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Post-Partum Hemoglobinuria (PPH) in Bovine

Navjot Singh Resum[1], Palneez Kour[2], Harbir Singh[3] and Neelesh Sharma*

[1]*Veterinary Officer Military Farm, Satwari, Jammu, J&K, India*
[2]*Division of Veterinary Public Health and Epidemiology, F.V.Sc. & A.H., SKUAST-J, R.S. Pura, Jammu, INDIA*
[3]*Ex. Vety. Superindentent, District Veterinary Hospital Poonch, J&K, INDIA*
[4]Division of Veterinary Medicine, *F.V.Sc. & A.H., SKUAST-J, R.S. Pura, Jammu, INDIA*

**Corresponding author: drneelesh_sharma@*yahoo.co.in

Abstract

Postpartum hemoglobinuria is a non-infectious haemolytic syndrome of adult cattle and buffaloes, a potent thread to these animals in India and Pakistan affecting considerable number of animals every year during advance pregnancy and early lactation. It is characterized by intra venous hemolysis, hemoglobinuria, severe anemia and death due to anemia and anoxia. The exact pathogenesis of this problem is not fully understood. The exhaustive studies have been undertaken and are still in progress to elucidate the exact cause of intravascular hemolysis which is the cause of hemoglobinuria in this disease. However, phosphorus deficiency in high yielding animals during early stage of lactation is widely believed to be associated with postpartum hemoglobinuria. A variety of risk factors have been reported to be associated with this disease in different part of world. Hematology and urinalysis are most commonly adopted diagnostic tools for the PPH. Moreover, Lecithin cholesterol acyltransferase (LCAT) activity may be used a more specific diagnostic indicator of PPH. Various studies have been suggested that administration of sodium acid phosphate along with supportive therapy with anti-oxidants and other important minsrals, can be used as a therapeutic protocol for management of PPH.

Keywords: post-partum hemoglobinuria, hypo-phosphataemia, cattle, buffalo

Post-partum hemoglobinuria (PPH) is commonly known as “Lahu mutna” or “Rakth mutna” in field condition, PPH is a metabolic disease of high yielding cows and buffaloes, usually occurs within 30 days of calving, commonly seen in adult dairy cattle during their third to sixth lactation (Blood *et al.,* 1989), caused due to the deficiency of phosphorus (Choudhary and Yadav, 2014) and is characterized by intravascular hemolysis, hemoglobinemia, hemoglobinuria and anemia (Akhtar, 2006; Gahlawat *et al.,* 2007; Akhtar *et al.,* 2007; Durrani *et al.,* 2010). Hypo-phosphataemia results in decreased red blood cell glycolysis and ATP synthesis which predisposes red blood cells to altered structure and function, and an increase in fragility and haemolysis, with resultant haemoglobinaemia and hemoglobinuria (Singari *et al.,* 1991). Copper deficiency is also an etiological factor for postparturient hemoglobinuria, as its deficiency reduces the activity of the copper containing enzyme, superoxide dismutase, which is part of the erythrocyte protection mechanism against oxidative stress (Heuer and Bode, 1998). Also, higher concentrations of molybdenum and low levels of copper interfere with copper absorption from the gut (Macwillims *et al.,* 1982). However, Mahmood *et al.* (2013) reported excessive molybdenum in soil and fodder reduces phosphorus contents of body by interfering with its absorption from gastro-intestinal tract and increasing its elimination

through urine leading to hypophosphataemia. Animals at the level of peak production during 3rd to 6th lactation resulting in stress on mineral balance (Akhtar, 2006). This stress is further intensified by pregnancy and late stage of gestation which coincides with ingestion of cruciferous plants in winter season resulting in development of parturient hemoglobinuria (Heuer and Bode, 1998). The disease has been reported in sporodiac cases affecting one or two animlas in a herd at a time. The disease has also got economic importance due to decrease in milk yield, cost of treatment and high case fatality rates (Sharma *et al.,* 2014).

Epidemiology and Risk factors

There are many risk factors such as age, lactation number, stage of pregnancy, postpartum period, previous history of hemoglobinuria and ingestion of cruciferous and/or toxic plants being putative risk factors of parturient hemoglobinuria (Mehmood *et al.*, 2012; Muhammad *et al.,* 2000; Khan and Akhtar, 2007; Radostits *et al.,* 2007). Under natural conditions hypophosphatemia is more commonly encountered compared to calcium, its homeostasis partner. There are reports in literature suggesting influence of some other factors like molybdenum, iron and aluminium on the availability of phosphorus to animals (Pyne, 1989). These are called *"conditioning factors"*. Environmental factors like leaching of soil by rains and man-made factors like constant removal by cropping contribute to low soil phosphorus levels and the resultant deficiency in plants and subsequently in animals feeding on them (Shupe *et al.*, 1988).

Digraskar *et al.* (1991) reported that in advanced gestation, more phosphorus and calcium are required for the developing foetus if supplementary phosphorus is not provided, thereby leading to hypophosphataemia. Moreover, high calcium to phosphorus ratio results in decreased phosphorus absorption from the intestinal tract and ultimately leads to hypo-phosphataemia. Akhtar *et al.* (2007) found that fodders grown on phosphorus deficient soils are consequently low in phosphorus content, and thereby prolonged feeding on such fodders can lead to hypophosphataemia. Kumar *et al.* (2014) reported that diet deficient in any cereals or concentrate resulted in dietry phosphorus deficiency leading to hemoglobinuria. Impaired absorption of phosphorus from gut due to wide Ca:P ratio, vitamin D deficiency and gastro-intestinal disease may contribute to occurance of hypophosphatemia (Bhikane and Syed, 2014). The transition between late pregnancy and early lactation, from calving until a 3 to 4 week postpartum, is a high-risk period for the occurrence of the disease in the dairy cow (Mahmut *et al.,* 2009). The risk is especially high around parturition (Jubb *et al.,* 1990; Macwillims *et al.,* 1982; Moore, 1997).

Chugh *et al.* (1996) hypothesized 3rd to 6th lactation, 6 months pregnancy, 1-28 days postpartum period, 10 litres daily milk yield, previous history of hemoglobinuria, berseem and cottonseed cake as risk factors of parturient hemoglobinuria. Heavy drainage of phosphorus through milk, particularly in high milk yielding animals, leads to hypophosphataemia (Bhikane *et al.*, 1995). However, other researchers have been reported that high milk yield is not associated with parturient hemoglobinuria (Mahmood *et al.,* 2012; Akhtar *et al.,* 2008). Mahmood *et al.* (2012) recorded highest prevalence at 5th lactation while the lowest one was recorded at the 1st lactation (1%). Similar findings were reported by Durrani *et al.* (2010) which might be attributed to lactational stress as the number of lactation increases (Kumar *et al.*, 2014). Post-parturient hemoglobinuria tends to occur during the winter months, especially when preceded by a dry growing season (Macwillims *et al.* 1982).

Soren *et al.* (2014) reported higher incidence of PPH in winter (87.50%) as compare to summer (12.50%). Similar findings were reported by Akhtar *et al.* (2006) who reported higher occurrence of PPH in winter season and lower

in autumn. However, Khan and Akhtar, 2007 strongly associated this disease with berseem feeding in the winter season. Also exposure to extreme cold weather may precipitate an attack of hemoglobinuria (Bhikane and Syed, 2014). The incidence of the disease in the total cattle population recorded is very low with a case fatality rate ranging from 10 to 50% (Macwillims *et al.*, 1982). However, in buffaloes case fatality was recorded to be 15% (Khan and Akhtar, 2007).

Etio-pathogenesis

PPH is a major problem of buffaloes in arid and semi-arid tracts of India, exhaustive studies have been undertaken and are still in progress to elucidate the exact cause of intravascular hemolysis which is the cause of hemoglobinuria in this disease. Though workers so far have not succeeded in pinpointing specific etiological factors and explaining the exact pathogenesis of the disease, yet hypophosphatemia, which is a consistent finding (Raza-Hassan and Singh, 1983) in diseased animals has been shown to be precipitating cause of this disease (Fig. 1). Hypophosphatemia in peri-parturient period of bovine dairy animals has now been linked to an important aspect of aerobic metabolism i.e. oxidative stress. It is defined as disturbance in the peroxidant- antioxidant balance in favour of the former. This aspect has been studied in detail in relation to many post-parturient diseases. How hypophosphatemia is actually related to oxidative stress is not fully understood at present but it is hypothesized (Mata and Bhardwaj, 1985) that it leads to low ATP production and subsequent weakening of antioxidant system of body which comprises of some enzymes (e.g. catalase, superoxide dismutase, glutathione peroxidase etc.) and some biological antioxidants viz. ascorbic acid (Vitamin C), alpha tocopherol (Vitamin E) and ceruloplasmin etc.

As the phosphorus is an essential element for cellular function. It is absorbed in the small intestine and excreted either *via* the faeces or urine. Factors reducing the flow of saliva,

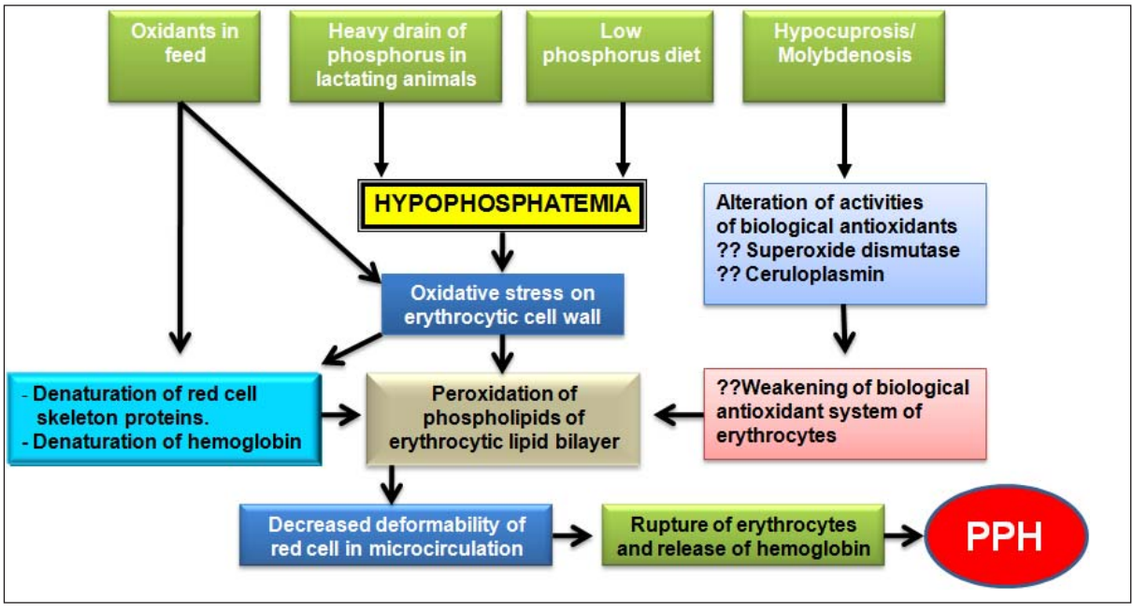

Fig. 1: Flow diagram showing probable inter-relationship of various factors leading to post-parturient hemoglobinuria

such as anorexia, may cause increased losses of phosphorus *via* urine (Reinhardt *et al.,* 1988). The etiology of PPH is believed to involve hypophosphataemia associated to primary dietary deficiency (Chugh *et al.,* 1998; Samad, 1997). Erythrocytes depend upon extracellular glucose for their energy requirement. The inorganic phosphorus promotes uptake of glucose by erythrocytes (Bhikane and Syed, 2014). Thus, hypo-phosphatemia results in decreased red blood cells glycolysis and ATP synthesis. Subnormal concentration of ATP predisposes red blood cells to altered function and structure, a loss of normal deformability, and an increase in fragility and hemolysis (Ogawa *et al.,* 1987). Decrease glucose utilization rate and ATP production by erythrocytes leads to decrease in synthesis as well as reduction of level of reduced glutathione which predispose erythrocytes to adverse effect of oxidants, which results in oxidative stress leading to lipid peroxidation of red cell membrane and eventually intravasucular hemolysis (Yadav *et al.,* 2014) with resultant haemoglobinaemia and hemoglobinuria. (Khan and Akhtar, 2007) (Fig. 2).

Clinical observations

Red, dark red or coffee colour urine depending upon the duration and severity of illness (Soren *et al.,* 2014) is often the premonitory clinical

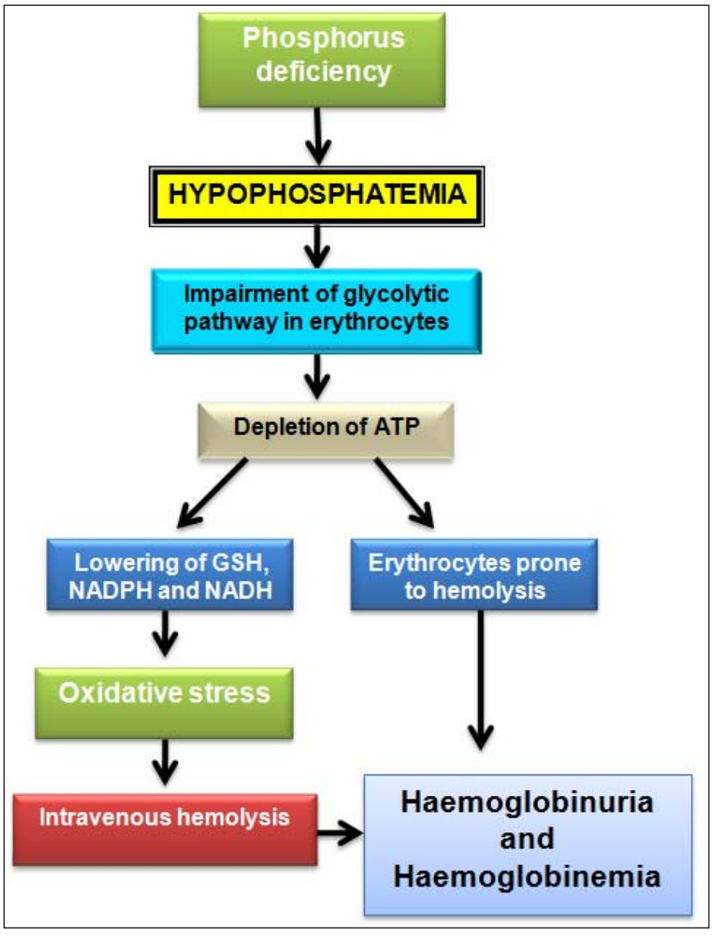

Fig. 2: Possible mechanism of Hemoglobinuria and haemoglobinemia

sign before anemia (Macwillims *et al.*, 1982). As the anemia develops, mucous membranes become pale and may become icteric (Bhikane *et al.,* 2004; Radostits *et al.*, 2007). Tachycardia, rapid and shallow breathing, depression, inappetence or normal appetite and decreased milk production are observed (Nagpal *et al.,* 1968; Macwillims *et al.*, 1982; Akhtar *et al.,* 2006; Soren *et al.,* 2014). Elevated temperature in early stage of the disease is a variable sign. Soren *et al.* (2014) and Reddy *et al.* (2014) recorded normal body temperature of buffaloes suffering for PPH but with increased heart and rapid respiration rate along with decreased rumen motility. Feces may be normal (Sridhar *et al.,* 2011), constipated (Raz *et al.,* 1988) dry and bilestained (Macwillims *et al.*, 1982) or fetid and diarrheic (Soren *et al.,* 2014). Laboured breathing and juglar pulsation can be observed during the terminal stage of disease (Soren *et al.,* 2014). Gangrene and sloughing of the extremities is reported sequel.

Diagnosis

Diagnosis is made on the basis of history of exclusive feeding of dry roughage to advanced pregnant or recently calved high yielding animals and characteristic clinical signs viz. coffee coloured urine, pale mucous membrane, straining while defecation with normal body temperature (Bhikane and Syed, 2014). Lecithin cholesterol acyltransferase (LCAT) activity may be used a diagnostic indicator of PPH (Ghanem and El-Deeb, 2010).

Urinalysis

Urinalysis is one the simple, most common and important aspect for the diagnosis of PPH. Khan and Akhtar (2007), reported that colour of urine in PPH affected animals varied from Red, dark red to coffee colour. Akhtar *et al.,* 2008 found that urine of PPH animals 100% positive for haemoglobin and 95% for albumin. Similar findings have been reported other researchers (Sharma *et al.,* 2014; Reddy *et al.,* 2014) who reported that urine of PPH affected animals was positive for protein. Higher pH of urine in hemoglobinuric animals has been reported by Soren *et al.,* 2014 and Akhtar *et al.,* 2008. Microscopic examination of urine of PPH animals shows uniformly reddish brown erythrocyte free urine (Jubb *et al.,* 1990; Soren *et al.,* 2014).

Hematology

Hematologically, PPH has the features of an acute intravascular haemolytic anemia. Morphologically, the anemia is characterized by evidence of intensified erythrogenesis. polychromasia, anisocytosis, macrocytosis, basophilic stippling, reticulocytosis and increased numbers of metarubricytes are commonly seen on stained blood films (Macwillims *et al.*, 1982). The packed cell volume falls rapidly to its lowest level four to nine days after the onset of hemoglobinuria (Macwillims *et al.,* 1982). Durrani *et al.* (2010) reported hemoglobinuria, mean erythrocyte count, haemoglobin concentration, and haematocrit were lower while their erythrocyte sedimentation rate was higher compared to the healthy buffaloes. Pandey and Misra (1987) reported a significant decrease in erythrocyte count, haemoglobin concentration, and haematocrit in affected buffaloes. Similar findings were also reported that decrease erythrocytic count, low Hb concentration and hemotocrit value (Soren *et al.*, 2014; Durrani *et al.,* 2010; Rateeb *et al.,* 2007; Sharma *et al.,* 2014 and Kumar *et al.,* 2014) and higher erythrocytic sedimentation rate resulted from intra venous hemolysis (Mahmood *et al.,* 2013).

Biochemical

Buffaloes suffering from post-parturient hemoglobinuria have been reported to exhibit severe hypophosphataemia (Chugh *et al.,* 1998). Samad (1997), reported phosphorus level less than 2 mg/dL indicates sever phosphorus deficiency in buffaloes. Mahmut *et al.* (2009)

reported deficiency of phosphorus could be responsible for the development of post-parturient hemoglobinuria in cows. Karapınar *et al.* (2006) detected low level of serum phosphorus in cows with hemoglobinuria (0.5 and 1.5 mg/dL). Durrani *et al.* (2010) found that serum phosphorus and copper rates were lower while molybdenum was higher in the postparturient hemoglobinuria affected buffaloes compared to the healthy buffaloes. Similarly, Kurundkar *et al.* (1981), Samad (1997) and Stockdale *et al.* (2005) also documented decreased serum phosphorus in affected buffaloes. Low serum inorganic phosphorus is a frequent finding in cows with postparturient hemoglobinuria (Ellison *et al.,* 1986; McCaughan, 1993). Durrani *et al.,* (2010) reported sulphides that are produced by micro-organisms in the rumen via the reduction of sulphate and degradation of sulphur amino acids. These sulphides react with molybdate to form thiomolybdates, which bind with copper and form an insoluble complex that does not release copper, even under acidic conditions, and renders it unavailable to the animal for utilization, resulting in copper deficiency, leading to hemoglobinuria. Durrani *et al.* (2010) reported higher urea and creatinine concentrations in the postparturient hemoglobinuria affected buffaloes. These higher level of urea and creatinine is also reported by Tewari *et al.* (2014) in PPH affected animals which might be due to the damage to kidneys resulting from anemic hypoxia due to extensive hemolysis (Digraskar *et al.,* 1991).

Treatment

Intravenous administration of 60g of sodium hydrogen ortho phosphate ($NaH_2PO_42H_2O$) dissolved in 5% dextrose solution through intravenous route followed by oral administration of same dose twice daily for three days (Singh *et al.,* 1989; Panday and Mishra, 1987). Shah *et al.* (1988) reported administration of sodium acid phosphate (20% solution) concurrently by i.v., s.c and oral route shows 100% results in 1-3 days. However, Durraini et al., 2010 reported better results when treated with toldimfos sodium along with sodium acid phosphate and tea leaves`. Soren *et al.* (2014) reported better response when given above treatment along with ascorbic acid as being antioxidant it help in reducing the oxidative stress of RBC and reducing intravascular hemolysis. Radostits *et al.* (2007) reported that PPH can be effectively treated with sodium acid phosphate 60 g intravenous along with supportive therapy. Copper glycinate (1.5 mg /Kg body weight dissolved in 500 ml NSS intravenously as single dose) has been recommended in cases where copper deficiency is suspected as the underlying cause. Copper sulphate 3.5 g orally or 500 mg dissolved in 500 ml NSS intravenously has been found to be 87.0% efficacious by some workers. However later reports did not find it efficacious at all. It is pertinent to point out that these animals were not hypocupremic. Transfusion of large quantity of whole blood is the best treatment for severely affected cows.

Fibrinolytic agents have also been suggested in the treatment of PPH (Chug *et al.,* 1987). Epsilon amino caproic acid (EACA) @ 20 g in 540 ml NSS intravenously. Efficacy up to 90% has been obtained. Para-amino methyl benzoic acid (PAMBA) @ 300 mg in 540 ml NSS intravenously with efficacy up to 92%. Botropase (snake venom derivative) @ 10 ml in 20 ml NSS intravenously as a single dose. May be repeated in persistent cases. Upto 95% efficacy has been reported.

Summary and Conclusion

Phosphorus deficiency plays a key role in causing hemoglobinuria which is manifested by acute intravascular hemolysis, hemoglobinuria, anemia, and hypophosphatemia. Postpartum, high-producing dairy cows in their third to sixth lactation are most commonly affected. Dietary phosphorus deficiency and/or rations containing cruciferous plants or beet products are suspected etiologies. The diagnosis of PPH can be made on the basis of the history, clinical and laboratory findings and after eliminating

other causes of intravascular hemolysis. Supplementation of deficient minerals during the last trimester of pregnancy or early lactation could be helpful in the prevention of parturient hemoglobinuria.

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