

## Ischemic Stroke Associated with Chronic Xylometazoline Nasal Spray Misuse: A Rare Avoidable Adverse Event

Sir,

A 54-year-old male presented with acute onset vertigo, with imbalance, with swaying towards the side with dysarthria, dysphonia, and dysphagia. On examination, he had decreased pain and temperature sensations in right upper and lower limbs, loss of pain, and temperature sensations on the left side of the face, truncal ataxia with swaying towards left, left-sided cerebellar signs and left Horner's syndrome. He did not have any conventional stroke risk factors like hypertension, diabetes mellitus, dyslipidemia, tobacco or alcohol use, or positive family history. His magnetic resonance imaging (MRI) of the brain was suggestive of acute left lateral medullary infarct with left vertebral artery stenosis [see Figures 1 and 2]. His blood pressure at admission and through the course, hemogram, liver function test, renal function test, glucose, lipid profile, electrocardiogram, 2D echocardiogram, and neck vessel angiography were normal. He was also screened for vasculitis and hypercoagulable states [erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), lupus anticoagulant, antiphospholipid

syndrome, antineutrophilic antibodies (ANA), factor V Leiden, antithrombin III, prothrombin mutation, level of protein C and S, level of homocysteine, thyroid-stimulating hormone (TSH)] but all reports were negative. On reanalyzing history, the patient had a habit of using xylometazoline (1 mg/ml) nasal spray 3–4 times a day for the last 5–6 years. It was prescribed to him before many years by a physician for an upper respiratory tract infection, but since then he had continued to use it continuously by purchasing it over the counter from local pharmacies. Thus, xylometazoline was considered to be the etiological factor for the cerebral vasospasm induced ischemic stroke in this case. The patient was advised to stop xylometazoline spray immediately and was treated with aspirin, clopidogrel, and statin for secondary prevention.

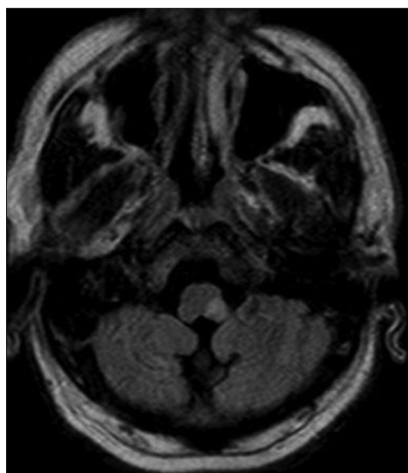
Ischemic stroke due to sympathomimetic drugs is a silent hidden healthcare problem. Though this association is relatively rare in the community, this association of stroke and sympathomimetic drug use is increasingly being described.<sup>[1,2]</sup> Common sympathomimetic drugs like pseudoephedrine,

phenylephrine (oral), and also xylometazoline, oxymetazoline, naphazoline, ephedrine, and tuaminoheptane (intranasal) are widely used over the counter (OTC) drugs in conditions like common cold, allergic rhinitis, sinusitis, and upper respiratory tract infection.<sup>[2]</sup> Common side effects of these drugs including xylometazoline are dryness, burning or stinging inside the nose, sneezing, runny nose whereas headache, dizziness, anxiety, palpitations, wheezing are some less pronounced side effects.<sup>[3]</sup> These OTC sympathomimetic drugs can also be an independent risk factor for ischemic and hemorrhagic stroke.<sup>[1]</sup>

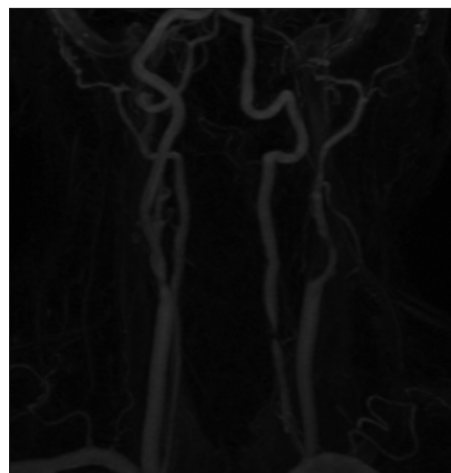
There are many pathophysiological presumptions for a cerebrovascular accident in our case. One of them and the most presumable is the vasoconstriction of cerebral arteries. Xylometazoline is an imidazoline derivative that causes a reduction in nasal mucosal edema by directly acting on adrenergic receptors or indirectly releasing more potent vasoconstrictor norepinephrine (NE), which in turn potentiates adrenergic tone and causes vasospasm of cerebral arteries.<sup>[1]</sup> Adrenergic receptors are diffusely located in the vascular walls including cerebral vessels and they play a very crucial role in cerebral blood flow.<sup>[4]</sup> Adrenergic receptors are mainly categorized into alpha 1 receptors, alpha 2 receptors, and beta receptors.<sup>[5]</sup> Cerebral arteries contract in response to alpha-adrenergic agonist and this contraction can be blocked by alpha-adrenergic antagonist.<sup>[4]</sup> Sympathomimetic agents (epinephrine, NE, naphazoline, and xylometazoline) can control vascular tone and/or permeability in the central nervous system (CNS) and this can lead to blood pressure alterations and associated central nervous system complications.<sup>[5]</sup> Ischemic stroke in our patient could be due to reversible cerebral vasoconstriction syndrome (RCVS) secondary to xylometazoline mediated central adrenergic receptor stimulation. RCVS is defined as reversible vasospasm of intracerebral arteries mainly brought on by the disturbance in vascular tone.<sup>[6]</sup> It presents as a severe thunderclap headache with or without focal neurological deficits.<sup>[6]</sup> It is triggered by pregnancy and its complications (eclampsia, pre-eclampsia), sympathomimetic drugs (pseudoephedrine,

oxymetazoline, xylometazoline), anti-depressants, illicit drug abuse, etc., Cerebral vasoconstriction in RCVS can lead to ischemic stroke (could be a mechanism in our case) and even intracerebral hemorrhage (intraparenchymal hemorrhage, sub-arachnoid hemorrhage) in some cases.<sup>[6]</sup>

The possible mechanism of hemorrhagic stroke due to sympathomimetic drugs is hypertensive crisis and vasculitis of the cerebral arteries which can also lead to subarachnoid and/or intracerebral hemorrhage.<sup>[1]</sup> Usage of phenylpropranolamine (nasal decongestant) has proven association with hemorrhagic stroke in 142 cases.<sup>[7]</sup> Phenylpropranolamine is used as appetite suppressants (in 16 cases) and common cold OTC medicine which leads to 22 cases of hemorrhagic stroke reported by the Food and Drug Administration (FDA).<sup>[8]</sup> Usage of naphazoline as nasal decongestant leads to hemorrhagic stroke in 1 case report with the possible mechanism of vasospasm or an increase in blood pressure.<sup>[9]</sup> It is presumable that the development of stroke would occur in a short interval of use or due to change in the pattern of dosage of sympathomimetic drugs. However, stroke has been described to occur after chronic use without any dosage modifications too as seen in our case. Leupold D, *et al.*,<sup>[1]</sup> Costantino G, *et al.*,<sup>[9]</sup> and Cantu C, *et al.*,<sup>[10]</sup> reported patients developing stroke with chronic use of nasal sympathomimetic drugs without any change of pattern as in our case. Amongst the cases of stroke associated with nasal sympathomimetic drugs, hemorrhagic strokes have usually been described following acute short-term use while ischemic strokes have been described with chronic use. It can be postulated that acute sympathomimetic use may lead to accelerated hypertension/hypertensive crisis leading to intracerebral hemorrhage, while chronic use of these drugs may be leading to central adrenoreceptors dysfunction predisposing to chronic vasculopathy manifesting as ischemic stroke. Such focal vasculopathy of nasal mucosa has been described with nasal decongestant spray use leading to rebound nasal congestion on stopping the use and this has been postulated to lead to chronic continuous use of such nasal decongestants by the patients. This phenomenon of “rebound congestion” has been described as



**Figure 1:** MRI brain showing left medullary infarct



**Figure 2:** MRI brain showing left vertebral stenosis

**Table 1: Case series of stroke reported because of nasal administration of sympathomimetic drugs**

Number	Gender/Age of patient	Nasal Drugs and Dosage	Duration of drug use	Type of stroke	CT/MRI findings	Reference
1	Male/34 year	Xylometazoline –(1 mg/ml) - 5 times/ day	10 years	Ischemic Stroke	Bilateral postero-inferior cerebellar artery (PICA) infarct	[1]
2	Male/44 year	Naphazoline nasal spray (0.125 g/100 ml) - 3 times/ day	5 days	Hemorrhagic stroke	Thalamic hemorrhage	[7]
3	Male/45 year	Naphazoline (0.125 g/100 ml) nasal spray - 20 times/ day	Several years	Ischemic Stroke	Right frontal subcortical infarct	[9]
4	Male/57 year	Phenylephrine (1 mg/ml) nasal spray - 3 times/day	4 months	Hemorrhagic stroke	SAH (subarachnoid hemorrhage), left temporal hemorrhage, right occipital infarct	[10]
5	Male/40 year	Oxymetazoline (1 mg/ml) nasal spray - daily	1 week	Hemorrhagic stroke	SAH	[10]
6	Male/36 year	Naphazoline (0.125 g/100 ml) nasal spray	2 week	Ischemic Stroke	Bilateral thalamic infarction	[12]
7	Male/35 year	Oxymetazoline (15 mg) every 3 days	20 years	Ischemic Stroke	Middle cerebral artery infarct	[13]
8	Male/40 year	Phenoxazoline (10 mg) every 5 days	15 years	Ischemic Stroke	Middle cerebral artery infarct	[13]
9	Young male	Oxymetazoline hydrochloride 0.5% (Afrin)	-	Ischemic Stroke	Retinal artery obstruction	[14]

Rhinitis medicamentosa and occurs due to inflammation of the nasal mucosa caused primarily by the prolonged use (more than 7 to 10 days) of topical nasal decongestant.<sup>[11]</sup> There are 2 cases reported having brain infarction and 1 case having retinal artery occlusion due to chronic nasal use of oxymetazoline and presumed mechanism is arterial occlusion.<sup>[10]</sup> A French pharmacovigilance survey reported 52 cases of stroke in association with nasal decongestant use.<sup>[2]</sup> Other than the survey, other cases of stroke due to short and long term use of nasal sympathomimetic drugs have also been reported in the medical literature [Table 1]. All the cases of stroke have been reported with the usual therapeutic doses of sympathomimetic drugs and no dose-dependent effect has been reported making it pertinent to be aware of this association as stroke can have major devastating long-term sequelae for the patients.

Even in India, xylometazoline nasal sprays are easily available as OTC medicines. Use of OTC sympathomimetic nasal spray can be an independent risk factor for stroke and this should be considered in the evaluation of causes of stroke. The rare risk of stroke associated with sympathomimetic nasal sprays should also be discussed with patients before prescription of such therapy.

### Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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### Conflicts of interest

There are no conflicts of interest.

**Jalpan Patel, Ishani Patel, Devangi Desai<sup>1</sup>, Soaham Desai<sup>2</sup>**

Physician Doctor, <sup>1</sup>Professor in Medicine Department and <sup>2</sup>Sr. Consultant Neurologist, Professor and Head, Neurology, Shree Krishna Hospital, Pramukhswami Medical College, Karamsad, Anand, Gujarat, India

**Address for correspondence:** Dr. Soaham Desai, Sr. Consultant Neurologist, Professor and Head, Neurology, Shree Krishna Hospital, Pramukhswami Medical College, Karamsad, Anand, Gujarat - 388 325, India.  
E-mail: drsoahamdesai@yahoo.com

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