



# Haemato- biochemical studies in spinal cord injured dogs treated with a combination of methylprednisolone sodium succinate and 4-aminopyridine or polyethylene glycol<sup>#</sup>

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## Abstract

The current study was conducted to compare the effect of 4-aminopyridine (4-AP) and polyethylene glycol (PEG) on haemato-biochemical parameters in methylprednisolone sodium succinate (MPSS) treated dogs for management of spinal cord injuries (SCI). The study was conducted on 14 dogs of different age, breed, sex and body weight, presented with clinical signs of SCI. Animals were randomly divided into two groups and subjected to two treatment protocols. One group was treated with MPSS and PEG intravenously on first day with oral follow up with prednisolone acetate, while the other group was treated with MPSS and 4-AP intravenously with oral follow up with 4-AP. All the selected dogs were subjected to detailed clinical, neurological, radiographic investigations at regular intervals to assess the effect of treatment upto eight weeks. Haematological and serum biochemical parameters were evaluated on the first day of treatment and then at fortnight intervals. The mean values of all the haematological parameters and serum biochemical parameters were found to be within the normal physiological range and were not significant. However a statistically significant increased serum alkaline phosphatase level was observed in the first group and a non-significant increase in second group throughout the period of study.

**Keywords:** Spinal cord injury, Methyl prednisolone sodium succinate, 4-aminopyridine, polyethylene glycol, neurological examination, haematology, serum biochemistry

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Spinal cord injury (SCI) is damage to the spinal medulla inflicted by a mechanical insult or ischemia (Bruce *et al.*, 2008). Although the annual incidence of SCI is low, this condition is associated with devastating neurological disorders accompanied with high morbidity and mortality in dogs. The most common causes of acute SCI are disc extrusion due to degenerative diseases of intervertebral disc, exogenous trauma and infarction due to ischemia (Sulla *et al.*, 2018). Clinical signs vary depending on the location, size, type and duration of spinal cord affections (Dewey, 2008). The pathophysiology involves a primary insult followed by a cascade of secondary events which can last upto months after the injury. Most of the therapeutic efforts in the medical and veterinary field are focused on reducing the degree of this secondary damage (Eminaga *et al.*, 2011). High dose methyl prednisolone sodium succinate (MPSS) was referred to as the golden standard drug in the treatment of acute spinal cord injury. It was known to produce satisfactory results when given in early stages of injury (Bracken *et al.*, 1997). Polyethylene glycol (PEG) is a hydrophilic polymer, which on intravenous administration, targets damaged membranes and act as a fusogen. The surfactant properties of PEG helps to seal damaged membranes, preventing intracellular leak of ions and subsequent axonal disruption and thus reducing many of the injury cascades (Shi and Borgens, 2000). 4-aminopyridine (4-AP) has been used to block voltage gated potassium channels specifically, restoring conduction to demyelinated axons in addition to improving synaptic transmission and muscle strength (Nashmi and Fehlings, 2001). These pharmacologic effects produced an electrophysiologic and functional improvement in experimental models of SCI and in human and canine patients with chronic SCI and multiple sclerosis (Blight *et al.*, 1989).

The study was conducted on 14 dogs of different age, breed, sex and body weight, presented with clinical signs of SCI to the surgery units of University Veterinary Hospitals at Mannuthy and Kokkalai, Kerala Veterinary and Animal Sciences University.

Preliminary clinical, neurological and radiological examinations were conducted in all

animals. Dogs of both the groups were subjected to a therapy with intravenous methyl prednisolone (MPSS) at the rate of 30 mg/kg body weight on the day of presentation. Animals of Group I were additionally administered intravenously with 30 per cent solution of polyethylene glycol (PEG) (M.W. 4000 Da), at the rate of 4 ml/kg body weight both on the day of presentation and after 48 hours. This was followed by an oral administration of prednisolone at the rate of 1 mg/kg body weight at divided and tapering doses for next 10 days. In Group II, the dogs were treated with 4-aminopyridine solution (4-AP) (0.5 per cent w/v) at the rate of 0.5mg/kg body weight intravenously on the first day of presentation. From the second day onwards, 4-AP at the rate of 1 mg/kg body weight in divided doses was administered orally for 10 days. All dogs were given supportive therapy with mecobalamine 1500 µg daily orally and analgesic gabapentin at the rate of 3 mg/kg body weight for 30 days. All animals were observed for a period of eight weeks for clinical and neurological changes. Haematological and serum biochemical parameters were estimated on the first day and at the 2<sup>nd</sup>, 4<sup>th</sup>, 6<sup>th</sup>, and 8<sup>th</sup> weeks. Venous blood was collected from each animal in EDTA vials for estimating total erythrocyte count ( $10^6/\mu\text{L}$ ), haemoglobin concentration (g/dL), volume of packed red cells (per cent), total leukocyte count ( $10^3/\mu\text{L}$ ) and total platelet count ( $10^3/\mu\text{L}$ ) using automatic haematology analyser. Estimation of erythrocyte sedimentation rate (mm/hr) by Wintrobe method and differential leukocyte count (per cent of individual cells) by manual method using blood smear was also done. Serum was separated and analysed for C-reactive protein (mg/L), creatinine phosphokinase (IU/L), alanine aminotransferase (IU/L), aspartate aminotransferase (IU/L), alkaline phosphatase (IU/L) and lactate dehydrogenase (IU/L) using suitable kits in semi-automatic serum biochemistry analyser. The collected data were compiled and statistically analysed using Student's t-test (SPSS Version 24). Haematological parameters of different animals before and after therapy are presented in Table 1. In all the dogs, the mean total erythrocyte count (TEC), haemoglobin and volume of packed red cells (VPRC) were moderately low on the day of presentation. This

**Table 1.** Observations on haematological evaluation of the animals (Mean  $\pm$  SE)

Parameter	Group	Day 1	Post treatment period				
			2 <sup>nd</sup> wk	4 <sup>th</sup> wk	6 <sup>th</sup> wk	8 <sup>th</sup> wk	
Total erythrocyte count (10 <sup>6</sup> / $\mu$ L)	I	4.88 $\pm$ 0.02 <sup>e</sup>	4.95 $\pm$ 0.03 <sup>d</sup>	5.18 $\pm$ 0.05 <sup>c</sup>	5.56 $\pm$ 0.08 <sup>b</sup>	5.62 $\pm$ 0.07 <sup>a</sup>	
	II	4.83 $\pm$ 0.02 <sup>e</sup>	4.94 $\pm$ 0.03 <sup>d</sup>	5.24 $\pm$ 0.02 <sup>c</sup>	5.46 $\pm$ 0.06 <sup>b</sup>	5.6 $\pm$ 0.05 <sup>a</sup>	
Haemoglobin concentration (g/dL)	I	10.31 $\pm$ 0.76 <sup>b</sup>	10.97 $\pm$ 0.50 <sup>b</sup>	11.44 $\pm$ 0.39 <sup>c</sup>	11.97 $\pm$ 0.34 <sup>b</sup>	12.54 $\pm$ 0.21 <sup>a</sup>	
	II	10.2 $\pm$ 0.63 <sup>b</sup>	11.31 $\pm$ 0.52 <sup>a</sup>	11.69 $\pm$ 0.51 <sup>a</sup>	11.67 $\pm$ 0.27 <sup>a</sup>	11.99 $\pm$ 0.12 <sup>a</sup>	
Volume of packed red cells (%)	I	26.33 $\pm$ 1.48 <sup>a</sup>	30.77 $\pm$ 1.24 <sup>d</sup>	33.66 $\pm$ 0.83 <sup>c</sup>	35.79 $\pm$ 0.35 <sup>b</sup>	37.1 $\pm$ 0.32 <sup>a</sup>	
	II	28.47 $\pm$ 2.01 <sup>c</sup>	33.00 $\pm$ 1.67 <sup>bc</sup>	34.84 $\pm$ 1.08 <sup>ab</sup>	35.84 $\pm$ 0.55 <sup>a</sup>	36.66 $\pm$ 0.40 <sup>a</sup>	
Total leukocyte count (10 <sup>3</sup> / $\mu$ L)	I	15.47 $\pm$ 2.83	14.86 $\pm$ 2.33	13.4 $\pm$ 1.89	13.23 $\pm$ 1.41	12.61 $\pm$ 1.49	
	II	17.86 $\pm$ 3.07	17.07 $\pm$ 2.32	15.13 $\pm$ 1.59	14.37 $\pm$ 1.62	13.7 $\pm$ 1.41	
Erythrocyte sedimentation rate (mm/hr)	I	3.14 $\pm$ 0.34	2.71 $\pm$ 0.18	2.57 $\pm$ 0.2	2.43 $\pm$ 0.3	2.5 $\pm$ 0.19	
	II	3.14 $\pm$ 0.34 <sup>a</sup>	2.71 $\pm$ 0.18 <sup>a</sup>	2.14 $\pm$ 0.14 <sup>b</sup>	2.71 $\pm$ 0.18 <sup>a</sup>	2.29 $\pm$ 0.18 <sup>ab</sup>	
Differential leucocyte count (per cent)	N	I	75.84 $\pm$ 1.84	76.67 $\pm$ 1.64	77.54 $\pm$ 1.7	77.39 $\pm$ 1.52	77.46 $\pm$ 1.63
		II	73.51 $\pm$ 2.21	71.27 $\pm$ 2.86	72.99 $\pm$ 2.28	73.37 $\pm$ 2.2	73.74 $\pm$ 2.05
	L	I	16.66 $\pm$ 1.47	16.14 $\pm$ 1.35	15.83 $\pm$ 1.14	16.09 $\pm$ 1.08	15.93 $\pm$ 1.21
		II	20.56 $\pm$ 2.23	21.33 $\pm$ 2.56	20.44 $\pm$ 2.11	20.01 $\pm$ 2.1	19.81 $\pm$ 2.1
	E	I	2.03 $\pm$ 0.58	1.69 $\pm$ 0.44	1.9 $\pm$ 0.64	1.76 $\pm$ 0.49	1.79 $\pm$ 0.53
		II	0.857 $\pm$ 0.459	0.50 $\pm$ 0.327	0.50 $\pm$ 0.362	0.79 $\pm$ 0.533	0.79 $\pm$ 0.58
	B	I	0.357 $\pm$ 0.18	0.071 $\pm$ 0.07	0.0 $\pm$ 0.00	0.0 $\pm$ 0.00	0.0 $\pm$ 0.00
		II	0.071 $\pm$ 0.07	0.0 $\pm$ 0.00	0.071 $\pm$ 0.07	0.0 $\pm$ 0.00	0.0 $\pm$ 0.00
Total Platelet count (10 <sup>9</sup> / $\mu$ L)	I	322.57 $\pm$ 7.23 <sup>b</sup>	325.57 $\pm$ 6.41 <sup>b</sup>	329.29 $\pm$ 5.45 <sup>a</sup>	332 $\pm$ 5.28 <sup>a</sup>	332.71 $\pm$ 5.10 <sup>a</sup>	
	II	313.14 $\pm$ 6.66 <sup>b</sup>	318.71 $\pm$ 5.64 <sup>a</sup>	321.71 $\pm$ 5.18 <sup>a</sup>	323.86 $\pm$ 6.1 <sup>a</sup>	325.57 $\pm$ 6.96 <sup>a</sup>	

\*\* Significant at 0.01 level; \* Significant at 0.05 level; ns non-significant ( $P > 0.05$ )

Means having different letter as superscript differ significantly

was in consonance with the findings of Hirsch *et al.* (1991) who pointed out that traumatic spinal cord injury was one among the causes of anaemia in human patients. There was no significant difference between the mean values of these parameters between groups but, the difference between observations within groups was statistically significant throughout observation period. A moderately high total leukocyte count was noticed among five dogs of both groups together on the day of presentation, but this subsided after a week, probably due to administration of antibiotics. Mean total leukocyte count in both the groups was within the normal range throughout the period of study. Variations in values within the group and between the groups were not significant statistically. Nithina *et al.* (2012) observed similar findings in a study on canine SCIs treated with methylprednisolone acetate (MPA) and PEG. Mean values of other haematological parameters *viz.*, erythrocyte sedimentation rate (ESR), differential leukocyte count (DLC) and total platelet count (TPC) in animals of both the groups throughout the study remained within the normal range and difference

between groups on different days of observation were not statistically significant. There was significant difference between mean ESR and total platelet count values within Group II and both groups respectively in different days of observation and the variations were within the referral range. Neither SCI nor the type of treatment produced any significant changes in the blood values. This was in accordance with the observations of Chandy (2006), Seena *et al.* (2010) and Sarmiento *et al.* (2014) when high doses of steroids were used for canine paraplegia. But Raskin *et al.* (2004) and Abhijith (2017) reported a possibility of stress leukogram after corticosteroid therapy. According to Carpenter *et al.* (1971) and Nithina (2012), there was no statistically significant change in haematology subsequent to intravenous administration of PEG. Mild thrombocytopenia observed in chronic SCI in one human patient under 4-AP treatment, was resolved within eight weeks after discontinuation of the drug (Grijalva *et al.*, 2003). Hayes (2004) also did not find any significant change in haematology after oral administration of 4-AP in human patients with SCI. According to Witsberger *et al.* (2012),

**Table 2.** Observations on serum biochemical parameters of the animals (Mean  $\pm$  SE)

Parameter	Group	Day 1	Post treatment period			
			2 <sup>nd</sup> wk	4 <sup>th</sup> wk	6 <sup>th</sup> wk	8 <sup>th</sup> wk
Creatinine (mg/dL)	I	1.09 $\pm$ 0.07 <sup>b</sup>	1.16 $\pm$ 0.06 <sup>a</sup>	1.10 $\pm$ 0.04 <sup>ab</sup>	1.05 $\pm$ 0.06 <sup>b</sup>	1.00 $\pm$ 0.05 <sup>c</sup>
	II	1.3 $\pm$ 0.13	1.27 $\pm$ 0.1	1.25 $\pm$ 0.1	1.2 $\pm$ 0.09	1.14 $\pm$ 0.09
C-reactive protein (mg/L)	I	1.62 $\pm$ 0.19 <sup>d</sup>	1.7 $\pm$ 0.19 <sup>c</sup>	1.77 $\pm$ 0.14 <sup>c</sup>	1.83 $\pm$ 0.15 <sup>b</sup>	1.92 $\pm$ 0.15 <sup>a</sup>
	II	1.30 $\pm$ 0.06 <sup>d</sup>	1.44 $\pm$ 0.08 <sup>d</sup>	1.52 $\pm$ 0.08 <sup>c</sup>	1.61 $\pm$ 0.08 <sup>a</sup>	1.67 $\pm$ 0.08 <sup>a</sup>
Creatine phosphokinase (IU/L)	I	77.14 $\pm$ 2.2 <sup>a</sup>	78.26 $\pm$ 1.83 <sup>a</sup>	76.49 $\pm$ 2.37 <sup>a</sup>	75.39 $\pm$ 2.55 <sup>a</sup>	74.53 $\pm$ 2.55 <sup>b</sup>
	II	65.29 $\pm$ 1.52 <sup>a</sup>	64.23 $\pm$ 1.48 <sup>a</sup>	63.71 $\pm$ 1.47 <sup>b</sup>	63.06 $\pm$ 1.50 <sup>c</sup>	62.61 $\pm$ 1.48 <sup>d</sup>
Alanine aminotransferase (IU/L)	I	56.23 $\pm$ 9.46	54.15 $\pm$ 6.4	58.71 $\pm$ 9.66	58.72 $\pm$ 9.17	58.07 $\pm$ 8.85
	II	64.02 $\pm$ 17.63	59.19 $\pm$ 14.34	59.23 $\pm$ 15.06	58.85 $\pm$ 15.37	60.13 $\pm$ 15.57
Aspartate aminotransferase (IU/L)	I	37.1 $\pm$ 2.67	35.51 $\pm$ 6.12	39.06 $\pm$ 2.6	39.39 $\pm$ 2.54	40.22 $\pm$ 2.56
	II	49.39 $\pm$ 9.41	48.16 $\pm$ 7.98	47.24 $\pm$ 6.72	46.69 $\pm$ 6.17	45.84 $\pm$ 5.49
Lactate dehydrogenase (IU/L)	I	194.829 $\pm$ 9.808	198.486 $\pm$ 9.916	200.3 $\pm$ 9.633	200.26 $\pm$ 9.25	199.59 $\pm$ 8.64
	II	185.871 $\pm$ 9.548 <sup>c</sup>	188.243 $\pm$ 9.595 <sup>b</sup>	192.086 $\pm$ 8.565 <sup>a</sup>	194.04 $\pm$ 7.96 <sup>a</sup>	198.37 $\pm$ 6.82 <sup>a</sup>
Alkaline phosphatase (IU/L)	I	161.19 $\pm$ 5.19 <sup>c</sup>	165.21 $\pm$ 3.99 <sup>b</sup>	169.8 $\pm$ 4.83 <sup>b</sup>	175.74 $\pm$ 6.66 <sup>b</sup>	179.14 $\pm$ 7.27 <sup>a</sup>
	II	242.17 $\pm$ 35.76	260.03 $\pm$ 40.37	245.29 $\pm$ 33.05	245.14 $\pm$ 31.69	239.53 $\pm$ 29.36

\*\* Significant at 0.01 level, \*Significant at 0.05 level; ns non-significant ( $P > 0.05$ )

Means having different letter as superscript differ significantly

the cerebrospinal fluid (CSF) biomarkers such as aspartate aminotransferase, creatine phosphokinase (CPK), lactate dehydrogenase (LDH) and myelin basic protein (MBP) were useful as prognostic indicators of acute SCI in dogs. The mean values of serum creatinine were within the normal range throughout the period of study in both the groups. Grijalva *et al.* (2003) also commented that administration of 4-AP in human patients did not cause any significant effect on the renal function. Variations observed between groups were not significant but significant within Group I on different weeks of observation. The mean values of alanine aminotransferase (ALT) and aspartate aminotransferase (AST) were found to be within the normal range in all the dogs in both the groups and variation within the group and between the groups was not statistically significant. Bloom and Freed (1989), reported an elevation in ALT and AST values of patients with acute SCI. A mild to moderate elevation of these enzyme levels were observed in human patients with long term spinal cord injury, under treatment with oral 4-AP, which resolved gradually after discontinuation of the drug (Grijalva *et al.*, 2003). Nagaraja (2007) observed an insignificant variation in the AST values and a physiologically normal ALT value in his study on surgical management of traumatic paraplegia in dogs. A significant increase was observed in the value of alkaline phosphatase (ALP) in

Group I whereas the increase was non-significant in Group II throughout the study period. In the first three weeks of observation there was significant elevation in mean ALP values in Group II over that in Group I. This was in accordance with the observations of Bloom and Freed (1989) in acute SCI patients and Nagaraja (2007) in dogs subjected to surgical management of SCI. Kim *et al.* (1980) and van Kujik *et al.* (2002) reported a significant elevation in the ALP level in patients with neurological heterotopic ossification. A dose and course dependant elevation of ALP was observed in experimental dogs following corticosteroid administration (Ginel *et al.*, 2002). A non-significant increase in ALP value was reported by Chandy (2006), Sharkey *et al.* (2007), Seena (2008) and Abhijith (2017) following steroid administration via different routes in paraplegic dogs. The mean value of C-reactive protein (CRP) remained within the normal range, without any significant changes, in both the groups throughout the study. Gibson *et al.* (2008) reported an elevated CRP value in patients with chronic SCI attributed to the chronic inflammation. CRP, an acute phase protein was considered as a real time marker of inflammation. (Catherine *et al.*, 2011). The mean value of lactate dehydrogenase (LDH) was within normal physiological range in both the groups throughout the study period. The difference in mean values between groups was

not statistically significant but, a significant difference in mean LDH values were observed in Group II and variations observed were limited to normal range. But, Nečas and Sedláková (1999) observed a higher amount of blood LDH and 10 times higher value in CSF in neurologic disease. Grijalva *et al.* (2003) also reported elevated levels of LDH in human SCI patients. The mean value of creatine phosphokinase (CPK) was within the normal range throughout the study in both groups. The variations between the groups were not statistically significant but, significant within both groups. A high CPK level was reported by Aktas *et al.* (1993) in dogs and by Grijalva *et al.* (2003) in human patients affected with spinal cord injury and that was attributed to the muscle damage and prolonged decubitus. On comparison between serum biochemistry of both the groups, no significant difference was found between values in both the groups except serum ALP. Similar findings were observed by Nithina and John Martin (2012) and Abhijith *et al.*, (2017) in methylprednisolone-PEG treated dogs for management of SCI. Carpenter *et al.* (1971) and Olby *et al.* (2009) in two separate studies, also did not observe any significant variation in serum biochemical values of dogs treated with PEG and 4-AP for SCI. The mean value of C-reactive protein (CRP) remained within the normal range, without any significant changes, in both the groups throughout the study. Gibson *et al.* (2008) reported an elevated CRP value in patients with chronic SCI attributed to the chronic inflammation. CRP, an acute phase protein was considered as a real time marker of inflammation. (Catherine *et al.*, 2011). The mean value of lactate dehydrogenase (LDH) was within normal physiological range in both the groups throughout the study period. But, Nečas and Sedláková (1999) observed a higher amount of blood LDH and 10 times higher value in CSF in neurologic disease. Grijalva *et al.* (2003) also reported elevated levels of LDH in human SCI patients. The mean value of creatine phosphokinase (CPK) was within the normal range throughout the study in both groups. The variations within and between the groups were not statistically significant. A high CPK level was reported by Aktas *et al.* (1993) in dogs and by Grijalva *et al.* (2003) in human patients affected with spinal cord injury and that was

attributed to the muscle damage and prolonged decubitus. On comparison between serum biochemistry of both the groups, no significant difference was found between values in both the groups except serum ALP. Similar findings were observed by Nithina and John Martin (2012) and Abhijith *et al.*, (2017) in methylprednisolone-PEG treated dogs for management of SCI. Carpenter *et al.* (1971) and Olby *et al.* (2009) in two separate studies, also did not observe any significant variation in serum biochemical values of dogs treated with PEG and 4-AP for SCI.

### Summary

Spinal cord injuries are common devastating conditions leading to permanent neurological dysfunction in canine patients. With timely intervention, medical management can reduce the severity of the symptoms and improve the quality of life in neurological patients. In the present study, both MPSS – PEG and MPSS- 4 AP combination therapies were found effective for the management of spinal cord injuries in dogs with minimal side effects. Current findings showed that the protocols were found to be safe in canine patients with non-significant variations in the haematological and serum biochemical values.

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### Conflicts of interest

There were no conflicts of interest reported by the authors.

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