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Research Article

Role of 10000-Fold Effect in Improving Urodynamic Parameters with Supra Spinal Cord Injury

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Abstract

Background*:* Spinal cord injury (SCI), whether complete or incomplete of supra-above D6 (SSCI as the autonomic supply of spinal cord is usually controlled and is situated here at D6 level) usually also presents with urinary problems of UMN type. Nitric oxide by virtue of its 10000-fold effect at synapse and neuromuscular junction has been shown excellent results in ASIA grading and also its predictability of improvements has been well demonstrated with the use of ALTENS (Acupressure Like Transcutaneous Epidermal Stimulation).

Objectives: To access the urodynamic urinary bladder parameter improvements via 10000-fold effect by Intrathecal Sodium Nitroprusside (ITSNP) superfusion, on patients with supra spinal cord injury cases.

Materials and Methods: A prospective one hospital-based study done on 9 patients from March 2014 to June 2020 with supra spinal cord injury. After taking written consent and video recording of the motor, sensory and bladder bowel involvement baseline ASIA, ALTENS and urodynamic study was performed, which was repeated after 2 hours. ASIA grading, ALTENS, Urodynamic parameters (like maximum detrusor filling pressures and maximum detrusor voiding pressures, maximum bladder capacity and bladder compliance) before after ITSNP were compared for final results..

Results: After ITSNP in all 9 patients, maximum bladder capacity 35.92%, bladder compliance 14.38%, maximum detrusor filling 9.14% and maximum detrusor voiding pressures 13% increase in urodynamic study. Less improvements noted in more than 5 months of bladder bowel involvement (BBI) cases than less than 5 months cases.

Conclusion: ITSNP is another modality via which ASIA grading 17.07%, ALTENS 25.55% and urodynamic parameters shows improvement such as maximum bladder capacity 35.92%, bladder compliance 14.38%, maximum detrusor filling 9.14% and maximum detrusor voiding pressures 13% increase, that is urinary bladder stores more urine with nearly same pressure, decreasing daily urination frequency.

Keywords: Intrathecal Sodium Nitroprusside; 10000-fold Effect; Suprasacral Spinal Cord Injury; Urodynamic Parameters

Key Message

10000-fold effect via nitric oxide donors improves the bladder UMN symptoms and signs.

Introduction

Spinal cord injury (SCI), whether complete or incomplete of supra (SSCI) or infra sacral injury (ISCI) (above or below D6 level -

SSCI as the autonomic supply of spinal cord is usually controlled and is situated here up to D6 level) presents with urinary as well as bowel dysfunctions in the form of lower urinary tract symptoms (LUTS) and loss of control of bowel defecation sense, which leads to significant morbidity and later on mortality [1]. Urodynamic studies are a gold standard to evaluate urinary tract dysfunction in SCI [2]. In this study we have studied the 10000-fold effect in SSCI. In our next study we will study the 10000- fold effect in ISCI cases and bowel dysfunctions in the form of lower urinary tract symptoms (LUTS) and loss of control of bowel defecation sense.

10,000-Fold Effect → In normal subjects, as the excitatory-impulse reaches at synaptic level, glutamate is released from presynaptic-membrane, which activates NMDA receptor at postsynaptic membrane. In turn NMDA activates nNOS (neuronal Nitric Oxide Synthetase) which releases NO_3. NO travels back in the synaptic cleft (forming NO cloud) [3], to bind with NO receptor (NOR)/sGC (soluble guanylyl cyclase enzyme) at presynaptic membrane, NO thus regulates anterograde neurotransmission (ANT), this process is called "retrograde-neurotransmission" (RNT) [3], allowing neural circuits to create feedback loops so called as chemical neuroregulation. NOR are 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 [3] (10,000-FOLD-EFFECT) completes in 20msec [4]. NO generation at postsynaptic membrane by nNOS via nitric oxide donor (NOD) {Sodium Nitroprusside (SNP)}, mimics ANT same as of normal ANT [3]. NO modulates that is it can up or down-regulate the oncoming impulses [3]. NO provides a simultaneous signal to both pre and postsynaptic elements, important in coordinating responses on the two sides of the synapse [3].

Efficacy of oral 5-Phospho Diesterase Enzyme (PDE5) inhibitors have been used in recent years for LUTS and has been shown benefit via urodynamic parameters in SCI [5,6]. At the synaptic level NO converts cyclic guanosine three phosphate to cGMP. cGMP decreases intracellular calcium concentration, then muscle relaxation. cGMP is being degraded by PDE5. The PDE5 inhibitors (Tadalafil) inhibits cGMP degradation, thereby raises the availability of cGMP and NO is directly involved in detrusor muscle relaxation [5,6].

Intrathecal sodium Nitroprusside (ITSNP) has shown marked recovery in various causes of paraplegias after proper surgical decompression of spinal cord and stabilization of vertebra [3]. Until now we were using clinical (complete or partial-ZPP Zone of Partial Preservation) or SSEP (Somato Sensory Evoked Potential) and MEP (Motor Evoked Potential) to predict the paraplegias' recovery bedside effectively. We have used Acupuncture-like TENS (AL-TENS) to predict ITSNP feasibility in paraplegics in previous paper [7].

In this study we are utilising this 10000-fold effect via ITSNP to get benefits as assessed by ASIA grading, ALTENS (not using MEP and SSEP) and urodynamic studies in SSCI cases in whom urological symptoms and signs are affected. The 10,000-fold effect has been checked by PNSAS (Pico Nano Second Absorption Spectroscopy), but we were unable to do so as this modality is not in our setup.

Aims/Study-Design

To access the ASIA grading, ALTENS and urodynamic parameter improvements via 10000-fold effect by Intrathecal Sodium Nitroprusside (ITSNP) superfusion, on patients with supra spinal cord injury (SSCI) cases (above D6 level).

Materials and Methods

A prospective pilot study, one hospital-based study done on 9 patients after taking proper local ethical committee clearance from March 2014 to June 2020 with supra spinal cord injury (above D6). The effect of ITSNP after 5th day to 22nd month of a decompressed spinal cord and stabilized vertebra was evaluated for urinary symptoms and signs. All the 9 patients were of partial paraplegia cases. After taking written consent and ASIA grading done with video recording of the motor, sensory and bladder bowel involvement baseline ALTENS and urodynamic study (Urodynamic parameters like maximum detrusor filling pressures and maximum detrusor voiding pressures, maximum bladder capacity and bladder compliance) was performed then ITSNP done, which was repeated after 2 hours and compared for final results.

Neurological clinical scoring was analysed on the basis of ASIA grading PRE ITSNP, after 2h, 24h, 1 week and 3 weeks of ITSNP

superfusion in all cases. All the selected cases were of partial paraplegia and injury above D6 level in which bladder and bowel control was lost and urodynamic studies showed a vast urinary neural tract disruption due to loss of autonomic dysfunction. The mean time for superfusion was 223 days overall and 43 days for less than 5 months and 426 days for more than 5 months cases. Written consent was taken from every patient telling all untoward reactions to the patients and their relatives too.

PREITSNP ALTENS was recorded in all cases in ward with "MEDILAP TWO CHANNEL TENS" machine and urodynamic studies done for maximum detrusor filling pressures and maximum detrusor voiding pressures, maximum bladder capacity and bladder compliance in urology department of ANGH. ITSNP was done in operation theatre then POST ITSNP ALTENS was again checked after 2 hours with urodynamic studies in ward.

The SNP injection (made with 200 ml of dextrose 5% with 50 mg of the SNP, 0.2 mg/kg body/weight) was superfused via Lumbar Puncture Route at L3/4 level i.e. around 8 ml of CSF was taken out and 8 ml of the SNP solution was put in slowly, about in 30 seconds. Waited for 10 mints and again superfusion was done slowly up to 0.8 ml per kg body weight and then the recovery is noted. Meticulous photoprotection and sterile technique were done for all aspects of delivery of the medication as well as its formulation.

Neurological assessment

The neurological assessment was performed PRE and POST ITSNP (2 hours), to get the exact improvement by ITSNP using ASIA grading system and according to method developed by [1] in ITSNP cases. Upon settling of nausea and apprehension by giving Ondansteron and mild sedative like Inj diazepam, patients returned to wards. Briefly, the neurological assessment was done by ASIA grading system after 2 hours along with full detailed urodynamic study. The scores of neurological assessments obtained after testing on each grade were summed up and denoted as neurological deficit score [1].

Measurement of the ALTENS score

PREITSNP and POSTITSNP ALTENS (2 hours, 24 hours, 1 week and 3 weeks) done to get the various neurological assessment. TENS employed here was AL-TENS.

Measurement of the urodynamics parameters

2 hours POST ITSNP urodynamics examination done to assess the maximum detrusor filling pressures, maximum detrusor voiding pressures, maximum bladder capacity and bladder compliance.

Results

The effect of ITSNP post 5th day in a decompressed spinal cord and stabilized vertebra was evaluated for urinary symptoms and signs. Neurological deficit (ND) scoring was analysed clinically on the basis of ASIA grading after 2h, 24h, 1 week and 3 weeks of superfusion in all cases. All the selected cases were of SSCI cases.

Our following work has been based on the following parameters based on Asia grading, Altens and urodynamic studies (Table 1 and 2).

POST ITSNP Asia gradings and urodynamics examination done and the results for all the 9 patients, ASIA grading 17.07%, POST ITSNP Altens 25.55%, maximum detrusor filling pressures got improved to 9.14% and maximum detrusor voiding pressures to 13%, maximum bladder capacity to 35.92% and bladder compliance to 14.38%.

Males were 7 and females were 2 patients. Males showed 32.5% and females showed 24.5% of ASIA gradings recovery.

Cases having less than or equal to 5 months presentation showed POSTITSNP TENS 25.55% and more than 5 months showed 20% benefit.

Post ITSNP urodynamics examination done and the results for female (n = 2) patients, ASIA grading 24.905%, POST ITSNP 35%, maximum detrusor filling pressures got improved to 12.035% and maximum detrusor voiding pressures to 10.675%, maximum bladder capacity to 24.335% and bladder compliance to 10.56%.

Post ITSNP urodynamics examination done and the results for male (n = 7) patients, ASIA grading 14.87%, POST ITSNP 22.85%, maximum detrusor filling pressures got improved to 8.31% and maximum detrusor voiding pressures to 13.36%, maximum bladder capacity to 39.23% and bladder compliance to 15.47%.

S no	Sex Age Name	Case briefings	Duration	Operation	PRE ITSNP Asia, Altens (mAmp). and urodynamics		POST ITSNP Asia, Altens (mAmp). and urodynamics after 2 hours		Percentage benefit in Post ITSNP Asia, and Altens (mAmp). urodynamics		p value
1	M/54 YRS	T4, T5 ligamental hypertrophy	12 months	T3, 4, 5, 6 Decompression (ITSNP done and then repeat ITSNP done after 21 days)	Asia (Motor) with BBI	80	Asia (Motor)	92	Asia (Motor)	15%	0. 212
					PREITSNP Altens	7	Post ITSNP Altens	4	Post ITSNP Altens	30%	0.0012*
					DFP	33.13	DFP	28.81	DFP	-9.51%	0.289
					DVP	62.01	DVP	52.05	DVP	-11.21%	0.416
					Capacity	252.41	Capacity	350.25	Capacity	+38.76%	0.009*
					Compliance	21.78	Compliance	32.25	Compliance	+15.94%	0.029*
2	F/36 YRS	T2/3 post traumatic wedge fracture with incomplete paraplegia below T4	7 days	T2/3 fixation	Asia (Motor) with BBI	84	ASIA (MOTOR)	96	ASIA (MOTOR)	14.2%	0.202
					PREITSNP Altens	6	Post ITSNP Altens	2	Post ITSNP Altens	40%	0.017*
					DFP	32.03	DFP	26.81	DFP	-14.51%	0.129
					DVP	60.11	DVP	50.05	DVP	-10.11%	0.156
					Capacity	256.11	Capacity	352.25	Capacity	+18.89%	0.019*
					Compliance	22.32	Compliance	31.25	Compliance	+10.95%	0.039*
3	M/55 YRS	T5 ligamentum hypertrophy with TCS	5th month	T 4, 5, 6 Laminectomy with decompression	Asia (Motor) with BBI	82	Asia (Motor)	92	Asia (Motor)	12.2%	0.218*
					PREITSNP Altens	5	Post ITSNP Altens	2	Post ITSNP Altens	30%	0.008*
					DFP	31.13	DFP	27.81	DFP	-8.51%	0.529
					DVP	61.01	DVP	51.05	DVP	-12.21%	0.516
					Capacity	242.41	Capacity	352.15	Capacity	+39.76%	0.008*
					Compliance	22.78	Compliance	32.20	Compliance	+14.94%	0.021*
4	M/15 YRS	T3/4 fracture with partial paraplegia below t6 with BBI	22 MONTHS	Decompression and fixation T3/4 (ITSNP done and then repeat ITSNP done after 21 days)	Asia (Motor) with BBI	80	Asia (Motor)	90	Asia (Motor)	12.5%	0.219
					PREITSNP Altens	6	Post ITSNP Altens	4	Post ITSNP Altens	20%	0.0211*
					DFP	30.23	DFP	28.87	DFP	-7.51%	0.189
					DVP	64.31	DVP	52.15	DVP	-21.21%	0.316
					Capacity	251.31	Capacity	350.85	Capacity	+41.76%	0.007*
					Compliance	22.48	Compliance	32.22	Compliance	+17.94%	0.005*

5	M/55 YRS	T2 neurofibroma with thoracic spinal cord compression	10 MONTHS	T1, 2, 3 Laminectomy and total excision of neurofibroma (ITSNP done and then repeat ITSNP done after 21 days)	Asia (Motor) with BBI	84	Asia (Motor)	92	Asia (Motor)	9.5%	0.242
					PREITSNP Altens	5	Post ITSNP Altens	3	Post ITSNP Altens	20%	0.0411
					DFP	31.73	DFP	28.78	DFP	-4.51%	0.299
					DVP	61.21	DVP	52.12	DVP	-17.21%	0.616
					Capacity	246.61	Capacity	350.22	Capacity	+37.76%	0.008*
					Compliance	22.88	Compliance	32.55	Compliance	+12.94%	0.011*
6	M/44 YRS	T4, 5, 6 thoracic pott's spine	12 months	T4, 5, 6 fixation and decompression (ITSNP done and then repeat ITSNP done after 21 days)	Asia (Motor) with BBI	86	Asia	94	Asia	9.3%	0.245
					PREITSNP Altens	7	Post ITSNP Altens	5	Post ITSNP Altens	20%	0.0024
					DFP	33.63	DFP	28.88	DFP	-9.11%	0.279
					DVP	62.11	DVP	52.15	DVP	-11.31%	0.626
					Capacity	252.71	Capacity	350.05	Capacity	+38.86%	0.007*
					Compliance	21.70	Compliance	32.22	Compliance	+15.24%	0.020*
7	F/45	Severe C5/6 PIVD (Left>right) with BBI	7th day	C5 and C6 anterior disectomy	Asia (Motor) with BBI	68	Asia (Motor)	92	Asia (Motor)	35.29%	0.008*
					PREITSNP Altens	7	Post ITSNP Altens	4	Post ITSNP Altens	30%	0.0007*
					DFP	33.00	DFP	28.24	DFP	-9.56%	0.289
					DVP	62.00	DVP	52.25	DVP	-11.24%	0.426
					Capacity	252.11	Capacity	350.15	Capacity	+29.78%	0.018*
					Compliance	21.70	Compliance	32.27	Compliance	+10.18%	0.059*
8	M/48 YRS	T1, 2 Ligamental hypertrophy with BBI	15 Months	C7, T1, 2 Laminectomy with decompression (ITSNP needed and then repeat ITSNP done after 21 days)	Asia (Motor) with BBI	70	Asia (Motor)	90	Asia (Motor)	28.57%	0.0084*
					PREITSNP Altens	6	Post ITSNP Altens	5	Post ITSNP Altens	10%	0.0012*
					DFP	33.33	DFP	28.87	DFP	-9.52%	0.389
					DVP	62.22	DVP	52.85	DVP	-11.31%	0.436
					Capacity	252.11	Capacity	350.35	Capacity	+38.96%	0.007*
					Compliance	21.22	Compliance	32.28	Compliance	+15.34%	0.019*

9	M/44 YRS	C4/5/6 Cervical canal stenosis with BBI	8th day	C3,4,5,6 Laminectomy	Asia (Motor) with BBI	82	Asia (Motor)	96	Asia (Motor)	17.07%	0.0216
					PREITSNP Altens	6	Post ITSNP Altens	3	Post ITSNP Altens	30%	0.0012*
					DFP	33.11	DFP	28.87	DFP	-9.52%	0.290
					DVP	62.09	DVP	52.25	DVP	-11.22%	0.471
					Capacity	252.21	Capacity	350.15	Capacity	+38.75%	0.008*
					Compliance	21.20	Compliance	32.26	Compliance	+15.98%	0.019*

Table 1: Case description.

SD: Standard Deviation.

Note: DFP = maximum detrusor filling pressure (cm H_2O); DVP = maximum detrusor voiding pressure (cm H_2O), CAPACITY = maximum bladder capacity (mL); COMPLIANCE = bladder compliance (ml/cm H_2O).

*Statistically significant value.

Variable in 9 cases	PRE ITSNP (mean ± SD)	POST ITSNP (mean± SD)	% change	p-Value
Asia grading	79.55	92.66	17.07%	0.152
ITSNP	6.1	3.55	25.55%	0.0104
DFP	31.92 ± 12.85	38.20 ± 11.88	-9.14%	0.133
DVP	55.12 ± 21.86	62.08 ± 21.448	-13%	0.029
Capacity	275.13 ± 113.79	332.17 ± 113.415	+35.92%	0.005*
Compliance	19.05 ± 6.73	22.333 ± 6.13	+14.38%	0.007*

Table 2: Overall urodynamics changes noted in SSCI.

SD: Standard Deviation.

Note: DFP = maximum detrusor filling pressure (cm H_2O); DVP = maximum detrusor voiding pressure (cm H_2O), CAPACITY = maximum bladder capacity (mL); COMPLIANCE = bladder compliance (ml/cm H_2O)

*Statistically significant value.

Post ITSNP urodynamics examination done and the results for the patients more than 5 months (n = 5), ASIA grading 14.97%, POST ITSNP 20%, maximum detrusor filling pressures got improved to 8.03% and maximum detrusor voiding pressures to 14.45%, maximum bladder capacity to 39.22% and bladder compliance to 15.48%. but these patients needed 2nd ITSNP injections on 21st day post ITSNP.

Post ITSNP urodynamics examination done and the results for the patients less than 5 months (n = 4), ASIA grading 19.69%, POST ITSNP 32.5%, maximum detrusor filling pressures got improved to 10.52% and maximum detrusor voiding pressures to 11.195%, maximum bladder capacity to 31.79% and bladder compliance to 13.01%.

Discussion

Urogenital and bowel disturbances have been one of the primary causes of morbidity and mortality [8,9] in SCI, also it has been uneasiness for the relatives in the form of smell of urine (if not catheterized) and faeces (due to loss of faecal control). This loss of

control of bladder emptying (LUTS causes detrusor areflexia and urinary retention then overactive detrusor and detrusor – sphincter dyssynergia) causes renal complications later on [11,12].

The availability of NO is responsible for 10000-fold effect mechanism [3]. NO after attaching with NOR in presynaptic membrane causes release of cGMP which modulates the oncoming anterograde neurotransmission [1] (in 2 hours of time) This cGMP is inactivated by phosphodiesterase (PDE5) enzyme at the synapse and thus oral PDE5 inhibitors (TADALAFIL) have a positive role too (also too in 2 hours of time) to improve urodynamic parameters [5,6]. Tadalafil causes smooth muscle relaxation, endothelial cell proliferation, better nerve activity and tissue perfusion by improving lower urinary tract oxygenation, negative regulation of proliferation and trans-differentiation of lower urinary tract stroma, reduction in bladder afferent nerve activity and downregulation of prostrate inflammation [5,6].

After ITSNP the NO causes 10,000-Fold effect at synapse at the injured portion of spinal cord. Thereafter the anterograde neurotransmission starts and the autonomic connections of urinary bladder and various sphincters gets the impulse. That causes the better urodynamic studies, well denoted by better and significant "p" value.

PREITSNP and POSTITSNP clinically by Asia grading and Altens with Urodynamic study showed bladder (27.95%) and bowel improvements (25.2%) also the paraplegic signs and symptoms is also relieved to a small extent (ASIA grading increased by 17.07%).

In urogenital conditions of partial SCI the urodynamic studies have used extensively by many studies [6]. We have also used the urodynamic studies for the bladder involvements in 9 cases of partial paraplegic patients in which bladder and bowel involvement was there in the form of maximum bladder capacity, bladder compliance, maximum detrusor filling and maximum detrusor voiding pressures.

In one case Tubercular case 6, extradural decompression was performed and fixation was done. Pre operatively patient had complete paraplegia and after decompression he improved partially in ASIA grading but bladder involvement was there up to 12 months (he didn't come for follow up to 12 months). After 12 months we did ITSNP and got excellent response in bladder symptoms and signs.

ITSNP done in male and female doesn't discriminated any sex difference as for as results were compared. NO is a gas and diffuses from CSF (Cerebro Spinal Fluid) to spinal cord and thereafter with 10000-fold effect the ANT is modulated and also NO enters the detrusor muscle and converts cyclic guanosine 3 phosphate to cGMP, the intracellular calcium is decreased so muscle relaxes properly. In our study, mean bladder capacity (MBC) showed increase by 35.2% after single ITSNP just after 2 hours. This MBC increased causes decrease daily frequency and well control of urination too leading to extra urinary storage time. This increases the quality of life and the attendants got relief of smell of not only urine but of faecal matter too (as the pathway are same). As the females also get benefit (the bladder capacity (24.335%), bladder compliance (10.56%), detrusor filling (12.04%) and detrusor voiding pressures (10.675%) with ITSNP, in our cohort of 9 cases in which 2 were females so this was a contrast from previous study of recent years in which only Tadalafil has been used[5]. We have noticed that the post ITSNP giving better motor scores in females (and not urinary functions) although overall urinary function was better in males (who did not have as much motor improvement) is also a finding in this study.

We have noticed from the table that the cases (case number 1, 4, 5, 6 and 8) which have lapsed the time of more than 5 months post-surgery of decompression of spinal cord and stabilisation of vertebra spine required repeat ITSNP and those cases responded not too well later on.

Limitations

The limitations of this study were

- Number is too small, being a pilot study
- we were not able to evaluate the 10,000-fold effect via pico nano second absorption spectroscopy (PNSAS) being non availability at our setup.
- We did not compare between AL-TENS and the SSEP and MEP, while performing this study.

Conclusion

ITSNP is a very swift procedure which enhances Asia grading (17.07%), PRE AND POST ITSNP Altens (25.55%), the bladder capacity (35.92%), bladder compliance (14.38%), detrusor filling (9.14%) and detrusor voiding pressures (13%) that is urinary bladder stores more urine with same pressure, decreasing daily urination frequency and no spillage so that one can hold the urine on his own will nearly equal in males and females.

Disclosures

All the writers disclose that there is no conflict in writing and preparing the manuscript.

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