

A CRITICAL REVIEW ON PHARMACOKINETICS OF NASYA

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ABSTRACT

Nose is considered as one among the *Panchagyanendriya*, whose functions are not only limited to olfaction and respiration but also considered as a pathway for drug administration. *Nasya Karma* is the special procedure where the drug is administered through nose. The medicine instilled through the nostrils easily penetrates the *Shringataka* and spreads to the Siras (arterioles) of Head (*Shira*), Eyes (*Netra*), Ears (*Shrotra*), Throat (*Kantha*) and expels out the impurities. Since nose is the gateway of the head, it is highly effective in curing a number of diseases pertaining to the head, if performed systematically. It cleanses and opens the channels of the head, thereby improving the process of oxygenation *Prana*, which has a direct influence on the functioning of brain. The olfactory nerves associated with the nasal pathway are connected with the higher centres of the brain i.e. limbic system, so the drugs administered through the nose stimulate higher centres of brain which in turn improves the endocrine and nervous system functions. Standardization of the *Nasya* with *Ayurveda* and modern scientific parlance is the need of the hour, and then only we would be able to do proper justification to this unique and noble treatment.

Keywords: Nose, *Panchagyanendriya*, Gateway, Olfactory nerves, *Shringataka*, *Nasya*

INTRODUCTION

Nasya is a therapeutic procedure, wherein the appropriate drugs in the form of *sneha* (unctuous substance), decoction, powder, processed milk, juice or medicated fumes are administered through the nose in a specific manner to cure various systemic diseases. The derivation of word *nasya* is from “*nasa*” dhatu. It conveys the sense of *gati* or motion. Many researches show that there is better absorption of drug in CSF through nasal route than any other route. Nasal drug delivery is superior to that of oral route because of hepatic first-pass metabolism and also drug degrada-

tion is absent; thus, nose-brain pathway leads to nearly immediate delivery of some nasal medications to the cerebral spinal fluid, bypassing the blood brain barrier. Nasal route is also the preferred route for some medications that are not absorbed orally and is a convenient route when compared with parenteral route for long-term therapy. Therapy through intranasal administration has been an accepted form of treatment in the Ayurvedic system of Indian Medicine. There is now that many drugs have shown to achieve better systemic bioavailability through nasal route than by oral ad-

ministration¹. Advances in biotechnology have made available a large number of protein and peptide drug for the treatment of a variety of diseases. These drugs are unsuitable for oral administration, because they are significantly degraded in the gastrointestinal tract or considerably metabolized by first pass effect in the liver. Even the parenteral route is inconvenient for long term therapy. Of many alternate routes tried, intranasal drug delivery is found much promising for administration of these drugs². As stated by Acharya Vagbhata, “*Nasa hi shirso dwaram*”³ which means the nasal passage is considered as the gateway to the brain and accordingly all drugs and measures introduced through the nose spread throughout the head and its constituent parts and may accordingly influence all the doshas and the diseases situated in these parts.

Anatomical And Physiological Considerations:

The Cribriform Plate Of Ethmoid Bone: It lies between the two orbital parts of the frontal bone. It separates the fossa from the nasal cavity, the roof of which it helps to form 1) foramen caecum 2) foramina in cribriform 3) anterior and posterior ethmoidal foramina. Through this anterior and posterior ethmoidal foramen the nerves and blood vessels are passed and forms connection from nasal cavity to cranial cavity. This is the passage between nose and cranium. The Shringataka marma has been explained as "middle cephalic fossa" ‘*shirasoantarmadhya*’ of the skull consisting of paranasal sinuses and meningeal vessels and nerves. The drug administered enters paranasal sinuses where the ophthalmic vein and other veins spread out. Due to vascularity, the drug is mainly absorbed through the capillaries (*raktavahini*). The capillaries of *Shleshmika kala* join venules which anastomose with each other to form plexus. Some of these venules open into the sphenopalatine veins. Others join facial vein, some end in ophthalmic vein, few communicate with siras and finally drain blood into systemic circulation. The *Shleshmika kala* of the *nasika* is continuous with frontal, maxillary, sphenoidal and ethmoidal sinus. Any drug, which is administered through the nose will certainly penetrate through the *Shleshmika kala* and will have its action on these sinuses⁴.

Stimulation Theory: Drugs present in *Nasya Kalpa* when come into contact with nasal mucosa irritate and stimulate the olfactory nerve cells lying in superior turbinate, which send efferent fibers to olfactory area in floor of cerebral cortex. The impulse from lateral olfactory stratum terminates at primary olfactory cortex, amygdaloid complex and many other areas. Efferent fibers from amygdaloid complex go to the hypothalamus and stimulate it, which in turn gives feedback to pituitary. Pituitary releases a ton of hormones that circulate our system and aid in maintaining our internal homeostasis⁵.

Factors influencing nasal drug absorption are:

1. Blood flow: Rich supply of blood and a large surface area makes the nasal mucosa an optimal location for drug absorption. The amount of blood flow influences the nasal absorption of a drug as it increases the amount of drug that passes through the membrane and hence reaching the general circulation. Therefore, proper *snehana* and *swedana* are required for proper vasodilatation that increases blood supply for better absorption.
2. Position: Head low position with slight elevation of legs helps medicine to reach deep inside olfactory mucosa and facilitates absorption.
3. Physiochemical properties of drug:
 - a. Lipophilicity: lipophilic drugs show better absorption. To achieve rapid diffusion through nasal mucosa, the lipid soluble drugs are preferred where the mucosal cilia are lipophilic in action.
 - b. Viscosity: Higher viscous formulation increases absorption of drug by increasing the contact time to nasal mucosa.
 - c. pH: pH of a drug also plays an important role. pH of the formulation should be near to human nasal mucosa i.e. (5 - 6.5) to prevent sneezing and for better absorption.
 - d. Volume: Quantity of nasya is mentioned in *Bindu pramana*. *Bindu* is the unit of measurement. *Bindu*¹⁰ is the unit of measurement and defined as the quantity of Drava (*Sneha*, *Swarasa*, *Kashaya* etc.) that dribbles down when the first two parts of index finger are dipped into it and taken out. Comment on this by Hemadri¹¹ proves beyond doubt that not just the first drop is one *Bindu*, but it is the total quantity dribbling

down from the index finger when immersed in the liquid should be considered as one Bindu⁶.

Advantages of nasal route drug administration are⁷⁻¹⁰:

Advantages of NDDS (Nasal Drug Delivery Systems) are: Drug degradation is absent in nasal drug delivery system which is present in case of oral intake of medicine. Hepatic first pass metabolism is absent. Also, there is seen rapid drug absorption and quick onset of action. Nasal bioavailability for smaller drug molecules is good. Instead, bioavailability of larger drug molecules can be improved by means of absorption enhancer or other approach.

- Avoidance of liver first pass effect.
- Fast onset of therapeutic effect.
- Rapid absorption.
- Higher bioavailability.
- Avoidance of metabolism by GIT.
- Non- invasive.

Research And Development In Nasal Drug Delivery¹¹:

Most of the over the counter nasal preparation are formulated as solution, to treat the nasal symptoms of allergic rhinitis and common cold. A simple drug solution is adequate for this purpose as it produces better dispersion over greater surface area. The nasal residence time of such formulation is short (3-20 min) and exhibit high inter individual variability. This route provides fast peak levels in circulation.

Breakthroughs of Nasal Drug Delivery System^{12,13}

1. Insulin administered through nasal route: Diabetes mellitus is a chronic disease that usually requires multiple insulin injections to achieve adequate glyce-mic control. This represents a major cause of reduced compliance to treatment. Consequently, other routes for insulin administration have been explored. During recent years, much progress in the development of inhaled insulin has been made. Inhaled insulin has favorable properties, such as rapid onset of action, improved bioavailability and good tolerability, thereby providing satisfaction and ease of administration. However, long-term safety of inhaled insulin needs to be assessed, and the cost would be higher than inject able insulin. Nasal, oral and transdermal insulin are undergoing early phases of pharmacological develop-

ment. The purpose of this review is to describe the latest developments in the area of non-invasive routes for insulin delivery. A large number of patients with diabetes worldwide require daily dose of insulin. Insulin therapy, using the vial and syringe method is complicated and time consuming. To find an alternative way to deliver insulin will elude the researchers to replace inject able insulin by more comfortable, non-invasive and less strenuous delivery method, which can provide in pharmacokinetically consistent manner. The present article reviews the various alternatives for insulin delivery.

2. Cancer pain management through nasal route:

Cancer pain management necessitates the use of opioids when pain is moderate or severe. Opioids need to be versatile and effective. Newer formulations may improve patient compliance and may be more conducive to the management of transient flares of pain; they also may be tailored to treat certain special populations and may be particularly effective in certain clinical situations.

3. Antibiotics and mucolytics are delivered to the nasal cavity:

Decongestants, antibiotics and mucolytics are delivered to the nasal cavity, their intended site of action. Due to its accessibility, relatively large surface area 160 cm² and rich vascular supply of the nasal mucosa, the nasal route of administration is attractive for many drugs for systemic absorption, including proteins and peptides. Due to rich blood supply, drugs absorbed via the nasal route have a rapid onset of action, which can be exploited for therapeutic gain. The nasal delivery is also recommended in order to avoid degradation in the gastro intestinal fluid, metabolization in the gastrointestinal tract or biotransformation by the first pass effect. The ease of administration via the nasal route may also lead to increased patient compliance. Nasal devices such as metered doses nasal sprays have been developed that are simple for patient to use. Patient with swallowing difficulty and/or children can be treated with less difficulty with nasal drug delivery system. Thus, Nasal drug delivery can:

- Promote rapid onset of action.
- Avoid gastrointestinal tract or first pass metabolism

- Enhance patient compliance

5. Microsphere as nasal drug delivery system: All types of microspheres that have been used as nasal drug delivery system are water insoluble but absorb water into the sphere matrix, resulting in swelling of the spheres and the formulation of a gel. The building materials in the microspheres have been starch, dextran, albumin and hyaluronic acid, and the bioavailability of several peptides and proteins has been improved in different animal models. Also, some low molecular weight drugs have been successfully delivered in microsphere preparations. The residence time in the cavity is considerably increased for microspheres compared to solutions. However, this is not the only factor to increase the absorption of large hydrophilic drugs. Microsphere also exerts a direct effect on the mucosa, resulting in the opening of tight junctions between the epithelial cells. Starch and dextran microspheres have been administered repeatedly and can be classified as safe dosage forms.

6. Utility of insoluble powder formulation for nasal systemic drug delivery: Insoluble powder formulations improve nasal bioavailability predominantly by retarding drug elimination from the absorption site and appear to be effective for nasal systemic drug delivery.

Mode Of Action Of Nasya:

According to *Acharya Chakrapani*, drug administered through *nasya karma* enters into head and draws out exclusively morbid *doshas* as *Ishika* is taken out after removing the fibrous coating of *Munja* adhered to it. In *Sushruta Samhita*, “*Mastulungagam*” (passage of brain matter i.e. CSF through nose) is a symptom mentioned in excess activity of *virechana nasya*¹⁴. This shows that *aacharya Sushruta* was already aware of the fact of relation between nose and brain.

In modern science, nasal route is easily accessible, convenient and reliable with a porous endothelial membrane that provides a rapid absorption of compounds into the systemic circulation. The nasal delivery seems to be a favorable way to bypass the obstacles for blood-brain-barrier allowing the direct drug delivery in the bio phase of CNS. It has also been considered as the route of administration of vaccines¹⁵.

The pharmacodynamics of Nasya karma can be explained as follows:

A. Vascular Pathway: The nasal passage is highly vascular structure. Rich vascular plexus permits topically administered drugs to absorb rapidly. Vascular path transportation is possible through the pooling of nasal venous blood into the facial vein which then communicates freely with the intracranial circulation. This is the natural phenomenon. Interestingly, facial vein has no venal valve present in between it. So, the pooling of blood from facial vein to the Cavernous Venous Sinus of brain is also possible due to gravity while lying in head lowered position in nasya karma. Thus, it is a point of consideration. In the support of this hypothesis it is described in modern medicine also that the infective thrombosis of facial vein may lead to infection of meninges easily, through this path. William et al. 1971 Pooling of the blood from paranasal sinuses is also possible in the same manner.

B. Neural Pathway: The adjacent nerves called Terminal nerves which run along the olfactory nerves have been reported but their functions are not identified. However, it is well known that these nerves are connected with the limbic system of brain including hypothalamus. Thus, drugs administered through nose may have an impact on immediate psychological functions by acting on limbic system through olfactory nerves. Moreover, hypothalamus is considered to be responsible for integrating the functions of endocrine system. Thus, endocrinal effects may be achieved through nasya karma.

C. Lymphatic Pathway: Pathways connecting the subarachnoid space containing CSF, Perineural spaces encompassing olfactory nerves and nasal lymphatics provide a gateway for intranasally applied therapeutics to the CSF and other areas of CNS. Along with olfactory nerve, the arachnoid matter sleeve is extended to sub mucosal area of nose. Correlation between them is understood by the fact that dye injected to arachnoid matter causes coloration of nasal mucosa within seconds and vice versa also. This pathway thus ensures the access of drugs to CNS after intranasal administration, moving from nasal passage to CSF. There is a body of evidence indicating that

tracers placed in the CSF will quickly move via the olfactory nerve to the nasal mucosa and then to the cervical lymph nodes. Organic and inorganic tracer materials and organisms as diverse as viruses, a bacillus, and an amoeba, when placed in the nasal cavity, have been shown to move from the nasal mucosa via the olfactory nerve to the olfactory bulb and the CSF.

CONCLUSION

The medicine given through nose reaches to brain and acts on higher centers of brain controlling different neurological, endocrinal and circulatory functions and thus showing various effects. The relevancy of “*Nasa hi Shirso Dwaram*” can be proved which ultimately explains the mode of action of *Nasya*.

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Source of Support: Nil

Conflict Of Interest: None Declared

How to cite this URL: Rishu Sharma & Gyanendra Datta Shukla: A Critical Review On Pharmacokinetics Of Nasya. International Ayurvedic Medical Journal {online} 2019 {cited September, 2019} Available from: http://www.iamj.in/posts/images/upload/1579_1583.pdf