

IS BRAIN DEATH REVERSAL POSSIBLE IN NEAR FUTURE: INTRATHECAL SODIUM NITROPRUSSIDE (SNP) SUPERFUSION IN BRAIN DEATH PATIENTS = THE 10,000 FOLD EFFECT

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ABSTRACT: BACKGROUND: Primary or secondary brain death is accompanied with vasospasm of the perforators & further exaggerating the anoxic damage, in the form of neuropraxia. In normal conditions the excitatory impulse propagates as anterograde neurotransmission (ANT) and at the level of synapse, glutamate activates NMDA receptors on postsynaptic membrane. Nitric oxide (NO) is produced by Nitric oxide Synthetase (NOS) in postsynaptic dendrite or cell body and travels backwards across a chemical synapse to bind to the axon terminal of a presynaptic neuron for regulation of ANT this process is called as the retrograde neurotransmission (RNT). Thus the primary function of NO is RNT and the purpose of RNT is regulation of chemical neurotransmission at synapse. For this reason, RNT allows neural circuits to create feedback loops. The haem is the ligand binding site of NO receptor (sGC) at presynaptic membrane. The affinity of haem exhibits >10, 000-fold excess for NO than Oxygen (THE 10, 000 FOLD EFFECT). In pathological conditions ANT, normal synaptic activity including RNT is absent. NO donors like sodium nitroprusside (SNP) releases NO by activating NOS at the level of postsynaptic area. NO now travels backwards across a chemical synapse to bind to the haem of NO receptor at axon terminal of a presynaptic neuron as in normal condition. NO now acts as impulse generator (at presynaptic membrane) thus bypasses the normal ANT. Also the arteriolar perforators are having Nitric Oxide Synthetase (NOS) at the adventitial side (outer border) on which sodium nitroprusside (SNP) acts; causing release of Nitric Oxide (NO) which vasodilates the perforators causing gush of blood in brain's tissue and reversal of brain death.

OBJECTIVE: In brain death cases we only think for various transplantations but this study being a pilot study reverses some criteria of brain death by vasodilating the arteriolar perforators. To study the effect of intrathecal sodium nitroprusside (IT SNP) in cases of brain death in which: Retrograde transmission = assessed by the hyperacute timings of reversal. The arteriolar perforator vasodilatation caused by NO and the maintenance of reversal of brain death reversal. **METHODS:** 35 year old male, who became brain death after head injury and has not shown any signs of improvement after every maneuver for 6 hours, a single superfusion done by SNP via transoptic canal route for quadrigeminal cistern and cisternal puncture for IV ventricular with SNP done. **RESULTS:** He showed spontaneous respiration (7 bouts) with TCD studies showing start of pulsations of various branches of common carotid arteries. **CONCLUSIONS:** In future we can give this SNP via transoptic canal route and in IV ventricle before declaring the body to be utilized for transplantations or dead or in broader way we can say that in near future it is possible to revert back from brain death or we have to modify our criterion.

KEYWORDS: Brain Death; Intrathecal Sodium Nitroprusside; Tcd Studies; Perforators; Vasodilatations; Retrograde Transmission; The 10,000 Fold Effect.

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INTRODUCTION: Understanding of brain death's etiopathogenesis has undergone a giant stride in past decades, so as the further management, from simple surfeit waiting for natural death to medical fraternity fostering stem cell transplantations in brain or various organ transplantations. Even doctors treat the patients frantically either from relevant court cases or due to loss of any further hope of survival.

This can only be eulogized and pertinent if the brunt of brain death cases be minimized and interventional therapeutic measures' aggrandizement noted which can show a ray of light in future. Primary or secondary brain deaths are associated with ischemia to some part of the brain and brain stem due to acute neurogenic shock or a cortical tissue disruption. The ischemia further leads to local axonal reflex stimulation which causes local perforators to go in spasm & further exaggerating the anoxic damage, in the form of neuropraxia along with infarcted area.

For physiological recovery we have to think at the gross root level i.e., synapses. For that we have to understand the normal and abnormal impulses well documented with nonclinical and clinical studies done previous in literature.

IN NORMAL CONDITIONS:

- 1) **GLUTAMATE RELEASE AT SYNAPSE UPTO NO DIFFUSION:** When an excitatory impulse, anterograde neurotransmission (ANT), spreads over the presynaptic terminal, the membrane depolarization causes glutamate release to synaptic cleft. Glutamate then activates NMDA receptors [~ 50 NMDA receptors dispersed over a 400-nm-diameter postsynaptic density¹ at postsynaptic membrane which further propagates excitatory impulse to cell body and also it activates calcium and calmodulin to bind with each other² and causes release of nitric oxide (NO) from nitric oxide synthetase (NOS) (One NOS molecule generates 20 NO molecules per second). NO diffuses in the synaptic cleft.³
- 2) **NO CLOUD FORMATION TO 10, 000 FOLD EFFECT:** As a result of diffusion, NO cloud is formed at synaptic cleft.^{1,3} NO travels backward across a chemical synapse to bind to the axon terminal (NO receptor/sGC) of a presynaptic neuron for regulation of ANT this process is called as the retrograde neurotransmission (RNT).⁴ NO receptors are equipped with a ligand binding site and a transduction domain but differ in some properties which are mesmerizing. The ligand binding site is an unremarkable haem group of the type used in hemoglobin for binding oxygen but, when incorporated into the receptor protein, it exhibits > 10, 000-fold excess of affinity for NO than oxygen^{5,6} (THE 10, 000 FOLD EFFECT).
- 3) **RNT ACTION OF NO TO IMPULSE GENERATION:** NO travels randomly and surprisingly quickly.⁷ So the primary function of NO is RNT and the purpose of RNT is regulation of chemical neurotransmission at synapse.¹ For this reason, RNT allows neural circuits to create feedback loops. RNT mainly serves to regulate typical ANT rather than to actually distribute any information, similar to electrical transmission. So NO can up regulate⁸ or down regulate^{9,10} the oncoming impulse. The endocannabinoids anandamide and/or 2-AG, acting through G-protein coupled cannabinoid receptors, are the primary retrograde messengers in the brain, and may also play an important role in retrograde signalling in long term potentiation (LTP) which is meant for memory and learning¹¹⁻¹⁴ as is nitric oxide. NO's RNT like action is also shown by carbon

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monoxide,¹⁵ platelet-activating factor,^{16,17} and arachidonic acid. NO provides a simultaneous signal to both pre- and postsynaptic elements, of probable importance in coordinating responses on the two sides of the synapse (bridging the microgaps by cloud of NO).^{3,18} In brain cells, NO switches on the associated guanylyl cyclase activity with no observable delay (with a 20-ms sampling time) and, on removal of NO, the activity decays with a half-time of 200ms¹⁹ generating and mimicking ANT where kinetics not dissimilar to that of NMDA receptors or glutamate receptors.^{18, 20}

Through subsequent activation of guanylyl cyclase and production of cGMP, NO production influences a variety of secondary processes. These include direct modulation of ion channels, stimulation of cGMP-dependent protein kinase, and both up-regulation or down-regulation of cAMP-phosphodiesterase. Downstream effects are then numerous and include up and down regulation of Ca²⁺ channels, increased excitability (increases neuronal firing rate), increased or decreased neurotransmitter release, and changes in neuron morphology.¹

NO produces the electrical impulses, also shown in vitro by an experimental study by O Dell et al (1991) on rats tissues where the exogenous NO donors increases frequencies of spontaneous miniature EPSPs.¹⁰ In brain, NO has a stellar role in neurotransmitter modulation, RNT, synaptic plasticity and a very potent vasodilator.

IN ABNORMAL CONDITIONS:

- 1) **IMPULSE TOO HIGH OR TOO LOW:** But in abnormal conditions like, if the impulse coming is of too much high in intensity as in schizophrenia,²¹ or Obsessive compulsive disorder²² NO will down regulate the impulse and in the cases of low impulses as in depression in which the serotonin levels are low then it will up regulate the impulse.²³
- 2) **IN ABSENCE OF IMPULSE:** If the impulse is not coming at all (as in ischemia) normal ANT including synaptic activity and thus RNT is absent. Then NO donors have shown a promising result in generating an impulse by NO via RNT in vitro in rats.²⁴ In this experimental study done by O Dell et al (1991) on rats' tissue the exogenous NO donors increase frequencies of spontaneous miniature EPSPs. NO now travels backward across a chemical synapse to bind to the axon terminal (NO receptor sGC) of a presynaptic neuron, as in normal condition, now acts as impulse generator (at presynaptic membrane) thus bypasses the normal ANT.

Primary or secondary brain death is accompanied with vasospasm of the perforators & further exaggerating the anoxic damage, in the form of neuropraxia and absent RNT. The various modalities for further management are for various transplantations but none of the studies were directed towards the vasodilation of vasospastic arteriolar perforators at ischemic zone and the very potent RNT by bypassing the ANT (THE 10, 000 FOLD EFFECT). The ANT is hampered due to absence of blood supply (because of vasospasm and/or obstruction) and also due to absence of any drives which can generate the ANT.

The vasodilator effect of SNP is known since the evolution of emergency treatment of hypertension.²⁵ The antihypertensive action is instantaneous; onset of action is in 30 seconds and peak in 2-5 mints in hypertensive cases.²⁶ The impact of the intrathecal and intraventricular

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administration in vasospastic cases is at the level of the microcirculation²⁷⁻²⁹ The impact of treatment on the larger-caliber conductance vessels appears to be minimal, while the decreased cerebral circulation time indicates improved cerebral blood flow by way of the microcirculation.

SNP as a NO donor has been administered by the arterial route for the treatment of ergotism in human beings³⁰⁻³³ and for cerebral vasospasm in dogs.³⁴ The return of acute cerebral vasospasm in dogs after 15 or 30 minutes following completion of the nitroprusside infusion in dogs suggests that the vasodilatation was secondary to the drug infusion and not to the spontaneous resolution of acute spasm.

Autoregulation by cerebral vessels was well documented in cats after intracarotid SNP.³⁵ Intracarotid injections in human beings have being given by many researchers^{36,37} and they found that SNP does not augment cerebral blood flow in human subjects. But these studies were done on normal human beings who were being subjected to DSA for other reasons. That may be due to the fact that NO is a regulator of ANT via RNT so it will not affect the CBF until any pathological condition causes either low or high impulses' situation like in Schizophrenia,²¹ OCD²² and depression.²³

The cloud of NO is being depleted by a highly efficient extracellular scavenger Superoxide, thus forming peroxynitrite which in turn is removed by serum superoxide dismutase (S.SOD). S.SOD level in patients with acute cerebral ischemic injury is inversely proportional to the size of infarction on CT and the severity of neurological deficits.³⁸ The decreased SOD activity recovered within 5 days after stroke to values found in serum of control patients by Chemiluminescence which was measured for 20 minutes in 1-minute cycles in BioLumat LB 9501.³⁸ Also in vitro (in rats) the NO donor results in generating an impulse of miniature EPSPs via RNT.²⁵

This same Principle of generation of impulses from presynaptic region to postsynaptic region by the 10,000 FOLD EFFECT of NO along with vasodilatation of the arteriolar perforators is the basis of authors' hypothesis to treat brain death cases. The intrathecal SNP (IT SNP) opens up the arteriolar perforators and also generates the ANT via the very potent RNT function of NO which may be one of the possibilities of instantaneous clinical recovery to some extent.

TCD has been recommended for assessing CBF in suspected brain-dead patients³⁹⁻⁴⁵ TCD is a noninvasive technique that measures local blood flow velocity and direction in the proximal portions of large intracranial arteries. TCD requires training and experience to perform it and interpret results; hence, it is typified as operator-dependent.^{46,47} In the ICU setting, intensivists or neurologists usually receive training to apply this technique using portable Doppler devices in suspected brain-dead cases. Oscillating flow, systolic spikes, or no flow patterns are typical Doppler-sonographic flow signals found in the presence of cerebral circulatory arrest, which if irreversible, results in BD.⁴⁸⁻⁵⁰

MATERIALS AND METHODS: The Ethical Committee clearance has been taken from the ethical committee of King George's Medical College Lucknow UP number 103/R cell 03 dated 03/10/2003. Potential benefits and significant risks, specifically the unresponsiveness to this new modality of treatment were discussed with all patients' families and a well written & video consent has been taken from the relatives of the patients for IT SNP, video recordings of pre and post injection phase with Trans Cranial Doppler (TCD).

35 year old male, who after head injury (CT SCAN having mild discrete contusions) became brain death on 14th day of injury (he fulfilled all the criterion of brain death i.e., GCS=E1VTM1, NO

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CRANIAL NERVE REFLEXES (PUPILLARY, RAPID HEAD IMPULSE TEST, OCULOCEPHALIC REFLEX, CORNEAL REFLEX, CALORIC REFLEX AND COMPLETE ABSENCE OF SPONTANEOUS RESPIRATION) and has not shown any signs of improvement after every maneuver for 6 hours. Cerebral circulatory arrest (CCA) is confirmed by TCD examination. Two examinations within a time lag of 30 minutes revealed missing flow signals in transcranial examination of intracranial arteries (figure 3).

Patient received IT SNP prepared meticulously by photo protecting and sterile technique was observed for all aspects of delivery of the medication as well as its formulation. Powdered SNP were sterilely reconstituted with 200ml of dextrose 5% with 50 mg of the SNP. Patient received 0.2 mg/kg of IT SNP up to a maximum of 8 ml (around 2 mg) was superfused via transoptic canal route (i.e., to insert 24 G LP needle in one of the supraorbital notch and proceeding forwards and inwards always touching the orbit's roof pointed towards ipsilateral optic canal and then feeling the give way as and when the quadrigeminal cistern is reached then drain the CSF and do the superfusion for quadrigeminal cistern superfusion and cisternal puncture for IV ventricular superfusion with SNP i.e., around 2 ml of CSF was taken out and 8 ml of the SNP solution was put in) slowly, about in 5 mints. Waited for 10 mints and again superfusion was done slowly and the recovery is noted.

Meticulous photoprotection and sterile technique were observed for all aspects of delivery of the medication as well as its formulation. Whole calculated dose was given as a bolus dose using sterile technique in 3 minutes by 24 G LP needle in carotid artery. We waited for 1.30 mints for the recovery along with continuous TCD studies.

RESULTS: Brain death was confirmed clinically with TCD examination (missing flow signals in transcranial examination of intracranial arteries). Brain death reversal signs are evident in the form of spontaneous respiration (SEVEN BOUTS figure 1, 2) with a single superfusion of SNP via transoptic canal route and 4th ventricular superfusion with SNP. YOU TUBE URLS;

<http://youtu.be/Y0h6WH27xu8>.

TCD studies shows start of pulsations of various branches of common carotid arteries (figure 3). Then he died after 24 hrs. due to cardiopulmonary arrest.

DISCUSSION: The brain death caused either by cranial pathology (primary brain death in which anatomical insult is main cause) or noncranial cause (secondary brain death in which decreased blood supply is the cause) is one of the dreadful conditions.

NO is a free radical, gas that freely diffuses through membranes and short-lived with a half-life measured in seconds and is therefore a highly reactive compound.

The various perforators of brain and brain stem, due to local axon reflex gets vasoconstriction thereby immediately decreasing the blood supply and producing the cranial shock or neuropraxia. Inj SNP superfusion which opens up the arteriolar perforators and vasodilatations thereby gush of blood in the brain and brain stem so the immediate (onset of action in 30 seconds and peak in 2-5 mints)⁽²⁶⁾ improvement of the functions of brain.

The cranial shock (which is having intact brain and without any anatomical disruption such as cranial contusion or compression) is recoverable with the Sodium Nitroprusside superfusion.

Thus the seven bouts of spontaneous respiration suggest something that we should proceed in the same direction and plan for a big study.

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We hypothesize that very potent retrograde transmission function of NO may be one of the possibilities of instantaneous clinical recovery.

In 2009, Regehr et al. proposed criteria for defining retrograde neurotransmitters. According to their work, a signaling molecule can be considered a retrograde neurotransmitter if it satisfies all of the following criteria: ⁴

1. The appropriate machinery for synthesizing and releasing the retrograde messenger must be located in the postsynaptic neuron.
2. Disrupting the synthesis and/or release of the messenger from the postsynaptic neuron must prevent retrograde signalling.
3. The appropriate targets for the retrograde messenger must be located in the presynaptic buttons.
4. Disrupting the targets for the retrograde messenger in the presynaptic buttons must eliminate retrograde signalling.
5. Exposing the presynaptic button to the messenger should mimic retrograde signalling provided the presence of the retrograde messenger is sufficient for retrograde signalling to occur.
6. In cases where the retrograde messenger is not sufficient, pairing the other factor(s) with the retrograde signal should mimic the phenomenon.

A special property of NO compared with conventional neurotransmitters is its free diffusion through aqueous and lipid environments, so it is not possible to predict where it will act after being synthesized in either pre- or postsynaptic sites from the standpoint of diffusion alone. Indeed, a special advantage of a messenger such as NO would be that it provides a simultaneous signal to both pre- and postsynaptic elements, of probable importance in coordinating responses on the two sides of the synapse (bridging the gap).⁴

The ligand binding site of NO receptor is having an unremarkable haem group of the type used in hemoglobin for binding O₂ but, when incorporated into the receptor protein, it exhibits > 10000-fold excess for NO than O₂ ^{5,6}. This action of NO probably causes mesmerizing instantaneous effect.

This study done has certain limitations to have CT Perfusion, DSA & MRA in pre and post injection period with DWI AND PWI but being a pilot study we were not able to get the resources and funding for these cases.

This preliminary data from a primary neurosurgical care center from a developing country shows that the use of vasodilating effect of SNP in brain death case is both feasible and useful. However, since the study is strictly observational, it may be taken as a pilot project to evaluate essentially the feasibility and safety. We accede that this is in a single case to draw any definite conclusions. A future trial needs to be undertaken with a blinded, controlled and randomized design to quantify the above findings.

The result depends on the various factors that are:

1. Time of presentation of disease and its decompression.
2. Status of brain stem seen at operation i.e., inflamed or contused (restoring anatomical structure).
3. Sub arachnoid space and the perforators' patency.

CONCLUSIONS: In future we can give this SNP via transoptic canal route and in fourth ventricle before declaring the body to be utilized for transplantations or brain dead or in broader way we can say that in near future it is possible to revert back from all the criterion of brain death or we have to modify our brain death criterion.

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Figure 1



Figure 2

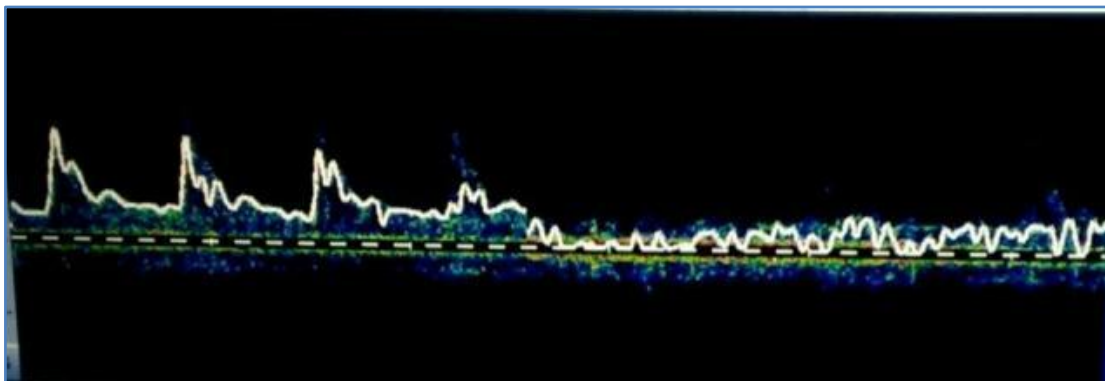


Figure 3

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