

***Nasya karma* (Intranasal therapy); An Alternative Route of Drug Administration into the Brain**

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Abstract

Ayurveda is the ancient system of Indian medicine in which the importance of both prevention and cure are highlighted. As per the Ayurvedic texts, The *tridoshas* are the main causative factors in the pathogenesis of any disease. Specific management for individual *doshas* have been elaborated in all Ayurvedic texts. In Ayurveda, a special procedure called *Nasya karma* has been mentioned. It is an alternative route of drug administration for most of the drugs that act on brain. *Nasya* is given in the form of oil, ghee, smoke, powder and herbal juice depending upon the nature of disease. Pharmacokinetics and pharmacodynamics of *Nasya* drugs and the connection of nose with brain is explained in the *Ayurvedic* classics. *Nasya karma* provides an alternative route to drug delivery to the brain with safe and efficacious formulations for simple, painless and long-term therapy.

Keywords

Nasya karma, intranasal therapy, nose, drug delivery to brain



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INTRODUCTION

These days many modern drugs have better systemic bioavailability through nasal route as compared to oral or systemic administration. Pharmacokinetics (drug absorption, distribution, metabolism, and excretion) and pharmacodynamics (the effect of a drug on its target site) reflects that intranasal drug delivery offers a promising alternative route for CNS drugs administration.¹ Many researches show that there is better absorption of drug in CSF through nasal route than any other routes.² Intranasal route for therapeutic purposes arises from the anatomical, physiological and histological characteristics of the nasal cavity, which provides rapid systemic drug absorption and quick onset of action. Nasal drug delivery is superior than that of oral because of hepatic first-pass metabolism and drug degradation is absent; nose-brain pathway leads to nearly immediate delivery of some nasal medications to the cerebral spinal fluid, bypassing the blood brain barrier.^{3,4} Drugs that are not absorbed orally may be delivered to the systemic circulation through nasal drug delivery system and it is a convenient route when compared with parenteral route for long term therapy.^{5,6}

Intranasal therapy has been an accepted form of treatment in the Ayurvedic system of Indian medicine. In Ayurveda, the word *Nasya* has been taken specifically to mention the route of administration of the drugs. As stated by *Sushruta* medicines or medicated oil administered through the nose is known as *Nasya*.⁷ *Acharyas Vagbhat* also said “*Nasa hi shirasodvaram.*”⁸ Means nose is the gateway of brain, because nose is indirectly connected with the brain centers in the head. This indicates there is a very close relationship between the nose and the brain. *Acharya Charaka* has mentioned one specific anatomical structure named *munja*, which is like type of grass which acts like *ishika* (i.e., like a painter’s brush). The *munja* structure can be thought for an olfactory bulb and the *ishika* for the numerous neurons join together to form the olfactory tract.⁹ During this explanation, classics have mentioned one more structure; the *shringatakamarma* (anatomical area in nose) which is the union point of *srotasa* (micro channels) of tongue, nose, eyes and ears.¹⁰ *Shringatakamarma* helps in assimilation and transportation of *Nasya* drug in local as well as general circulation.¹¹ *Acharya Charaka* says the *snehapradhananavana* drug (lipophilic

drug), gets absorbed in the *shringataka* region.¹² That means lipid soluble drugs are much more efficiently absorbed by nasal mucosa. *Nasya karma* is used both to manage the local and general disorders. In

this article we have discussed about the Ayurvedic anatomy, physiology of nose and mode of action of *Nasya karma* and its correlation with modern science.

Application of nose anatomy with reference to *Nasyakarma*^{13,14,15}

Facts	Interpretation
1. Nose serves as important communication centre. Channels from all sinuses, Eustachian tube and Naso-lacrimal duct open inside the nasal cavity.	Enables the <i>Nasya</i> medicines to reach all sinus cavities, middle ear and Palpebral fissure.
2. Mucous membrane lining of all these areas are histologically one and the same continuous sheath.	This makes mucous membranes of all these sites to respond as single unit for any sort of stimuli.
3. Receptor cells of olfactory mucosa are the only neurons which are projected to external world.	Enables direct contact of <i>Nasya</i> medicines.
4. Nasal villi of receptors show special absorption property.	Enables direct entry of <i>Nasya</i> medicines to brain, bypassing blood brain barrier.
5. One division of olfactory pathway by passes thalamus and olfactory systems have connection with limbic system.	Stimulation from <i>Nasya</i> medicines can influence over – Mood, Sexual behavior, Memory pattern, Endocrinal functions.
6. Special features of blood supply: <ul style="list-style-type: none"> • Arterio venous blood shunting • Fenestrated capillaries • Rich pooling of blood in sinusoids Enables direct absorption and <ul style="list-style-type: none"> • Efficient heat exchange ability. 	Enables direct absorption and distribution of drug through circulatory route.

Nasya drug: *Mridu paka*¹⁶ (preparation of the medicine using lipid and water base)

medicine which has having hydro-lipophilic nature is used for *Nasya* procedure; the

Nasya medicine contains water soluble as well as lipid soluble active principles. The aqueous part of the active principle gets absorbed through mucous membrane (Nasal mucosa, olfactory mucosa) and fat soluble active principle can be easily assimilated through nerve endings (Trigeminal and olfactory).¹⁷ This has the relevancy in facilitating the stimulation as well as the absorption of the drug. Fat-soluble drugs are usually absorbed more rapidly than are water-soluble drugs.¹⁸ To achieve rapid diffusion through nasal mucosa the lipid soluble drugs are preferred where the mucosal cilia are lipophilic in action. In humans, large particles (>4 µm) and small particles (0.5 to 1.0 µm) tend to deposit in the nasopharyngeal structures, whereas intermediate particles (1 to 4 µm) reach distal airways. Water-soluble drugs tend to remain on the tissues of the upper airway and fat-soluble drugs are more likely to reach distal airways.¹⁹

Importance of *Purvakarma* (preoperative) and *Pachchhatkarma* (postoperative procedures) of *Nasya*

Poorva karma plays a major role in the access of the drug into the body. The lowering of the head, elevation of lower extremities and fomentation of face seems to

have an impact on blood circulation of the head and face.²⁰ As the efferent vasodilator nerves are spread out on the superficial surface of the face, receives stimulation by fomentation and it may engender the increased blood flow to the brain. Lowering of head plays a major role in the spread of medicine to the nose and adjoining structure i.e. sinus ostia. After the absorption of the drug it may follow neural (olfactory and trigeminal)²¹ and circulatory (cavernous sinus) course to reach the site of action. It can influence the psychic level (limbic system), sensory level, motor level (Trigeminal nerve) and general circulation and ultimately produce the action (excitation or sedation). Massage to the frontal, temporal, maxillary, mastoid regions are recommended after *Nasyakarma*.²² The absorption of the drug is also facilitated by the *pachchhat karma* followed during the procedure.

Importance of long Duration of *Nasya*:

The duration of the *Nasyakarma* course ranges from 7-21 days. It differs for each classification of *Nasya karma*. Many days are needed for the action of the drug and to achieve required symptoms. Because of the quantity of the drug, very minimal and continuous stimulation to the olfactory

neurons should facilitate the stimulation of the higher centre (i.e., to the olfactory bulb). Once this area is stimulated, then this stimulation is continued to the parts of Amygdala, Hypothalamus, to the parts of Basal Ganglia and to the brain stem also.²³ This whole system is called the limbic system, which controls emotional reactions, visceral somatic, behavioral changes, motivation, biological rhythms, and respiratory, circulatory, and endocrine changes.²⁴

Pharmacokinetic of *Nasya* drug -

Absorption, distribution and metabolism of *Nasya* drugs explore the local and systemic effects of *Nasya karma*. The olfactory epithelium is a gateway for substances entering the CNS and the peripheral circulation. The neural connections between the nasal mucosa and the brain provide a unique pathway for the non-invasive delivery of therapeutic agents to the CNS.²⁵ The transport of drugs across the nasal membrane and into the bloodstream may involve either passive diffusion of drug molecules through the pores in the nasal mucosa or some form of non-passive transport.²⁶

Factors influencing nasal drug absorption²⁷

The following factors affect drug absorption:

1) Nasal physiological factors: Nasal mucosa also have the metabolic capability of converting endogenous materials into compounds that are eliminated more readily. Mucociliary clearance (MCC) is the self-clearing mechanism of the bronchi. When MCC increases permeation rate of drug is decreased.²⁸ Also the rich supply of blood and a large surface area make the nasal mucosa an optimal location for drug absorption.²⁹

2. Physicochemical properties of drugs:^{30,31} Nasal absorption is affected by molecular weight, size, formulation pH, pKa of molecule, and delivery volume among other formulation characteristics. Lipophilic drugs are absorbed quickly and efficiently across the nasal membrane via transcellular mechanisms. This observation is better for lipophilic compounds having molecular weight lower than 1 kDa. On the other hand, the rate and degree of nasal absorption of polar drugs is low and highly dependent of the molecular weight. Whenever lipophilicity is too high, the drug permeation through the wall may be reduced because drug does not dissolve easily in the aqueous environment of nasal cavity. Shape is also

important. Linear molecules have lesser absorption than cyclic-shaped molecules.

3. Effect of drug formulation: Formulation with higher viscosity has a better contact time thus increases the absorption. At the same time, high viscosity enhanced the permeability of drugs.^{32,33} pH is also an important formulation factor for drug

absorption. However, the pH of formulation should be near on human nasal mucosa (5.0-6.5) to prevent the sneezing.^{34,35} Volume and concentration are also important considerations. The delivery volume is limited by the size of the nasal cavity. An upper limit of 25 mg/dose and a volume of 25 to 150 mL/nostril have been suggested.³⁶

Ayurvedic view of pharmacokinetic of *Nasya* drug.

Pharmacokinetics	Ayurvedic comparison
1. Access -the drug absorb into the body may be through a. Receptor cells of olfactory mucosa. b. Sensory receptors of trigeminal nerve. c. Cavernous sinus	<i>Shringataka marma</i>
2. Course - Neuronal pathway a. olfactory b. Trigeminal	<i>Prana</i> (vital energy)
3. Target - Site where effect is produced	
• Limbic System	Psychic level of <i>Prana</i>
• Sensory and motor area of trigeminal	Sensory level of <i>Prana</i>
• Whole body through circulation	Physical level of <i>Prana</i>
4. Theory - Behind action a. Excitation b. Sedation	Accessed and Regulated through <i>shringatakamarma</i>

Probable mode of action of *Nasya Karma*

A clear description regarding the mode of action of *Nasyakarma* is not available in Ayurvedic classics. *Acharya Charaka* described that nose is the doorway of head.³⁷ So, the medicine administrated through *Nasya* can easily spread to head and get absorbed. *Acharya Vagbhata* has given some more details about the mode of action.

It is explained that nose being gateway to head (brain), the drug administrated through nostrils reaches *shringataka*, a *sirahmarma* (vital vascular structure) by micro channels and spreads in the brain and scratches the morbid *doshas* in upper part of body and extract them from nose.³⁸ Extraction of morbid *dosha* by *shirovirechan* type of *Nasya* is explain by *Charaka*.he has given

the example of *ishika* which is the slender fine stalk of *munja* grass, according to *Charaka* the recipe administered by *Nasya* therapy enters into the head and draws out exclusively the morbid matter as the pith (*ishika*) is taken out after removing the fibrous coating of *munja* (a type of grass) adhered to it.³⁹ The *munja* structure can be thought for an olfactory bulb and the *ishika* for the numerous neurons join together to form the olfactory tract. *Acharya Gangadhara* explains that *Nasya* medicine enters into micro channels and removes *doshas* which are adherent to *majjapeshi* (brain tissue).⁴⁰

According to modern science the olfactory area is the only place in the whole human body where there is direct contact between the outer surface and central nervous system.

Intranasal administration may rapidly achieve therapeutic brain and spinal cord (CNS) drug concentrations. If the nasally administered medication contacts the olfactory mucosa, there is good evidence that suggests molecule transport can occur directly across this tissue and into the cerebral spinal fluid.^{41,42} Thus to understand the action of *Nasya* drug on central nervous system it is necessary to know the probable

pathways of action of *Nasya* medicines. The drug transport to CNS probably by three pathways

- a) By vascular path
- b) By lymphatic path
- c) By Neural path

a) Drug transportation by vascular path:

Nasya drug is transported from nasal vein to meninges nasal vein and ophthalmic vein drain in to facial vein. It is interesting that both facial and ophthalmic veins have no venial valve in between. As a result the blood may drain on either side.⁴³ It means blood from facial vein can enter in cavernous venous sinus of the brain in reverse direction. Such a pooling of blood in the brain is more possible in head lowered position due to gravity. Thus the absorption of drug in meninges and related intra-cranial organ is considerable point. *Shringataka marma*, mentioned by *Acharya Vagbhatta* can also be explained by above description.

b) Drug transportation by lymphatic path:

Pathways connecting the subarachnoid space containing CSF, perineurial spaces encompassing olfactory nerves and nasal lymphatics provide a gateway for intranasally applied therapeutics to the CSF and other areas of the CNS.⁴⁴ Along with olfactory nerve; the

arachnoid matter sleeve is extended to sub-mucosal area of the nose. There are direct connections between CSF and nasal lymphatics, the injected antigen into the subarachnoid space appears in both superficial and deep cervical lymph nodes, suggesting the drainage of this antigen from the subarachnoid space to extra cranial lymphatic vessels along olfactory nerves.⁴⁵ These pathways also ensure the access of drugs to the CNS after intranasal administration, moving from nasal passages to the CSF. In humans' neuro therapeutics are directly delivered to the CSF after intranasal delivery, without entering the blood to a significant extent.⁴⁶ Acharya Sushruta also aware of connection between nose and subarachnoid space containing CSF. In *Sushrutsamhita*, 'mastulungagam' (leakage of CSF through nose) is symptom mentioned in *atiyoga* (excess activity) of *Virechananasya*.⁴⁷

c) Drug transportation by transneuronal

Path : The olfactory region is situated at the roof of the nasal cavity in humans and which is about 2.5 cm² in each cavity or about 3% of the nasal surface area.⁴⁸ The olfactory nerve pathway; where drug is taken up into the neuronal cell by endocytosis or pinocytosis mechanisms and transported by

intracellular axonal transport to the olfactory bulb.⁴⁹ The olfactory neural pathway provides both an intraneuronal and extraneuronal pathway into the brain.^{50,51} The intraneuronal pathway involves axonal transport and requires hours to days for drugs to reach different brain regions. While the extraneuronal pathway probably relies on bulk flow transport through perineural channels, which deliver drugs directly to the brain parenchymal tissue and/or CSF. The extraneuronal pathway allows therapeutic agents to reach the CNS within minutes.⁵² Another possible pathway is through adjacent nerves called terminal nerves which run along the olfactory nerves. It is well-known that these nerves are connected with limbic system of the brain including hypothalamus, which is having control over endocrinal secretions. Hypothalamus is also responsible for integrating the function of the endocrine system and nervous system. Hypothalamus is directly connected with posterior lobe of pituitary by nerve fibers.⁵³

Acharya Charaka might know the concept of trans-neuronal and para-neuronal pathway of drug delivery from nose to brain therefore he has given example of *munja-ishika*. The *munja* structure can be correlated with

olfactory bulb and the *ishika* for the numerous neurons join together to form the olfactory tract.

CONCLUSION

Intranasal delivery bypasses the BBB to target CNS, reducing systemic exposure of drug, thereby reducing the systemic side effects. It also bypasses the hepatic first-pass metabolism and drug can directly enter into systemic circulation. It is an attractive option of drug delivery due to its non-invasiveness. A variety of neurotherapeutic agents including small drug molecules, proteins, peptides, hormones and biological cells such as stem cells can be delivered by this route, thereby yielding new insights into prevention and management of different neurological disorders. It is found that the intranasal administration of drugs is an effective way for systemic availability of drugs and the drug through nasal route may have extended efficacy compared to oral route. Thus the *Nasya karma* provides future potential for several drugs through the development of safe and efficacious formulations for simple, painless and long-term therapy.

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