Application of Modest Hypothermia in Patients with Acute Traumatic Cervical Spine Injury: A Pilot Study

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Abstract:

Introduction: This prospective randomized controlled study aimed to examine the role of modest systemic hypothermia in individuals with acute cervical spinal cord injury (SCI) regarding neurological improvement. Studies have shown that the application of hypothermia is safe and that it improves neurological outcomes in patients with traumatic spine injury. Hypothermia helps in decreasing a secondary damage to the cord.

Methods: Twenty cases of acute post-traumatic cervical SCI with AISA were selected and randomly divided into two treatment groups: Group A-Hypothermia with surgical decompression and stabilization; and Group B-Normothermia with surgical decompression and stabilization. American Spinal Injury Association (ASIA) motor and sensory scores were evaluated at presentation; post-surgery; and at a 2-week, 6-week, and 12-week follow-up.

Results: At the final follow-up, the change in ASIA motor scores of Group A was 46 (11.5-70.5) and Group B 13 (4.5-58.0), whereas ASIA sensory scores were 118 (24.75-186.5) and 29 (15.25-124.0) in Group A and Group B, respectively. ASIA scores between the two groups were statistically significantly different at a 2-week follow-up (ASIA motor p=0.04, ASIA sensory p=0.006), showing early improvement in the hypothermia group. There was no significant difference between the two groups on further follow-up.

Conclusions: Hypothermia can be applied safely to subjects with acute SCI. Our study showed that hypothermia was beneficial in the early improvement of functional outcomes in acute cervical SCI.

Keywords:
- hypothermia, cervical, spinal cord injury, hypothermia, improvement, American Spinal Injury Association score

Introduction

Damage to the spinal cord often results in a neurological deficit such as loss of movement and sensation below the spinal cord injury (SCI). This type of injury has many socio-economic implications and emotional repercussions for subjects, their caregivers, and the health care system. Mathur et al.¹ thus conducted a prospective observational study in a tertiary care center (SMS, Jaipur) between January 2000 and December 2008 to examine the epidemiological factors in traumatic SCI in the Indian population. During this study, a total of 8178 cases were admitted in the department, out of which 2716 cases (23.2%) were SCI. Cervical SCI included 1400 cases, out of which 557 involved complete paralysis. Patients with SCI become involuntarily a heavy burden on their families and healthcare system, not just during the initial phase, but after many years following injury. Examples of this are numerous secondary complications such as bedsores, which require hospitalization; the need for an extra caretaker or home nursing services or a fellow family member and extra hospital follow-ups; and many other complications in SCI (e.g., psychological disorders). The natural history of recovery in complete SCI spontaneously is very rare, but some degree of neurological recovery is expected in...
some subjects, peaking at around 3 months. Spontaneous recovery occurring in SCI can be considered as a confounder to the therapeutic benefits of other agents. Thus, Steeves et al. in their retrospective study showed that among the subjects who were classified as neurologically complete cervical SCI, around 60% regained sensations without motor recovery, and 10% regained some degree of motor functions. The physiological dysfunction following SCI results from both tissue damage, which is produced by the primary insult of trauma, as well as a range of secondary injury mechanisms.

Treatment of SCI includes surgical stabilization, decompression, and rehabilitation. Surgical stabilization, critical care, and rehabilitation programs might not be enough to provide a significant amount of recovery of sensory and motor function after any SCI to most of the individuals. The role of steroids in SCI remained a controversy for many days. Recently a meta-analysis showed that the use of methylprednisolone was not associated with any significant short- or long-term improvements. The use of hypothermia is neuroprotective and improves outcomes following SCI. The various protective mechanisms of mild to moderate hypothermia are the slowing down of cellular metabolism, reducing free radical generation, decreasing excitotoxicity, inhibiting apoptosis, decreasing inflammation, preserving the blood spinal cord barrier, decreasing astrogliosis, increasing angiogenesis, decreasing the damage to axons, and increasing the chances of neurogenesis. Hypothermia can also be used along with antioxidants, alkalinization, and stem cell transplantation which can provide additional benefits.

Cooling was done at 32°C-33°C, as in previous studies, to improve power in both upper and lower limbs and decrease the white and gray matter damage. Dididze et al. established a safety profile of systemic hypothermia and its efficacy in an acute traumatic cervical SCI with the use of an endovascular catheter. However, no multicentric randomized studies have demonstrated, to the best of our knowledge, the therapeutic effects of systemic hypothermia, which makes it still an experimental procedure. After an exhaustive search of the literature, we only found 4 clinical studies on the therapeutic effect of hypothermia in subjects with SCI, and none of them in the Asian population. We have not find even a single randomized clinical trial on this topic. Thus, in our study, we hypothesize that modest hypothermia of 33°C for 24 h in subjects with acute traumatic SCI is neuroprotective and thus limits the neurological dysfunction caused by the trauma.

Materials and Methods

This was a prospective randomized controlled clinical trial that included subjects aged 18-65 years having a traumatic closed lower sub-axial complete SCI (C3-C7) with a GCS of 15. Subjects presenting to the Orthopedic Emergency in the Advanced Trauma Center, PGIMER, Chandigarh, India, requiring surgical decompression and fixation of the spine using anterior cervical disectomy and fusion or by lateral mass fixation were assessed for eligibility and recruited. The study lasted from January 1st, 2019, to March 31st, 2020. We registered our study with clinical trial registry India ref. no. CTRI/2020/02/023146, and it is available at www.ctri.nic.in.

Exclusion criteria

Subjects with incomplete SCI, polytrauma subjects, those presenting with hyperthermia of >38.5°C, having complete cord transection on magnetic resonance imaging, or having a history of severe bleeding, coagulopathy, thrombocytopenia, cardiac disease, pancreatitis, and Raynaud syndrome were excluded from the study.

After written informed consent was obtained, a general health check-up and a neurological examination were performed for every subject immediately on presentation in the orthopedics emergency in advanced trauma center. The examination included the ATLS primary survey, secondary survey, general physical examination, American Spinal Injury Association (ASIA) scoring, lab tests (hemoglobin, total leucocyte count, platelet count, prothrombin time, international normalized ratio, activated partial thromboplastin time, serum electrolytes, renal function tests), resting ECG, and chest X-ray. Subjects who improved their ASIA scores within 48 h were excluded from the study. Subjects were asked about any other comorbidities. The principal investigator enrolled all the subjects who met with inclusion criteria.

Randomization

The principal investigator used a simple randomization technique to allocate subjects equally in the ratio of 1:1 into both groups. The principal investigator prepared 20 sealed envelopes marked with numbers from 1 to 20. After meeting the inclusion criteria, subject’s attendant was asked to pick any one of the sealed envelopes. Subjects receiving odd numbers were allocated to Group A, and subjects receiving even numbers were allocated to Group B. Participants, operating surgeon, and outcome assessor were blinded.

Group A (Hypothermia)

Individuals enrolled in the study were shifted to the High Dependency Unit, and the NiBP, SPO2, and ECG monitors were attached to the subjects. Temperature monitoring was conducted through a nasopharyngeal probe. All patients were immediately temporarily stabilized by skull traction, and reduction was achieved preoperatively.

Modest hypothermia (defined as 33°C in this study; a range of 32°C-34°C) was achieved using intravenous cold saline, and in addition, cold sponging and cold packs were also applied.

Phases of Hypothermia (Supplementary file 1)

Anti-shivering protocol was considered in this study as a precautionary measure, but as the patients were fully quadri-
plegic, the temperature regulation by the hypothalamus was impaired, and it was found that there was no shivering in the patients upon application of therapeutic hypothermia; hence, the drugs in the anti-shivering protocol were not used.

Surgical procedure and rewarming phase

Subjects were taken up for surgery (anterior cervical discectomy and fusion or by lateral mass fixation) after the maintenance phase. Subjects were rewarmed slowly to near-normal temperature peri-operatively. Rewarming was done slowly with a vigilant watch for side effects such as vasodilatation caused due to rewarming on various organ systems. Thus, a controlled rate of 0.3°C/hour rise of core body temperature was conducted. General anesthesia was administered to all subjects, and standard ASA monitors were attached. An invasive arterial line was placed, ABG analysis was done, and subjects were extubated only when all extubating criteria were fulfilled and the body temperature was >35°C. Others were shifted to the HDU on ventilator support and extubated later. Thus, the total time required to reach 35°C was approximately 6 h, but the total duration of rewarming (to reach 37°C) was approximately 12 h.

Group B

Subjects remained at their normal body temperature (37°C) and were immediately temporarily stabilized by skull traction, and reduction was achieved preoperatively and were subsequently operated similarly as in Group A. The neurological examination included an assessment of ASIA scores, and it was done regularly. Demographic, clinical, and surgical data were collected. We characterized the subjects’ socio-demographic characteristics and injury. Each subject was followed up for a minimum period of 3 months. Each follow-up consisted of a general physical and neurological examination, and the ASIA score was calculated.

1st follow-up: Immediately post-surgical procedure in the post-operative room
2nd follow-up: 2 weeks from the surgery
3rd follow-up: 6 weeks from the surgery
4th follow-up: 12 weeks (~3 months) from the surgery

Outcome parameters: Neurological improvement using ASIA motor and sensory scores, complications.

The sample size was calculated using a one-tailed statistical t-test, the mean difference between two dependent means (matched pairs), given α=0.05 and power 0.95 with a treatment effect size of 0.80. Using this, we obtained a total sample size of 18. Calculating for attrition, we used a total of 20 subjects with 10 in each group.

Statistical analysis

All statistical analysis was done using MS Excel and SPSS version 22 (IBM SPSS Statistics, Somers NY, USA). Categorical data were represented in the form of frequencies and proportions. Data were analyzed for normality using the Kolmogorov-Smirnov test and the Shapiro-Wilk test and found to be non-normal in distribution. Thus, the Mann-Whitney U test was used to compare the means between the two groups. A chi-squared test was used as a test of significance for qualitative data. A p-value <0.05 was considered statistically significant after assuming all the rules of statistical tests.

Results

After checking for the inclusion criteria, 20 subjects were included in our study with 10 subjects in each group. Participant flow is illustrated in Fig. 1. Subjects were not changed from their allocated groups. Subjects were mainly men (75%), and the mean age of all the subjects in the study was 42.4±12.7. Among all cases, 40% of injuries were due to fall from height followed by road traffic accidents 35%. The most common levels of injury were C5-C6 and C6-C7, each having 30% of the total subjects in the study, the next common being C5 body fracture in this study. The spine stabilization was majorly done anteriorly (75%), as compared to posterior stabilization (25%). There was no significant difference between the two groups regarding demographic parameters (Table 1).

All subjects were assessed immediately on presentation in the orthopedics emergency in advanced trauma center and immediately post-operatively, at 2, 6, and 12 weeks. ASIA motor and sensory scores were noted at each follow-up. We used the Friedman test to see the improvement in ASIA scores at final follow-up. According to the Friedman test, there was a significant improvement in the ASIA motor and sensory scores of both the groups when tested individually (Table 2). In Group A, the mean ASIA motor score at pre-op was 4.80±1.68 [CI 3.71-5.88], and at final follow-up, it was 45.80±28.85 [CI 26.02-65.57]. In Group A, the mean ASIA sensory score at pre-op was 26.80±1.13 [CI 26.08-27.52], which improved to 132.8±78.16 [CI 82.84-182.75] at final follow-up. In Group B, the mean ASIA motor score at pre-op was 5.00±1.51 [CI 3.79-6.20], which improved to 31.25±30.31 [CI 9.14-53.36] at 3 months. In Group B, the mean sensory score at pre-op was 27.13±0.99 [CI 26.32-27.93], which improved to 86.25±69.54 [CI 30.39-142.10] at final follow-up. We used the Mann-Whitney test to compare the ASIA score between the two groups at each follow-up (Table 3, 4). There was a significant difference between the two groups at 2 weeks showing better improvement in Group A, and a p-value of 0.04 and 0.006, for ASIA motor and sensory, respectively (Table 3, 4). There was no significant difference between the two groups on further follow-up. This indicates early improvement in Group A compared to Group B.

The change in ASIA motor scores between pre-op and final follow-up was 46 (11.50-70.50) and 13 (4.50-58.00) in Group A and Group B, respectively. Similarly, the change in ASIA sensory scores between pre-op and final follow-up was 118 (24.75-186.50) and 29 (15.25-124.00) in Group A and Group B, respectively (Table 5).
Table 1. Showing Demographic Parameters, Mode of Injury, Level of Injury, and Surgical Procedure Performed.

|                  | Group A     | Group B     | P-value |
|------------------|-------------|-------------|---------|
| Age              | 43±14.2     | 41.9±11.7   | 0.87    |
| Mode of Injury   | 0.78        | 0.78        |         |
| Fall from height | 4           | 4           |         |
| Fall on level ground | 3       | 1           |         |
| RSA              | 2           | 5           |         |
| Others           | 1           | 0           |         |
| Level of injury  | 1.00        | 1.00        |         |
| Up to C5         | 3           | 4           |         |
| Below C5         | 7           | 6           |         |
| Surgery performed| 0.61        | 0.61        |         |
| ACDF             | 8           | 7           |         |
| LMSF             | 2           | 3           |         |

Table 2. Showing the Improvement in Serially Measured ASIA Motor and ASIA Sensory Scores in Groups A and B (Friedman Test).

|                  | FRIEDMAN TEST         |
|------------------|-----------------------|
|                  | ASIA Motor Mean Ranks | ASIA Sensory Mean Ranks |
|                  | Group A | Group B | Group A | Group B |
| Time             |         |         |         |         |
| Pre-op           | 1.50    | 1.50    | 1.50    | 1.63    |
| Immediate post-op| 1.50    | 1.50    | 1.50    | 1.63    |
| 2 weeks          | 3.05    | 3.19    | 3.00    | 2.94    |
| 6 weeks          | 4.05    | 4.00    | 4.00    | 3.88    |
| 12 weeks         | 4.90    | 4.81    | 5.00    | 4.94    |
| Chi square       | 39.42   | 30.93   | 40.00   | 29.94   |
| P-value          | 0.01    | 0.01    | 0.01    | 0.01    |

We also assessed the number of subjects who improved to AIS Grade C or D. Five subjects in Group A and two in Group B improved to AIS grade C or D at 3 months with an odds ratio of 3 and 95% CI 0.4-22.71. There were two deaths in Group B at the final follow-up. This was not statistically significant (p=0.46).
Table 3. Differences in ASIA Motor Scores between Groups A and B at Each Follow-up (Mann-Whitney Test).

| Time   | Group A Mean Rank | Group A Sum of Ranks | Group B Mean Rank | Group B Sum of Ranks | MVU | P-value |
|--------|-------------------|----------------------|-------------------|---------------------|-----|---------|
| Pre-op | 9.90              | 99.00                | 11.10             | 111.00              | 44.00 | 0.59    |
| Post-op| 9.90              | 99.00                | 11.10             | 111.00              | 44.00 | 0.59    |
| 2 weeks| 13.10             | 131.00               | 7.90              | 79.00               | 24.00 | 0.04    |
| 6 weeks| 12.15             | 121.50               | 8.85              | 88.50               | 33.50 | 0.20    |
| 12 weeks| 10.55             | 105.50               | 8.19              | 65.50               | 29.50 | 0.34    |

Table 4. Differences in ASIA Sensory Scores between Groups A and B at Each Follow-up (Mann-Whitney Test).

| Time   | Group A Mean Rank | Group A Sum of Ranks | Group B Mean Rank | Group B Sum of Ranks | MVU | P-value |
|--------|-------------------|----------------------|-------------------|---------------------|-----|---------|
| Pre-op | 9.65              | 96.50                | 11.35             | 113.50              | 41.50 | 0.48    |
| Post-op| 9.65              | 96.50                | 11.35             | 113.50              | 41.50 | 0.48    |
| 2 weeks| 14.10             | 141.00               | 6.90              | 69.00               | 14.00 | 0.006   |
| 6 weeks| 12.75             | 127.50               | 8.25              | 82.50               | 27.50 | 0.09    |
| 12 weeks| 11.15             | 111.50               | 7.44              | 59.50               | 23.50 | 0.14    |

Table 5. Changes in ASIA Motor and ASIA Sensory Scores at Final Follow-up when Compared to Pre-op.

| Change in ASIA Scores at Final Follow-Up When Compared to Pre-op | Group A | Group B |
|-----------------------------------------------------------------|---------|---------|
| Change in motor score                                           | 46 (11.5–70.5) | 13 (4.5–58.0) |
| Change in sensory score                                          | 118 (24.75–186.5) | 29 (15.25–124.0) |

Acronyms: IQR, interquartile range

Complications

There was one subject who had arrhythmia in Group A, and one subject from the same group had gastrointestinal bleeding. No subjects in both groups had pneumonia, pleural effusion, or ARDS. No subjects developed DVT in both groups. There were two deaths in Group B and no deaths reported in the hypothermia group. Six patients from Group A and eight patients from Group B developed bedsores.

Discussion

The common procedure in the treatment of acute cervical spine injury is surgical stabilization with the spinal cord decompression. No drug to date has been effective in minimizing cord damage. Many large multicentric trials have been conducted to improve neurological outcomes and decrease the complications associated with residual paralysis. Various regenerative techniques are found in literature, which include biomaterial scaffolds, neurotrophin delivery, or stem cells implantation. These techniques were used individually and in combination. These studies showed promising results in improving functional recovery in patients with acute SCI after surgery. A systemic review was conducted to assess the outcomes of patients with acute SCI after treatment with methylprednisolone. This review showed the pooled outcomes of included studies and recommended that there is no role of methylprednisolone infusion after 8 h of injury. In many developing countries, it is difficult for a patient with acute SCI to reach specialized hospital in such a short span. There have SCI cord injury. The results favor the use of hypothermia. According to a multicentric distribution study by Goldberg et al. in the United States, dislocations occurred most commonly at the C5-C6 (25.11%) and C6-C7 (23.37%) levels, whereas atlantooccipital and C7 and T1 dislocations occurred infrequently. Spine stabilization was majorly done anteriorly (75%) as compared to posterior stabilization (25%), depending on the pattern of injury. All the subjects included in this study were of the AIS Grade A. The preliminary diagnosis was done at presentation to the hospital, but the diagnosis was confirmed on post-operative Day 1, which was nearly 48 h after injury, and only when
there was no improvement in the ASIA scores and the return of bulbocavernous reflex, the confirmatory diagnosis was made.

In a study conducted by Steeves et al.\(^9\), including mainly the individuals with C4-C7 AIS A, 70% regained at least one motor level in the injured cervical cord within 1 year following SCI. Of these individuals, a smaller proportion (30%) recovered two or more motor levels. In the same study, it was recorded that at 4 weeks, nearly 20% of subjects spontaneously converted from AIS A to AIS B or more, and a further 30% improved from AIS A to AIS B or more, at 8-12 weeks. In our study, all subjects enrolled in both the groups were AIS A at presentation. Among the subjects in Group A, five out of ten persons improved to AIS grade C or D, and in Group B, two out of eight subjects improved to AIS grade C or D at the end of 3 months. In a study by Dididze et al.\(^8\), recruited 21 acute SCI subjects prospectively and combined them with the 14 cervical SCI subjects from Levi et al., retrospectively\(^3,16,17\), representing the largest number of cases (n=35) of cervical SCI subjects treated with systemic hypothermia\(^10\). Fifteen out of 35 subjects (43%) had an improved neurological score of at least one grade according to the International Standards for Neurological Classification of SCI impairment scale at the 1-year follow-up, reflecting that the results were consistent with their previous study\(^7\). The neurological recovery gained in the hypothermia group was higher than that in the control group, in which only three out of 14 subjects (21.4%) experienced neurological recovery of at least one grade with standard care\(^5\). The neurological improvement in hypothermia-treated subjects exceeded the baseline expectation in the improvement of sensory or motor power spontaneously after complete cervical SCI reported in other multicenter trials\(^3,16,17\). In our study, mean motor and sensory scores in the hypothermia group were significantly improved at 3 months when compared to pre-op levels. In addition, there was no significant improvement in the non-hypothermia group. This shows hypothermia helps in improving functional outcomes. While comparing both groups, the hypothermia group showed statistically significant improvement in ASIA motor and sensory scores at 2 weeks. Furthermore, the difference was not statistically significant on further follow-up indicating early improvement in the hypothermia group.

In a study by Levi et al.\(^7\), they reported that pulmonary, cardiac, and thromboembolic complications occurred at rates similar to that of historic, uncooled, age, and injury-matched SCI subjects, which suggests that the majority of the complications that were encountered were secondary to SCI itself, rather than hypothermia. Our study also showed no significant difference between the two groups. Earlier studies showed that earlier surgery might improve neurological outcomes\(^10\), but there is no definite evidence of timing of surgery. Few studies mentioned early surgery as <72 h and few as <24 h\(^9,20\). Studies also demonstrated no significant difference between length of intensive care unit stay and in-hospital mortality\(^21\). In this study no patient underwent surgery within 24h after admission, as we have to maintain hypothermia for 24 h.

In summary, all the previous studies have shown that systemic hypothermia can be a feasible option to enhance the neurological recovery if given as soon as the patients reach the emergency, and systemic hypothermia if monitored well has very less side effects as seen in the previous studies, as well as in our study.

The limitations were in that this study had a low sample size as we conducted this as a pilot study. The results may change as the number of sample size increases for some parameters, which did not have a significant difference. The cases were operated after 24 h in both the groups to decrease any confounders between the groups. This study involved only a single center. Further studies with a large number of subjects focusing on residual disability or disability-adjusted life years, rehabilitation of subjects, morbidity, and mortality are required.

In conclusion, using modest hypothermia is a safe procedure in subjects with acute cervical SCI. It improves functional outcomes early when compared to non-hypothermia group individuals, but it was not statistically significant in our long-term follow-up.

**Conflicts of Interest:** The authors declare that there are no relevant conflicts of interest.

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**Author Contributions:**

1. PBS: Primary investigator of the study
2. SSD: guide of the primary investigator, periodically assessed study progression and approved final study
3. VK: periodic changes in subjects included, protocol design and clinical trial registration
4. AKS: operated on all included subjects
5. DN: final manuscript preparation and changes according to journal policies
6. TS: providing hypothermia and critical care management and ventilatory support.
7. KJ: critical care management.

**Ethical Approval:** This study was approved by the Institutional Ethics Committee of PGIMER, Chandigarh vide letter no. INT/IEC/2019/001031 in their meeting held on 29/04/2019. If we certify that all applicable institutional and governmental regulations concerning the ethical use of human volunteers/animals were followed during the course of this research.

**Informed Consent:** Written and informed consent taken from all the participants

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