



Intracarotid Sodium Nitroprusside with Double Dose Platelet Rich Plasma In Sub Acute Ischemic Stroke Cases (From 5th To 21st Post Stroke Day) To Prevent Post 24 Hours Power Decrease – Pilot Study In 7 Cases

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Abstract

Background: Tissue Plasminogen Activator (tPA) showed a level 1 benefit in acute stroke (within 4.5 hours). But for more than 4.5 hours cases (if they fail to qualify for clot retrievers) Intracarotid/Intraarterial sodium nitroprusside (ICSNP/IASNP) has been studied by the author previously from 5th day to 21st day has shown promising results. Actually, most of the cases in developing and even in developed countries are there which arrives to clinicians after this time window of 4.5 hours. But after giving IASNP in those cases and activating the 10,000-fold effect those cases show decrease in power after 24 hours. Platelet rich plasma (PRP) is thereby utilized to provide growth factors at the cyton level to maintain and restore the raw materials for the synaptic flow of 10,000-fold effect along with ICSNP via the same port.

Aims/Study Design: Post 24 hours IASNP activation (10,000-fold effect) causes decrease in power of the recovered area which is restored by the PRP at the cyton level are the basis of the authors' hypothesis to treat sub-acute stroke cases from 5th day to 21st day. Pilot study on 7 cases prospective study.

Materials and Methods: The population included 7 stroke patients. The mean time for superfusion was 8 days post-stroke. Pre- and post-IASNP with Double dose PRP (IASNP with DD-PRP) status was monitored by NIHSS, MRI-DWI, ALTENS.

Results: After 2 hours of IASNP with DD-PRP, the mean change in the NIHSS score was a decrease of 9.5 points; after 2 h, there was a decrease of 2 points; after 24 h, there was an decrease of 2.5 points, at 7 days there was an 3-point decrease, at 3 weeks there was a decrease of 0 points; at 3 month there was a 0-points decrease, well documented by NIHSS, MRI and ALTENS study.

Conclusions: IASNP causes improvement in neurological deficit in these 7 cases but after giving PRP via same port we didn't find any decrease in benefitted neurological deficit.

Keywords: Brain Infarcts; Intracarotid Sodium Nitroprusside; Perforators' Vasodilations; Retrograde Neurotransmission; The 10,000-Fold Effect, PRP. NIHSS, MRI-DWI, ALTENS

Introduction

Gold standard treatment for Acute stroke remains to be rTPA as recommended by NINDS and Indian study too but within 4.5 hours [1-3]. What will be the fate of those patients who arrive clinicians after this critical time window of 4.5 hours be it developed or developing country. Except clot retrievers for large artery blocks that too within 12 hours is highly recommended now a days [4].

We have proved IASNP as treatment modality for sub-acute stroke cases from 5th to 21st post stroke day 1st in rats [5] then in humans [6].

In our publications [5,6] on IASNP alone in sub-acute ischemic stroke cases (from 5th to 21st post stroke day), we have pointed out that there was a decrease of power after 24 hours of IASNP always in nearly each case. Then after vigorous search of literature we didn't find any remedy for it. We attended many conferences including Regenerative medicine conferences and stem cell conferences in India. We came across the Platelet Rich Plasma extraction technique [7].

Which provided multiple growth factors contained in platelets' Alpha granules of platelets are having Brain-derived neurotrophic factor (BDNF), a major neurotrophin and vascular endothelial growth factor (VEGF) in large quantities. BDNF and VEGF can both be found in the brain, their ability to cross the blood brain barrier is not straightforward. BDNF can cross the BBB, but its transport may be limited and influenced by factors like the specific region of the brain and the presence of other molecules. VEGF's ability to cross the BBB is also complex, with some studies suggesting it can cross under certain conditions or via specific mechanisms. BDNF is in maximum concentration in platelets of humans, VEGF is in moderate concentration in platelets. BDNF is having larger structural unit (27 KDA) which cannot effectively penetrate through the BBB (BBB permeates only those molecules which are less than 20 DA) [8-10].

With this hypothesis, first of all we did IASNP to enlarge the BBB via eNOS activity and then we gave PRP via the same port, causing BDNF and VEGF fluent entry and provides raw material for neurotransmitters to be used at synapses.

Aim: To give 1ASNP with PRP in sub-acute ischemic stroke cases from 5th to 21st post stroke day.

Materials and Methods

This is a pilot study in 7 cases between Mar-2025 and Aug-2025, treated at Advance Neuro and General Hospital Lucknow prospectively. 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 with PRP injection and NIHSS score, ALTENS, MRI with DWI brain and Video-recordings of pre- and post-injection phases.

Mean age of our patients was 61years (range 45-72). Out of the 7 patients who were given IASNP, 4 were males and 3 were females. Co-morbid-illnesses in form of hypertension, diabetes, hypercholesterolemia were present in all 7 patients. There was no history of prior stroke in any patient. Mean-blood-pressure at admission was 180/100 and mean-maximum-pretreatment was 150/90 mmHg. 2 of 7 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, NIHSS score, ALTENS, MRI and Video-recordings of pre- and post-injection phases. 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.

Patient's venous blood samples 15 ml in 4 test tubes is taken and placed them upright in the test tube, waited for half an hour [1]. Do the multiple spins in an appropriate centrifugation machine and get the plasma then add calcium gluconate at the ratio of 1:10 in it and do one more spin so that activated PRP is ready to use. Around 12 ml of double dose PRP is prepared [2].

Patients received pretreatment for nausea in form of ondansetron HCl (32.0 mg IV push) 15 minutes before treatment. Meticulous photoprotection, sterile technique were observed for all aspects of delivery of medication as well as its formulation. Powdered SNP was sterilely reconstituted with 200ml 5% dextrose with 50 mg of the SNP. Patients were hydrated and ICSNP was given via 20 G Viggo at the ipsilateral carotid artery of MRI DWI indicating hyperintensity at the dose of 0.01 mg/kg body weight up to a maximum of 2ml (0.5mg) with simultaneous Double dose PRP (freshly prepared from the blood of the patient himself). As and when hypotension is encountered IV injection of 1 ml Mephenterine is given, based on titration of hypotension. We waited for 2 hours for the recovery. NIHSS scores were recorded at baseline, 2-h, 24-hrs, 7-days, & 2-months. The mRS was recorded at 2 months.

This study corroborates earlier impressions regarding the safe limits of doses of SNP in humans. Heparin/aspirin/clopidogrel/Antihypertensives were given during hospital stay. High-protein (arginine-rich) diets were started as was in our previous human studies.

Table 1 intracarotid sodium nitroprusside with double dose platelet rich plasma (iasnp with dd-prp) in sub acute stroke cases to prevent post 24 hours power decrease.

S. NO	BAMFORD'S GROUPS-4	7 CASES	DURATION	PRE- ICSNPALTENS	POST- ICSNPALTENS	% CHANGE	PRE ICSNP NIHSS GRADING	POST (2 hrs) ICSNP NIHSS GRADING	POST (24 hrs) ICSNP NIHSS GRADING	POST (7 days) ICSNP NIHSS GRADING	POST (21 DAYS) ICSNP NIHSS GRADING	POST (3 MONTHS) ICSNP NIHSS GRADING
1	LACS (LACUNAR STROKES)	3	7 DAYS	5 to 6 mAmp	2 to 3 mAmp	25%	28	12	8	7	4	4
2	PACS(PARTIAL ANTERIOR CIRCULATION STROKES)	2	10 DAYS	6 to 7 mAmp	3 to 4 mAmp	25%	24	10	8	7	4	4
3	TACS (TOTAL ANTERIOR CIRCULATION STROKE)	1	7 DAYS	more than 8 mAmp	more than 8 mAmp	0%	32	32	32	32	30	30
4	POCS (POSTERIOR CIRCULATION STROKES)	1	8 DAYS	5 to 7 mAmp	4 to 5 mAmp	25%	30	18	16	8	4	4

Table 1: Intracarotid Sodium Nitroprusside with Double Dose Platelet Rich Plasma in Sub Acute Stroke Cases to Prevent Post 24 Hours Power Decrease.

Using Oxford stroke classification (BAMFORD's classification), LACS(LACUNAR- STROKE) was found in 3/7 patients, PACS (PARTIAL-ANTERIOR-CIRCULATION- SYNDROME) was found in 2/7, TACS (TOTAL-ANTERIOR-CIRCULATION-STROKE) was found in 1/7 and POCS (POSTERIOR-CIRCULATION-SYNDROME) was found in 1/7.

Mean time of INTRACAROTID-SODIUM-NITROPRUSSIDE injection was 9.5 days (range 7-10) after stroke onset. Mean length of

hospitalization was 5 days. The MEAN BASELINE NIHSS SCORE was 28.11(range 24-32). Pre IASNP and post IASNP clinical examination NIHSS was video recorded. MRI-DWI were performed in each case. Post IASNP done.

Results

We obtained telephone or clinic follow-up with patients and caregivers in cases for next two months and assessed mRS scale.

For analysis based on NIHSS GRADING, results were as follows

- NIHSS 25-30 (4/7) 3 patients were of LACS and 1 patient was of POCs with NIHSS at 28 AND 30 respectively. Where IASNP with DD-PRP was given on 7th AND 8th post stroke day respectively and after 2 hours the NIHSS came to at 12 and 18 respectively after 24 hours NIHSS came to 8 and 16 respectively. Then after a week NIHSS was at 7 and 8 respectively, after 21 days at 4 and after 3 months at 4 in all cases. The ALTENS study was remarkable from 5 - 6 mAmp to 2 - 3 mAmp and from 5 - 7 mAmp to 4 - 5 mAmp respectively after 24 hours. The modified RANKIN SCORE (mRS) was 1.
- NIHSS 30-35 (1/7) the patient was of TACS with NIHSS at 32. Where IASNP with DD- PRP was given on 7th post stroke day and after 2 hours the NIHSS came to at 32 and no change in NIHSS and remained at 32 even after 3 months. The ALTENS study remained from 8 mAmp to 8 mAmp even after 24 hours. The modified RANKIN SCORE (mRS) was 4.
- NIHSS 20-24 (2/7) both the patients were of PACS with NIHSS at 24. Where IASNP with DD-PRP was given on 10th post stroke day and after 2 hours the NIHSS came to at 12 and after 24 hours NIHSS came to 8. Then after a week NIHSS was at 7, after 21 days at 4 and after 3 months at 4. The ALTENS study was remarkable from 6 - 7 mAmp to 3 - 4 mAmp after 24 hours. The modified RANKIN SCORE (mRS) was 2.

Discussion

NINDS study gave a brain salvaging time of 4.5 hours. A significant difference in our experience was the effectiveness of treatment within an average of 8 days, and, due to very potent 10,000-fold effect, IASNP with DD-PRP. IASNP generates the anterograde neurotransmission via retrograde neuro regulation. We choose only those patients who were out of range for thrombolysis (from 4.5 hours onwards). None of our patients developed any form of intracerebral hemorrhage (as found in the NINDS study), which suggests a good safety profile for IASNP and DD-PRP.

3 cases with LACS out of 7 cases having baseline NIHSS-scores of 28, IASNP with DD- PRP was given on 7th post stroke day. After 2 hours of IASNP NIHSS came to 12 and After 24 hours NIHSS came to 8 so he improved excellently. Then after a week NIHSS was at 7 and after 21 days it came to be at 4 which continued at 3 months.

In MRI DWI there was mild change noticed from pre IASNP and DD-PRP then post IASNP and DD-PRP upto 1 week. But ALTENS immediately done after 2 hours was significantly improved from 5 - 6 mAmp to 2 - 3 mAmp.

The modified RANKIN SCORE (mRS) was 1 after 3 months of follow up. Video recordings also showed remarkable improvements at 2 hours, 24 hours, 7 days, 3 weeks and 3 months that also coincided with the MRI-DWI and NIHSS clinical scoring.

2 cases with PACS out of 7 cases having baseline NIHSS-scores of 24, IASNP with DD- PRP was given on 10th post stroke day. After 2 hours of IASNP NIHSS came to 10 and After 24 hours NIHSS came to 8 so he improved excellently. Then after a week NIHSS was at 7 and after 21 days it came to be at 4 which continued at 3 months. In MRI DWI there was mild change noticed from pre IASNP and DD-PRP then post IASNP and DD-PRP upto 1 week. But ALTENS immediately done after 2 hours was significantly improved from 6 - 7 mAmp to 3 - 4 mAmp.

The modified RANKIN SCORE (mRS) was 2 after 3 months of follow up. Video recordings also showed remarkable improvements at 2 hours, 24 hours, 7 days, 3 weeks and 3 months that also coincided with the MRI-DWI and NIHSS clinical scoring.

1 case with TACS out of 7 cases having baseline NIHSS-scores of 32, IASNP with DD- PRP was given on 7th post stroke day. After 2 hours of IASNP NIHSS remained at 32 and After 24 hours NIHSS remained to 32 so there was no improvement. Then after a week NIHSS remained at 32 and after 21 days it came to be at 30 which continued at 3 months denoting that was spontaneous recovery due natural disease regression. In MRI DWI there was no change noticed from pre IASNP and DD-PRP then post IASNP and DD-PRP upto 3 weeks. Even ALTENS also done before and after 2 hours was same from more than 8 mAmp indicating the importance of ALTENS in these cases. The modified RANKIN SCORE (mRS) was 4 after 3 months of follow up. Video recordings also showed no improvements at 2 hours, 24 hours, 7 days, 3 weeks and 3 months that also coincided with the MRI-DWI and NIHSS clinical scoring.

1 case with POCs out of 7 cases having baseline NIHSS-scores of 30, IASNP with DD- PRP was given on 8th post stroke day. After 2

hours of IASNP NIHSS came to 18 and After 24 hours NIHSS came to 16 so he improved marginally. Then after a week NIHSS was at 8 and after 21 days it came to be at 4 which continued at 3 months. In MRI DWI there was mild change noticed from pre IASNP and DD-PRP then post IASNP and DD-PRP upto 1 week. But ALTENS immediately done after 2 hours was marginally improved from 5 – 7 mAmp to 4 – 5 mAmp. The modified RANKIN SCORE (mRS) was 2 after 3 months of follow up. Video recordings also showed remarkable improvements at 2 hours, 24 hours, 7 days, 3 weeks and 3 months that also coincided with the MRI-DWI and NIHSS clinical scoring.

So, from these findings one can easily find out the importance of PRP after giving IASNP in these sub-acute ischemic stroke cases where PRP provides different growth factors namely BDNF and VEGF to enter in BBB after giving IASNP and enlarging the BBB via eNOS and SNP works via 10,000-fold effect and the growth factors enters the cyton of the neurons and provides the raw material to form the various neurotransmitters needed for further synaptic activity. To prove this whole cascade needs further studies in the form of RCT IIA and then RCT IIB. Also, it is emphasized further that authors have used PRP alone in 6 cases of sub- acute ischemic stroke. But no improvements were noted either after 2 hours later or on the 24 hours later. So, authors have concluded from that unpublished series that in humans pores of BBB is to be enlarged first by ISNP using eNOS then PRP is to be injected via the same route, so that the various growth factors enter the BBB and reach cyton and thus raw material be available for further manufacturing of synaptic neurotransmission.

The present study has certain limitations, such as not having fMRI (Functional MRI study) in the pre- and post-injection periods with DWI, due to the unavailability of higher-end MRI at our setup. Also in our next study we will include the various biomarkers ("Inflammatory biomarkers (IL-6 and TNF- alfa) and neurodegenerative biomarkers {S100-Beta and Neuron specific enolase) at CISR-IITR LUCKNOW". We plan to conduct a broader study including all of the above investigations in the future. No patient was given blood transfusion.

Conclusions

IASNP with DD-PRP treatment is highly effective at mean of 9.1 days post-stroke (5th to 21st post-stroke day). It prevents the detrimental response after 24-hrs shown by the author's previous study followed by an incremental response until the seventh-day with a Barthel-score of 75.88% after two-months. A larger, double-blinded, controlled, multicentric, randomized trial study is needed to quantify the effect of IASNP with DD-PRP in Sub-acute ischemic stroke cases from 5th to 21st post stroke day.

Disclosures

This study was sent for ICMR Proposal to do RCT IIA recently and the approval is awaited (IIRPIG-2025-01-00275).

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