Steroids in Acute Spinal Cord Injury

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Spinal cord injury (SCI) is a devastating condition, leaving the most productive group of population disabled for the rest of their lives. over the years, attempts have been made to enhance recovery. Search for a drug that prevents or reduces secondary spinal injury by counteracting oxygen free radicals is going on. On this endeavor, steroid was initially used empirically based on animal studies for almost three decades before controlled trials were started to find efficacy especially of methylprednisolone succinyle succinate (MPSS).

The landmark study was National Spinal Cord Injury Study (NASCIS) which concluded the benefit of MPSS in acute SCI if used within 8 hours and it quickly became an implied standard of care. There were many other studies conducted during and after NASCIS trial which independently analyzed the trial. Most of the studies stressed concerns about the statistical analysis, randomization, and clinical end points and put question marks on its statistical validity and the clinical benefits of MPSS. The role of the steroid was questioned once again and MPSS has become no more than a treatment option only in many trauma centers.

Nepalese people are at high risk group of spinal cord injury but ironically the geographical and economical condition has made it almost impossible for them to use whatever the advantage of MPSS would have. In this article review of relevant literature has been done in the context of Nepal.

Key words: methylprednisolone ,National Spinal Cord Injury Study (NASCIS), spinal cord injury, steroid

Spinal cord injury is one of the most devastating injuries leaving annually almost 40 million,[11] mostly young males, disabled to various extent. Spinal cord injuries were initially considered not amenable to therapy intended to improve neurological functions and were left unattended. However, it was later realized that, for a problem as common and devastating as spinal cord injury, even a moderate improvement in the degree of disability made a great difference on the quality of life and the functional status of the injured. Thus attempts were made from different aspect of management to improve the neurological status and to reduce the extent of paralysis in these patients. The prospect of these patients has changed ever since then.

Over the years, the patho-physiology of spinal cord injury has been better understood. The primary insult occurring during the accident involved both vascular and neuronal injuries. These injuries initiate a cascade of secondary events that include ischemia, inflammation and calcium-mediated cell injuries. Of the important byproducts of the reactions are calcium, nitrous oxide and reactive oxygen species. These byproducts activate lipases, endonucleases and proteases like calpain,[3,22,57]causing degradation of membrane lipids, fragmentation of DNA, and loss of cytoskeleton and alteration of the expression of genes, thus causing further neuronal injury, collectively called secondary spinal cord injury.[1,2] The treatment of primary spinal cord injury is prevention only. Thus the most important component of the management of spinal cord injury is the prevention of secondary injury by interfering with the pathway of chains of reactions involved in the production of the byproducts, mainly the reactive oxygen species. Many pharmacological agents like tirilazad mesylate, naloxone, Interleukin-10, Glutamate (AMPA) Receptor Blockers, 4-Aminopyridine, steroid, GM-1-ganglioside[2,27] and other neuroprotective treatments, have been used to achieve the above goal but only steroid has stood up against the test of time.

Steroids have been used very widely for almost three decades in acute spinal cord injuries (ASCI), on empirical basis, encouraged by the improvement of outcome in cerebral edema.[28,56] Animal experiments had suggested that among all the steroids, only Methylprednisolone succinyl succinate (MPSS- pregna – 1,4 –diene-3,20 – dione, 11,17, 21 –trihydroxy-6-methyl,(6á ,11â), a Glucocorticoid, exhibited potential neuro-protective effects by its anti-inflammatory and oxygen free radical scavenging action. It inhibits lipid peroxidation and calcium influx, thus stabilizing membrane, maintaining the blood-spinal cord barrier, reducing oedema, increasing blood flow and maintaining electrolyte homeostasis.[1,59] Methylprednisolone succinyl succinate (MPSS) was thus used widely though there was no scientific study or evidence to support the benefit of the steroid in closed acute spinal cord injury till the late 1980's. Many studies were then started to establish a scientific basis of the use of steroid in acute closed spinal cord injury. One of the important of these studies was National Spinal Cord Injury Study (NASCIS) which was conducted in USA and was initiated in 1979.[2]

NASCIS was a multicentre, prospective, randomized, double-blind trial carried out in ten different centers of USA. It studied the efficacy of MPSS in acute closed spinal cord injury. The study was conducted in three stages. In the stage 1 of the trial, 330 patients with acute spinal cord injury were divided into two treatment groups. In treatment group 1, 100 mg bolus dose of MPSS was given which was followed by 25 mg every 6 hours for 10 days. In the treatment group 2, 1000 mg bolus dose of MPSS was given followed by 250 mg every 6 hours for 10 days. There was no control group. NASCIS I examined the change in motor function in specific muscles and changes in light touch and pinprick sensation from baseline.

The result of NASCIS I was published in 1984.[4,5] It showed improvement in the motor and functional recovery in the group receiving one gram of MPSS but the result was found to be statistically not significant. In addition, there was statistically significant increase in wound infections (9.3% vs. 2.6%, p=0.01), sepsis, pulmonary embolism and death in the high-dose group. Animal studies subsequently determined that the dose of MPSS used in NASCIS 1 was below the therapeutic threshold to observe any potential beneficial effect.[14,15,20,26] The study found no benefit from methylprednisolone, though the dose was considered to be below the therapeutic threshold determined from animal experiments. The study was concluded as negative.

The stage two of the study (**NASCIS 2) was initiated in 1985 and had three treatment groups with closed** ASCI**. The first group included 162 patients** presenting within the first twelve hours of the injury. They received 30 mg / kg bolus dose of MPSS followed by an infusion at the rate of 5.4 mg / kg per hour for the next 23 hours. The second group of 154 patients studied the effect of Naloxone (5.4 mg/kg bolus followed by 4 mg/kg/hr for 23 hours). The third group with 171 patients was a placebo control group. They excluded children and injuries below L1 level. They followed up 427 patients (95%) up to 1 year (deaths excluded). Patients were examined at admission, 6 weeks, 6 months and at 1 year intervals. Motor strength was measured using the American Spine Injury Association (ASIA) 0-5 scale in 14 muscle groups. Pin prick & touch sensation were assessed in 29 dermatomes. Analysis only used scores from the right side of the body. There was no mention of left-sided scores, although both sides were examined. The study was started in the late 1980's and the result was published in 1990.[6] The authors concluded that treatment with study dose of MPSS administered within the first 8 hours of injury improved neurological outcome and was therefore indicated in the treatment of patients with ASCI.[7,60] Treatment with MPSS beyond 8 hours after injury was not recommended.[12]

However there were many and serious criticism on the methodology, scientific and statistical issues of the study.[19, 33,34,39, 48, 49, 50,51,61] The Level 1 evidence from this data was that there was no difference between MPSS and placebo groups in the outcome of spinal cord injury. All the reported positive results from the NASCIS 2 trial were from post-hoc subgroup analysis. Data from post-hoc subgroup analyses cannot be classed as Level 1 or 2 evidence (or even level 3). The result of the post-hoc analysis was that the patients receiving steroids within 8 hours had a statistically significant improvement of 5 points on the motor score at 6 months and 1 year (p=0.03) though this much of difference may not be clinically significant. Patients treated with steroids more than 8 hours after injury had a worse neurological outcome though it was statistically insignificant. There was a statistically significant improvement in pinprick (3.4/58) and light touch (3.8/58) scores at 6 months in post-hoc analyses but at one year the result was not statistically significant. Wound infection and pulmonary embolus were doubled in the steroid group. NASCIS 2 allowed for 78 potential discrete post-hoc subgroup analyses based on time of administration. By chance, 1 in 20 of these would be expected to be statistically significant at a p value of 0.05. Furthermore, the NASCIS 2 statistical analysis included over 60 t-tests for comparing neurological outcomes. There were no corrections for multiple comparisons or analysis of variance and multivariate statistical techniques were not employed. Additionally, much of the data was thought to be non-parametric, and hence the t-test was not appropriate. Thus if correct statistical methodology had been used, it was unlikely that any statistical significance would be observed. No outcome measures involving patient's functional recovery was used.[19,34,39,61] They did not require minimum motor impairment for inclusion and included even those with minimal or no neurological deficits.[27]

Therefore, there was no statistically significant benefit overall in the MPSS group; however, post hoc analyses detected a small gain in the total motor and sensory score in a subgroup of patients who had received the drug within 8 hours after their injury.

In the **NASCIS 3**, 499 patients with ASCI were included who were treated within the first eight hours. The study excluded children. They had three study groups. In the treatment group 1, 166 patients presenting within the first three hours of injury were given 30 mg/Kg bolus dose of MPSS within 15 minutes and were maintained at 5.4 mg/kg/hr for the next 23 hours. In the second group, 157 patients

presenting between three to eight hours of the injury received the same bolus but the maintenance dose was further extended to forty eight hours. The duration of 0-3 hours or 3-8 hours was completely arbitrary though the 8 hour criterion was explained to be based on the median treatment time that divided the patient population into approximately equal halves'.[60] The third group 166 patients received Tirilazad mesylate at the dose of 2.5 mg/kg every 6 hours for 48 hours. Tirilazad mesylate is a 21-aminosteroid non-glucocorticoid LP inhibitor and has potent antioxidant properties.[30] There was follow-up of 459 patients (92%) at 1 year. Patients were examined at admission, 6 weeks, 6 months and at 1 year. Motor strength was measured using (ASIA) 0-5 scale in 15 muscle groups. Pin prick & touch sensation were assessed in 29 dermatomes. Disability was scored using the Functional Independence Measure (FIM). Only right sided deep pain & pressure and left side light touch & motor scores were used in analyses, despite both sides being examined.

In NASCIS 3, statistical analysis included over 100 t-tests for comparing neurological outcomes .[8] There was no correction for multiple comparisons and analysis of variance. Multivariate statistical techniques were not employed. Additionally, much of the data was thought to be non-parametric, and hence the t-test was not appropriate. Only in patients treated between 3 to 8 hours of injury, there was a 5-point improvement in motor scores at one year (p=0.053). There was no difference in sensory outcome. Disability as measured by FIM was also unchanged at 1 year. There was a statistically significant improvement in sphincter control of 1/14 points at 6 months which was lost at 1 year. Mortality due to respiratory complications was 6 times higher in the 48-hour group (p=0.056) and there was 4 times increase in severe sepsis in the 48-hour group compared to the 24-hour group.

The result of NASCIS 3 was published in 1998[9] and overall it was a negative study. As with NASCIS 2, the Level 1 evidence from the data was that there was no difference between the three groups in the outcome of spinal cord injury. All the reported positive results from the NASCIS 3 trial were from post-hoc subgroup analysis. The data from post-hoc analyses cannot be classed as Level 1 or 2 evidence (or even level 3). The meta-analysis of these data from post-hoc analyses showed improved motor recovery of 1 full neurological grade, better functional outcome and improved sphincter control at 6 weeks (P=.09) and 6 months (P=.07) after the injury in the 48 hours MPSS group. With Tirilazad group, the motor recovery rates were equivalent to that of MPSS group.

Despite considerable criticism of the validity of such a post hoc analysis, after the NASCI study, MPSS was accepted as the only pharmacological agent useful in ASCI and quickly became an implied standard of care in many hospitals and trauma centers around the world. The patients with ASCI who are diagnosed within the first eight hours of the injury received a bolus dose of MPSS at the rate of 30mg/Kg body weight. Those diagnosed within the first three hours of the injury received the maintenance infusion of MPSS at the rate of 5.4 mg /Kg for 23 hours and those diagnosed between 3 to 8 hours after injury, were maintained on steroid at the same dose for 48 hours.[10]

With so many questions raised in the NASCI Study and its results, the role of steroid, namely MPSS, was simultaneously being studied at many other centers and had been producing conflicting reports. The important once that supported NASCIS were Japanese and Cochrane Database systemic reviews.

A Japanese multicenter, prospective, randomized, unblinded trial was led by Otani K in 1994.[40] They studied the effect of MPSS as being done in NASCIS II, i.e. Methylprednisolone 30 mg/kg bolus followed by maintenance dose of 5.4 mg/kg/hr for 23 hours. There were total of 158 patients. Among them, 117 patients were available for 6-months' follow-up. Neurological assessment was almost identical to the NASCIS 2 study. They reported improved function at 6 months in a larger number of muscles and sensory dermatomes among subjects who received high-dose MPSS infusion than among those who received only low doses of the MPSS or no drug. However, the study lacked details about randomization and outcome measures, and it included only 74% of the enrolled subjects in the outcome analysis. There was no statistical significant difference in outcome between the treatment groups and there was a trend towards an increase in septic complications in the MPSS group (66% vs. 45%) though this did not achieve statistical significance. **Post-hoc analyses** identified a statistically significant increase in improvement in sensation for those patients who received steroids (68% vs. 32%). The pitfall of this study was that the 41 exclusions after randomization (primarily for protocol violations) made it impossible to clearly identify this result and study as Level 1 evidence. Admission characteristics between the two groups were different in terms of severity of spinal cord injury (Frankel grade) and neurological scores for motor and pinprick. Thus analysis in depth of this study does not produce a satisfactory support in favor of the use of steroid in spinal cord injury.[42] Another retrospective single-center study done in Japan led by Tsutsumi et al, also gave conclusion in favour of NASCIS trial.[58]

In 2002, Cochrane Database systemic review led by Bracken MB analyzed all the studies, research and papers, both published and not published till that date and came up with the conclusion that significant improvement in neurological outcome occurred in one year with MPSS therapy if it was administered within the first eight hours of the injury. It showed benefit in terms of motor functions and functional status, if the steroid was continued for 48 hours. This report supported NASCI study results.[11,13] Rasool et al also supported the result of NASCI study in their paper.[47]

A French study lead by Pointillart Petitjean[44] from 1998 to 2000 is also a popular study on this subject. It was a single centre, prospective, randomized, single-blind study, which studied the effect of Methylprednisolone, Nimodipine and Placebo. They included 106 patients hospitalized within eight hours of spinal injury. They had three treatment groups. In the first group, bolus dose of Methylprednisolone was given at 30 mg/kg bolus followed by 5.4 mg/kg/hr for 23 hours. In the second group, Nimodipine was given at the rate of 0.5 mg/kg/hr for two hours followed by infusion at the rate of 0.03 mg/kg/hr for seven days. The third group was a placebo one. Patients

were examined at admission and at one year by a trained neurologist blinded to the treatment. 100 patients were available for follow-up at one year. There was no significant difference in ASIA score between treatment groups at one year. There was also no significant difference overall in those patients who received steroids and those who did not. Two-way ANOVA showed no evidence of interaction between methylprednisolone and nimodipine. However there was a trend towards an increase in septic complications in the methylprednisolone group (66% vs. 45%) although this did not achieve statistical significance. They concluded that there was not even a trend of improvement in outcome in this study.

Likewise many other retrospective studies and papers were subsequently published which created lot of doubts on the efficacy and usefulness of MPSS though none of the papers were strong enough to give a universal and uncontroversial data to readily change the deep rooted result of NASCI study. Some of the negative conclusions of the major studies were as follows:

- High dose MPSS could be harmful to the patients, the use of MPSS in acute spinal cord injury cannot be recommended and cannot be considered a standard of care. It is an **unproven standard of care.**[18]

- The reporting of the NASCIS studies has fallen far short of the guidelines of the ICH/FDA and of the Evidence-based Medicine Group. These shortcomings have denied physicians the chance to use confidently a drug that many were enthusiastic about and have left them in an intolerably ambiguous position in their therapeutic choices, in their legal exposure, and in their ability to perform further research to help their patients.[19]

- The numbers, tables, and figures in the published reports are scant and are inconsistently defined, making it impossible even for professional statisticians to duplicate the analyses, to guess the effect of changes in assumptions, or to supply the missing parts of the picture. [19]

- The NASCIS group has not left anyone the means to verify the published interpretations or to evaluate alternative interpretations. The SCI community must accept or reject the published conclusions as stated, and they are offered no evidence for making this choice other than faith. Science is not faith.[19]

- We have not been able to determine its efficacy from the published reports. We have been denied the opportunity to use with confidence a drug that many of us were enthusiastic about when reports of the success of NASCIS II first appeared. Since then, excitement has turned to frustration as the years have gone by; promise has not been followed by public confirmation, and we have been left in an ambiguous clinical, legal, and scientific position.[19]

- Until the raw patient data from NASCIS II is made available for independent review, the actual benefit of intensive steroid therapy will remain elusive.[20]

- **There was no difference in neurological outcome between the two sets of patients on or off steroid in the outcome analysis with a higher rate of pneumonia (79% versus 50%), and longer hospital stays.**[23]

- Clinical improvement in the outcome of SCI has not been consistently identified with the use of MPSS.[24]

- There were no significant differences in neurological outcomes, using the Frankel classification system, between those who received MPSS and those who did not. [25]

- There was significant increase in the incidence of pneumonia and in the duration of ventilation and ICU stay in the MPSS group.[26]

- **NASCIS show little effect of steroids in spinal injury.**[41,29]

- High-dose methylprednisolone for acute closed spinal cord injury is only a treatment option. It is not an evidence-based standard of care for patients with such an injury. [31]

- Methylprednisolone for acute spinal cord injury is not a standard of care.[32]

- Methylprednisolone for acute spinal cord injury is an inappropriate standard of care. NASCIS could still be considered experimental.[33]

- Use of MPSS cannot be recommended for routine use. Use of MPSS in acute spinal cord injury was of investigational (unproven) status only. Prolonged administration of high-dose steroids (48 hours) is harmful to the patient. Until more evidence is forthcoming, MPSS should be considered to have investigational (unproven) status only. [34]

- Analyses have been made on subgroups of the study-populations and the results are based on statistical artefacts. This, combined with the failure to show improved functional recovery, puts into question earlier conclusions drawn on the efficacy of MPSS on ASCI. The recent literature concludes that there is no scientific evidence to support MPSS as standard treatment in ASCI.[36]

- Use of steroid is not proven as a standard of care.[37]
- The potential adverse effects of high-dose steroid administration in trauma patients were increased incidence and severity of infectious and septic complications like respiratory complications,

gastrointestinal hemorrhage, pancreatitis, pulmonary embolism, worsening of head injury outcome, and possibility of missed hollow viscous injury due to 'masking' of abdominal signs.[38]

- Neither of NASCIS 2 or 3 convincingly demonstrate the benefit of steroid and the clinical benefits are questionable. There are concerns about the statistical analysis, randomization, and clinical points.[39]
- There was no difference in disability outcome between those patients who received steroids and those who did not.[43]
- There was absence of benefit of pharmacological therapy in this indication.[44]
- High-dose methylprednisolone may do more harm for spinal cord injury.[45]
- High-dose methylprednisolone may cause myopathy in acute spinal cord injury patients.[46]
- **High dose of methyleprednisolone cannot be justified as a standard treatment in acute spinal cord injury within current medical practice.[50]**
- The use of high dose methylprednisolone in the management of acute spinal cord injury cannot be supported.[52]
- The evidence provided in the literature supports 'the recommendation that high dose methylpredisolone be excluded from consideration as an intervention for acute spinal cord injury. The study does not support the use of steroid to improve neurological recovery.[52]
- The NASCIS data is insufficient to support the use of high-dose methylprednisolone as a treatment standard or as a guideline for treatment following an acute closed spinal cord injury. The data may support the treatment as optional, but the high evidence of complications should be kept in mind.[53]
- The use of MP in patients with acute SCI is not associated with an improvement in outcome or neurological function. Moreover, the use of MP is associated with an increased risk of infectious and metabolic complications.[54]
- There is insufficient evidence to support the use of methylprednisolone as a standard treatment in acute spinal cord injury.[55]

All these studies were done in famous trauma centers with adequate number of cases and were analyzed using scientific and dependable statistical methodologies. So, these conclusions can not be ignored though none of the trials reported here, fulfill all the current standards for study design, conduct of trial, analysis and presentation. The serious and increasing complications relating to the use of steroids have further dampened the enthusiasm of its use. A committee comprising of Canadian neurosurgical and orthopedic spine specialists, emergency physicians and physiatrists, have reviewed the evidence and concluded that high-dose methylprednisolone infusion is not an evidence-based standard of care for patients with such an injury. They have concluded that a high-dose of methylprednisolone, after an acute closed spinal cord injury, is not a standard treatment nor a guideline for treatment but, rather, a treatment option, for which there is very weak level II and III evidence.[16,17,31,32] Thus use of MPSS in acute spinal cord injury needs lot of thoughts and consideration. Steroids are nowadays used because of pressure of fear of medical litigation in many trauma centres.[35]

Nepal has its own unique problem for using MPSS in closed ASCI. Nepalese people are at a high risk of sustaining spinal injuries due to its geographical structure and risky life style. Most of the people live in hills and mountains where they work in tall trees and difficult steep cliffs. They live in unscientifically built houses with inadequate safety measures and travel in overloaded high speed and ill-maintained vehicles. All these situations render them high risk of spinal injuries. Most of the spinal injuries in Nepal occur following fall from height which usually occurs in remote places and at times, remain undetected for days. Due to the problems like, difficult geographical situations, problem of transport, poverty, very limited numbers of centers specialized to take care of SCI patients, widely prevalent ignorance among people including even the medical personals about the management of the injurirs, they arrive at the hospital much after the golden eight hours of NASCI study. The time frame for the beneficial use of MPSS is practically impossible to meet under these circumstances. One full course of MPSS costs US$ 215 if the diagnosis is made within three hours and US$ 360 if detected within 8 hours of the injury. For a country whose annual per capita income is only US$ 300, it is very difficult to use such an expensive medicine whose benefit has recently become very controversial and carries a lot of inherent complications even if they arrive within eight hours. In addition, due to its high cost, the drug is not freely available in peripheral medical centers. With all these unique additional problems in Nepal, the use of MPSS in closed acute spinal injury is very limited.

After considering the above facts, it is clear that more research is required to decide in favor or against the use of MPSS in spinal injury, like decided by many other review meetings around the world.[21] The draw backs like inadequate numbers of patients to achieve statistical power, a placebo group as one of the treatment arms, standardized medical protocols, careful collection of relevant outcome data, especially functional outcomes, and appropriate statistical analyses need to be further strengthened. With the world now divided on the usefulness of MPSS in the injury, the question of using MPSS has to be very thoughtfully individualized with open mind and heart. The use of MPSS as a treatment option, even after arriving within the first

eight hours, has become difficult in Nepalese patient by financial issues and unavailability of the drug. Thus, treatment option in these individuals with MPSS, in our situation, is guided by many other factors rather than all those scientific data alone.

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