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Pharmacological therapy of spinal cord injury during the acute phase

V Pointillart*,[1], ME Petitjean[2], L Wiart[3], JM Vital[1], P Lassié[2], M Thicoipé[2] and P Dabadie[2]

[1]Unité de Pathologie Rachidienne, Hôpital Pellegrin, 33076 Bordeaux Cedex, France; [2]Département des Urgences, Hôpital Pellegrin, 33076 Bordeaux Cedex, France; [3]Service de Rééducation et Réadaptation Fonctionnelle, Hôpital Pellegrin, 33076 Bordeaux Cedex, France

Study design: Prospective, randomized clinical trial.
Setting: France.
Objectives: To evaluate the safety and effect on neurological outcome of nimodipine, methylprednisolone, or both *versus* no medical treatment in spinal-cord injury during the acute phase.
Method: One hundred and six patients who had spinal trauma (including 48 with paraplegia and 58 with tetraplegia) were randomly separated into four groups: M = methylprednisolone (30 $mg \cdot kg^{-1}$ over 1 h, followed by 5.4 $mg \cdot kg^{-1} \cdot h^{-1}$ for 23 h), N = nimodipine (0.015 $mg \cdot kg^{-1} \cdot h^{-1}$ for 2 h followed by 0.03 $mg \cdot kg^{-1} \cdot h^{-1}$ for 7 days), MN (both agents) or P (neither medication). Neurological assessment (ASIA score) was performed by a blinded senior neurologist before treatment and at 1-year follow-up. Early spinal decompression and stabilization was performed as soon as possible after injury.
Results: One hundred patients were reassessed at 1 year. Neurological improvement was seen in each group ($P < 0.0001$), however no additional neurological benefit from treatment was observed. Infectious complications occurred more often in patients treated with M. Early surgery (49 patients underwent surgery within 8 h of their accident) did not influence the neurological outcome. The only predictor of the latter was the extent of the spinal injury (complete or incomplete lesion).
Conclusion: The present study confirms the absence of benefit of pharmacological therapy in this indication. Because of the paucity of clinical studies that demonstrate the efficacy of pharmacological treatment in spinal injury during the acute phase, systematic use of pharmaceutical agents should be reconsidered.
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Keywords: spinal cord injury; nimodipine; methylprednisolone

Introduction

The complexity of pathophysiologic mechanisms at play in the immediate aftermath of spinal cord injury explains the diversity of pharmacological protocols that have been tested and suggests that various associations of pharmaceutical agents warrant consideration.[1–11] The initial results concerning neurological improvement after early administration of heavy doses of methyprednisolone to spinal injury victims appeared very promising.[12,13] However, clinical studies that followed dampened the initial enthusiasm. In France, for example, no pharmacological treatment is currently recommended in this indication.[14–18] The present trial assessed neurological recovery 1 year after administration, within 8 h of spinal-cord injury, of methylprednisolone, nimodipine, or the two combined, in comparison with no pharmacological treatment. The side effects of these treatments and the impact of early spinal surgery on functional recovery were also evaluated.

Patients and Methods

The present prospective randomized was conducted between November 1990 and March 1995 with the consent of the medical ethics committee of our institution. Patients were included only after written consent was obtained from the patient, the patient's family, or both. Inclusion criteria were age older than 15 years and younger than 65 years, and hospitalization within 8 h of vertebral trauma with spinal cord involvement.

Exclusion criteria were a pattern of nerve-root involvement, cauda equina syndrome, open spinal lesions, pregnancy, multiple trauma, head injury with Glasgow score lower than 13, pulmonary contusion, hemodynamic instability that persisted despite volume

*Correspondence: V Pointillart, Unité de Pathologie Rachidienne, Hôpital Pellegrin Tripode, 7ème étage, Place Amélie Raba Léon, 33076 Bordeaux Cedex, France

expansion, mean arterial pressure (MAP) less than 60 mmHg, previous treatment by corticoids or calcium channel blockers, or a history of diabetes mellitus, stomach ulcer, liver failure, or cardiovascular disorders such as high blood pressure or coronary disease. The protocol was discontinued if the patient refused to participate in the study or if the MAP remained lower than 60 mmHg for more than 1 h.

The following data were noted: age, sex, circumstances of the trauma, results of neurological examination at admission and 1 year later according to the classification of the American Spinal Injury Association (ASIA), and the amount of time between the accident and the administration of the treatment.[19] The level of consciousness was evaluated according to the Glasgow coma scale. The injury severity score (ISS) was also recorded. It is based upon the abbreviated injury scale (AIS), which classifies traumatic lesions according to their nature, location, and severity on a scale of 1–5.[20] The ISS corresponds to the sum of the squares of the highest AIS lesions observed in three of the six regions of the body (head and neck, face, thorax, abdomen and pelvis, extremities and pelvic girdle, and the skin). The maximum possible score is 75. For the patients who necessitated surgery during the first 24 h, the amount of time between the accident and the operation was recorded as was the amount of intraoperative bleeding. Complications were noted, including metabolic (hyperglycemia), infectious (pneumonia, septicemia, urinary tract infections), cardiovascular and digestive disorders. The duration of assisted ventilation and that of the overall hospital stay were recorded.

Plain anteroposterior and lateral films of the spine were obtained for all patients. Spinal computed tomography (CT), CT myelography, or magnetic resonance imaging was obtained as needed.

The neurological examination at admission and 1 year later were carried out by a senior neurologist who was blind with respect to the treatment administered to the patient as was the orthopedic surgeon who managed the patient. This examination was performed in the emergency room within the first few hours following admission and before any surgery. Patients meeting the inclusion criteria were randomly separated into four groups, each of which received a different treatment. Group M received methylprednisolone at a dose of 30 $mg \cdot kg^{-1}$ over 1 h, followed by 5.4 $mg \cdot kg^{-1} \cdot h^{-1}$ for 23 h, Group N received nimodipine at a dose of 0.15 $mg \cdot kg^{-1} \cdot h^{-1}$ for 2 h followed by 0.03 $mg \cdot kg^{-1} \cdot h^{-1}$ for 7 days. Group MN received both methylprednisolone and nimodipine at the same doses used in groups M and N; and patients in group P received neither medication. The designation of a patient to a group was decided using a random selection cycle that started over after every series of eight subjects to yield groups that were balanced in number.

Results for the quantitative values that concerned all the patients are expressed as mean $\pm$ standard deviation. The quantitative values for each group are expressed as median and are provided with the 25th to 75th percentile range. The statistical analysis was carried out using chi2, Fisher, or Kruskal-Wallis nonparametric tests as appropriate. The effect of treatment upon the outcome at 1 year according to the complete or incomplete nature of the spinal cord lesion and the usefulness of early spinal surgery were evaluated using two-way analysis of variance; $P < 0.05$ was considered to be significant.

Results

Between November 1990 and March 1995, 106 patients, including 48 paraplegic patients and 58 tetraplegic patients were included in this study. Forty-eight patients (45%) had complete cord lesions. Ninety per cent of the patients were men. Motor vehicle accidents were the most frequent (46%) cause of spinal cord trauma, followed by falls (29%) and sports accidents, predominantly diving accidents (25%). The four groups had no significant differences with respect to age, initial Glasgow score, ISS, or delay between trauma and the administration of treatment (Table 1). There were also no significant differences among the groups in terms of initial ASIA motor scores (ASIAmO), pinprick sensation scores (ASIAsO), or pain scores (ASIApO) (Table 2).

Neurological examination after one year was possible in 100 of the patients. Five patients died within 1 year of their accident. One paraplegic patient died due to pulmonary embolism in the early aftermath of the accident. Two tetraplegic patients (47 years old and 65 years old) died from septicemia and multiorgan failure. One paraplegic patient committed suicide, and one tetraplegic patient succumbed to respiratory failure following a second

Table 1 Principal epidemiological characteristics

	No medication	*nimodipine*	*Methyl-prednisolone*	*Methylpred. and nimodipine*
Patients (*n*)	25	27	27	27
Age (years)	28 (25–42)	32 (26–47)	32 (25–44)	28 (20–39)
ISS	25 (20–25)	25 (25–25)	25 (16–29)	25 (25–25)
Time from accident to medication (h)	3 (2–3)	3.5 (2.3–5.3)	4 (3–5)	4 (3–6)

The values are expressed as average with the 25th and 75th percentile in parentheses. ISS = injury severity score

Table 2 ASIA scores at admission and at 1 year

	No medication	*Nimodipine*	*Methyl-prednisolone*	*Methylpred. and nimodipine*
Motor (entry)	50 (23–51)	50 (21–58)	50 (20–58)	50 (10–58)
Motor (1 year)	67 (50–95)*	72 (50–94)*	57 (43–92)*	50 (50–97)*
Touch (entry)	65 (27–98)	64 (40–88)	56 (24–90)	52 (20–92)
Touch (1 year)	82 (60–110)*	76 (62–104)*	76 (44–106)*	72 (42–104)*
Pin prick (entry)	65 (27–96)	64 (40–65)	60 (24–90)	52 (20–62)
Pin prick (1 year)	82 (60–110)*	76 (62–104)*	76 (44–106)*	72 (42–104)*

The values are expressed as average with the 25th and 75th percentiles in parentheses. *$P < 0.001$

Table 3 Complications observed during intensive care according to use or non-use of methylprednisolone

Complications	*Methylprednisolone (n = 35)*	*No methylprednisolone (n = 30)*
Urinary tract infections	8	4
Septicemia	4	1
Pulmonary disorders	11	9
Gastrointestinal bleeding	2	0
Hyperglycemia	16	1*

*$P < 0.05$; methylprednisolone = patients who received either methylprednisolone with or without nimodipine; no methylprednisolone = patients who received nimodipine alone or no medication

Table 4 Average duration of stay in intensive care and of mechanically assisted ventilation

	No medication	*Nimodipine*	*Methyl-prednisolone*	*Methylpred. and nimodipine*
Days in intensive care unit	16 ± 27	16 ± 28	14 ± 21	16 ± 19
Days of mechanical ventilation	15 ± 32	7 ± 7	13 ± 20	6 ± 5

motor vehicle accident. One patient refused to come back for a 1 year follow-up examination. In all four groups, there was a significant improvement in neurological scores at 1 year ($P < 0.0001$), regarding ASIA motor, sensibility, and pain scores (ASIAm1, ASIAs1, and ASIAp1) (Table 2). At 1 year, there were no significant differences among the four groups in terms of any of the ASIA scores. Two-way analysis of variance showed no interaction between methylprednisolone and nimodipine. Only the complete or incomplete nature of the spinal cord lesion was correlated with sublesional recovery ($P < 0.0001$).

Sixty-five patients, most of whom (72%) were tetraplegic, were cared for in a traumatologic intensive care unit. The analysis of infectious, cardiovascular, metabolic, and gastrointestinal complications concerned only these patients. Although the incidence of infectious complications was higher in the patients who received methylprednisolone (66% *versus* 45%), this difference was not significant (Table 3). Two patients treated with methylprednisolone had a bleeding gastroduodenal ulcer that required only medical treatment. Thirteen of the patients in intensive care (representing all four groups) experienced episodes of bradycardia of less than 40 beats min^{-1}. No patient was excluded due to persistent arterial hypotension (MAP < 60 mmHg). Hyperglycemia occurred in 16 out of 35 patients treated with methylprednisolone (46%) as compared to only one out of 30 patients who did not receive methylprednisolone (3%) and this difference was significant (Table 4). These cases of hyperglycemia appeared early necessitating intravenous administration of insulin, but did not last longer than 3 days. Although motor recovery was less complete in the patients who were treated with methylprednisolone and who initially developed hyperglycemia (ASIAml: 56 *versus* 62), the difference was not significant. Overall, these various complications affected neither the duration of stay in the intensive care unit nor that of mechanically assisted ventilation (Table 4).

Eighty patients (76%) underwent surgery within 24 h of the accident (average interval of time, 7.5 ± 4.2 h). Among these patients, 49 (61%) were

operated on within 8 h. The surgical procedures were performed to decompress the spinal cord and stabilize the spine in order to limit the extensiveness of the cord lesions. There was no significant difference in the neurological recovery of the patients who underwent surgery within 8 h (ASIAml = 64) and that of those who either were operated on between 8 and 24 h after the accident or did not undergo surgery (ASIAml = 65). There was no difference in intraoperative bleeding among the four groups, although this value was highest in the patients who received nimodipine. Except for one case of transient arterial hypotension noted in one of the patients who received nimodipine, no intraoperative hemodynamic complication occurred. The isolated case of hypotension developed immediately after induction of anesthesia with propofol. Its treatment by volume resuscitation delayed surgery less than 1 h.

Discussion

The complexity and multiplicity of the pathophysiologic mechanisms involved in the aftermath of a spinal-cord injury, explains to a large degree the diversity of experimental pharmaceutical approaches to this disorder.[11] Nonetheless, three lines of research are currently in the forefront: lipid peroxidation inhibitors, calcium channel blockers, and more recently, antagonists of N-methyl-D-aspartate receptors, which mediate the neurotoxic effects of glutamate. In contrast, there have been few published clinical trials. At present, the only one that has had an impact on the management of spinal-cord injuries is the NASCIS II study.[12,13] Unfortunately, only moderate progress has been made, and it is reasonable to assume that, given the diversity of the pathophysiologic phenomena, use of more than one medication might enhance this progress.

In the present trial, the neurological status of the patients was improved at the 1-year follow-up visit in all four groups. Only patients with a normal state of consciousness were included in the study to avoid potential underestimation of the initial ASIA scores related to patients' inability to cooperate. Consequently, the validity of the observed improvement after 1 year is a reliable finding. In the patients with complete spinal-cord injury, this improvement, when present, involved the level of the lesion and the two adjacent caudal levels to various degrees. The greatest amelioration was noted in the patients who had incomplete cord lesions. In contrast with the findings NASCIS II, there was no difference in the improvement of the patients who received methylprednisolone compared to that of those who received no specific treatment. Similarly, the administration of nimodipine or the methylprednisolone-nimodipine combination had no influence on neurological recovery in comparison with that of the control group. These results must be interpreted with caution since the number of patients in each group may have been insufficient. However, even though the absence of interaction between methylprednisolone and nimodipine enabled us to double the number of patients in the two groups that received one of the two agents (52 patients M+, 48 patients M−, 51 patients N+, and 49 patients N−), no significant difference or tendency was found. The present results obtained with methylprednisolone confirmed those of several recently published clinical trials.[14,18] However, comparison of the latter results and the present findings is not straightforward for two reasons. Since 1991 in the United States the administration of methylprednisolone has become a standard procedure in the management of spinal cord injury, even though the Food and Drug Administration has not yet authorized its use in this indication. Methylprednisolone has not been authorized for marketing in this indication in France either.[11] Consequently, the most recent studies are retrospective. The second obstacle to comparing studies is the absence of consensual terminology in the initial neurological evaluation. The currently recommended scores proposed by the ASIA allow a very precise analysis of spinal cord involvement, but the use of ASIA scores is not yet widespread. Moreover, their determination requires full patient cooperation. Nonetheless, functional recovery of patients treated by corticoids has been reported to be similar to that of patients who did not receive corticoids regardless of the scales or classifications of recovery that were used.

In the present trial, nimodipine was used for the first time in this indication in humans. Ischemia is a final mechanism common to most spinal cord lesions and vascular changes are directly involved in this process. In several experimental models of spinal cord injury, the early administration of nimodipine reduced the drop in spinal cord blood flow in the proximity of the lesion compared to placebo, but the benefit in terms of neurological recovery remains to be demonstrated.[2–6] The current patients showed good hemodynamic tolerance for nimodipine, probably because of the systematic preliminary volume resuscitation. At 1 year, neurological improvement was not significantly different from that of the methylprednisolone group or controls. Maintaining MAP above 60 mmHg may be insufficient. Studies in which the minimum MAP is 70 mmHg, or perhaps even 80 mmHg might be warranted, regardless of the pharmacological approach.

The incidence of infectious complications was higher among patients treated with corticoids (66% *versus* 45%). This tendency has been observed in other studies.[14,18] The action of corticoids on the immune system is well known, but their direct responsibility should be tempered.[21,22] Over the last few years, complex interactions among the immune system, central nervous system and endocrine system have been discovered. Patients with a neurological dysfunction have been shown to have a deficient lymphocyte response and impaired natural killer cytotoxic activity, which would at least partially explain their increased

susceptibility to infection.[23] In the present series the rate of pulmonary disorders was similar in the groups M+ and M−. The neurological level of the cord injury is certainly one of the elements that should be considered among factors predisposing to pulmonary complications. In our series there was no significant difference among the four groups in the level of neurological lesions.

Even more surprising is the absence elsewhere[12,13,24] of metabolic complications, in particular of hyperglycemia in view of the fact that 31% of the present M+ patients had severe, but transient hyperglycemia. The role of hyperglycemia in the exacerbation of ischemic lesions is still the subject of debate.[25,26] In the M+ group neurological recovery was poorer in the patients who had initial hyperglycemia, even though no patient had deterioration at the level of the initial neurological lesion. Consequently, early detection and treatment of this complication is probably warranted. These metabolic and infectious complications affected neither the average duration of stay in intensive care nor that of mechanical ventilation and they should not be considered as an obstacle to the use of a medication if its therapeutic effectiveness is demonstrated.

The usefulness of early surgery remains in the forefront of the treatment of spinal-cord injury. It has been shown experimentally that the persistence of spinal cord compression is correlated with neurological worsening.[27,28] Furthermore, an unstable vertebral lesion presents a risk of secondary displacement. Although there is relative consensus concerning the need for surgery of patients who have spinal injury with incomplete neurological deficit, in complete lesions the type and timing of surgical intervention are unsettled issues.[29–31] In the present study, the neurological improvement of the patients who underwent surgery within 8 h of the spinal cord injury was not significantly different from that of those who had later or no surgical treatment. An insufficient number of patients might explain this result. Given the importance of osteosynthesis in reducing the risks of microtrauma to the nervous tissue, facilitating patient care, and preventing complications of the decubitus position and secondary spinal deformations that hamper rehabilitation, the authors advocate this technique in most cases of complete spinal lesions. Neither the pharmacological approach, nor early surgery influenced functional recovery in the present series. The complete or incomplete nature of the primary spinal-cord lesion was the only factor that was correlated with functional recovery.

Conclusion

In contrast with previous findings in the literature,[12] the present authors found no benefit from the early use of methylprednisolone in spinal-cord injuries. Nimodipine, which was tested for the first time in this indication, was also ineffective. Early decompression with osteosynthesis failed to influence neurological recovery. The only factor correlated with neurological recovery was the complete or incomplete nature of the initial spinal-cord lesion. A precise assessment of motor and sensory deficits such as that proposed by the ASIA, is an essential prerequisite for pharmacological studies of such patients. Methylprednisolone, nimodipine, or both failed to alter the course of spinal-cord injury and their use in this indication should be reconsidered.

References

1 Tator CH, Fehlings MG. Review of the secondary injury theory of acute spinal cord trauma with emphasis on vascular mechanisms. *J Neurosurg* 1991; **75:** 15–26.
2 Guha A, Tator CH, Piper I. Effect of a calcium blocker on posttraumatic spinal cord blood flow. *J Neurosurg* 1987; **66:** 423.
3 Fehlings MG, Tator CH, Linden RD. The effect of nimodipine and dextran on axonal function and blood flow following experimental spinal cord injury. *J Neurosurg* 1989; **71:** 403–416.
4 Guha A, Tator CH, Smith CR, Piper 1. Improvement in posttraumatic spinal-cord blood flow with a combination of a calcium channel blocker and a vasopressor. *J Trauma* 1989; **29:** 1440–1447.
5 Petitjean ME, Pointillart V. Effet de l'administration continue de nimodipine à la phase aiguë d'un traumatisme médullaire chez le babouin. *Ann Fr Anesth Réanim* 1992; **11:** 652–656.
6 Ross IB, Tator CH. Further studies of nimodipine in experimental spinal cord injury in the rat. *J Neurotrauma* 1992; **8:** 229–238.
7 Francee PC *et al*. Limiting ischemic spinal cord injury using a free radical scavenger 21-aminosteroid and/or cerebrospinal fluid drainage. *J Neurosurg* 1993; **79:** 742–751.
8 Geisler FH, Dorsey FC, Coleman WP. Past and current clinical studies with GM-I ganglioside in acute spinal cord injury. *Ann Emerg Med* 1993; **22:** 1041–1047.
9 Haghighi SS, Stiens T, Oro JJ, Madsen R. Evaluation of the calcium channel antagonist nimodipine after experimental spinal cord injury. *Surg Neurol* 1993; **39:** 403–408.
10 Ross IB, Tator CH. Spinal cord blood flow and evoked potential responses after treatment with nimodipine or methylprednisolone in spinal cord-injured rats. *Neurosurgery* 1993; **33:** 470–477.
11 Greene KA, Marciano FF, Sonntag VKH. Pharmacological management of spinal cord injury: current status of drugs designed to augment functional recovery of the injured human spinal cord. *J Spinal Disord* 1996; **9:** 355–365.
12 Bracken MB *et al*. A randomized controlled trial of methylprednisolone or naloxone in the treatment of acute spinal-cord injury. *N Engl J Med* 1990; **322:** 1405–1411.
13 Bracken MB *et al*. Methylprednisolone or naloxone treatment after acute spinal cord injury: One year follow-up data. *J Neurosurg* 1992; **76:** 23–31.
14 Galandiuk S, Raque G, Appel S, Polk HC. The two-edged sword of large-dose steroids for spinal cord trauma. *Ann Surg* 1993; **218:** 419–427.
15 Prendergast MR *et al*. Massive steroids do not reduce the zone of injury after penetrating spinal cord injury. *J Trauma* 1994; **37:** 576–580.
16 George ER *et al*. Failure of methylprednisolone to improve the outcome of spinal cord injuries. *Am Surg* 1995; **61:** 659–664.
17 Gerhart *et al*. Utilization and effectiveness of methylprednisolone in a population-based sample of spinal cord injured persons. *Paraplegia* 1995; **33:** 316–321.
18 Gerndt SJ *et al*. Consequences of high-dose steroid therapy for acute spinal cord injury. *J Trauma* 1997; **42:** 279–284.
19 Ditunno F, Young W, Donovan WH, Greasey G. The international standards booklet for neurological and functional classification of spinal cord injury. *Paraplegia* 1994; **32:** 70–80.

20 Greenspan L, McLellan BA, Greig H. Abbreviated Injury Scale and Injury Severity Score: A scoring chart. *J Trauma* 1985; **25:** 60 – 64.
21 Braun SR, Levin AB, Clark KL. Role of corticosteroids in the development of pneumonia in mechanically ventilated head trauma victims. *Crit Care Med* 1986; **14:** 198 – 201.
22 Williams MD *et al*. Steroid use is associated with pneumonia in pediatric chest trauma. *J Trauma* 1992; **32:** 520 – 525.
23 Campagnolo D *et al*. Alteration of immune system function in tetraplegics: A pilot study. *Am J Phys Med Rehabil* 1994; **73:** 387 – 393.
24 Aubrun F *et al*. Enquête auprès des médecins de Samu sur l'application du protocole de methylprednisolone en traumatologie médullaire. *JEUR* 1996; **9:** 62 – 67.
25 Lam AM, Winn HR, Cullen BF, Sundling N. Hyperglycemia and neurological outcome in patients with head injury. *J Neurosurg* 1991; **75:** 545 – 551.
26 Robertson C *et al*. The effect of glucose administration on carbohydrate metabolism after head injury. *J Neurosurg* 1991; **74:** 43 – 50.
27 Levi L *et al*. Anterior decompression in cervical spine trauma: Does the timing of surgery affect the outcome? *Neurosurgery* 1991; **29:** 216 – 222.
28 Delamarter RB, Sherman J, Carr JB. Pathophysiology of spinal cord injury. Recovery after immediate and delayed decompression. *J Bone Joint Surg* 1995; **77:** 1042 – 1049.
29 Bravo P *et al*. Outcome after vertebral fractures with neurological lesion treated either surgically or conservatively in Spain. *Paraplegia* 1993; **31:** 358 – 366.
30 Kiwerski JE. Neurological outcome from conservative or surgical treatment of cervical spinal cord injured patients. *Paraplegia* 1993; **31:** 192 – 196.
31 Petitjean ME *et al*. Thoracic spinal trauma and associated injuries. Should early spinal decompression be considered? *J Trauma* 1995; **39:** 368 – 372.