

THE 10,000 FOLD EFFECT OF RETROGRADE NEUROTRANSMISSION, A NEW CONCEPT FOR STROKE REVIVAL: USE OF INTRACAROTID SODIUM NITROPRUSSIDE

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ABSTRACT: BACKGROUND: Tissue Plasminogen Activator (tPA) showed a level 1 benefit in acute stroke (within 3-6 hrs). Intracarotid sodium nitroprusside (ICSNP) has been studied in this context with a wide treatment window, fast recovery and affordability. This work proposes two mechanisms for acute cases and one mechanism for chronic cases, which are interrelated, for physiological recovery. **RETROGRADE NEUROTRANSMISSION (acute cases): Normal excitatory impulse:** at the synaptic level, glutamate activates NMDA receptors, with nitric oxide synthetase (NOS) on the postsynaptic membrane, for further propagation by the calcium-calmodulin complex. Nitric oxide (NO, produced by NOS) travels backward across the chemical synapse and binds the axon-terminal NO receptor/sGC of a presynaptic neuron, regulating anterograde neurotransmission (ANT) via retrograde neurotransmission (RNT). Heme is the ligand-binding site of the NO receptor/sGC. Heme exhibits >10, 000-fold higher affinity for NO than for oxygen (the 10, 000-fold effect) and is completed in 20 msec. **PATHOLOGICAL CONDITIONS:** normal synaptic activity, including both ANT and RNT, is absent. A NO donor (SNP) releases NO from NOS in the postsynaptic region. NO travels backward across a chemical synapse to bind to the heme of a NO receptor in the axon terminal of a presynaptic neuron, generating an impulse, as under normal conditions. **VASOSPASM (acute cases):** Perforators show vasospastic activity. NO vasodilates the perforators via the NO-cAMP pathway. **LONG-TERM POTENTIATION (LTP) - (chronic cases):** The NO-cGMP-pathway plays a role in LTP at many synapses throughout the CNS and at the neuromuscular junction. LTP has been reviewed both generally and with respect to brain regions specific for memory/learning. **AIMS/STUDY DESIGN:** The principles of "generation of impulses from the presynaptic region to the postsynaptic region by very potent RNT (10, 000-fold effect) and "vasodilation of arteriolar perforators" are the basis of the authors' hypothesis for treat stroke cases. Case-control prospective study. **MATERIALS AND METHODS:** The experimental population included 82 stroke patients (10 patients were given control treatments without super fusion or with 5% dextrose super fusion, and 72 patients comprised the ICSNP group). The mean time for super fusion was 9.5 days post-stroke. Pre- and post-ICSNP status was monitored by NIHSS, MRI and TCD. **RESULTS:** After 90 seconds in the ICSNP group, the mean change in the NIHSS score was a decrease of 1.44 points, or 6.55%; after 2 h, there was a decrease of 1.16 points; after 24 h, there was an increase of 0.66 points, 2.25%, compared to the control-group increase of 0.7 points, or 3.53%; at 7 days, there was an 8.61-point decrease, 44.58%, compared to the control-group increase of 2.55 points, or 22.37%; at 2 months in ICSNP, there was a 6.94-points decrease, 62.80%, compared to the control-group decrease of 2.77 points, or 8.78%. TCD was documented and improvements were noted. **CONCLUSIONS:** ICSNP is a swift-acting drug in the

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treatment of stroke, acting within 90 seconds on day 9.5 post-stroke with a small decrease after 24 hours. The drug recovers from this decrease quickly.

KEYWORDS: Brain Infarcts; Intracarotid Sodium Nitroprusside; Perforators; Vasodilations; Retrograde Transmission; The 10, 000-Fold Effect.

INTRODUCTION: Time is Brain. NINDS study on thrombolytic therapy approved rTPA (recombinant-Tissue-Plasminogen-activator) in 1995¹ for hyperacute-stroke. However, owing to its narrow window^{2, 3} and its price, only a fortunate few eligible patients are able to receive it. Also low-frequency TCD (2-MHz-kHz) with rtPA-thrombolysis in acute-stroke^{4, 5} and use of various stents have also been advocated but in acute stage.

The early start of pulsations with physiological recovery (by electrical impulse generation) is the goal of any intervention performed on infarcted brain. This pilot study serves the ultimate goal of physiological recovery.

For physiological recovery, we must attempt to understand the normal and abnormal impulses, synapses and the generation of action potential cascade that are well documented by clinical and nonclinical studies. Two mechanisms for acute, and one for chronic cases is being proposed here.

FOR-ACUTE (3-7days) CASES-RETROGRADE-NEUROTRANSMISSION-THEORY: In normal excitatory-impulses (at synapse), glutamate (from presynaptic-membrane) activates NMDA receptors (associated with nitric-oxide synthetase (NOS) on postsynaptic-membrane for further propagation by calcium-calmodulin-complex.⁶⁻⁸ NOS produces NO and then NO cloud at synapse thus bridging the microgaps.⁸⁻¹¹ NO travels backward across this chemical synapse⁸ to bind to its receptor (NO receptor/sGC-soluble guanylyl cyclase), regulating anterograde-neurotransmission; this process is called "retrograde neurotransmission"^{7, 12} and allows neural circuits to create feedback-loops.

NO-receptors (well equipped with a ligand-binding-site and a transduction-domain) differ in some interesting properties. The ligand-binding site (heme, such as hemoglobin in blood) when incorporated into the receptor-protein, exhibits >10, 000-fold higher affinity for NO than for oxygen (THE 10, 000 FOLD EFFECT)^{13, 14} and is completed in 20 msec⁹ decays in 200 msec.¹⁵ This retrograde-neurotransmission-like action of NO^{11, 16} is also shown by carbon monoxide¹⁷ and platelet-activating factor.^{10, 18}

ABNORMAL CONDITIONS:

IMPULSES TOO-HIGH/TOO-LOW: NO can up¹⁹ or down regulate^{20, 21} the oncoming-impulses. In conditions of high-intensity impulses such as schizophrenia²² and obsessive-compulsive disorder,²³ NO downregulates the impulses; in conditions of low-intensity impulses such as depression with low-serotonin levels, NO upregulates the impulses²⁴ (FIGURE I A).

IN THE ABSENCE OF IMPULSES: In cases with no impulse (NORMAL-ANTEROGRADE-NEUROTRANSMISSION, including synaptic activity, with no RETEROGRADE-NEUROTRANSMISSION), NO-donors have shown promising results in generating impulses by increasing the frequency of spontaneous miniature EPSPs by NO via RETEROGRADE-NEUROTRANSMISSION in vitro in rats²⁵

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thus bypassing normal ANTEROGRADE-NEUROTRANSMISSION (FIGURE I B). This cascade relaxes the smooth-muscles of perforators.

FOR-ACUTE (3-7 days) CASES-VASOSPASM-THEORY: NO is a very potent vasodilator²⁶⁻²⁸. SNP excels in emergency treatment of hypertension²⁹ by vasodilation, which is instantaneous (onset within 30 seconds; peak in 2-5 minutes).³⁰ Intrathecal-sodium-nitroprusside has been used in vasospasms induced by subarachnoid-hemorrhage. SNP acts on NOS present at the adventitial side of perforators, triggering NO release thus relaxes smooth muscles of perforators via cAMP pathway.

The impact of the intrathecal^{31,32} and intraventricular³³ SNP in vasospastic cases on the larger-caliber vessels appears to be minimal, and the decreased cerebral circulation time indicates improved cerebral blood flow via microcirculation.³⁴⁻³⁶ Oral Sildenafil have been studied but only to relieve vasospasms caused by SAH.³⁷⁻³⁹ Studies on intra-arterial(for ergotism patients⁴⁰⁻⁴³ and intracarotid (for measurements of cerebral blood flow)were conducted on dogs,⁴⁴ cats⁴⁵ and then on normal human beings who were subjected to DSA for other reasons.^{46,47}

Various treatment options available are for salvaging the penumbra region and to relieve obstruction via thrombolysis, but no study for vasodilation of perforators at penumbra and to induce electrical impulses by EPSPs²⁵ via the very potent RETEROGRADE-NEUROTRANSMISSION by bypassing the ANTEROGRADE-NEUROTRANSMISSION is available.

FOR-CHRONIC (>7 days) CASES: LTP (LONG-TERM-POTENTIATION): Endocannabinoids-anandamide and 2-AG are primary-retrograde-messengers in brain and may also play an important role in retrograde-signaling in long-term-potential, which is crucial for memory &/or learning^{9,19,20,21,48,49,26-28,50-53} as nitric-oxide.^{19,20} The NO-cGMP pathway plays a role in LTP at many synapses throughout the CNS and even at neuromuscular-junction.

This same principle of "generation of impulses from presynaptic-region to postsynaptic-region by highly-potent RETEROGRADE-NEUROTRANSMISSION (10,000-FOLD-EFFECT), the vasodilation of arteriolar perforators and long-term-potential are the bases of the authors' hypotheses for treating acute/chronic stroke cases.

MATERIALS AND METHODS: Clearance was obtained from the local-ethical-committee (number-02/NC/SUL/2012). Potential benefits and significant risks, specifically uneasiness/vomiting /retching/diaphoresis/apprehension/restlessness/perspiration/muscle twitching/ palpitation /dizziness and abdominal pain and possible hypotension, were discussed with all patients and/or their families. Written and video consent were obtained from relatives of patients for INTRACAROTID-SODIUM-NITROPRUSSIDE and video-recordings of pre- and post-injection phases with Trans-Cranial-Doppler (TCD).

The stroke team was notified of 178-patients suspected of having strokes of >3days previously; 96 were disqualified, and 82 qualified for the study. The most common reasons for disqualification from INTRACAROTID-SODIUM-NITROPRUSSIDE therapy were intracerebral-hemorrhage (n=48), acute stroke diagnosis in which thrombolysis was acutely needed (rTPA given) (n=32), a non-stroke diagnosis (n=10) and minor or rapidly resolving symptoms (n=6).

82-stroke-patients, the control-group (10/82) and INTRACAROTID-SODIUM-NITROPRUSSIDE- group (72/82) were formed. Control-group was subdivided into two subgroups.

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First-subgroup (5/10) did not undergo any super fusion, and the other (5/10) super fused with Dex5% between Dec-2012 and Feb-2014, treated at NEURO-CENTER prospectively. INTRACAROTID-SODIUM-NITROPRUSSIDE-GROUP (72-patients) was subdivided according to BASELINE-NIHSS score. Three groups (5-15, moderate; 16-20, moderate to severe; and 21-42, severe) were formed based on the NIHSS-Score. All the NIHSS-grades were again subdivided according to time of infusion, from 3-7 days and >7 days.

Mean age of our patients was 63.75 years (range45-72). Out of the 72-patients who were given INTRACAROTID-SODIUM-NITROPRUSSIDE, 52 were males. Co-morbid-illnesses in form of hypertension/diabetes/hypercholesterolemia were present in 72(100%)/52(72.22%)/72(100%) patients, respectively. Additionally, atrial fibrillation/congestive-heart-failure/coronary-artery-disease were present in 10(13.88%)/5(6.94%)/28(38.88%) patients, respectively.

There was a history of prior stroke in 4patients (5.55%). Mean-blood-pressure at admission was 170/98 and mean-maximum-pretreatment was 182/100 mmHg. Fifty-four (75%) of 72-patients were smokers. Detailed blood-pressure monitoring was performed due to the possible hypotensive action of SNP.

Variables recorded: time of symptom onset, arrival time, CT scan and/or MRI and TCD and INTRACAROTID-SODIUM-NITROPRUSSIDE administration time. Extensive-neurological-examination including BASELINE-NIHSS was performed in all patients. Other parameters noted were demographic profile, stroke risk-factors, ECG-examination, baseline CT-scan findings/MRI-study, platelet-aggregation-activity monitoring (bleeding-time), PT/PC/APTT and INR level.

Using TOAST-criteria, patients were classified into: large-artery-atherosclerotic=32; cardioembolic=16; small-vessel-occlusion=8; other-determined-etiology=4; undetermined-etiology=12.

Inclusion and exclusion criteria are shown in (TABLE I).

Patients received pretreatment for nausea in form of ondansetron HCl (32.0mg/IVpush) 15-minutes before treatment. Meticulous photoprotection/sterile techniques were observed for all aspects of delivery of medication as well as its formulation. Powdered-SNP was sterilely reconstituted with 200ml 5%dextrose with 50mg of the SNP. Patients were hydrated and INTRACAROTID-SODIUM-NITROPRUSSIDE given with simultaneous IV injection of 1 ml mephentermine to combat the ensuing SNP-related hypotension.

Each of our patients received 0.01mg/kg of INTRACAROTID-SODIUM-NITROPRUSSIDE, up to a maximum of 2ml (0.5mg), based on titration of hypotension (stopping at the very point at which the anesthetists declared hypotension had started). The whole calculated dose was given as a bolus dose using sterile technique, injected slowly over 3 minutes through a 25 G LP needle directly into the ipsilateral-carotid-artery.

We waited for 90 sec for the recovery, while conducting continuous TCD studies. NIHSS-scores were recorded at baseline/90-sec/2-h/24-hrs/7-days/&/2-months. The Barthel-index was recorded at 2-months.

This study corroborates earlier impressions regarding the safe limits of doses of SNP in intrathecal,^{32,33} intraventricular,³⁴ intra-arterial for ergotism³⁸⁻⁴¹ and intracarotid^{44,45} administration. We injected only 0.5mg (2ml of reconstructed fluid, i.e., 0.01mg/kg/bo/wt). This study also supports safety of INTRACAROTID-SODIUM-NITROPRUSSIDE in intensive care/emergency room.

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Heparin/aspirin/clopidogrel/&/Antihypertensives were given during hospital stay. High-protein (arginine-rich) diets were started. Peak blood pressure was recorded during INTRACAROTID-SODIUM-NITROPRUSSIDE administration as well as during the first 24 h after INTRACAROTID-SODIUM-NITROPRUSSIDE.

Using Oxford stroke classification (BAMFORD's classification), LACS (LACUNAR-STROKE) was found in 16/72 patients (22.22%), PACS (PARTIAL-ANTEROGRADE-NEUROTRANSMISSIONERIOR-CIRCULATION-SYNDROME) was found in 36/72(50%), TACS (TOTAL - ANTEROGRADE-NEUROTRANSMISSIONERIOR-CIRCULATION-STROKE) was found in 12/72(16.66%) and POCS(POSTERIOR-CIRCULATION-SYNDROME) was found in 8/72(11.11%).

Mean time of INTRACAROTID-SODIUM-NITROPRUSSIDE injection was 9.5days (range 3-24) after stroke onset. (TABLE II: CLINICAL CHARACTERISTICS (PRE-TREATMENT)). Mean-length-of-hospitalization was 4-days. The MEAN-BASELINE-NIHSS-SCORE was 21.11(range 10-33). Pre-INTRACAROTID-SODIUM-NITROPRUSSIDE and post - INTRACAROTID-SODIUM-NITROPRUSSIDE clinical examination was video-recorded.

MRIs were performed (FIGURE II A TO D, FIGURE III A TO D, FIGURE IV A TO D AND FIGURE V A). TCD was noted in pre-(FIGURE V B; PRE INTRACAROTID-SODIUM-NITROPRUSSIDE) and post-INTRACAROTID-SODIUM-NITROPRUSSIDE(FIGURE V C AND D; POST INTRACAROTID-SODIUM-NITROPRUSSIDE).

TABLE III: BASELINE AND POST-INTRACAROTID-SODIUM-NITROPRUSSIDE CHARACTERISTICS WITH NIHSS CHANGES.

TABLE IV: BAMFORD'S CLASSIFICATION AND CHANGES AFTER INTRACAROTID-SODIUM-NITROPRUSSIDE.

RESULTS: We obtained telephone or clinic follow-up with patients and caregivers in cases for next two months and assessed Barthel Index of Activities of Daily Living.

For analysis based on NIHSS GRADING, results were as follows:

1. **NIHSS 5-15(12/72-CASES/16.66%):** INTRACAROTID-SODIUM-NITROPRUSSIDE-GROUP had a MEAN-BASELINE-NIHSS-SCORE 10-points, whereas CONTROL (no superfusion;dex5%) scored 19.14/20.2 points, respectively. Patients were given INTRACAROTID-SODIUM-NITROPRUSSIDE at 11-days poststroke. After 90-sec, MEAN-MOTOR-CHANGE in NIHSS of INTRACAROTID-SODIUM-NITROPRUSSIDE-group was 2.4points/21.81%decrease. 2-hrs, 5.26%decrease. 24-hrs, 0.43%increase, which decreased until 2-months after stroke. At 2-months, Barthel's-score was 85%, and mRS was 0-1.
2. **NIHSS (16-20(24/72CASES/32.33%):** INTRACAROTID-SODIUM-NITROPRUSSIDE-GROUP had a MEAN-BASELINE-NIHSS-SCORE 18.33points. Patients were given INTRACAROTID-SODIUM-NITROPRUSSIDE at 10.16-days poststroke. After 90-sec, MEAN-MOTOR-CHANGE in INTRACAROTID-SODIUM-NITROPRUSSIDE-GROUP MEAN-BASELINE-NIHSS-SCORE was 2.17POINTS/18.33% decrease. After 2-hrs, 11.83%decrease and after 24-hrs 12% increase, decreased until 2-months. At 2-months, Barthel's-score was 88.33%, and mRS was 1.
3. **NIHSS BETWEEN 21 and 42 (36/72 CASES, 50%):** INTRACAROTID-SODIUM-NITROPRUSSIDE GROUP had a MEAN-BASELINE-NIHSS-SCORE 28.33points. Patients were given INTRACAROTID-SODIUM-NITROPRUSSIDE at 8.88 days poststroke. After 90-sec, MEAN-MOTOR-CHANGE in INTRACAROTID-SODIUM-NITROPRUSSIDE-GROUP

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MEAN-BASELINE-NIHSS-SCORE was 3.33 POINTS/11.75% decrease. After 2-hrs, 7.15% decrease and after 24 hrs, 3.34% increase decreased until 2-months. At 2-months, the Barthel's-score was 72.50% and mRS was 2.

For analysis, we defined outcomes as follows:

- 1) EXCELLENT-OUTCOME-NIHSS of ≥ 3 in 90-sec and Barthel-Index of $\geq 80\%$ after 2-months.
- 2) GOOD-OUTCOME-NIHSS of 1-2 in 90-sec and Barthel-Index of 70-80% after 2-months.
- 3) FAIR-OUTCOME only subjective/TCD showed improvement of one-grade in 24-hrs, with the improvement sustained/increased even after 7-days, with Barthel-Index of 60-70% after 2-months.
- 4) POOR-OUTCOME patient shows no improvement clinically/TCD for up to 7-days, with Barthel-Index of 50-60% after 2-months.

For video verifications, the case-videos can be viewed on YouTube, at URLs provided in online supplement.

- 1) **EXCELLENT-OUTCOME-CASES (16/72-CASES; 22.22%):** INTRACAROTID-SODIUM-NITROPRUSSIDE-GROUP with MEAN-BASELINE-NIHSS-SCORE 19-points compared to CONTROL (no superfusion/dex5%), which scored 19.14/20.2 points respectively. Patients were given INTRACAROTID-SODIUM-NITROPRUSSIDE at 8.75days post-stroke. After 90sec, the MEAN-MOTOR-CHANGE in INTRACAROTID-SODIUM-NITROPRUSSIDE-GROUP NIHSS was 3.5POINTS/18.42%decrease. After 2-hrs, 14.51% decrease and after 24-hrs/43%increase was noted. Mean-recovery was decreased (5.75 POINTS/30.26%) from BASELINE-INTRACAROTID-SODIUM-NITROPRUSSIDE-NIHSS-SCORE but increased compared to 2-hrs POST-INTRACAROTID-SODIUM-NITROPRUSSIDE. Comparing CONTROL (no superfusion/dex 5%) to INTRACAROTID-SODIUM-NITROPRUSSIDE-GROUP, mean change in NIHSS was 1/0.4-POINTS, 5.15/1.98% decrease, respectively, which decreased until 2-months after stroke.
- 2) **GOOD-OUTCOME-CASES (28/72-CASES;38.88%):** INTRACAROTID-SODIUM-NITROPRUSSIDE -GROUP had MEAN-BASELINE-NIHSS-score 18.71points. Patients were given INTRACAROTID-SODIUM-NITROPRUSSIDE at 7-days post-stroke. After 90-sec, MEAN-MOTOR-CHANGE in INTRACAROTID-SODIUM-NITROPRUSSIDE-GROUP NIHSS 1.71 POINTS/9.13% decrease. After 2-hrs 1.71 POINTS/10.11% decrease, after 24-hrs 0.71 POINTS/4.71% increase. Mean recovery was decreased POST-BASELINE INTRACAROTID-SODIUM-NITROPRUSSIDE-NIHSS-SCORE (1 POINT/5.88%) but increased POST-2-hrs-INTRACAROTID-SODIUM-NITROPRUSSIDE then decreased until 2-months after stroke.
- 3) **FAIR-OUTCOME-CASES (8/72 CASES/11.11%):** INTRACAROTID-SODIUM-NITROPRUSSIDE - GROUP had MEAN-BASELINE-NIHSS-score 19.5-points. Patients were given INTRACAROTID-SODIUM-NITROPRUSSIDE at 22days post-stroke. No recovery was noted after 90-sec or after 2-hrs. After 24-hrs, 1 POINT/1.12% decrease, at 7-days 3-POINTS/2.37% decrease and at 2-months 1.5-POINTS/1.01% decrease.
- 4) **POOR-OUTCOME-CASES (20/72 CASES/27.77%):** INTRACAROTID-SODIUM-NITROPRUSSIDE -GROUP had MEAN-BASELINE-NIHSS-score 30.4-points. Patients were given INTRACAROTID-SODIUM-NITROPRUSSIDE at mean 22 days poststroke. No recovery noted after 90-sec, 2-hrs or 24-hrs. At 7-days, there was a decrease of 1.8-POINTS/2.92%, at 2-months decrease of 1.75-POINTS/2.18%.

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COMPARISON OF DIFFERENT COMBINATIONS OF POSTSTROKE DAYS OF INTRACAROTID-SODIUM-NITROPRUSSIDE:

- a) 3 DAYS-<7days: Mean time was 4.72-days. MEAN-BASELINE-NIHSS-SCORE was 23 points (range10-32). After 90-sec, MEAN-CHANGE was 3.09-points/13.47% (range2-5). After 2-hrs, 1.27-points/4.28%. After 24-hrs, 0.27-points/1.01%. After 7-days, 4.72-points/7.16%. After 2-months, 7.72-points/10.61%.
- b) >7 days: Mean time was 17-days. MEAN-BASELINE-NIHSS-SCORE was 20.71points. After 90-sec, MEAN-CHANGE was 2.28points/11.05%(range 0-5). After 2-hrs 1.57-points/8.52%. After 24-hrs, 0.44-points/0.28%. After 7-days, 1.28-points/5.93%. After 2-months, 2-points/7.1%.

Considerable reduction in stroke-severity was noted in 44/72 patients (MEAN-CHANGE-NIHSS after 90-sec, 2.6-points/13.85%(range1-3). This reduction was accompanied by changes in TIBI flow grades on TCD as well as in clinical assessment of limb strength.

A remarkable clinical course was noted in cases numbered 11, 44 and 71, who presented with a right-sided weakness due to an occlusion in left middle cerebral artery at post-stroke mean-day-4.6.

Complete instantaneous improvement (power increased from grade 0 to grade 2-3) was noted, as seen in video recordings, after only 90 sec of INTRACAROTID-SODIUM-NITROPRUSSIDE with TCD-PULSATATIONS.

Using Oxford stroke classification (BAMFORD's-classification).

LACS (LACUNAR-STROKES)12/72-patients(16.66%), with BASELINE-NIHSS-SCORE 13.33-points; MEAN-CHANGE 90-sec/3.3 points/24.98%; at 2-hrs, 2.34-points/23.40%; at 24-hrs, 1.67-points/21.80%; at 7-days 5.67-points/60.77%; BARTHEL's-SCORE was 85%.

PACS(PARTIAL-ANTERIOR-CIRCULATION-SYNDROME)36/72-patients(50%), with BASELINE-NIHSS- SCORE 23.44-points; MEAN-CHANGE at 90-sec 2.89-points/12.32%; at 2-hrs, 1.33-points/6.47%; at 24-hrs, 0.78-points/4.05%; at 7-days, 15.12-points/75.60%; BARTHEL's-SCORE was 80.55%.

TACS (TOTAL-ANTERIOR-CIRCULATION-STROKE) 16/72-patients (22.22%), with BASELINE-NIHSS- SCORE 30-points; MEAN-CHANGE 90-sec 3.25-points/7.47%; at 2-hrs, 2-points/7.47%; at 24-hrs, 0.75-points/3.03%; at 7-days, 20.5-points/80.39%; BARTHEL's-SCORE was 71.66%.

POCS (POSTERIOR-CIRCULATION-SYNDROME)8/72-cases(11.11%), with a BASELINE-NIHSS- SCORE 13.5-points; MEAN-CHANGE 90-sec 0.5-points/3.70%; at 2-hrs, 0-points, at 24-hrs, 0.5-points/3.84%; at 7-days, 5.5-points/44%; BARTHEL's-SCORE was 85%.

TCD-STUDY:

TACS (16-patients). In 9-cases, ICA was stenosed and produced a focal significant flow-velocity-increase (70cm/s at terminal ICA-bifurcation (temporal-window). ICA-MFV (mean-flow-velocity)was greater than in the MCA and contralateral ICA. In 7-cases, ICA-SIPHON was OCCLUDED, producing no signals at 62-70 mm via transorbital-approach. More findings included were collateral flow in posterior and Anterior communicating arteries and a blunted MCA signal and contralateral ICA compensatory velocity increase.

PACS (36 patients). In 14-cases, MCA-STENOSIS was observed associated with MFV (100 cm/s). There was also some turbulence/murmur/decreased flow resistance distal to stenosis, and increased unilateral A1-ACA-flow-velocities. M1-MCA-stenosis in 12-cases produced a significant

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focal increase in MFV-80 cm/s, and PSV-140 cm/s, and an interhemispheric MFV-difference of >30% was noted. ACA-stenosis in 5-cases produced focal significant flow-velocity increase (80cm/s, ACA>MCA). MCA-OCCLUSION-In 8-cases of M1-MCA-occlusion, there were no signal at any depth (45-65 mm) via transtemporal-approach. M2-MCA-occlusion in 5-cases produced a unilateral MFV-decrease of >30% M1-MCA and a high-resistance waveform (PI 1.2). There was also a compensatory flow-velocity-increase in ACA. ACA-occlusion in 5-such cases, no-signals were found at depths of 62-74mm.

POCS (8 patients). In 4-cases, PCA-stenosis produced a focal significant increase in flow velocity >50 cm/s, and PCA MFV >ACA, ICA, or MCA MFV. Stenosis of the basilar artery in 4-cases at depths ranging from 80mm (proximal) to 100mm (distal) noted. Focal significant flow-velocity increase >60 cm/s and BA MFV>MCA MFV. Terminal VA-stenosis 1-case produced a focal significant flow-velocity increase (50 cm/s and VA MFV>BA MFV).

For LACS, we were not able to insonate deeply enough and therefore relied on MRI and CT findings from the pre-INTRACAROTID-SODIUM-NITROPRUSSIDE phase.

Of these 72 patients, 75.88% of the Barthel Index scores indicated near-normal functional status.

DISCUSSION: NINDS study gave a brain salvaging time of 3 hrs for anterior circulation and 6 hrs for posterior circulation. A significant difference in our experience was the effectiveness of treatment within an average of 9.5days, and, due to very potent 10, 000-fold effect, INTRACAROTID-SODIUM-NITROPRUSSIDE generates ANTEROGRADE-NEUROTRANSMISSION via RETEROGRADE-NEUROTRANSMISSION action thus bypassing the normal ANTEROGRADE-NEUROTRANSMISSION(which is usually absent in stroke). We did not deviate from the standard protocol of thrombolysis within the specified time by choosing only those patients who were out of range for thrombolysis (from 3rd day onwards). None of our patients developed any form of intracerebral hemorrhage (as found in the NINDS study), which suggests a good safety profile for INTRACAROTID-SODIUM-NITROPRUSSIDE.

Just after 90-sec, cases with moderate NIHSS-scores (5-15) improved excellently (21.27%)compared to moderate to severe cases (9.11%)and severe cases (2.36%) if INTRACAROTID-SODIUM-NITROPRUSSIDE was performed within 3-7 days (18.92%)versus >7 days (11.05%). This means that results with INTRACAROTID-SODIUM-NITROPRUSSIDE, if administered between 3-7 days, are 1.71 times better than those for >7 days. Further, LACS showed the best results (24.98%), followed by PACS (12.32%)and then the other types of stroke. Video recordings also showed remarkable results of increases of 3.3points in LACS, 3.25points in TACS and 1.33points in PACS within 90-sec. These patients all invariably showed a decremental decrease after 2-hrs (patient improvement) and an increase in NIHSS(patient deterioration)after 24-hrs.

Those patients who showed deterioration in their NIHSS scores at 24-hrs post-INTRACAROTID-SODIUM-NITROPRUSSIDE return back to 7-day NIHSS-status after 24-hrs. This deterioration might be due to superoxide (SO) formation in pathological brain region. The level of serum superoxide dismutase (SOD) is inversely correlated with size of infarction on CT scan and severity of the neurological deficits. Decreased SOD activity recovered within a mean of 5-days to serum values of control patients.⁵⁴ Our second hypothesis proposed that synaptic vesicles were swiftly used up by ANTEROGRADE-NEUROTRANSMISSION and RETEROGRADE-

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NEUROTRANSMISSION, creating local depletion, pulling raw material(L-Arginine/&/oxygen⁵⁵ from cell body, approximately within a week.⁶⁻⁸ We therefore advised an arginine-rich-diet. Our clinical findings (7 days post-INTRACAROTID-SODIUM-NITROPRUSSIDE)show a decrease in NIHSS-score after 7-days, supporting above two hypotheses-superoxide-ions is washed away by serum SOD along with restoration of material from cell-body.

Four-cases (POCS) did not respond until 24-hrs after treatment, as they were given INTRACAROTID-SODIUM-NITROPRUSSIDE at mean of 20.22-days post-stroke; further, they had brainstem(minute left-pontine or right-midbrain)infarcts(POCS), and we injected into the common-carotid-artery, which is separate from posterior-circulation.

They started moving their upper/lower-limbs after 24-28 hrs, perhaps because of the long-term-potential function of NO,^{21,48} yet to be evaluated. The NO-cGMP pathway forms the basis of memory and learning in the brain. These patients were walking with support by 3-4 days POST-INTRACAROTID-SODIUM-NITROPRUSSIDE, and their NIHSS-SCORES averaged 10.22points on the 7th day POST-INTRACAROTID-SODIUM-NITROPRUSSIDE (Youtube video-URL attached).

INTRACAROTID-SODIUM-NITROPRUSSIDE-GROUP TIME-COMPARISON study reveals definite and quick improvement in the 3-7day group (INTRACAROTID-SODIUM-NITROPRUSSIDE at 90 sec/3-POINTS/13.47%) compared to the >7th day group (INTRACAROTID-SODIUM-NITROPRUSSIDE at 90 sec/2.28-POINTS/11.05%).

Comparative study of patients with EXCELLENT and GOOD RESULTS showed a swifter improvement (90 sec/2.6-points/13.85%) than the fair group (24 hrs/1-POINT/5.12%), and there was no response in the poor group within 7 days of treatment.

Comparative study, as per BAMFORD's classification (56), showed a specific correlation between the site of blockage and the POST-INTRACAROTID-SODIUM-NITROPRUSSIDE effect. The best response was observed with the LACS patients (3.3-points/24.98%), followed by PACS (2.89-points/12.32%), and then TACS (3.25-points/10.83%), with the smallest response in POCS patients (0.5-points/3.70%,). This discrimination may be because the posterior circulation is too far from the carotid arteries, but the cause has yet to be evaluated. In future, we plan to superfuse fourth ventricle in POCS cases.

In cases of TACS, the TCD in the PRE-INTRACAROTID-SODIUM-NITROPRUSSIDE phase in ipsilateral ICA showed minimal flow signals, but soon after INTRACAROTID-SODIUM-NITROPRUSSIDE, it showed dampened flow signals (pulsatile signal with normal acceleration and mean flow velocity of 30% with positive end diastolic flow compared to the normal side GRADE 2 TIBI grading system); in two cases (case numbers 15 and 60), blunted flow signal was detected with delayed systolic flow acceleration and mean flow velocity of less than 30 cm/sec(57, 58)perhaps because the perfusion performed was on day,^{24,42} and the BASELINE-NIHSS was.³³

The present study has certain limitations, such as not having CT perfusion, DSA & MRA in the pre- and post-injection periods with DWI and PWI, due to the unavailability of higher-end MRI and CT perfusion-enabled software for CT scanning at our setup. We plan to conduct a broader study including all of the above investigations in the future. No patient was given blood transfusion.

CONCLUSIONS: INTRACAROTID-SODIUM-NITROPRUSSIDE treatment is effective at mean of 9.5 days post-stroke (3-24 post-stroke-day) within 90-seconds; it shows a small detrimental response after 24-hrs followed by an incremental response until the seventh-day with a Barthel-score of 75.88% at

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two-months. SNP is a very potent RETEROGRADE-NEUROTRANSMISSION (via the 10, 000-FOLD-EFFECT) safe (does not cause hemorrhage-acts at microcirculation), universally available, affordable and administrable in a wide time period. A larger, double-blinded, controlled, multicentric, randomized trial study is needed to quantify the effect of INTRACAROTID-SODIUM-NITROPRUSSIDE in stroke.

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FIGURE 1A: SHOWS THE NORMAL REGULATION OF ANTEROGRADE NEUROTRANSMISSION BY NITRIC OXIDE AND IN VARIOUS ABNORMAL CONDITIONS WELL SUPPORTED BY VARIOUS PAPERS.

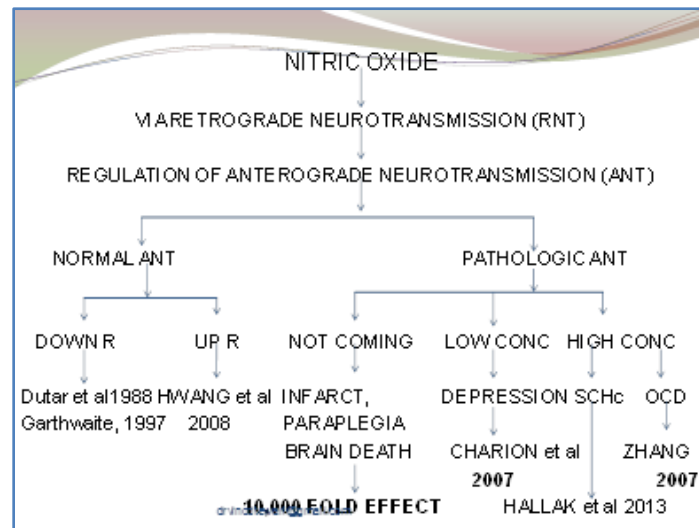


Figure 1A

FIGURE 1B: SHOWS THE MECHANISM OF ACTION OF NITRIC OXIDE AT THE SYNAPSE LEVEL.

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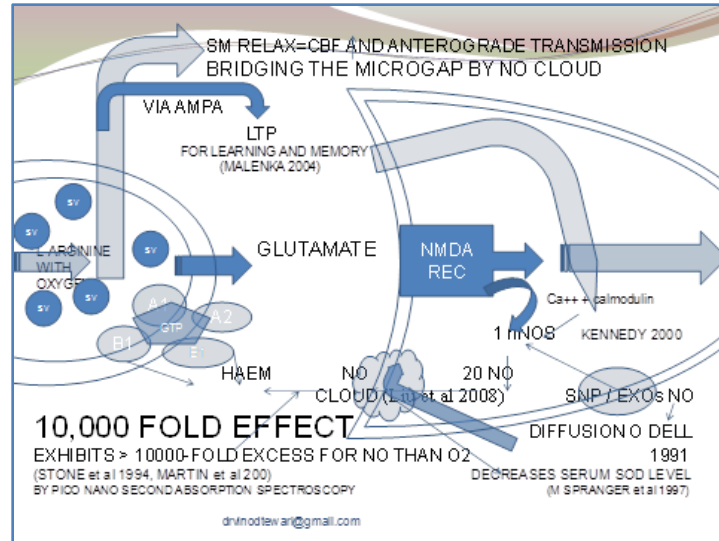


Figure 1B

TABLE 1; CRITERIA FOR USE OF ICSNP IN TREATING ACUTE ISCHEMIC STROKE:

CLINICAL INCLUSION CRITERIA:

1. Patient / caregiver able to give informed written and video recordings consent before and video recordings after the study procedure.
2. Age \geq 18 years
3. Onset of symptoms of ischemic stroke from 3rd poststroke day to more than 7 days.
4. Measurable neurological deficit defined as impairment of language, motor function, cognition and/or gaze, vision or neglect, comprehension.
5. Score of Stroke severity \geq 4 on the National Health Stroke Scale (NIHSS).

CLINICAL EXCLUSION CRITERION:

1. Minor stroke symptoms (NIHSS score $<$ 4) or those that are rapidly improving.
2. Patients fit for rTPA thrombolysis (3 hrs for anterior and 6 hrs for posterior circulation).
3. Seizure at onset unless the treating physician is convinced that the neurological deficit is due to stroke and not due to seizure.
4. Previous known intracranial hemorrhage.
5. Hemorrhage in pretreatment CT scan of the brain.
6. Uncontrolled baseline hypertension ($>$ 180/110).
7. Myocardial infarction in past 30 days.
8. Recent ($<$ 1 days) surgery, major arterial puncture, trauma or ulcerative wounds.
9. Known and clinical evidence of chronic or acute hepatic or renal disease.
10. Known bleeding diathesis/coagulopathies.
11. Patients on anticoagulants.
12. Pregnancy, lactation and parturition within previous 30 days.
13. Hypoglycemia, hyperglycemia (baseline serum glucose level must be between 50mg%-400mg%).

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COMPUTED TOMOGRAPHY (CT) OR MRI (MAGNETIC IMAGING) EXCLUSION CRITERIA:

1. Evidence of acute or chronic intracranial bleeding on CT.
2. Likely etiology other than acute brain ischemia.

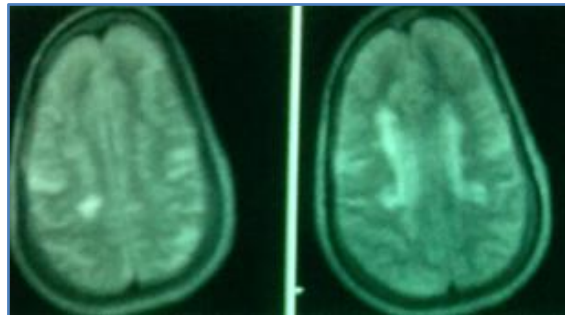
Age	63.75 years (45 to 72)
Sex M:F	13:5
MEAN DAYS OF ICSNP	9.5 (RANGE 3 TO 22 DAYS)
HYPERTENSION	72 (100%)
DIABETES MELLITUS	36 (50%)
HYPERCHOLESTEROLEMIA	72 (100%)
AF	NIL
CHF	NIL
CAD	28 (38.88%)
PRIOR INFARCT	4 (5.5%)
SMOKING	68 (94.44%)
MEAN ADMISSION BP	170/98 mm of Hg
MEAN MAXIMUM PRETREATMENT BP	182/100 mm of Hg
MEAN BASELINE NIHSS	Mean 21.11 (range 10 to 33)
TCD	IMMEDIATE IN EMERGENCY ROOM

TABLE 2 CLINICAL PRETREATMENT CHARACTERISTICS

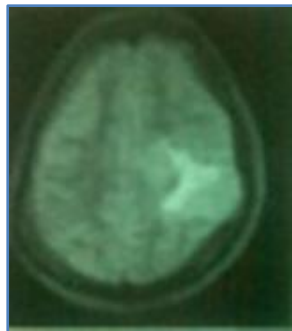
FIGURE III MRI / CT SCAN INVESTIGATIONS



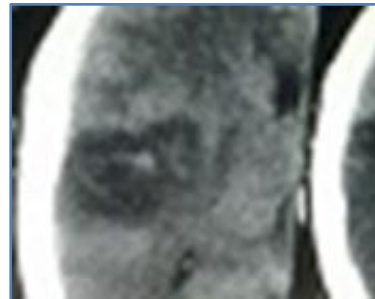
A) PRE ICSNP MRI SCAN CASE NUMBER 2;



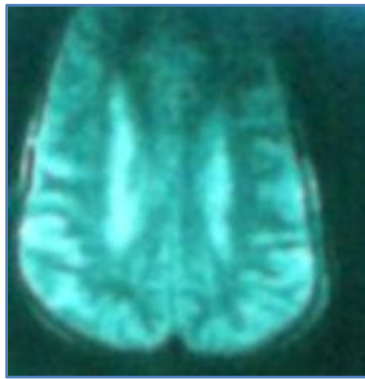
B) PRE ICSNP MRI CASE NUMBER 4;



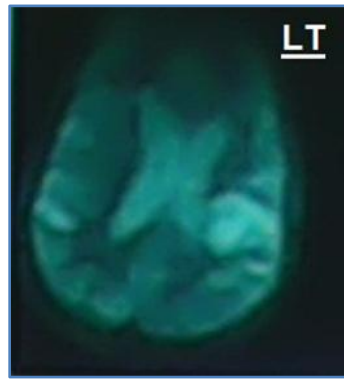
C) FIGURE III C PRE ICSNP MRI CASE NUMBER 5;



D) PRE ICSNP CT SCAN CASE NUMBER 7

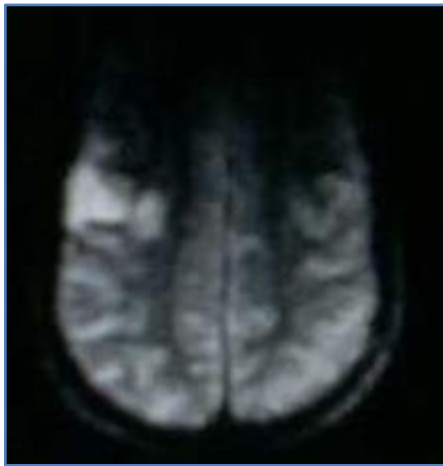


E) PRE IC SNP CT SCAN CASE NUMBER 9

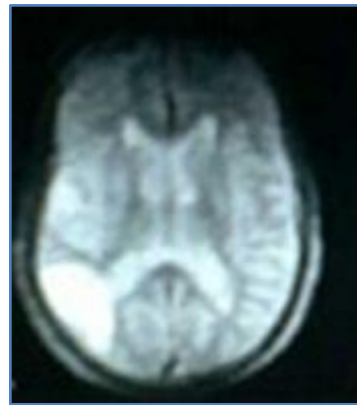


F) MRI AXIAL VIEW OF CASE NUMBER 11

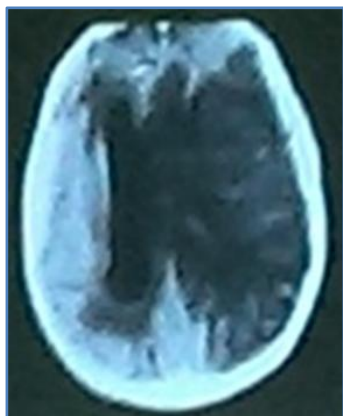
FIGURE IV



(A) MRI AXIAL VIEW OF CASE NUMBER 12



B) PRE ICSNP MRI SCAN CASE NUMBER 13;

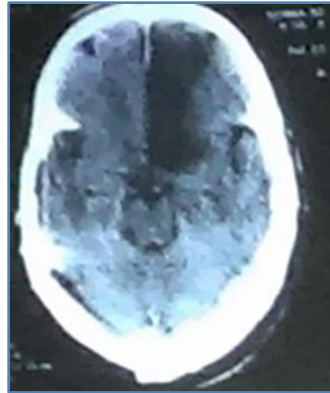


C) PRE ICSNP CT SCAN CASE NUMBER 15



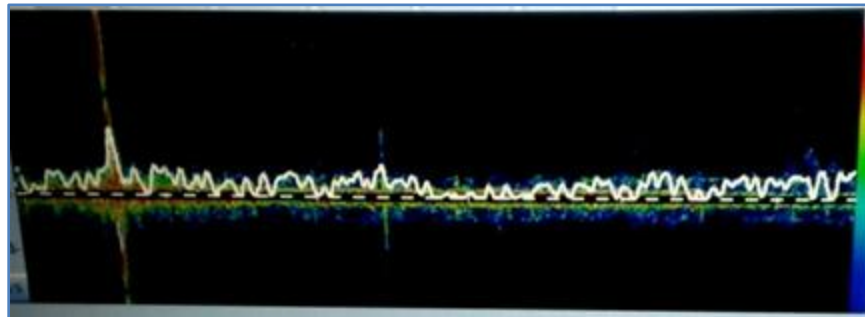
D) PRE ICSNP MRI SCAN CASE NUMBER 16

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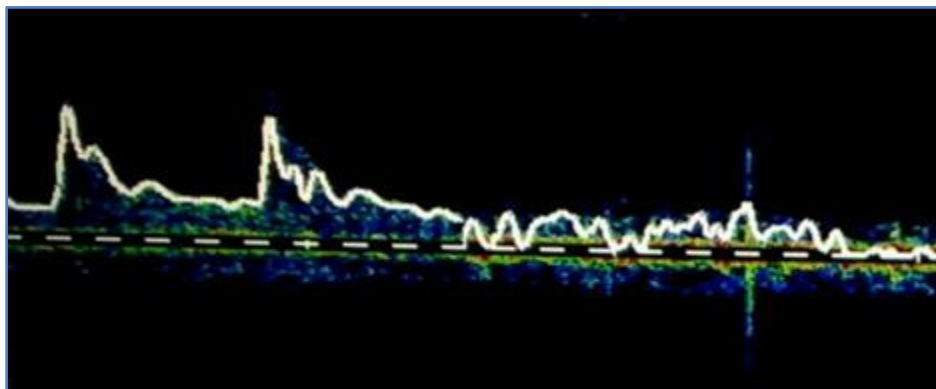


E) PRE ICSNP MRI CASE NUMBER 18

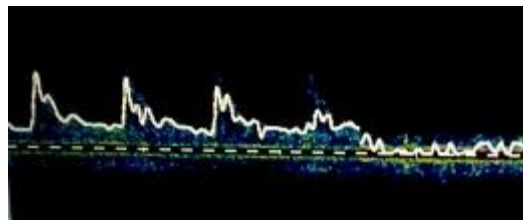
FIGURE V



A) TCD STUDIES PACS CASES: PRE ICSNP TCD

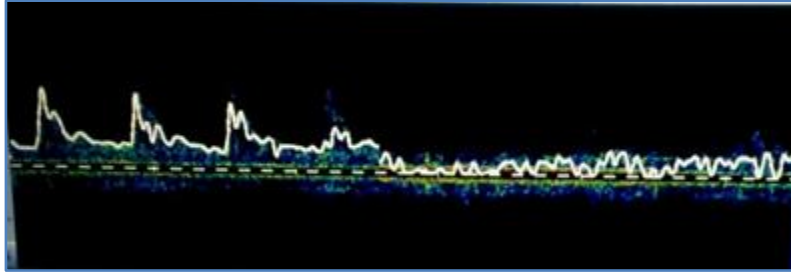


B) POST ICSNP TCD STUDIES IN PACS

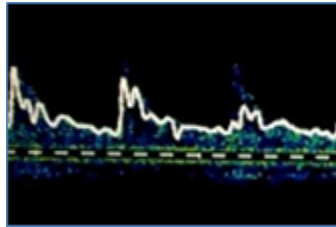


C) POST IC SNP PACS

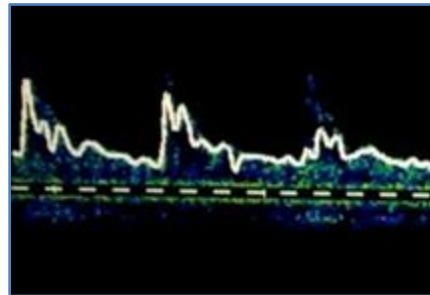
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D) POST IC SNP PACS



E) POST IC SNP PACS



F) POST IC SNP PACS

CASES 82 Pts	NIHSS	Cases	ICSNP (Day)	NIHS score Baseline	POST IT SNP NIHS SCORE					BARTHAL'S SCORE	
					1.30 MINTS	2 HOURS	24 HOURS	7 DAYS	2 MONTHS	2 MONTHS	
ICSNP (72/82)	5 TO 15	12	10	11	8.66	7.66	8	3	1.33	85%	
	16 TO 20	24	12.16	18.33	16.16	14.66	15.66	4.66	2.83	88.33%	
	21 TO 42	36	6.55	28.33	25	23.33	24.11	5.33	3.25	72.5%	
Control (10/82)	NO Injection	5	0	19.14	19.4	19.4	18.4	13.2	10.75	60%	
	Dex 5% Injection	5	15	20.2	20.2	20.2	19.8	17.2	14.2	65%	

TABLE 3: CLINICAL BASELINE NIHSS AND CHANGES

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CASES 82 Pts	BAMFORD'S	Cases	ICSNP (Day)	NIHS score Baseline	POST IT SNP NIHS SCORE					BARTHAL'S SCORE
					1.30 MINTS	2 HOURS	24 HOURS	7 DAYS	2 MONTHS	2 MONTH
ICSNP (72/82)	LACS	12	6.33	13.33	10	7.66	9.33	3.66	2	85
	POCS	8	20	13.5	13	13	12.5	5	2	85
	PACS	36	8.11	23.4	20.5	19.22	20	4.88	3.11	80.55
	TACS	16	9.75	30	26.7	24.75	25.5	5	3	71.66
Control (10/82)	NO Injection	5	0	19.14	19.4	19.4	18.4	13.2	10.75	60%
	Dex 5% Injection	5	15	20.2	20.2	20.2	19.8	17.2	14.2	65%

TABLE 4: BAMFORD'S CLASSIFICATION AND CHANGES AFTER ICSNP

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