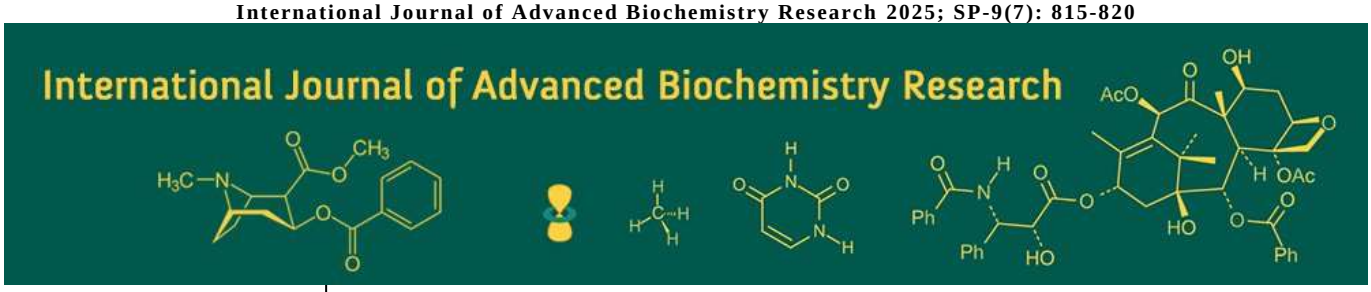

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Effect of darbepoetin-alfa on haemato-biochemical parameters after sciatic nerve crush injury in rats

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Abstract
This study investigates the therapeutic effects of darbepoetin alfa on hematological and biochemical profiles in a rat model of sciatic nerve crush injury. Twenty-four male rats (8-10 weeks old) and 200-250 g weight were randomly assigned to three groups (n=8): sham control, saline control and treatment administered with darbepoetin alfa (5000 IU/kg, intraperitoneal, for 3 days). Blood samples were collected before treatment and on days 3, 7 and 21 to assess hematological and biochemical parameters using automated analyzers. Hematological analysis revealed significantly higher total erythrocyte counts (TEC) and hemoglobin levels in the treatment group on day 3 and 7 (p<0.01) compared to the saline control, with no significant differences by day 21, confirming darbepoetin alfa's hematopoietic effects without inducing polycythemia. No notable changes were observed in total leucocyte count or packed cell volume. Biochemical analysis demonstrated significantly lower levels of aspartate aminotransferase, alanine transaminase, alkaline phosphatase, blood urea nitrogen, serum creatinine, bilirubin, total cholesterol and low-density lipoprotein in the treatment group on days 7 and 21 (p<0.01), alongside elevated albumin, total protein and high-density lipoprotein levels (p<0.01) compared to saline controls. These findings suggest hepatoprotective and nephroprotective effects, including reduced liver and kidney injury, improved hepatocyte function and enhanced protein synthesis. Darbepoetin alfa also improved motor and sensory functions, with no adverse clinical signs despite transient hematocrit elevation. These results, consistent with prior studies, highlight darbepoetin alfa's potential as a safe and effective therapeutic agent for peripheral nerve injury repair, supporting hematopoiesis and hepatorenal function, warranting further exploration for clinical applications.

Keywords: Darbepoetin alfa, sciatic nerve, crush injury, Neuroprotective

1. Introduction
Peripheral nerve injuries, such as sciatic nerve crush, result in significant structural and functional damage (Govindappa *et al.*, 2020) [8]. These injuries often occur due to sudden blunt force from objects like surgical clamps or other crushing mechanisms, without completely severing the nerve (Ding *et al.*, 2018 and Li *et al.*, 2019) [6, 11]. Common causes include motor vehicle accidents or physical assaults. Such injuries disrupt local neural structures and trigger widespread physiological changes, including shifts in blood and biochemical markers. The sciatic nerve crush model in rats is widely used to study the mechanisms of nerve damage and evaluate potential therapies for nerve repair and functional restoration (Caillaud *et al.*, 2019 and Seddighi *et al.*, 2016) [4, 15].
Erythropoietin (EPO) is a glycoprotein hormone primarily produced by kidney peritubular cells in adults, crucial for red blood cell production. It binds to erythropoietin receptors (EPOR) on erythroid progenitor cells in the bone marrow, promoting their survival, proliferation and differentiation (Tsagalis, 2011) [18]. This process increases hematocrit levels by releasing reticulocytes into the bloodstream, where they mature into erythrocytes (Priyadarshi and Shapiro 2006) [14]. Advances in recombinant DNA technology have led to the development of erythropoiesis-stimulating agents (ESAs), such as recombinant human EPO (rhEPO) (Kalantar-Zadeh 2017) [9]. Beyond blood cell production, EPOR is found in non-hematopoietic tissues like the brain, heart and skeletal muscle, indicating EPO's potential in neuroprotection, cardioprotection and tissue repair (Suresh *et al.*, 2020) [17].

The use of EPO in severe peripheral nerve injuries is limited due to risks of blood clotting and cardiovascular issues tied to its hematopoietic effects. Darbepoetin alfa, an EPO-derived molecule, offers a longer half-life, reduced side effects and enhanced biological activity compared to EPO. It supports red blood cell survival, promotes blood vessel formation and encourages the growth of smooth muscle and vascular tissues (Lykissas *et al.*, 2007) [12]. Unlike EPO, darbepoetin alfa requires higher doses for cytoprotection than for hematopoiesis, but its extended half-life makes it a promising candidate for neuroprotection. Research suggests that agents like darbepoetin alfa, which aid nerve regeneration, may reduce motor end plate loss and muscle atrophy. While its use in anemia treatment is well-documented, its potential in musculoskeletal and neuromuscular repair, skin healing, angiogenesis, anti-inflammatory effects, antioxidant properties and myelin sheath formation is underexplored.

The present study aims to investigate the effects of darbepoetin alfa administration on both hematological and biochemical profiles in a rat model of sciatic nerve crush injury. By analyzing these systemic parameters, this research seeks to elucidate the extent to which darbepoetin alfa confers protective effects at the organismal level, thereby contributing to a more comprehensive understanding of its therapeutic utility in peripheral nerve injury contexts.

2. Materials and Methods

2.1 Experimental animals

The study was conducted on a total of 24 healthy eight to ten-week-old male rats, procured form central laboratory animal house, at the department of Veterinary Pharmacology and Toxicology, College of Veterinary Science and A.H. Jabalpur, NDVSU, Jabalpur Madhya Pradesh, India. The experimental animals were maintained as per the institute animal ethical guidelines and all necessary management procedures were adapted to keep the rats free from stress. All the experimental rats were kept under constant observation during the entire period (21 days) of experiment. All the experimental rats were randomly divided into three groups (I: Sham control, II: Saline control, III: Treatment) containing 8 rats in each. Rats from treatment group received darbepoetin alfa at dose rate of 5000 IU/kg body weight for a period of 3 days.

2.2 Sample collection

The 2 ml blood was collected aseptically by retro orbital plexuses with the help of heparinized capillary tube before treatment and on day 3, 7 and 21 in heparinized and non-heparinized sterile test tubes for haematological and biochemical studies following standard procedure described by Archar and Riley (1981) [3] respectively. Serum was separated after centrifugation of clotted whole blood at 3,500 rpm for 20 min. Collected serum and heparinized blood was kept at 4 °C till further analysis (Miraghaee *et al.*, 2011).

2.3 Sample estimation

Total Erythrocyte Count (TEC) (10^6/µl)), Total Leucocyte Count (TLC) ($\times 10^3$/µl), Haemoglobin (Hb) (g/dl) and Packed Cell Volume (PCV) (Per cent) were assessed by using automatic haematology analyzer and Aspartate Aminotransferase (AST) (IU/L), Alanine Transaminase (ALT) (IU/L), Alkaline Phosphatase (ALP) (IU/L), Blood Urea Nitrogen (BUN) (mg/dl), Serum Creatinine (mg/dl), Albumin (g/dl), Bilirubin (mg/dl), Total Protein (g/dl), Total Cholesterol (mg/dl), Low Density Lipoprotein (LDL) (mg/dl) and High Density Lipoprotein (HDL) (mg/dl) were analyzed by using semi-automatic biochemical analyzer .

2.4 Data analysis

The data were analyzed using one way analysis of variance and difference among treatments was compared by Post hoc Duncan's Multiple Range Test (DMRT) following standard statistical design outlined by Snedecor and Cochran (1994) [16].

3. Results and Discussion

Clinical signs such as hunched posture, inactivity, respiratory distress, limb edema, or bleeding were absent and the animals remained active throughout the study. Moreover, they exhibited significant improvements in both motor and sensory functions. These findings suggest that the new darbepoetin-alfa dosing regimen is safe, effective and non-toxic in rats.

The effect of IP administration of darbepoetin-alfa on hematological parameters including Total Erythrocytes Counts (TEC), Total Leucocyte Counts (TLC), haemoglobin and Packed Cell Volume (PCV) have been shown in table 1, 2, 3 and 4.

Haematological parameters were assessed at baseline on day 0 (before treatment) and following darbepoetin alfa administration on day 3, 7 and 21, thereby enabling as comprehensive evaluation of the potential effects of the darbepoetin-alfa dosing regimen in rats. The total erythrocyte counts and haemoglobin level in the rats treated with darbepoetin-alfa on day 3 and 7, were significantly higher ($p<0.01$) than those in the rats treated with normal saline, while on day 21 no significant ($p<0.05$) difference was observed, which is in agreement with the findings of Lee *et al.* (2020) [10]. No change was observed in total leucocyte count and packed cell volume in rats treated with darbepoetin-alfa on day 7 and day 21. The primary function of darbepoetin-alfa is to stimulate the production of red blood cells (RBCs) in the bone marrow (Chateauvieux *et al.*, 2011) [5]. The elevated haemoglobin and total erythrocyte count (TEC) in the rats treated with darbepoetin-alfa confirm its hematopoietic effect. Importantly, no adverse events were observed in the rats despite a transient increase in hematocrit (HCT) levels.

The effect of IP administration of darbepoetin-alfa on biochemical parameters including, Aspartate Aminotransferase (AST) (IU/L), Alanine Transaminase (ALT) (IU/L), Alkaline Phosphatase (ALP) (IU/L), Blood Urea Nitrogen (BUN) (mg/dl), Serum Creatinine (mg/dl), Albumin (g/dl), Bilirubin (mg/dl), Total Protein (g/dl), Total Cholesterol (mg/dl), Low Density Lipoprotein (LDL) (mg/dl) and High Density Lipoprotein (HDL) (mg/dl) have been shown in table 05, 06, 07, 08, 09, 10, 11, 12, 13, 14 and 15.

Biochemical parameters were assessed at baseline on day 0 (before treatment) in sham control, saline control as well as in darbepoetin-alfa treated group. The aspartate aminotransferase, alanine transaminase, alkaline phosphatase, blood urea nitrogen, serum creatinine, bilirubin, total cholesterol and low-density lipoprotein level in the rats treated with darbepoetin-alfa on day 7 and 21,

were significantly lower (p<0.01) as compared to rats from control group, while albumin, total protein and high density lipoprotein level in the rats treated with darbepoetin-alfa on day 7 and 21, were significantly higher (p<0.01) as compared to rats from saline control group. The results of present study are in close agreement with the findings of Alaasam and Janabi (2023) [2]; Abiodun (2023) [1] and Golshani *et al.* (2019) [7]. The significantly decreased level of aspartate aminotransferase, alanine transaminase, alkaline phosphatase, blood urea nitrogen, serum creatinine, bilirubin, total cholesterol and low-density lipoprotein are suggestive of hepatoprotective effect, reduced mitochondrial injury in liver cells, improvement in bile flow and hepatobiliary integrity, improved bilirubin clearance and hepatocyte function as well as increased level of albumin and total protein indicated improved protein synthesis by hepatocytes and supports restored liver synthetic function.

Table 1: Effect of darbepoetin-alfa on Total Erythrocyte Count (10^6/µl) in rats (n=8)

Group		Day			
		0	3	7	21
G-I	Sham control	06.31±0.11	06.22^{a}±0.10	05.90^{a}±0.14	06.05±0.12
G-II	Saline control	06.17±0.13	05.82^{a}±0.16	06.04^{a}±0.15	05.82±0.13
G-III	Treatment	06.11±0.14	07.31^{b}**±0.15	07.46^{b}**±0.16	06.02±0.11

Values indicate Mean ± S.E. Mean values in the same column bearing different superscripts differ significantly (p≤0.05)

Table 2: Effect of darbepoetin-alfa on Total Leucocyte Count (10^3/µl) in rats (n=8)

Group		Day			
		0	3	7	21
G-I	Sham control	04.46±0.09	03.98±0.16	03.86±0.13	03.86±0.13
G-II	Saline control	04.39±0.10	04.01±0.10	03.95±0.11	03.79±0.13
G-III	Treatment	04.22±0.14	03.87±0.12	03.96±0.12	03.85±0.12

Values indicate Mean ± S.E.

Table 3: Effect of darbepoetin-alfa on Haemoglobin level (g/dl) in rats (n=8)

Group		Day			
		0	3	7	21
G-I	Sham control	14.63±0.24	14.45a±0.17	14.06a±0.17	14.22±0.17
G-II	Saline control	14.11±0.15	14.15a±0.15	14.04a±0.21	14.04±0.17
G-III	Treatment	14.29±0.14	15.10b*±0.16	15.40b**±0.20	14.50±0.20

Values indicate Mean ± S.E. Mean values in the same column bearing different superscripts differ significantly (p≤0.05)

Table 4: Effect of darbepoetin-alfa on Packed Cell Volume (per cent) in rats (n=8)

Group		Day			
		0	3	7	21
G-I	Sham control	43.79±0.77	43.27±0.60	41.14±0.53	41.72±0.77
G-II	Saline control	42.25±0.45	42.10±0.56	41.30±0.65	36.89±4.71
G-III	Treatment	42.93±0.58	44.80±0.38	41.55±3.78	43.30±0.50

Values indicate Mean ± S.E.

Table 5: Effect of darbepoetin-alfa on Aspartate Aminotransferase (AST) (IU/L) in rats (n=8)

Group		Day		
		0	7	21
G-I	Sham control	093.88±07.24	099.50^{b}±08.14	107.85^{b}±05.28
G-II	Saline control	099.69±08.16	125.87*^{c}±04.73	130.19^{c}**±02.97
G-III	Treatment	100.35±06.08	055.04^{a}**±01.55	049.96^{a}**±00.36

Values indicate Mean ± S.E., *-Significant (p<0.05), **-Highly significant at (p<0.01) and (p<0.001). Mean values in the same column bearing different superscripts differ significantly (p≤0.05)

Table 6: Effect of darbepoetin-alfa on Alanine Transaminase (ALT) (IU/L) in rats (n=8)

Group		Day		
		0	7	21
G-I	Sham control	70.28±03.24	59.18^{b}±4.66	62.55^{b}**±04.06
G-II	Saline control	75.85±01.99	78.82^{c}**±1.15	81.06^{c}±00.95
G-III	Treatment	73.06±02.39	36.47^{a}**±1.60	33.60^{a}**±01.61

Values indicate Mean ± S.E., *-Significant (p<0.05), **-Highly significant at (p<0.01) and (p<0.001). Mean values in the same column bearing different superscripts differ significantly (p≤0.05)

Table 7: Effect of darbepoetin-alfa on Alkaline Phosphatase (ALP) (IU/L) in rats (n=8)

Group		Day		
		0	7	21
G-I	Sham control	94.46±09.73	189.12^{b}±20.10	189.45^{b}**±17.45
G-II	Saline control	97.65±09.71	235.71^{c}*±11.05	257.48^{c}±08.46
G-III	Treatment	76.44±11.61	95.43^{a}**±01.47	81.33^{a}**±01.42

Values indicate Mean ± S.E., *-Significant (p<0.05), **-Highly significant at (p<0.01) and (p<0.001). Mean values in the same column bearing different superscripts differ significantly (p≤0.05)

Table 8: Effect of darbepoetin-alfa on Blood Urea Nitrogen (BUN) (mg/dl) in rats (n=8)

Group		Day		
		0	7	21
G-I	Sham control	16.47±00.54	17.73^{b}±00.94	18.84^{b}±1.26
G-II	Saline control	15.97±00.38	16.87^{b}±00.44	22.80^{c}±00.85
G-III	Treatment	15.30±01.15	10.71^{a}**±00.52	11.00^{a}**±00.40

Values indicate Mean ± S.E., *-Significant (p<0.05), **-Highly significant at (p<0.01) and (p<0.001). Mean values in the same column bearing different superscripts differ significantly (p≤0.05)

Table 9: Effect of darbepoetin-alfa on Serum Creatinine (mg/dl) in rats (n=8)

Group		Day		
		0	7	21
G-I	Sham control	00.31±00.02	00.37^{b}±00.03	00.38^{b}±00.03
G-II	Saline control	00.33±00.03	00.30^{b}±00.02	00.45^{b}±00.01
G-III	Treatment	00.27±00.01	00.18^{a}**±00.01	00.14^{a}**±00.01

Values indicate Mean ± S.E., *-Significant (p<0.05), **-Highly significant at (p<0.01) and (p<0.001). Mean values in the same column bearing different superscripts differ significantly (p≤0.05)

Table 10: Effect of darbepoetin-alfa on Albumin (g/dl) in rats (n=8)

Group		Day		
		0	7	21
G-I	Sham control	04.15±00.15	03.61^{a}±00.16	04.20^{b}±00.14
G-II	Saline control	03.88±00.30	03.86^{a}±00.09	03.36^{a}*±00.26
G-III	Treatment	04.29±00.35	05.24^{b}**±00.09	05.55^{c}**±00.19

Values indicate Mean ± S.E., *-Significant (p<0.05), **-Highly significant at (p<0.01) and (p<0.001). Mean values in the same column bearing different superscripts differ significantly (p≤0.05)

Table 11: Effect of darbepoetin-alfa on Bilirubin (mg/dl) in rats (n=8)

Group		Day		
		0	7	21
G-I	Sham control	00.25±00.02	00.21^{b}±.02	00.27^{b}**±00.03
G-II	Saline control	00.22±00.02	00.19^{b}±00.01	00.58^{c}±00.01
G-III	Treatment	00.22±00.02	00.10^{a}**±00.006	00.14^{a}**±.01

Values indicate Mean ± S.E., *-Significant (p<0.05), **-Highly significant at (p<0.01) and (p<0.001). Mean values in the same column bearing different superscripts differ significantly (p≤0.05)

Table 12: Effect of darbepoetin-alfa on Total protein (g/dl) in rats (n=8)

Group		Day		
		0	7	21
G-I	Sham control	05.47±00.43	05.40^{a}±00.40	07.06^{b}±00.26
G-II	Saline control	05.47±00.43	05.47^{a}±00.43	03.66^{a}**±00.21
G-III	Treatment	06.14±00.42	06.14^{b}*±00.42	07.38^{b}±00.26

Values indicate Mean ± S.E., *-Significant (p<0.05), **-Highly significant at (p<0.01) and (p<0.001). Mean values in the same column bearing different superscripts differ significantly (p≤0.05)

Table 13: Effect of darbepoetin-alfa on Total Cholesterol (mg/dl) in rats (n=8)

Group		Day		
		0	7	21
G-I	Sham control	65.06±07.07	65.06^{b}±07.07	64.34^{b}**±6.20
G-II	Saline control	81.05±11.39	81.05^{c}**±11.39	121.22^{c}±01.23
G-III	Treatment	87.03±09.91	87.03^{a}**±09.91	39.01^{a}**±00.95

Values indicate Mean ± S.E., *-Significant (p<0.05), **-Highly significant at (p<0.01) and (p<0.001). Mean values in the same column bearing different superscripts differ significantly (p≤0.05)

Table 14: Effect of darbepoetin-alfa on Low Density Lipoprotein (LDL) (mg/dl) in rats (n=8)

Group		Day		
		0	7	21
G-I	Sham control	30.62±04.37	30.62^{b}±04.37	23.10^{b}**±02.07
G-II	Saline control	29.22±04.91	29.22^{c}**±04.91	48.52^{c}±2.51
G-III	Treatment	20.85±02.07	20.85^{a}±02.07	12.62^{a}**±00.64

Values indicate Mean ± S.E., *-Significant (p<0.05), **-Highly significant at (p<0.01) and (p<0.001). Mean values in the same column bearing different superscripts differ significantly (p≤0.05)

Table 15: Effect of darbepoetin-alfa on High Density Lipoprotein (HDL) (mg/dl) in rats (n=8)

Group		Day		
		0	7	21
G-I	Sham control	78.46±02.58	78.46^{a}±02.58	59.30^{b}**±02.34
G-II	Saline control	81.83±02.06	81.83^{a}±02.06	43.09^{a}±02.47
G-III	Treatment	80.26±02.74	80.26^{b}**±02.74	81.77^{c}**±01.06

Values indicate Mean ± S.E., *-Significant (p<0.05), **-Highly significant at (p<0.01) and (p<0.001). Mean values in the same column bearing different superscripts differ significantly (p≤0.05)

4. Conclusion

The darbepoetin-alfa treatment protocol in rats proved safe, efficacious and non-toxic, markedly elevating red blood cell counts and hemoglobin concentrations on days 3 and 7 without adverse effects despite a temporary rise in hematocrit. Additionally, it enhanced motor and sensory capabilities, decreased biomarkers of hepatic and renal injury and promoted liver and kidney. These results, aligning with previous research, underscore its potential for therapeutic use in supporting hematopoiesis and hepatorenal function.

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