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PATHO-PHYSIOLOGY OF ENDOTOXEMIC BUFFALO CALVES BEFORE AND AFTER I/V INFUSION OF HYPERTONIC SALINE, DEXTRAN-40 AND FLUNIXIN MEGLUMINE

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ABSTRACT

Five apparently healthy male buffalo calves aged between 6 months to one year with body weight range of 70-140Kg were used in the present investigation. Endotoxic shock was produced by i.v. infusion of Escherichia coli endotoxin @5µg/kg BW/hr for 3 hours and were further observed up to day four. Endotoxin infusion to the animals caused restlessness, respiratory distress, snoring, diarrhoea, profuse salivation along with the significant hypoproteinemia, hypoalbuminemia, hypokalemia and decrease in globulins. The treatment with HSS, flunixin meglumine and dextran – 40 to the affected calves significantly raised the circulating glucose level at 4.5 hr and fibrinogen at 6.5 hr and at day 2 of observation. A significant hypoproteinemia, hypoalbuminemia, hypokalemia, hypocalcaemia, hypophosphatemia, hyponatremia and decrease in globulin was found before and afters treatment. The plasma phosphorus and sodium showed a general non-significant change during endotoxin infusion but after treatment at 5.5 hr, plasma phosphorus and sodium level showed a significant decrease Four out of five endootoxemic buffalo calves died between day 3 to 4 of the observation period. The necropsy was performed on all dead animals. The gross lesions included haemorrhages, congestion and emphysema in lungs, haemorrhages in intestines, gall bladder and reddish discolouration of kidneys, Epicardial and sub-endocardial haemorrhages and mild catarrhal enteritis. Histopatholgically, the common findings in all the animals were congestion, haemorrhages, emphysema, mild interstitial pneumonia, sloughing of bronchiolar mucosa and hyaline membrane formation in the alveoli of lungs. Over all the lungs appeared to be like 'shock lung'. Necrotic enteritis with mononuclear cell infilteration, congestion and lower nephron nephrosis in kidneys mild sinusoidal congestion and hepatocellular necrosis in liver were also found.. Wide spread gross and microscopic damage in most of the organs, particularly in lungs and heart indicated vascular collapse and hypoxia associated with endotoxemia resulting in the death of buffalo calves. Endotoxemia is a very common manifestation of gram negative sepsis and its treatment is elusive, therefore, this study assumes significance.

INTRODUCTION

The pathogenesis of sepsis and endotoxemia involves a myriad of complex alterations (Green and Adams 1992). Endotoxins cause endothelial injury directly or indirectly, and thereby expose subendothelial collagen and tissue thromboplastin, initiating the intrinsic and extrinsic coagulation cascades, respectively (Morris1991). Endotoxemia, a potentially severe complication of several diseases of cattle, including enteric disease, septicemia, metritis, mastitis and pneumonia. It causes a variety of adverse effects such as cardiovascular compromise, lactic acidosis, leucopenia, glucose dyshomeostaisis, hemostatic alterations and gastrointestinal, respiratory and renal disturbances. These complications of endotoxemia may result in considerable animal mortality or morbidity nd thereby economic loss to the farmers (Semrad 1993). The treatment of endotoxemia is difficult because of the numerous mediators involved in the body's response to endotoxin. The three possible approaches in treating endotoxemia include increasing target cell tolerance, decreasing plasma endotoxin concentrations and interfering with endotoxin binding (Hardie and Krusse-Elliott 2008). However, in vivo experimental studies on induction of endotoxemia and its treatment response in buffalo calves are sparse. Therefore, the present investigation was planned at studying patho-physiological changes during induced endotoxemia in buffalo calves and to study the effect of i/v infusion of hypertonic saline solution, Dextran-40 and Flunixin meglumine subsequently.

MATERIAL AND METHODS

Five apparently healthy male buffalo calves of 6 months to one year with body weight of 70-140 Kg procured from local market were used in the present investigation. These calves were kept under the good managemental conditions and nourishment. All the animals were dewormed and vaccinated against endemic diseases sbefore the start of experiment. The

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Endotoxin[1] was reconstituted by dissolving it in normal saline solution (0.9% NaCl acq.) to make a stock solution of 1mg/ml. Endotoxin concentration of 5µg/ml was prepared by dissolving 1 ml of stock solution in 199 ml of normal saline to make total volume 200ml. The animals were casted in right lateral recumbency on operation table. Before endotoxin infusion, an area over jugular furrow was shaved and disinfected with savlon. The local anesthetic Lignocaine (2%) @ 90-120 ml was injected subcutaneously and intra-muscularly before catheterization of the jugular vein and carotid artery to alleviate pain. The skin was incised to expose and catheterize carotid artery and jugular vein. In all the animals, the endotoxin was infused intravenously through jugular vein @ 5µg/kg BW/hr for 3hours, followed by the subsequent treatment and these animals were observed further for 3 hours to study the physio-pathological changes. The blood samples from the jugular vein of buffalo calves were collected immediately before and after 1.5, 2.5, 3.5, 4.5, 5.5, 6.5 hrs of start of endotoxin infusion, followed by samples at 24 hr interval of the last sample of day 1 upto 4th day. Heparin was used as an anticoagulant for collection of various samples. Following intravenous administration of endotoxin for 3 hrs these animals were subjected immediately to infusion of HSS @ 4 ml / Kg body weight, Dextran-40 @ 10 ml / Kg body weight, & Flunixin Meglumine @ 1.1mg / Kg Body weight as one time infusion. All the animals were given rapid intravenous infusion of Hypertonic Saline Solution **(HSS)** @ 4ml/kg body weight and HSS was adminstered within 6 minutes after completion of endotoxin infusion. The HSS was prepared by dissolving the 72 gm of sodium chloride in one liter of double distilled water (7.2% Nacl aqueous solution). The HSS was autoclaved at a pressure of 15 lbs for 20 minutes 16-18 hrs prior to infusion.

The physiological parameters estimated were plasma Total Protein, Albumin, Fibrinogen, Total Globulins, Alkaline phosphatase, Creatinine, Glucose, Sodium, Potassium, Calcium and Phosphorus. All the above mentioned parameters were determined by Dry stat clinical dry chemistry analyser[2]. Plasma Fibrinogen was estimated using a portable refractometer by comparing the protein in non-heated plasma and that in the same sample heated to 56° to 58° Celsius for 3 minutes. (Thomas 2000). The data so generated was pooled & analysed with CRD Anova (Snedecor and Cochran, 1976). All the values obtained were compared with the normal pre-infusion values.

All the experimental animals that died during observation period were subjected to necropsy examination in order to study the pathological changes. For histopathology 1-2 cm thick tissue slices from heart, lung, kidney, liver, gall bladder, intestines and brain were collected in 10% neutral buffered formalin. After fixation in 10% formalin for 48 hours, the tissues were thoroughly washed in running water; dehydrated in ascending grades of alcohol and acetone; cleared in benzene and embedded in paraffin at 58° Celsius. The paraffin embedded tissues were sectioned at five microns thickness and stained by haematoxylin and eosin (H&E) method (Lillie 1965). Slides were examined under bright field using BX-53 Olympus microscope[2].

RESULTS AND DISCUSSION

Clinical signs observed due to endotoxemia consisted of restlessness, respiratory distress, forceful abdominal respiration, diarrhoea and profuse salivation and death. Only one endotoxemic buffalo calf survived beyond the observation period. The normal mean total protein ranged between 6.22±0.08g/dl (Table-1) which is close to 6.40 ±0.19 g/dl (Singh *et al* 2004) and lower than 7.54 ± 0.25 g/dl (Kumar 1989).A significant (P< 0.05) hypoproteinemia was observed during endotoxin infusion in all buffalo calves. Nagaraja *et al* (1979) observed hypoproteinemia on *E.coli* endotoxin infusion in cow calves. Singh *et al* (1997) also reported a slight decrease in plasma protein in endotoxemic calves. The hypoproteinemia as observed in present investigation was perhaps due to increased protein break down and ability of carbon skeleton of amino acids to enter kreb cycle. Additionally, the decreased ability of anoxic liver to metabolize amino acid to synthesize proteins may also partially contribute to hypoproteinemia (Singh *et al* 2004).

A significant (P< 0.05) hypoproteinemia was found even after treatment i.e., at 4.5, 5.5 and 6.5 hr. Hypoproteinemia after treatment can be attributed to the rapid plasma volume expansion and redistribution of cardiac output towards splanchnic region, following hypertonic saline solution infusion (Constable *et al* 1991a). The HSS acutely increases the plasma osmolarity and draws intracellular and interstitial water into the vascular space. A volume expansion of 3ml for every 1ml of hypertonic saline infused has been reported by Jean *et al* (1993). The normal plasma albumin was 2.54±0.10g/dl (table-1) which is lower that 3.29 ± 0.13 g/dl as reported by Kaneko *et al* (1997) and 3.20 ± 0.19 g/dl (Ghuman and Singh 2009a). A significant (P< 0.05) hypoalbuminemia was observed throughout endotoxin infusion in all the animals. Hypoalbuminemia persisted even after treatment throughout till day 2 of observation. Singh *et al* (2004) also observed significant (P< 0.05) hypoalbuminemia in buffalo calves after *E.coli* endotoxin administration.

The fall in albumin can be attributed to loss of blood and plasma, gastrointestinal diseases, diarrhoea besides other cases (Kaneko *et al* 1997). Albumin decrease may also be due to exudation of fluid into peripheral tissues as evidenced by edema in various organs. The normal mean plasma fibrinogen was found to be 0.24±0.04g/dl which is lower than 0.30 to 0.8gm/dl (Thomson 2000) and 0.35 to 0.60 g/dl (Deldar *et al* 1984).Non-significant alteration in fibrinogen was found in all groups of endotoxemic buffalo calves during endotoxin infusion. After i.v. infusion of HSS, Dextran-40 and Flunixin meglumine, a significant (P< 0.05) increase in fibrinogen level at 6.5 hr and day 2 in endotoxemic buffalo calves was observed. (Table-1) This increase may be due to the fact that endotoxin accelerates fibrinogen synthesis rate (Wycoff 1970) and fibrinogen is an acute phase protein released in response to tissue injury and inflammation. Thus increase in fibrinogen may be acute phase inflammatory responses. The normal mean plasma globulins were found to be 3.56±0.21g/dl which are closer to 3.90 ±0.39 g/dl (Singh 2000) but higher than 3.24 ± 0.24 g/dl as reported by Kaneko *et al* (1997), 2.34 ±0.25 g/dl (Ghuman and Singh 2009a) and 2.79 ± 0.13 g/dl(Ghuman and Singh 2009b). A significant (P<0.05) fall in plasma globulins was observed during endotoxin infusion at 3.5 hr i.e., at the

[1] *Escherichia coli* endotoxin Lyophilized (Phenol extracted) 0111:B4 lipopolysacharide, SIGMA Chemicals U.S.A.

1. Dry stat clinical dry chemistry analyser, Johnson &Johnson, U.S.A.

2.Olympus Microscope, Model No. BX61, Japan

end of endotoxin infusion. After administration of treatment, a significant (P< 0.05) fall in globulins at 4.5hr, 5.5hr and day 2 of observation was found, which may be due to the increased protein breakdown or sequestration of globulins in tissues from plasma. The normal mean circulating glucose was found to be 74.80±6.82 mg/dl, which is closer to 67.50 ± 1.74 to 81.74 ± 6.98 mg/dl (Singh 2000) and slightly lower than 75.30 ±0.97 to 89.74 ± 6.98 mg/dl as reported by Singh *et al* (2004). In the present study, the plasma glucose level showed non-significant alteration in all animals during i.v. infusion of endotoxin. However, after treatment, a significant (P< 0.05) hyperglycemia at 4.5 hr was observed in all endotoxemic buffalo calves, suggesting probable beneficial effects of Dextran-40 which gets converted into glucose through metabolism in the liver. Hyperglycemia may also be due to release of epinephrine due to the stress and glycogenolysis.

The normal mean plasma creatinine level was found to be 0.96±0.02mg /dl, which is within the physiological range of 1-2 mg/dl (Kaneko *et al* 1997) and close to 1.10 ± 0.10 to 1.30 ± 0.10 mg/dl (Constable *et al* 1991a) but lower than 1.20 ± 0.20 to 2.38 ± 0.40 mg/dl reported by Singh (2000). No significant variation in plasma creatinine was observed during and after the intravenous infusion of the endotoxin and the treatment given thereafter.

The normal mean plasma sodium was found to be 135.20±1.83mmol/l which is similar to 136.6 ± 5.51 mmol/l (Ghuman and Singh 2009a), 134.48 ± 4.07 mmol/l (Kumar 1989) and 133.40 ± 3.19 mmol/l (Singh *et al* 2007). Non-significant change in sodium was found during and after endotoxin infusion and after treatment except that a significant (P< 0.05) hyponatremia at 5.5 hrs. In the present study, the significant hyponatremia is most likely due to the infusion of HSS, which causes the rapid expansion in plasma volume and redistribution of the cardiac output towards the splanchanic circulation in calves given *E. coli* endotoxin (Constable *et al* 1991a). The mean sodium levels at the end of the observation period was almost equal to pre infusion level. Absence of any significant increase in plasma sodium even after infusion of HSS is an advantage as it does not cause hypernatremia, which makes the infusion of HSS very safe (Singh *et al* 2007).

The normal mean plasma potassium was found to be 3.50 ±0.19mmol/l .which is similar to 3.60 ± 0.2 mmol/l (Celly and Prasad 1987) but higher than 2.28 ± 0.18 mmol/l (Kumar 1989). A significant (P< 0.05) hypokalemia was observed at 1.5 and 2.5 hr of endotoxin infusion, which continued even after treatment at 4.5, 5.5 and 6.5 hours. The fall in potassium level may be a part of the mechanism whereby endotoxins promote the release of endogenous pyrogens from leucocytes, since experiments have shown this process is inhibited by physiological concentration of this element. Decrease in potassium level could be attributed to release of histamine during endotoxic shock, increasing the capillary permeability leading to reduction in the potassium level (Singh *et al* 1994). Hypokalemia after treatment can be attributed to rapid volume expansion following HSS infusion (Constable *et al* 1991a). Decrease in circulating levels of sodium and potassium in whole blood can also be attributed to the greatly diminished active transport of sodium and potassium through the cell membrane. As a result, sodium and chloride accumulate in the cell. (Singh *et al* 1994).

The normal mean plasma calcium was found to be 8.70±0.50mg/dl, which is within the physiological range of 8.7-11.4 mg/dl as reported in cows by Kaneko *et al* (1997). In the present study, a significant (P<0.05) hypocalcaemia was observed throughout period of observation. The normal mean plasma phosphorus was found to be 6.54±0.27mg/dl, which is close to physiological value of 5.6-6.5 mg/dl in cattle serum (Radostits *et al* 2000). In present study, the plasma phosphorus showed a general non-significant change during endotoxin infusion, but after treatment at 5.5 hr, plasma phosphorus level showed a significant decrease. However, Allen *et al* (1970) observed a significant decrease in serum phosphorus at six to 10 hours following intravenous administration of *E.coli* endotoxin O111:B4 in cattle. Decrease in plasma Sodium, Potassium, Calcium and Phosphorus may be due to loss of electrolytes through body fluids and /or haemodilution as a consequence of i.v. fluid infusion.

The normal mean plasma Alkaline phosphatase was observed to be 63.40 ±18.62 U/l, which is lower than 173 ± 40 U/l as reported by Constable *et al* (1991a). In the present study, plasma samples showed non- significant variation in plasma Alkaline phosphatase throughout the period of observation.

The gross lesions in the dead buffalo calves were Epicardial and sub-endocardial haemorrhages in three endotoxemic buffalo calves (Fig.1) and mild catarrhal enteritis in two animals were also recorded. Epicardial and sub-endocardial haemorrhages were previously reported by Singh *et al* (1996) and Nagaraja (1979) in endotoxemic calves, which were suggestive of either hypoxia or septicaemia or toxaemia or massive respiratory distress. Mild to clear cut haemorrhages along with congestion and emphysema in lungs in two endotoxemic buffalo calves, besides haemorrhages in intestines, gall bladder and reddish discolouration of kidneys (Figs.3,5 & 7).

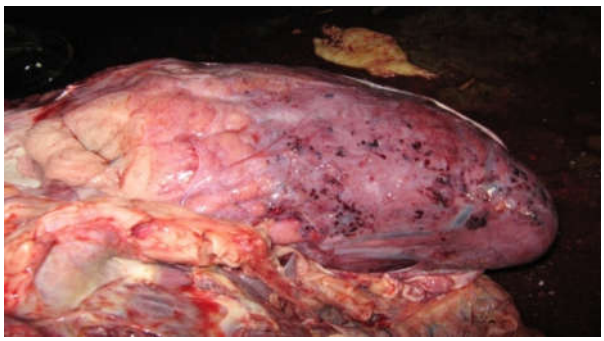

Fig 1 Heart - Epicardial haemorrhages

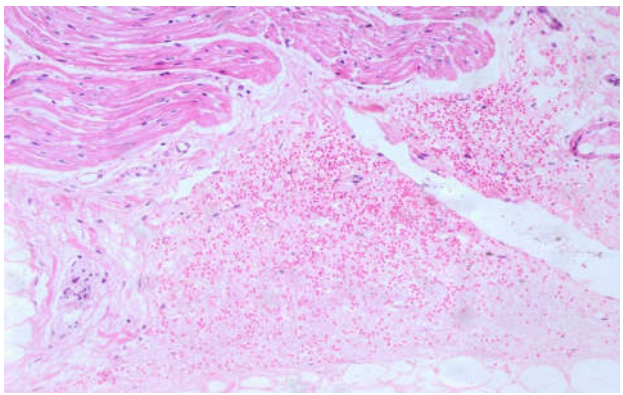

Fig 2 Heart histopathology-Epicardial haemorrhages (H.E.X150).

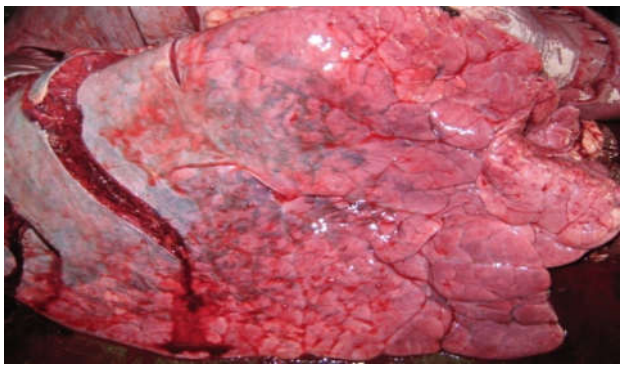

Fig 3 Lung -Haemorrhages and Emphysema

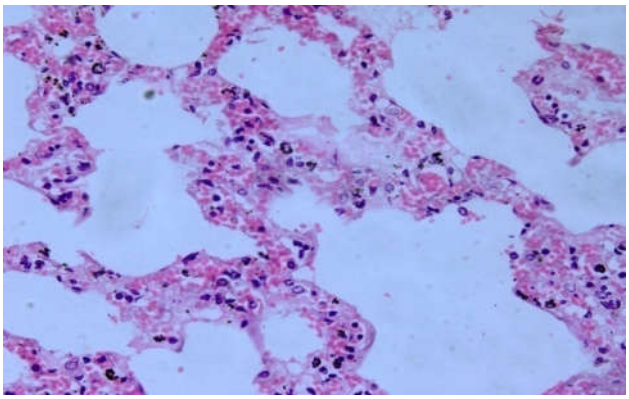

Fig 4 Lung histopathology-Congestion, edema and hyaline membrane formation, the so called 'shock lung' (H. E.X300).

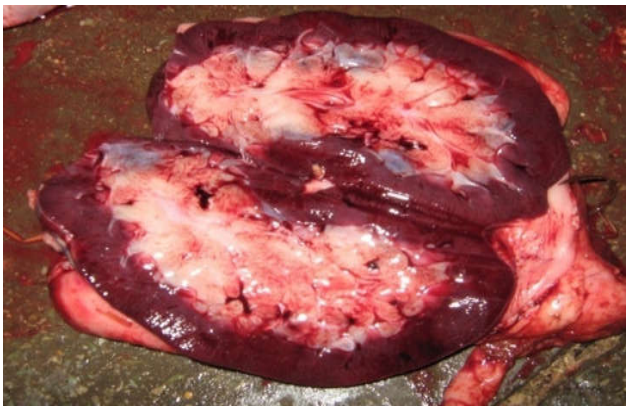

Fig 5 Kidney – Marked congestion in cortex

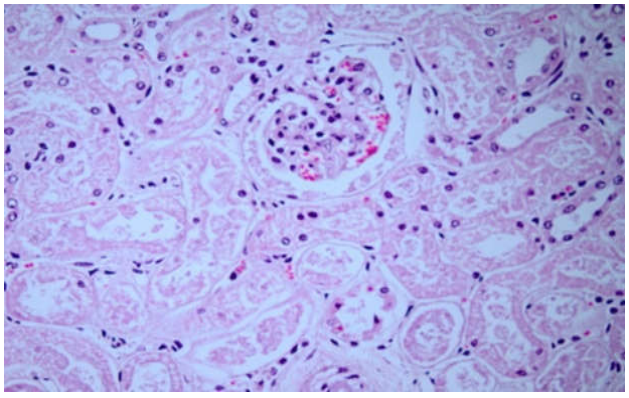

Fig 6 Kidney histopathology-Marked diffuse degeneration and necrosis of tubular epithelium (lower nephron nephrosis) along with congestion in a glomerulus (H. E.X300).

Fig 7 Intestines - Serosal congestion, oedema and dilatation due to fluid exudation

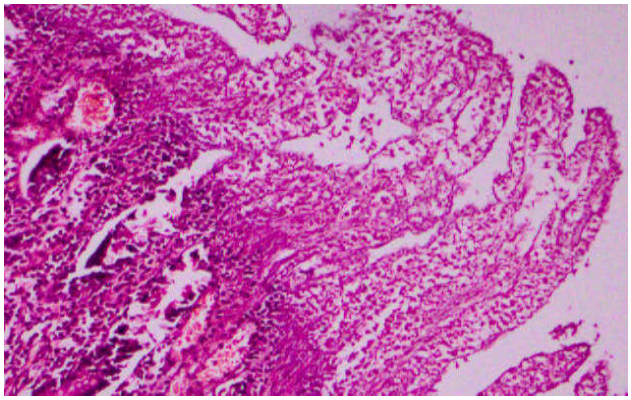

Fig 8 Intestine histopathology- Ischemic superficial necrosis of villi (H. E.X150).

The major histopathological changes were noticed in lungs, kidneys, heart, liver and intestines. Histopatholgically, the common findings in all the animals were generalized congestion, haemorrhages, besides emphysema in lungs (Fig.5), necrotic enteritis due to ischemia (Figs.8,) with mononuclear cell infiltration, lower nephron nephrosis in kidneys (Fig.6), mild sinusoidal congestion and hepatocellular necrosis in liver. The changes were more prominent in lungs. More prominent bronchio-interstitial changes in lungs included mild interstitial thickening, sloughing of bronchiolar mucosa, haemorrhages, congestion and marked emphysema (Figs.3). In some bronchioles, bacterial colonies surrounded by neutrophils were also observed. Apart from these changes, hyaline membrane formation was also noticed in the alveoli in two endotoxemic buffalo calves. Over the lungs appeared to be like 'shock lungs' in affected cases. (Fig.4) Epicardial, sub-endocardial and myocardial haemorrhages noticed grossly were also prominent histopathologically (Fig.-2). In one animal, there was degeneration and necrosis of cells of the zona fasciculata of adrenal glands possibly related to stress, hyper production of corticosteroids and thereby exhaustion of cells in this zone. Nagaraja (1979) also observed small haemorrhages in the zona fasciculata of adrenal glands of endotoxemic calves while Sobti (1991) reported darkened, congested and discoloured adrenal glands in bovine septic shock.

In nutshell, induced endotoxemia in buffalo calves caused acute vascular injury and collapse leading to multi-organ damage as evidenced on gross and histopathologic evaluation and the eventual outcome being death due to cardio-pulmonary failure.

Table 1 Biochemical parameters at different stages of endotoxic shock and after i.v. infusion with HSS, Dextran-40 and Flunixin meglumine

Group	Endotoxic shock			After treatment				
	0 h	**1.5h**	**2.5h**	**3.5h**	**4.5h**	**5.5h**	**6.5h**	**Day2**
Total protein(g/dl)	6.22 ±0.08	5.64* ±0.36	5.30* ±0.24	4.52* ±0.16	4.74* ±0.41	4.66* ±0.29	5.10* ±0.31	5.54 ±0.36
Albumin(g/dl)	2.54 ±0.10	1.94* ±0.17	1.76* ±0.09	1.40* ±0.05	1.52* ±0.15	1.48* ±0.10	1.56* ±0.08	1.78* ±0.15
Fibrinogen(g/dl)	0.24 ±0.04	0.28 ±0.05	0.32 ±0.05	0.24 ±0.04	0.32 ±0.08	0.44 ±0.10	0.52* ±0.08	0.84* ±0.19
Globulins(g/dl)	3.56 ±0.21	3.60 ±0.11	3.18 ±0.20	2.80* ±0.15	2.92* ±0.32	2.82* ±0.23	3.00 ±0.19	2.96* ±0.21
Glucose(mg/dl)	74.80 ±6.82	68.80 ±11.47	62.20 ±9.60	79.00 ±7.06	133.00* ±25.80	105.40 ±15.47	83.20 ±2.35	84.00 ±2.26
Creatinine(mg/dl)	0.96 ±0.02	0.92 ±.08	1.00 ±0.06	1.06 ±.05	1.12 ±0.07	0.98 ±0.10	1.00 ±0.06	0.98 ±0.06
Sodium(mmol/L)	135.20 ±1.83	129.00 ±2.43	130.20 ±2.22	131.00 ±0..84	138.80 ±3.18	123.60* ±8.35	133.60 ±3.14	134.40 ±2.11
Potassium	3.50 ±0.19	2.64* ±0.20	2.70* ±0.21	2.88 ±0.37	2.70* ±0.21	2.48* ±0.20	2.62* ±0.15	2.94 ±0.19
Calcium(mg/dl)	8.70 ±0.50	6.94* ±0.33	6.78* ±0.20	6.10* ±0.28	6.54* ±0.22	6.36* ±0.41	6.36* ±0.44	6.86* ±0.24
Phosphorus(mg/dl)	6.54 ±0.27	6.14 ±0.23	6.12 ±0.17	5.68 ±0.07	6.24 ±0.33	5.22* ±0.21	5.70 ±0.62	5.92 ±0.60
Alkaline Phosphatase (U/L)	63.40 ±18.62	70.60 ±21.95	71.40 ±19.35	78.00 ±26.90	78.00 ±15.90	74.20 ±20.95	84.80 ±21.0	77.80 ±19.20

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