosal-level vaccines to induce potent immune responses at the infection sites[5].

Owing to the benefits of local immunity in the nasal mucosa, researchers at Charité-

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Universitätsmedizin-Berlin have developed a live attenuated intranasal vaccine and state that intramuscular vaccines with two doses perform significantly worse in protecting the nasal mucosa because the virus can damage the upper layers of the tissue[6].

Accordingly, Diallo *et al.* determined in their experimental vaccine (IM/IN) that antibodies induced with the ancestral sequence (WT) of the S-protein were less effective in neutralizing Omicron. On this bases, using newer versions of the S-trimer or adding other antigens such as nucleocapsid, ORF, and other proteins that are less mutated than Spike in future formulations is needed. Since viral variants escape antibodies more readily than T cells, a vaccine that induces both T cells and antibodies, particularly in the respiratory tract, may have a significant advantage, suggesting that a nasal protein vaccine formulated with a potent adjuvant may be a suitable approach to provide long-term protection against SARS-CoV-2 in humans[7].

Thus Tang J *et al.* argue that current COVID-19 vaccines are highly effective against the development of severe disease, probably through recruitment of circulating B and T cell responses during reinfection, but offer limited protection against advanced infection, especially for Omicron; with mucosal booster vaccination being necessary to establish robust sterilizing respiratory immunity against SARS-CoV-2[8].

Zhong *et al.* describe how intramuscular vaccine administration creates a global economic burden as low-temperature storage and trained health personnel are required for administration. On the other hand, intranasal administration can be performed through disposable devices with minimal storage requirements for mass vaccination, resulting in a viable option for developing countries[9].

It is the case for El Salvador and the reason why it is crucial to continue research on intranasal inoculation since it is not yet possible to conclude on its clinical effectiveness in humans, nor the safety profile of the intranasal vaccine since it is still in the clinical evaluation phases. Therefore, it is advisable to continue conducting studies to consolidate the effectiveness and safety of the intranasal route, as it is a promising route of administration that needs further studies in humans.

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