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ORIGINAL ARTICLE

THE 10,000-FOLD-EFFECT-RETROGRADE NEUROTRANSMISSION-A NEWER CONCEPT FOR PARAPLEGIAS PHYSIOLOGICAL REVIVAL-USE OF INTRATHECAL SODIUM NITROPRUSSIDE

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ABSTRACT: BACKGROUND: Methylprednisolone-level-1-benefit (20%) in paraplegia (8hrs). Patient's wait-long-duration for physiological-recovery. Intrathecal-Sodium-Nitroprusside (ITSNP) has been used-in vasospasm-due-to-subarachnoid-hemorrhage. ITSNP-has been studied-here for wide-window-period-range for-treatment, fast-recovery/affordability. 2-mechanisms for acute-cases-and 1-mechanism-for chronic-cases, which-are-interrelated, are being-proposed-for-physiological-recovery. A) RETROGRADE-NEUROTRANSMISSION: (acute-cases). 1) Normal-excitatory-impulse: At synaptic-level, glutamate-activates NMDA-receptors, having-Nitric-Oxide-Synthetase (NOS) on-postsynaptic-membrane, for-further propagation-by-calcium-calmodulin-complex. NITRIC-OXIDE (NO-produced-by-NOS) travels-backward-across-chemical-synapse, binding-to-axon-terminal (NO-receptor/sGC) of-a-presynaptic-neuron, regulating-Anterograde-Neurotransmission (ANT) called-Retrograde-Neurotransmission (RNT). The-haem-is-the-ligand-binding-site-of-NO-receptor/sGC. The-affinity-of-haem-exhibits 10, 000-fold-excess-for-NO-than-Oxygen (THE=10, 000-FOLD-EFFECT) completes-in-20msec. 2) Pathological-conditions**:** Normal-ANT, synaptic-activity including-RNT is-absent. NO-donor (SNP) release NO from NOS at postsynaptic-region.NO-travels-backward across a chemical-synapse to bind to the haem of NO-receptor at axon-terminal of a presynaptic-neuron, generates-impulse, as in normal-condition. B) VASOSPASM: (acute-cases) c) Perforators-show vasospastic-activity. NO-vasodilates the-perforators by NO-Camp-pathway. D) LONG-TERM-POTENTIATION-(LTP): (chronic-cases) NO–cGMP-pathway-plays-a-role-in-LTP-at-many-synapses-throughout-the-CNS, and-at-neuromuscular-junction. The-LTP-has-been-reviewed both-generally and with-respect to specific-brain regions for memory/learning. **AIMS/STUDY-DESIGN:** Principle-of "generation-of-impulses from presynaptic-region to postsynaptic-region by-RNT, vasodilatation of arteriolar-perforators and LTP is the basis-of-authors' hypothesis to treat-acute-and-chronic-paraplegia-cases**.** Case-control-prospective-study. **MATERIAL/METHODS:** 82 paraplegia-patients (10patients taken as control-no super fusion or dextrose5% superfusion and 72patients as ITSNP-group). The mean time for super fusion was 14.11 days. ITSNP administered at a dosage of 0.2 mg/kg bo wt. Pre/post ITSNP monitored by SSEP/MEP. **RESULTS:** AFTER-2-HOURS in ITSNP-group MEAN-CHANGE-FROM-BASELINE-ASIA MOTOR/SENSORY-SCORE 13.84%/13.10%, after-24-hours MOTOR-1.27-points decrease(3.77%) and SENSORY 10.5points-increase(6.22%)as compared to Control-group no-change noted upto 24-hours, **At-7days** ITSNP motor/sensory;11.56%/6.22% as compared to Control-group 7.60/4.48%, At-2-months in ITSNP 27.69%/6.22% as compared to Control-group 16.02/4.5%. SSEP/MEP-documented-improvements-noted. **CONCLUSIONS:** ITSNP, a-swift-acting-drug in treatment-of-paraplegia, is effective within-two-hours (mean-change-MOTOR-13.84%andSENSORY-13.10%) on-

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mean14.11th postparaplegia-day with a small-detrimental-response after-24-hours which-recovers-fast.

KEYWORDS: Paraplegias; intrathecal sodium nitroprusside; retrograde transmission; the 10,000 fold effect; perforators; vasodilatations; long term potenciations.

INTRODUCTION: Anatomical continuity and stabilized spine are the goals of spine surgeons. But functional recovery always remains in dark which can be achieved by generating electrical impulse.

For management of acute paraplegia, methylprednisolone (MP) is approved by USFDA in 1995,[1] limitations are: narrow window period (<8 hours), clinician's fear of steroid related complications and slow improbable recovery. Physiological recovery still remains in dark.

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.

a) FOR ACUTE CASES-RETROGRADE-NEUROTRANSMISSION-(RNT): 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.[2,3] Nitric oxide (NO produced by NOS), travels backward (forming a cloud of NO) across chemical synapse[4] to bind to axon terminal (NO receptor/sGC) of a presynaptic neuron, regulating anterograde-neurotransmission (ANT), process called "retrograde-neurotransmission"(RNT),[2,5] allowing neural circuits to create feedback loops. NO-receptors, well equipped with a ligand binding site and a transduction-domain. The ligand-binding-site (haem-like haemoglobin of blood) when incorporated into the receptor protein, exhibits >10, 000-fold excess affinity for NO than Oxygen (THE 10, 000-FOLD-EFFECT)[6,7] completes in 20msec.[8] In brain cells, NO switches on the associated guanylylcyclase activity with no observable delay, a 20-msec sampling-time,[4] and on NO removal, the activity decays with half-time of 200 msec,[29] generating and mimicking ANT where kinetics not dissimilar to that of NMDA receptors or glutamate-receptors.[28,30] NO can up[9] or down-regulate[10,11] the oncoming impulses. NO's RNT like action is also shown by carbon-monoxide[25] and platelet-activating factor.[26,27] NO provides a simultaneous signal to both pre and postsynaptic elements, important in coordinating responses on the two sides of the synapse (bridging micro gaps by cloud of NO).[4,8,28]

b) ABNORMAL CONDITIONS:

1) **IMPULSE TOO-HIGH OR TOO-LOW**: In conditions of high-intensity-impulse (Schizophrenia (32), Obsessive compulsive disorder (33), NO down-regulates the impulse; in conditions of low-intensity-impulses (Depression with low-serotonin levels), NO up-regulates the impulse (34) (**FIGURE 1**).

2) **IN ABSENCE OF IMPULSE:** In cases with no-impulse (normal-ANT, including synaptic-activity and hence RNT is absent), NO-donors have shown promising result in generating an impulse by NO via RNT in vitro in rats (31).The study by O Dell-et-al (1991) on rats' tissue shows exogenous NO-donors increase frequencies of spontaneous miniature EPSPs. Now NO travels

DOI: 10.14260/jemds/2014/2891

backward across a chemical synapse, binding to axon terminal (NO-receptor/sGC) of presynaptic-neuron, acts as impulse-generator, as in normal condition, thus bypassing the normal ANT (FIGURE-2).This cascade relaxes the smooth muscles of perforators thus causing vasodilatation.

b) FOR ACUTE CASES-VASOSPASM; Vasospasm, demonstrated after experimental spinal-cord injury in laboratory by scanning[35,36] and transmission-electron-microscopy.[37,38] NO is a very potent-vasodilator.[14,15,16] SNP excels in emergency treatment of hypertension[39] by vasodilation action which is instantaneous (onset-within 30seconds; peak in 2-5minutes).[40] Intrathecal-Sodium-Nitroprusside (ITSNP) has been used in vasospasm due to subarachnoid-hemorrhage (SAH). SNP acts on NOS present on the adventitial-side of the perforators, triggering NO-release. NO vasodilates the spinal arterioles (in resting and compressed states of the spinal-cord[37,38] causing gush of blood into spinal-cord.

The impact of the Intrathecal[41,42] and intraventricular[43] administration in vasospastic cases is at the level of the microcirculation. Studies on Intraarterial (for ergotism patient's[44,45,46,47] and intracarotid (for cerebral blood flow measurements) in normal subjects[48,49,6,7,50,51,53] are noted. Oral NO-donor like Sildenafil was studied but to relieve SAH's vasospasm.[52,53,54]

C) FOR CHRONIC CASES-LTP (LONG TERM POTENTIATION) The endocannabinoids anandamide and 2-AG are the primary retrograde messengers in the brain and may also play an important role in retrograde signaling in long-term-potentiation (LTP), meant for memory and learning [12,13,14,15, 16,17,18,19,20,21,22,23, 24] as is nitric-oxide.[13,14] NO–cGMP pathway plays a role in LTP at many synapses throughout the CNS, and even at the neuromuscular junction. The LTP has been reviewed both generally[16,17,18,19] and with respect to specific brain regions.[20,21, 22,23,24]

This same Principle of "generation-of-impulses from presynaptic-region to postsynaptic-region by the very potent RNT (10, 000-FOLD-EFFECT), vasodilatation-of-arteriolar-perforators and LTP is the basis of authors' hypothesis to treat acute and chronic paraplegia cases respectively.

MATERIALS AND METHODS: The Ethical-Committee-acceptance has been taken from King-George's-Medical-College-Lucknow; UP INDIA (Number: 13389/GA; dated: 15/03/2002). Potential benefits and significant risks (uneasiness, nausea, vomiting, headache and hypotension) were discussed with all patients/relative and written & video consent has been taken for ITSNP, video-recordings of pre & post injection phase with Somato Sensory Evoked Potential (SSEP) and Motor Evoked Potential (MEP) studies.

We were able to treat 82 paraplegia patients prospectively, in which 10 patients were taken as a control and 72 patients were given ITSNP. Control-group is again subdivided into two subgroups. First (5/10) was treated without any super fusion and other subgroup (5/10) super fused with Dextrose 5% in the same amount. ITSNP-group (72-patients) is subdivided into operative group (48/72) (restored anatomical continuity with or without stabilization) and the second non-operative group (24/72). ITSNP-group again divided into two-subgroups. First-subgroup in which ITSNP was given from 3-21days and second in which ITSNP was given beyond 21 days.

The variables that were specifically recorded for each patient in this study were: time-of-symptom/accident for paraplegia onset, time-of-arrival in the emergency department, baseline-MRI,

DOI: 10.14260/jemds/2014/2891

SSEP and MEP studies, operation done/not and the time of ITSNP administration. An extensive neurological examination including the baseline ASIA paraplegia scale[55,56] was performed in all patients. Other parameters noted were the demographic profile, mean arterial blood pressure and temperature before and after SNP treatment.

The ITSNP-protocol has the inclusion and exclusion criteria as shown in table 1.

PRETREATMENT: Acute-traumatic-paraplegia-cases (<8 hours) were given MP in the same dosages as advocated by NASIS-III.[1] For nausea Ondansetron HCl 32.0 mg IV, was given 15 minutes before treatment. Meticulous photoprotection and sterile-technique were observed for all aspects of delivery of the medication as well as its formulation. Powdered-SNP was sterilely reconstituted with 200 ml of dextrose5% with 50 mg of the SNP. Control-group either did not receive any super fusion (5/28) or was superfused-with-5%DEXTROSE (5/28). Each of ITSNP-GROUP (18/28) patients received 0.2 mg/kgbodywt of SNP. After lumber puncture (LP) with 24G LP needle at L3/4 level around 8-ml of cerebro spinal fluid (CSF) drained and then 8-ml of the SNP/DEXTROSE put in, waited for 3-minutes, repeated the same procedure for two times. We waited for two hours for the further study on recovery along with SSEP and MEP studies. Post ITSNP 2 hours, 24 hours, 7 days and 2 months noted.

This study corroborates earlier impressions regarding the safe limits of doses of SNP in Intrathecal.[42, 43] This study also supports the safety of administration of ITSNP in the intensive care unit or in emergency-room.

High protein (ARGININE RICH) diet started in all cases after ITSNP.

MRI was done in all cases. (Figure 3 a and b saggital and axial). SSEP and MEP done in pre and post-ITSNP (figure 4 a, b and 5 a, b). Mean length of hospitalization in our patients was nine days. We obtained telephone or clinic follow-up with the patient and caregiver for 2 months and assessed the outcome using the ASIA outcome score.

RESULTS: The mean age of our patients was 42.38 years (range 42-56); 48 were males. Co-morbid illnesses in the form of hypertension and diabetes were present in 8 and 3 patients respectively. The mean blood pressure (MAP) at admission was 124/88 mm of Hg, there was no change in MAP in PRE or POST ITSNP. The temperature remained same in post-super fusion status either in Control-group or ITSNP group. The paraplegia team was notified of 892 patients suspected of having paraplegia during the period 2007-2014.

The common reasons for disqualification from study were medical causes (GB Syndrome, transverse myelitis, periodic paralysis), minor or rapidly resolving symptoms (ASIA-D or E), postoperative improving cases upto 3 days, traumatic-paraplegia with head injury, traumatic-paraplegia with abdominal and pelvic injury and traumatic paraplegia cases who reported within 8 hrs in whom methylprednisolone was given.

DOI: 10.14260/jemds/2014/2891

TABLE 2 = MEAN MOTOR AND SENSORY CHANGES

CASES 82	Super fusion	DAYS	Mean DAYS	Motor	POST ITSNP MOTOR				Sensory	POST ITSNP SENSORY			
				Baseline	2 hrs	24 hrs	7 DAYS	2 months	Baseline	2 hrs	24 HRS	7 days	2 months
Control 10 Cases	NO SUP 5/10		0	42.2	42.2	42.2	43	61.33	114.8	114.8	114.8	150	154
	DEX 5% 5/10		13.6	47.2	47.2	47.2	53.2	73.5	143.6	143.6	143.6	176	186
POTT'S 28/72	ITSNP OP 20/72	3-<21 DAYS	6.6	60.33	71.66	66	76	100	165.33	178	188.66	188.66	224
		>21 DAYS	24.5	42.5	56	47.5	65	81	97.5	130.5	140.5	170.5	207
	ITSNP NONOP 8/72	3-<21 DAYS	6	64	76	74	80	88	172	200	210	224	224
		>21 DAYS	33	50	50	50	50	L	72	77	77	77	L
Pyogenic 4/72	ITSNP 4/72	3-<21 DAYS	4	58	70	66	74	96	172	210	224	224	224
Traumatic 40/72	ITSNP OP 16/72	3-<21 DAYS	5.75	42.5	42.5	49.5	53	70.66	115.5	125.5	135.75	162.5	203.33
		>21 DAYS	27	58	74	68	75	90	163	210	224	224	224
	ITSNP NONOP 16/72	3-<21 DAYS	5.5	53.5	59.5	60	63.5	78.5	171	182	189	193	197
		>21 DAYS	27	50	50	50	53	54	152	153	155	155	148
			14.11	51.72	58.72	57.61	64.27	82.07	141.16	159.66	168.72	179.22	207.85

L= LOST TO FOLLOW UP
ITSNP=INTRATHECAL SODIUM NITROPRUSSIDE

MEAN STUDY RESULTS: AFTER-2-HOURS in ITSNP group (as a whole) MEAN-CHANGE-FROM-BASELINE-ASIA MOTOR/SENSORY SCORE 13.84%/13.10%, after-24-hours MOTOR 3.77% decrease and SENSORY 6.22% increase as compared to Control-group no change noted upto 24 hours, At-7days ITSNP motor/sensory; 11.56%/6.22% as compared to Control-group 7.60/4.48%, At-2-months in ITSNP 27.69%/6.22% as compared to Control-group 16.02/4.5%.
For result analysis, we defined:

A) EXCELLENT-OUTCOME increase of two grades better than pre ITSNP within two hours.
B) GOOD-OUTCOME one grade better within two hours.
C) FAIR-OUTCOME subjective improvement or SSEP and MEP shows improvement of one grade in 24hours and sustains/increases after 7days.
D) POOR-OUTCOME no improvement clinically or SSEP and MEP upto 7days.

The various results may be understood by the following data:

1) EXCELLENT-RESULTS' CASES (24/72CASES; 33.33%)

ITSNP-GROUP patients with excellent results had MEAN-BASELINE-MOTOR/SENSORY-ASIA-SCORE of 53.83/154.83 points. Patients were given ITSNP on 5.33 mean days, giving time for natural recovery.

MOTOR/SENSORY-RECOVERY: After 2hrs MOTOR/SENSORY-MEAN-CHANGE was 30.03%/17.57% increase respectively. After-24-hours motor/sensory; 11.2%/7.07% increase respectively. Motor

DOI: 10.14260/jemds/2014/2891

recovery was increased post BASELINE-ITSNP-ASIA-SCORE (8.33POINTS;15.47% RANGE 1-18) but detoriated (7.84POINTS;11.2%RANGE 4-13) as compared to post-ITSNP 2hrs this motor recovery showed a incremental increase thereafter upto 2-months but sensory didn't detoriated.

2) **GOOD-RESULTS' CASES (12/72CASES; 16.66%):** ITSNP-patients with good results had a MEAN-BASELINE-ASIA-MOTOR/SENSORY-SCORE of 62.66/169.33. Patients were given ITSNP on 6.33 mean days.

MOTOR/SENSORY-RECOVERY: After 2-hrs MOTOR/SENSORY-MEAN-CHANGE was 17.02%/22.04% increase respectively. After-24-hrs MOTOR/SENSORY was 9.09%/6.13% increase respectively. Motor recovery was increased again post BASELINE-IT-SNP-ASIA-SCORE(6.67 POINTS;9.09%RANGE 2-10) but detoriated (5.45%)as compared to post-ITSNP-2hrs this motor recovery showed a incremental increase thereafter upto 2-months without sensory deterioration. as compared to CONTROL (no superfusion/dex5%) motor1.89%/6.71%; and sensory 3.48%/5.29%.

1) **FAIR-RESULTS' CASES (16/72 CASES; 22.22%):** ITSNP-patients with fair results MOTOR/SENSORY-MEAN-CHANGE was 42.55/133 respectively. Patients were given ITSNP on 25 mean days.

MOTOR/SENSORY-RECOVERY: In ITSNP-group after-2hrs no change noted in motor but 8.27% increase in sensory noted. After-24-hours=20%/8.15% increase in motor/sensory respectively and no detoriation noted in motor as compared to post ITSNP 2hrs. At-7days- in ITSNP-group motor/sensory was 6.86%/18.13% increase which increased upto 2 months as compared to CONTROL (no superfusion/dex5%)-motor 1.89%/6.71%; and sensory 3.48%/5.29%.

2) **POOR-RESULTS CASES (20/72CASES; 27.77%):** ITSNP-patients with poor results MOTOR/SENSORY-MEAN-CHANGE was MOTOR/SENSORY-MEAN-CHANGE was 50/113.6 respectively. Patients were given ITSNP on 20.6 mean days.

MOTOR/SENSORY-RECOVERY: In ITSNP-group after-2hrs no change noted in motor but 2.28% increase in sensory noted. After-24-hours motor/sensory was 0.8%/0.68% increase respectively. At 7 days motor/sensory was 2.38%/0.68% increase which increased upto 2 months as compared to CONTROL (no-superfusion/dex5%)-motor 1.89%/6.71%; and sensory 3.48%/5.29%.

PARAPLEGIA PATIENTS HAVING NORMAL SPINAL-CORD 36/72: ITSNP-group after-2hrs motor/sensory was 14.34%/19.48% increase which increased upto 2 months.

PARAPLEGIA PATIENTS HAVING ABNORMAL SPINAL-CORD 36/72: Both in ITSNP-GROUP and CONTROL-GROUP no response was seen in MOTOR upto 2 hours but in IT-SNP group SENSORY-ASIA-SCORE improved slightly after-2-hours i.e., 5.17%. After-24hrs in ITSNP-group motor/sensory was 8.57%/9.81% increase respectively which increased upto 2 months.

DOI: 10.14260/jemds/2014/2891

PARAPLEGIA PATIENTS IN WHICH ITSNP DONE FROM 3 DAYS TO 21 DAYS (44/72): After-2hrs in ITSNP-group motor/sensory was 21.11%/17.66% increase which increased upto 2 months.

PARAPLEGIA PATIENTS IN WHICH ITSNP DONE IN MORE THAN 21 DAYS (68/72): In ITSNP-group no improvement noted after-2hrs in MEAN-MOTOR-ASIA-SCORE but MEAN-SENSORY-ASIA-SCORE improved slightly (5.24%) which increased upto 2 months.

PARAPLEGIA PATIENTS IN WHICH ITSNP DONE POSTOPERATIVE (48/72): In ITSNP-group after-2hrs motor/sensory was 13.99% both improved which increased upto 2 months.

PARAPLEGIA PATIENTS IN WHICH ITSNP DONE IN NONOPERATIVE GROUP 24/72: In ITSNP-group after-2-hours motor/sensory was 14.54%/12.13% both improved which increased upto 2 months.

PARAPLEGIA PATIENTS IN WHICH ITSNP DONE IN CERVICAL CASES (8/72): In ITSNP-group after-2-hours motor/sensory were 43.58%/59.70% improved which increased upto 2 months.

PARAPLEGIA PATIENTS IN WHICH ITSNP DONE IN THORACIC SPINE CASES (52/72): In ITSNP-group after 2hours motor/sensory was 12.65%/13.52% increase which increased upto 2 months.

PARAPLEGIA PATIENTS IN WHICH ITSNP DONE IN LUMBER SPINE CASES (12/72): In ITSNP-group after-2hrs motor/sensory was 12.24%/7.01% increase which increased upto 2 months.

SIDE EFFECTS ENCOUNTERED: After ITSNP nausea (95%), vomiting (85%), headache mild (25%) to moderate (45%), uneasiness (95%), warmness or coldness of involved extremities (45%), retching(5%), diaphoresis (55%), apprehension (15%), restlessness (65%), perspiration (65%), palpitations (25%), dizziness (10%). None of the patient had hypotension.

DISCUSSION: The methylprednisolone, to be effective, should be given in 8 hrs. We didn't deviate from standard protocol of use of methylprednisolone within specified time. We chose only those patients who were out of range for methylprednisolone (i.e., from 3rd day to >21 days). A significant difference in our experience was treatment within an average of 14.11TH postparaplegia day. Due to its very potent 10, 000 fold effect ITSNP generates ANT via RNT action.

Methylprednisolone targets mainly the edema part of spinal-cord insult. But vasospasm and thereby generation of impulses from presynaptic to postsynaptic neuron was the purpose of this study by the use if ITSNP without neglecting methylprednisolone's role and obtaining the physiological recovery.

In ITSNP-group, just after two hours of superfusion the mean MOTOR/SENSORY-ASIA-SCORE was13.84%/13.10% as compared to Control-group (both subgroups) showing no improvement upto 24 hours. In ITSNP group this response (clinically by ASIA GRADING coincided with ZPP in pre-clinical examination and the SSEP and MEP studies) shows an overwhelming response due to that

effect of nitric oxide (released due to NOS activation) which expedite the synaptic activity i.e., ANT via RNT and by vasodilatation of the arteriolar-perforators.

This generation of impulses i.e., ANT via RNT, in vitro, has been shown to produce miniature EPSPs in rats by O Dell in 1991(31) that too in 20 msec, shown experimentally by Bellamy et al in 2001 (4).

In ITSNP-24 hrs, a slight deterioration in motor score (not in sensory) is observed (mean decrease of 3.77% in acute cases) followed by an increment (9.15%) by 7th day.

In excellent and good results' showed deterioration in mean-motor-score, after 24 hour, returned back to 7th day ASIA status. This deterioration was might be due to superoxide (SO) formation at the pathological spinal cord. A study done on serum superoxide dismutase (S-SOD) level in infarct cases, of brain, showed the level of S-SOD is inversely correlated with the size of infarction on CT scan of brain and the severity of neurological deficits.

The decreased SOD-activity recovered within mean 5 days to control serum values.[57] Second hypothesis proposed: synaptic vesicles were swiftly used up by ANT and RNT, creating local depletion, pulling raw material (L-Arginine and oxygen[58] from cell body, approximately within a week time.[2,3,4,5] So we advised Arginine rich diet after ITSNP. Our clinical findings (post ITSNP-24 hrs) show a decrease in ASIA-SCORE, then after 7 days, recovered, supporting above two hypotheses, i.e., superoxide ion is washed away by the S-SOD along with restoration of the raw material from the cell body.

SENSORY-ASIA-SCORE level showed no detoriation POST-24-hours-ITSNP may be because the area per volume (AREA PER VOLUME HYPOTHESIS) of posterior column and lateral spinothalamic tract (and hence the no. of synapses) is more as compared to corticospinal tract and for RNT, more the synapses, more the effect and consistent recovery (yet to be evaluated).

Fair results' (ITSNP on 25th day), showed no deterioration after-24-hours; instead the maximum incremental response was after 7th day (MOTOR 24.56% and SENSORY 26.96%) because after that duration NO released would have acted via the mechanism of LONG-TERM-POTENTIATION (LTP) which is responsible for learning and memory in brain [15,16,17,18,19,20, 21,22,23,24] (yet to be evaluated).

Poor results' in ITSNP-GROUP with abnormal spinal-cord having small level of ZPP, contused or damaged spinal cord in MRI, and during intraoperative inspection, no improvement is seen in motor level but there is a mild improvement in sensory after-7-days. This improvement was upto the level of ZPP and corroborates recovery from Control-group in which spinal-cord is transacted.

ITSNP-group time comparison study revealed definite & quick improvement on super fusion done between 3-21days (ITSNP 2 hrs motor 21.11%, sensory17.66%) than >21days group (ITSNP 2hours motor-no response, sensory-6.86%).

ITSNP-group op/non-operative comparison study reveals definite & quick improvement on super fusion done in operative group (ITSNP-2hrs motor/sensory; 13.99% both) than non-operative group (ITSNP-2hrs motor/sensory; 9.84/10.12% respectively).

Region-wise comparative study showed maximum response from cervical then thoracic and lumber region. Post-2hrs ITSNP cervical::thoracic::lumber; motor 3.56::1.03::1 & sensory 8.51::1.92::1 (supporting AREA PER VOLUME HYPOTHESIS). These responses showed an incremental response upto ZPP in next 7 days.

DOI: 10.14260/jemds/2014/2891

This preliminary data from a developing country shows that the use of SNP in paraplegia is feasible and useful. This study may be taken as a pilot project to evaluate essentially the feasibility and safety in future. In future we plan to combine methylprednisolone (for hyperacute spinal injury) and after subsidence of spinal edema, ITSNP for maximum recovery.

CONCLUSION: The ITSNP is fast acting drug for paraplegia revival (within 2hrs) and effective (mean change in motor/sensory:13.84%/13.10% on mean 14.11^{th} post paraplegia day) with small deterioration after 24hours (3.77% in motor) and then incremental response to 2 months. For acute cases (3-21 days), SNP works via very potent retrograde neurotransmission (10, 000FOLD-EFFECT), with vasodilator effect and for chronic cases (>21 days) SNP works via long term potentiation effect. SNP is safe, universally available, very cheap, and administered in a wide time window and vasodilates the arteriolar-perforators for further maintenance of anterograde neurotransmission. A double blinded, controlled, multi-centric and randomized study in future is needed to quantify the effect of SNP in paraplegias.

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

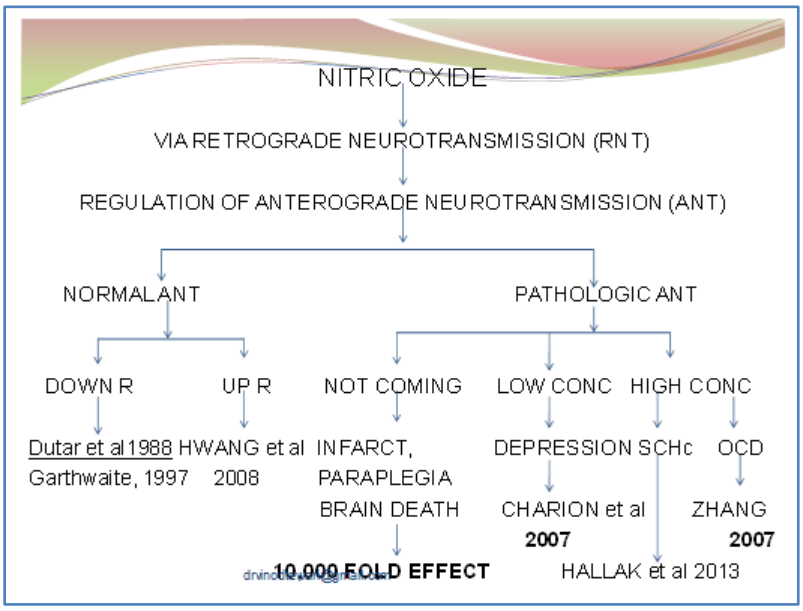

Figure 1

FIGURE 2 SHOWS THE MECHANISM OF ACTION OF NITRIC OXIDE AT THE SYNAPSE LEVEL.

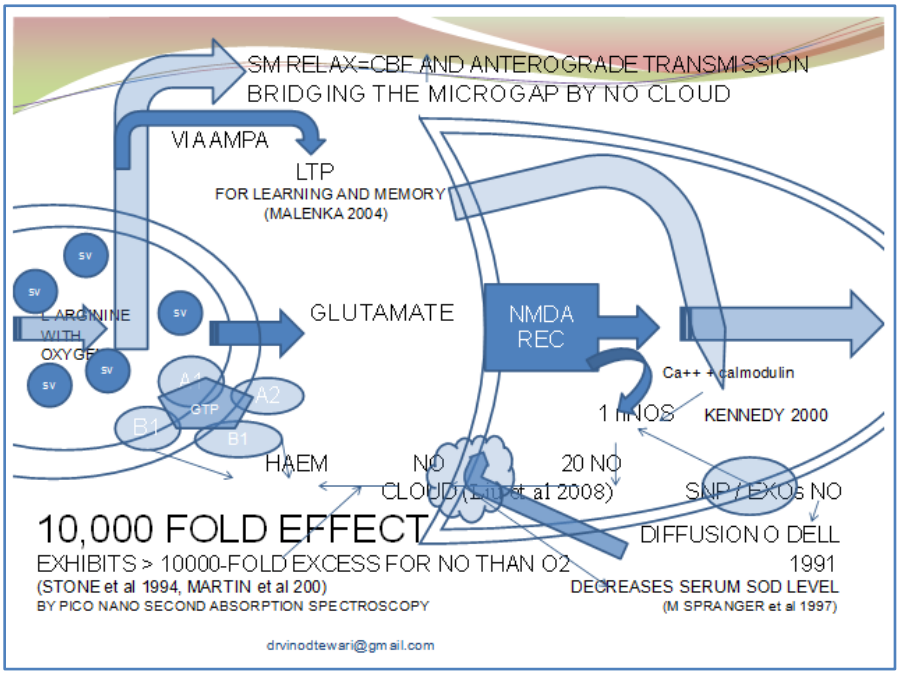

Figure 2

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TABLE 1: CRITERIA FOR USE OF ITSNP IN TREATING VARIOUS CASES PARAPLEGIA.

CLINICAL INCLUSION CRITERIA:

1. Patient/ caregiver able to give informed written and vedio recordings consent before and Vedio recordings after the study procedure.
2. Age >= 18years
3. Two groups
    a) Operative cases = two groups based on time period.
        i. No response postsurgery upto 3 days (3 days to 21 days subgroup).
        ii. More than 21 days postsurgery.
    b) Nonoperative cases
        A. Not responding from 3 days to 21 days.
        B. More than 21 days.
4. American Spinal Injury Association (ASIA) Classification ASIA A, B OR C (i.e., patient should be of complete (A) or incomplete (B, C) grading in ASIA group).

CLINICAL EXCLUSION CRITERION:

1. ASIA D or E.
2. Medical causes like G B Syndrome, transverse myelitis or periodic paralysis.
3. SCIWORA
4. Post-operative improving cases upto 3 days.
5. Pregnancy, lactation and parturition within previous 30 days.

MRI (MAGNETIC IMAGING) EXCLUSION CRITERIA:

1. Evidence of acute or chronic intraspinal bleeding on MRI.
2. Acute spinal contusion with bleeding.

FIGURE 3 a: CASE 1 operative case MRI SAGGITAL VIEW AND AXIAL VIEW:

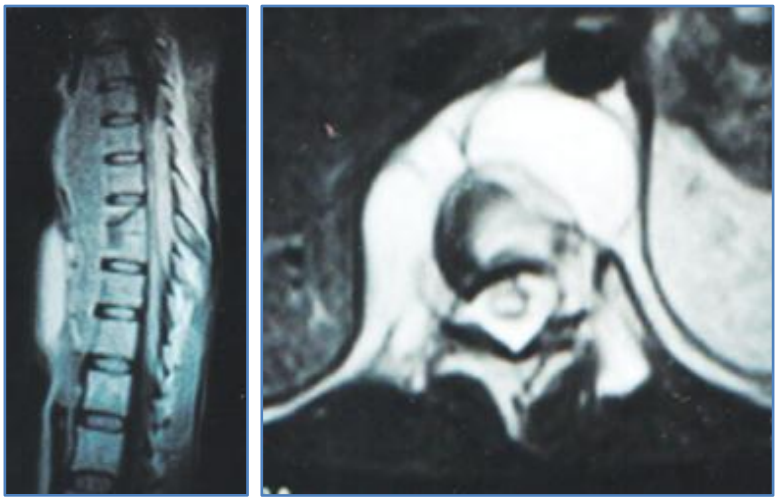

Figure 3 a

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FIGURE 3 b: CASE non-operative case MRI SAGGITAL VIEW AND AXIAL VIEW:

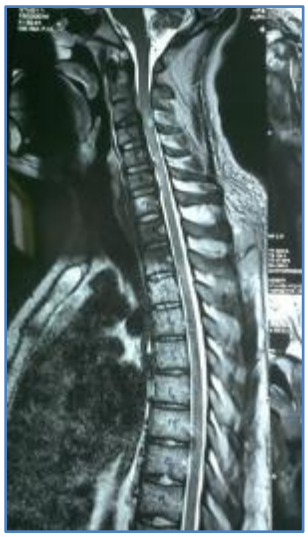

Figure 3 b

FIGURE 4 (A): CASE 1 PRE STUDY SSEP AND MEP:

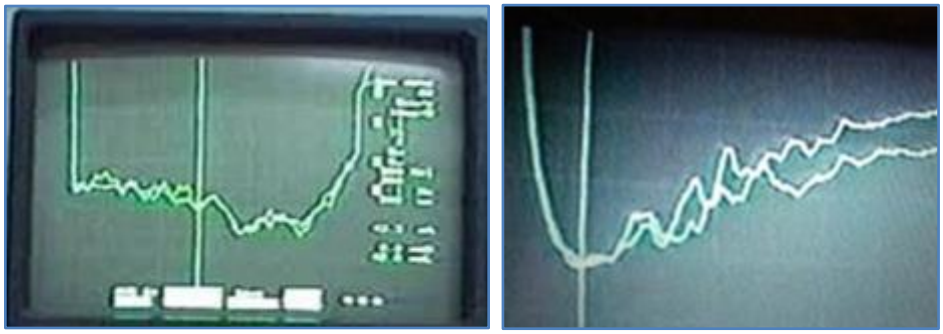

Figure 4 (A)

FIGURE 4 (B): CASE 1 POST SSEP AND MEP:

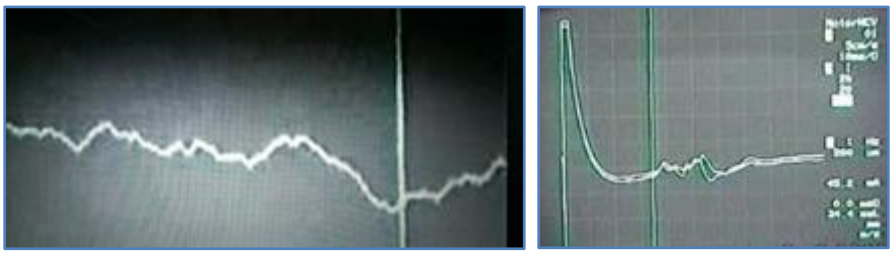

Figure 4 (B)

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FIGURE 5 (A): CASE 2 PRE STUDY SSEP AND MEP:

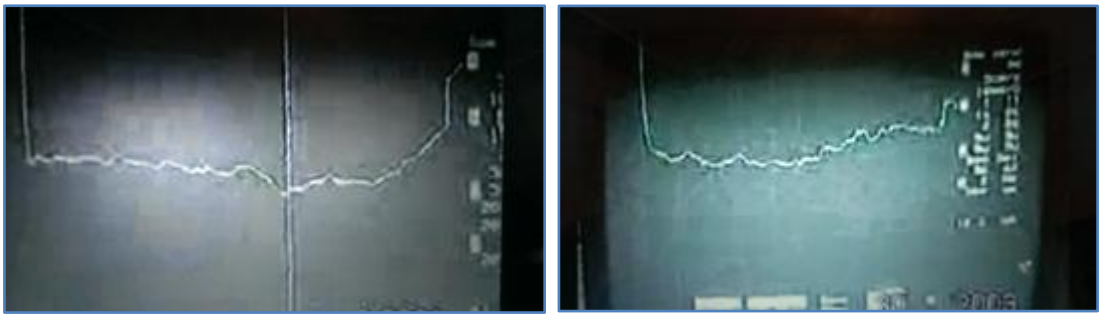

Figure 5 (A)

FIGURE 5 (B): CASE 2 POST SSEP AND MEP:

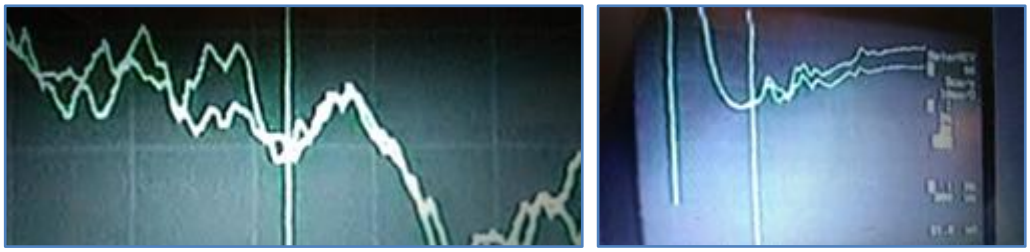

Figure 5 (B)

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