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Efficacy and Safety of Inosine Monophosphate, Agmatine Sulphate and L-Carnosine (NUREWIRE®) Therapy for The Management of Spinal Cord Injury

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ABSTRACT

Aims: To evaluate efficacy and safety of Inosine Monophosphate, Agmatine Sulphate, And L-Carnosine (Nurewire®) therapy for the management of spinal cord injury to standard rehabilitation protocol in patients with SCI undergoing rehabilitation.

Methods: An open-label study of 255 patients with registration of the total SCIM and of the four subscales. Clinical significance was calculated per several distribution-based approaches. The calculated clinical significance was compared with improvements by the patients to determine the percentage of patients who achieved significant improvement. The total study population was divided into two groups namely group 1 (n=127) receiving standard care and group 2 (n=128) receiving Nurewire® along with standard protocol.

Results: An improvement of at least 4 points of the total SCIM is needed to obtain a small significant improvement and 10 points to obtain a substantial improvement. Based on these results, the percentages of patients who achieved an improvement in Group 1 varied from 71% to 79% as compared to group 2 who achieved improvement varied from 91% to 94%, which is statistically significant.

Conclusion: The Nurewire® trial evaluated a novel oral combination therapy for spinal cord injuries (SCI), showing significant improvements in functional independence when administered alongside standard treatment and rehabilitation. Patients receiving Nurewire® demonstrated notable enhancements in self-care and mobility with a favorable safety profile compared to standard treatment alone. These findings indicate promising benefits for SCI patients, necessitating further research to validate long-term efficacy and underlying mechanisms.

Keywords: Nurewire®; Inosine Monophosphate; Agmatine Sulphate, L-Carnosine; SCI

INTRODUCTION

Spinal cord injury (SCI) is a serious medical condition, which often results in severe morbidity and permanent disability. It occurs when the axons of nerves consecutively through the spinal cord are disrupted, leading to loss of motor and sensory function below the level of injury. Injury is usually the result of major trauma, and primary

injury is often irreversible.[1] These injuries are particularly costly and disabling as they disproportionately affect patients that lead to significant functional impairment for the remainder of the individual's life, and put the individual at risk for numerous complications leading to increased morbidity and mortality.[2] While advancements have been made in the management and rehabilitation of SCI, there are still several unmet medical needs in this field. Some of the key areas of unmet medical need in spinal cord injury include neuroprotection and neural repair following a spinal cord injury, there is a complex cascade of secondary injury processes that can further damage the spinal cord tissue. Developing neuroprotective strategies to minimize secondary damage and promoting neural repair mechanisms is an important unmet need.[3] This includes interventions to enhance axon regeneration, remyelination, and neuroplasticity. Moreover, functional recovery and rehabilitation, maximizing functional recovery, and improving the quality of life for individuals with spinal cord injury is a significant challenge. There is a need for more effective rehabilitation interventions and therapies that can enhance motor function, sensory perception, bladder, bowel control, and other essential activities of daily living. This includes the development of advanced assistive technologies and neurorehabilitation approaches, also bladder, bowel management and common complications of spinal cord injury. Although various management strategies exist, there is a need for improved methods for neurogenic bladder and bowel control, including better control mechanisms, minimally invasive interventions, and regenerative therapies.[4]

Existing traditional treatment focus on surgical intervention, pharmacological treatment includes methylprednisolone, which reduces inflammation, and minimize secondary damage; other medication may use to manage spasticity, bladder and bowel dysfunction.[5]

Previous studies demonstrated To axon regeneration and central nervous system (CNS) rewiring, novel strategies are required to effectively suppress or regulate growth-inhibiting factors such as NMDAR and Glutamate,[6] competitive i-NOS inhibition,[7] and Mobile/ionic Zn^{++} chelators[8] Additionally, stimulating or activating axon growth and sprouting factors is essential, including Mst3b activation [9] and the activation or secretion of plasticity proteins like NGF (Nerve Growth Factor), BDNF Nerve Growth Factor), NTF3 (Neurotrophic Factor 3) and GAP 43 (Growth Associated Protein 43).[10] These approaches aim to create an environment conducive to neural repair and regeneration, facilitating functional recovery in individuals with spinal cord injury and other neurological conditions.

Nurewire® is a patented formulation comprising key components aimed at promoting neural repair and regeneration. It contains Inosine monophosphate (IMP), which activates the Mst3b master receptor responsible for controlling axon outgrowth and upregulates GAP 43, a crucial regulator of axon regrowth. Additionally, Nurewire® includes Agmatine sulfate at 250 mg, which inhibits NMDAR and glutamate, competitively inhibits iNOS to prevent the release of mobile/ionic Zn++, and activates plasticity proteins such as BDNF, NGF, and NTF3. Furthermore, L-Carnosine at 50 mg binds to mobile/ionic Zn++ in the central nervous system (CNS), minimizing neuron damage. This combination offers a comprehensive approach to enhancing neural plasticity and promoting functional recovery in individuals with spinal cord injury and other neurological conditions. Hence this trial aims to investigate whether Nurewire® is an effective and safe medication for patients with spinal cord injury compared to traditional treatment (Standard of care).

MATERIALS & METHODS

Study Design

An open-label study was undertaken to evaluate the effectiveness of a novel oral fixed-dose combination of Nurewire® containing (Inosine monophosphate, Agmatine sulfate, and L-carnosine) as an adjunctive therapy for spinal cord injury. This study was conducted across multiple centers. Participants were recruited from the neurology department and rehab patients were followed up until the end of the study period and informed consent was obtained from all participants. The study included both male and female participants aged 18 years and older.

Inclusion Criteria

Participants eligible for this study must be male or female adults aged 18 years or older who have been diagnosed with a spinal cord injury (SCI), confirmed through clinical evaluation and imaging studies such as MRI or CT scans. The injury must have occurred within the past six months. Eligible participants should have a stable neurological status, evidenced by sensory and/or motor deficits corresponding to the injury level. They must be capable of providing informed consent and willing to comply with all study procedures and follow-up assessments. Additionally, they should be able to receive the investigational therapy, Nurewire®, as part of the trial protocol. Participants must also possess the ability to understand and communicate in the language used for the study procedures and assessments.

Exclusion Criteria:

Participants will be excluded from the study if they have severe cognitive impairment or psychiatric disorders that could interfere with their ability to provide informed consent or comply with study procedures. Those who have participated in other clinical trial investigating investigational therapies for spinal cord injury within the past six months will also be excluded. Individuals with a history of significant allergic reactions or hypersensitivity to any components of the investigational therapy (Nurewire®) are not eligible. Known cases of gout, determined by hyperuricemia with serum uric acid levels above 10 mg/dL, will result in exclusion, as will pregnancy or breastfeeding. Participants with a history of malignancy within the past five years, except for adequately treated non-melanoma skin cancer or carcinoma in situ of the cervix, are excluded. Chronic use of medications that are known to affect neurological function or interfere with the interpretation of study outcomes will also disqualify potential participants. Additionally, individuals with unstable medical conditions, including uncontrolled hypertension, uncontrolled diabetes mellitus, or significant cardiovascular disease, are not eligible. Finally, the presence of conditions that may independently contribute to neurological deficits or impairments in sensory or motor function unrelated to spinal cord injury will lead to exclusion from the study.

Intervention:

During the intervention phase of the study, participants were randomly divided into two groups in a 1:1 ratio. The intervention group was prescribed a fixed-dose combination (FDC) of Nurewire®, taken orally once daily for a duration of six months. This adjunctive treatment regimen aimed to assess the effectiveness and tolerability of Nurewire® in conjunction with the participants' existing medication regimen and the standard rehabilitation protocol for spinal cord injury. The control group received the standard treatment and followed the standard rehabilitation protocol for spinal cord injury. The primary objective of this intervention phase was to evaluate the clinical relevance of Nurewire® regarding overall improvement in patients, focusing on the effectiveness and tolerability of the adjunctive treatment regimen compared to the standard treatment. Both groups were monitored

and assessed over six months to measure outcomes such as improvements in sensory and motor function, the tolerability of Nurewire®, and overall clinical improvement.

Assessment:

The assessment of the spinal cord independence measure (SCIM) focused on both the total SCIM score and the scores of its three subscales: self-care, respiration, sphincter management, and mobility. Clinical significance was calculated using several distribution-based approaches. These methods helped determine meaningful changes in SCIM scores, allowing for a comparison between calculated clinical significance and actual patient improvements. The percentage of patients who achieved significant improvement was then determined by comparing these clinical significance thresholds with the observed improvements in SCIM scores. This assessment provided a comprehensive evaluation of the effectiveness of the intervention by identifying the proportion of patients who experienced substantial functional gains.

Data Analysis:

All statistical evaluations were performed using SPSS 12 for Windows (Chicago, IL). Data were evaluated by number and percentage. Descriptive values, expressed as mean ± standard deviation (s.d.), were provided for all continuous clinical data. The differences between admission and discharge scores of all patients were analyzed using paired t-tests. This approach enabled the comparison of scores to assess the effectiveness of the treatment.

RESULT

The study included 255 patients, divided into two groups: Group 1 (n=127) standard group and Group 2 (n=128) Nurewire® group. The average age of the participants was 41.9 ± 18.4 years, consistent across both groups. The gender distribution was 199 males and 56 females, with Group 1 comprising 99 males and 28 females, and Group 2 comprising 100 males and 28 females. The mean time since the lesion was 51.6 ± 36.8 days for both groups. The average length of rehabilitation stay was 123.6 ± 86.3 days. Regarding the type of spinal cord injury, 157 patients were paraplegic, and 98 were tetraplegic, with Group 1 having 78 paraplegic and 49 tetraplegic patients, and Group 2 having 79 paraplegic and 49 tetraplegic patients. The distribution of AIS (American Spinal Injury Association Impairment Scale) grades was as follows: Grade A (97 patients), Grade B (40 patients), Grade C (52 patients), and Grade D (66 patients), evenly distributed between both groups. Additionally, the study population included 171 patients with traumatic spinal cord injuries and 84 with non-traumatic injuries, with Group 1 having 65 traumatic and 42 non-traumatic cases, and Group 2 having 66 traumatic and 42 non-traumatic cases as mentioned in table no 1.

Table 1. Characteristics of the populations of the databases

	Overall	Group 1 (n=127)	Group 2 (n=128)
Total Patients	255	127	128
Age (Years)	41.9+/-18.4	41.9+/-18.4	41.9+/-18.4
Male/Female	199/56	99/28	100/28
Mean distance from the lesion (Days)	51.6+/-36.8	51.6+/-36.8	51.6+/-36.8
Mean length of rehabilitation stay (Days)	123.6+/-86.3	123.6+/-86.3	123.6+/-86.3
Paraplegic/Tetraplegic	157/98	78/49	79/49
AIS Grade			
A	97	48	49
B	40	20	20
C	52	26	26
D	66	33	33
Traumatic/non traumatic	171/84	65/42	66/42

The results of the study demonstrated significant improvement in the functional independence of patients. Specifically, 94% of the patients in the Nurewire® group, who received the fixed-dose combination along with standard treatment and rehabilitation protocol, showed an improvement of at least 4 points on the SCIM scale. This included enhancements in self-care, respiration, and sphincter management, mobility within the room and to the toilet, as well as mobility indoors and outdoors on even surfaces. These improvements were notably statistically significant ($p<0.005$) compared to the standard treatment group, indicating the added effectiveness of Nurewire® in conjunction with standard rehabilitation practices mentioned in Figure no 1. (Proportional improvement)

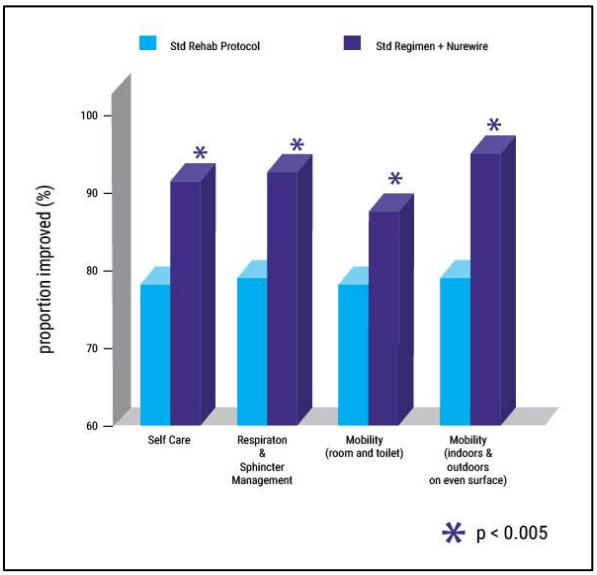

Figure no 1: Comparison of proportion of SCIM scale improvement of at least 4 points: standard protocol vs Nurewire® group

Moreover, 91% of patients in the Nurewire® group, who received the fixed-dose combination along with the standard treatment and rehabilitation protocol, showed a substantial improvement of at least 10 points on the SCIM scale. This significant enhancement encompassed self-care, respiration and sphincter management, mobility within the room and to the toilet, as well as mobility indoors and outdoors on even surfaces. These substantial improvements were highly significant ($p<0.0001$) compared to the standard treatment group, underscoring the added benefit of incorporating Nurewire® into the standard rehabilitation regimen for patients with spinal cord injuries mentioned in Figure no 2

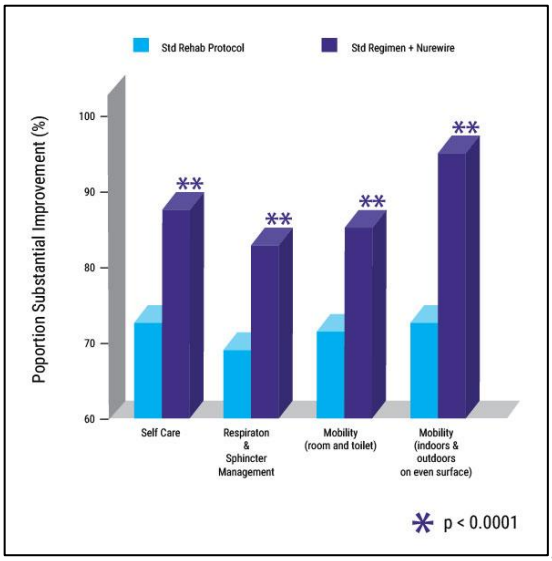

Figure no 2: Comparison of proportional Substantial improvement in SCIM Scale of at least 10 points: Standard Protocol vs Nurewire® Group

Safety Measures:

The evaluation of adverse events (AEs) revealed notable differences between Group 1 (n=127) and Group 2 (n=128). In Group 1, comprising patients receiving standard treatment alone, serious AEs were reported in 30.7% of cases, with notable occurrences including acute coronary syndrome (3.15%), pneumonia (4.72%), and suicide ideation (5.5%). Additionally, AEs of special concern, such as palpitations (1.57%) and tachycardia (2.36%), were observed in 5.51% of patients. In contrast, Group 2, receiving Nurewire® alongside standard protocol, exhibited a lower incidence of serious AEs at 3.12%, with pneumonia being the most prevalent (2.34%). AEs of special concern were also less frequent at 3.12%, with gout-like symptoms being the primary concern, affecting 1.56% of patients. These findings underscore the importance of considering the safety profile of adjunctive therapies like Nurewire® while also recognizing the overall safety of standard treatment protocols mentioned in Table no 2.

Table 2: Serious adverse events and adverse events of special concern

Adverse Events (AEs)	Group 1 (n=127)	Group 2 (n=128)
A) Serious AEs	**30.7% (39)**	**3.12% (4)**
Acute coronary syndrome	3.15% (4)	0%
Cholecystitis	0%	0%
Pneumonia	4.72% (6)	2.34% (3)
Urosepsis	3.15% (4)	0%
Cervical fracture	1.57% (2)	0.78% (1)
Arthritis	2.36% (3)	0%
Synovial cyst	0.78% (1)	0%
Radiculopathy	3.15% (4)	0%
Cerebrovascular accident	1.57% (2)	0%
Depression	3.15% (4)	0%
Nephrolithiasis	0%	0%
Suicide Ideation	5.5% (7)	0%
Pulmonary Fibrosis	1.57% (2)	0%
B) AEs of special concern	**5.51% (7)**	**3.12% (4)**
Palpitations	1.57% (2)	0%
Tachycardia	2.36% (3)	0%
Atrial fibrillation	0.78% (1)	0%
Gout like symptoms-Arthralgia of toe	0%	1.56% (2)
Gout like symptoms-Swelling of toe	0%	0.78% (1)
Hematuria	0.78% (1)	0.78% (1)

DISCUSSION

The results of this study shed light on the promising role of Nurewire® as an adjunctive therapy in the rehabilitation of patients with spinal cord injuries, offering valuable insights into both its efficacy and safety profile. The findings demonstrate a significant improvement in functional independence among patients receiving Nurewire® in conjunction with standard treatment and rehabilitation protocols. Notably, a vast majority of patients (94%) exhibited notable improvements of at least 4 points on the SCIM scale, indicative of enhancements across critical domains such as self-care, respiration and sphincter management, and mobility indoors and outdoors. These findings align with previous studies highlighting the neuro regenerative potential of inosine monophosphate (IMP), a key component of Nurewire®, which has been shown to stimulate neuronal growth and facilitate functional recovery in various neurological conditions.[11] Furthermore, a substantial proportion (91%) of patients demonstrated significant improvements of at least 10 points on the SCIM scale, underscoring the robust efficacy of Nurewire® in facilitating substantial functional gains. This efficacy is supported by previous research indicating IMP's ability to up-regulate genes associated with axon growth and enhance neural plasticity, ultimately

contributing to improved functional outcomes.[12] Additionally, the inclusion of Agmatine Sulphate and L-Carnosine in Nurewire® further complements its neuroprotective and neuroregenerative effects, offering potential benefits such as improved bladder control and competitive inhibition of neurotoxic pathways.[13] The statistical significance of these improvements compared to standard treatment reaffirms the added therapeutic value of Nurewire® in enhancing rehabilitation outcomes for individuals with spinal cord injuries. Moreover, the safety analysis reveals a favorable safety profile of Nurewire® with a lower incidence of serious adverse events and adverse events of special concern compared to standard treatment alone. This suggests a potential protective effect or reduced risk associated with Nurewire® when administered alongside standard protocols, highlighting its safety and tolerability. These findings underscore the potential of Nurewire® as a promising adjunctive therapy for improving functional outcomes and enhancing the safety profile of rehabilitation protocols in patients with spinal cord injuries. However, further research, including larger-scale studies and long-term follow-up, is warranted to validate these findings and elucidate the underlying mechanisms of action.

CONCLUSION

In conclusion, the Nurewire® trial investigated the efficacy and safety of a novel oral combination therapy for spinal cord injuries (SCI), demonstrating significant improvements in functional independence among patients receiving Nurewire® alongside standard treatment and rehabilitation protocols. The study revealed notable enhancements in key areas such as self-care and mobility, with a favorable safety profile compared to standard treatment alone. These findings suggest that Nurewire® may offer promising benefits for individuals with SCI, although further research is needed to validate its long-term efficacy and elucidate underlying mechanisms.

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