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Clinical Features of Post-Parturient Hemoglobinuria in Dairy Cattle and Buffaloes: A Review

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Abstract

Postpartum hemoglobinuria (PPH) is a sporadic noninfectious syndrome which normally seen in bovine around the world. PPH is most commonly affecting high-productive cows and buffaloes during the early pregnancy and early lactation period. PPH stands as a serious threat to the dairy cattle and buffaloes in Afghanistan, Pakistan, and India, affecting a considerable number of animals every year. It is characterized by hemoglobinuria, intravenous hemolysis, severe anemia, and death due to anemia and hypoxia. However, the exact mechanism of the mentioned illness is not completely understood. Lots of comprehensive studies have been done and/or still are in progress in order to find the exact causes of intravascular hemolysis that is responsible for hemoglobinuria in the mentioned disease. But, hypophosphatemia in the high productive milking cows during the early stage of milk production is widely confident to be associated with PPH. In different parts of the world, many risk factors had been reported to be associated with PPH. Decreasing the level of phosphorous in blood serum, interrupted the phospholipid layers of red blood cells resulting in hemoglobinuria, a decrease in milk production, anorexia, and the death of animals in the cause if remained untreated. Urinalysis and hematology findings are the most commonly suitable diagnostic tools for this disease. Lots of studies have been suggesting that injection of sodium acid phosphate along with important minerals and supportive therapy with anti-oxidants can be used as the therapeutic protocol for the management of PPH.

Keywords

Hypophosphatemia, Anemia, Post-Partum Hemoglobinuria, Cattle and Buffalo

1. Introduction

Post-parturient hemoglobinuria (PPH) is a common problem for dairy cattle in Afghanistan. This problem had been seen in highly productive animals and endemic disease of cattle and buffaloes which is characterized by intravascular hemolysis, anemia, and hemoglobinuria [1]. This condition is common among animals in their third to sixth lactation periods [2]. According to [3] and [4] studies, the more risk period for incidence of the PPH in dairy cattle and buffaloes is the periods of late pregnancy up to early lactation and from calving up to one month after parturition. However, the risk is also elevated during the parturient period. Moreover, hypophosphatemia in cattle is also incident at the beginning of lactation is widely believed that along with parturient downer cow syndrome and milk fever [5]. The incidence of hemoglobinuria was found to be higher in buffalos comparing to the cross bread cows in their third lactation with the maximum incidence in the winter season [6]. The PPH is usually had been seen in adult cattle during their third-sixth lactations. Post-parturient hemoglobinuria tends to be occurred during the winter months, especially when preceded by a dry growing season. The PPH along with a lot of similarities has been reported in sheep, Egyptian and Indian buffaloes, and goats [7]. The exact cause of post-parturient hemoglobinuria is unknown, but phosphorus depletion or hypophosphatemia, as well as, copper deficiency and possible hemolyzing substances contained in the certain feed have been reported as potential causative or predisposing factors [2]. However, phosphorous deficiency plays an important role in causing PPH, which is manifested by hemoglobinuria, intravascular hemolysis, hypophosphatemia, and anemia [8] [9] and [10] [11]. Phosphorous deficiency can cause decreased red blood cells (RBC) glycolysis and Adenosine triphosphate (ATP) synthesis which predisposes the RBC to change its function and structure, that increment in brittleness and hemolysis of RBC, which result in the hemoglobinaemia and hemoglobinuria [10]. Haemato-biochemical alterations are the indicators of the severity of the mentioned disease. The PPH has been reported as a sporadic disease [12] that affecting one or two dairy cattle and buffaloes in a herd at one time. The disease has also economic losses that they including the cost of treatment decrease in milk yield and high case mortality rates. The epidemiology, etiology, risk factors, pathogenesis, clinical finding, clinical pathology, diagnosis, therapy, and prevention strategies are described below.

2. Epidemiology

Post-parturient hemoglobinuria normally happens as a sporadic disease in cattle herd [13], and its incidence among the animal population is relatively uncommon. The sporadic occurrence of PPH has been reported from Iraq in Iraqi indigenous cows [14], from Egypt in buffaloes [15], from India [16] [17], Pakistan [9] [18], Brazil [19], Sri-Lanka [20] and Iran [21] in both buffaloes and cows. Adult cows and buffaloes are usually affected with higher frequency especially, during their advanced pregnancy stage (8 - 9 months) and/or early lactation pe-

riod (1 - 60 days post-partum) [7] [17] [21] [22]. But, a rare case of PPH has also been reported in a buffalo at 16 weeks of post-partum [13]. However, in beef cattle the PPH does not commonly occur. A long period of phosphorous deficiency is thus considered to be a predisposing factor for the incidence of PPH [2]. Although, [10] reported that the incidence of PPH is very high in late pregnancy and early lactation, from calving unlit one month post-partum is the high-risk period for the incidence of the disease in the dairy cows. But, the risk is very serious near the parturition. The disease tends to be occurred during winter months, especially, when it is preceded by dry growing season [7]. According to [23] the incidence of PPH syndrome in winter is higher (87.50%) as compared to summer (12.50%). The incidence of this problem is very high in 3rd-6th lactation [24]. The incidence of PPH in the milking cows is very low, with a case mortality rate is from 10% - 50%, while its incidence in the buffaloes is higher than cattle, with a case fatality rate of 15% [10]. In Europe and North America, the PPH is more common during a prolonged period of housing, but in the areas with severe phosphorous deficiency, it may occur at the cattle feeding in the pasture. Moreover, drinking cold water and exposure to cold weather may also cause hemoglobinuria in dairy cattle and buffaloes [2].

3. Etiology

Causes of PPH are multifactorial and yet it is poorly understood. As the putative causes for the PPH syndrome have been reported as phosphorous deficiency or hypophosphatemia [17]. But, in many countries like USA, India, and Pakistan, diets with low phosphorous or unsupplemented feed with phosphorous are usually known to be related with this problem in dairy cows and buffaloes. In New Zeeland, one form of the PPH is perhaps associated with copper and selenium in nutrition. Copper deficiency has been considered as an important etiological factor for PPH, because in the marginally copper deficient areas, supplementations of feed with copper, resulted in reduction of the mentioned disease incidence [2] [10]. There are some reports confirming that the presence of some plants such as *Cruciferous* in feed is associated with the disease incidence. The feeding of some hemolytic agents, such as some plants (*Rape*, a plant of cabbage family), but some plants are not the causes of erythrocyte lysis in some conditions [2].

However, the ratio of dietary cation-anion seems to be very important in the maintaining of phosphorous and calcium hemostasis in serum. During periods of calcium stress or deficiency, activities of parathyroid hormone increase the renal and saliva functions, these activities can be harmful to the preservation of the normal concentration of phosphorous. This is one of the main reasons that animals with calcium deficiency tend to be phosphorus deficient [17] [25]. Some studies have been reported that hypophosphatemia can induce a variety of structural and functional disorders, such as liver functional abnormalities, decreased hepatic oxygenation, muscle weakness, RBC hemolysis and rigidity, ce-

rebral and platelet disorders [5] [26].

4. Risk Factors

According to different studies, it has been shown that pregnancy (≥7 months), lactation number (≥3), age (≥7 months), post-partum period (≤60 days), have a significant role in the incidence of PPH in cows and buffaloes, while the role of other factors such as use of mineral mixture of drugs, ingestion of cottonseed cake, previous history of other diseases than parturient hemoglobinuria are non-significant [1] [10] [17] [27]. Furthermore, low production of adenosine tries phosphate (ATP) is also associated with the reduction in the antioxidant system; comprising of enzymes and some biological antioxidants such as vitamin C (Ascorbic acid) and etc. Moreover, ingestion of hemolytic or oxidative plants such as cruciferous plants, berseem (Saponins), sugar beets and green forage are also associated with the incidence of PPH [18]. According to [17] buffaloes are more prone to PPH compared to hypocalcemia. The highest incidence of PPH in the mentioned animals have been observed at 5th lactation period, but the lowest level of PPH was recorded at the first lactation (1%) [7] [10]. According to a study by [10] leaching of soil by rains or man-made like constant removal by cropping are contributed to the low phosphorous levels in soil, which resulted in the deficiency of phosphorous in the plants grown on it, and subsequently the feeding of animals from such plants resulted in the incidence of PPH in them. But, in cattle, phosphorous evacuation without any factors is unlikely to cause intravascular hemolysis of RBC and the plasma inorganic phosphorous concentration is invalid surrogate parameters to the intravascular inorganic phosphorous concentration of RBC [28]. However, [16] founded that the low phosphorous in the organism is responsible for the development of PPH in buffaloes. But, in New Zealand, one form of this problem may be related to copper and selenium nutrition deficiency [2]. Also, with copper absorption from the gut, higher concentration molybdenum and a low level of copper will interfere with this problem [7].

5. Pathogenesis

Although the etiology and pathophysiology of PPH are not unequivocally clarified, this problem is widely believed to be the result of phosphorous deficiency, so the incidence may be increasing at the beginning of lactation in high productive dairy animals [10] [28]. Because some studies have been reported that most of the animals that are suffering from phosphorous deficiency do not develop intravascular hemolysis [17]. In recent study [23] showed that a high decrease in hemoglobin concentration, erythrocyte level, and PCV in PPH affected buffaloes caused intravascular hemolysis of RBC that may take place due to impaired glycolytic pathway and evacuation of ATP in RBC [17] [29]. Some researchers [10] reported that hypo-phosphatemia cased decrease in the RBC glycolysis and ATP synthesis, which decrease in the concentration of ATP; predisposing RBC to al-

ter their function and structure that cases increase in their brittleness and hemolysis. A recent study [18] reported that RBC for control cell volume and its deformability by active Sodium extrusion needs ATP. Therefore, in phosphorous deficient erythrocytes decrease in the ATP concentration about 15% of normal values resulted in the reduction of their osmotic (**Figure 1**) resistance and ultimately cases their intravascular hemolysis. In addition to them, exposure to extremely cold weather and drinking cold water has also been associated with hemoglobinuria in cows and buffaloes [2]. However, circulating oxidants also may starting point for erythrocyte damage which may be predisposed by phosphorous deficiency [30]. A recent study has been found that in hypophosphatic animals; the phospholipid structure of erythrocyte membrane changed and their membrane liquidity inflexible. Therefore, the phosphorous deficiency might destroy the erythrocyte integrity and their working characteristic in dairy cattle and buffaloes [5], however, severe intracellular phosphorous evacuation is recognized to increase the osmotic friability of the RBC.

In phosphorous deficiency animals, all erythrocyte cell membranes become destroyed and damaged. Therefore, the concentration of total bilirubin and indirect bilirubin, ALT and AST are significantly higher than those in control group. In the phosphorous deficient group the proteins of erythrocyte membranes become damage and significantly change in both structure and functions [5] [31].

6. Clinical Finding

The first remarkable clinical sign in the affected buffaloes and dairy cows is change in the color of urine from red to brown [1] [9] [10] [16] [17] [23] and an increase in the rectal temperature from 101˚F to 103˚F within 20 ± 10 before and after parturition. Feces of the affected cows are usually dry and firm [2]. However, the affected buffalo looks uninteresting to go and sad, and completely anorectic with colorless mucous membranes. The production of milk is decreasing significantly. Furthermore, the affected buffalos are also having hemoglobinuria

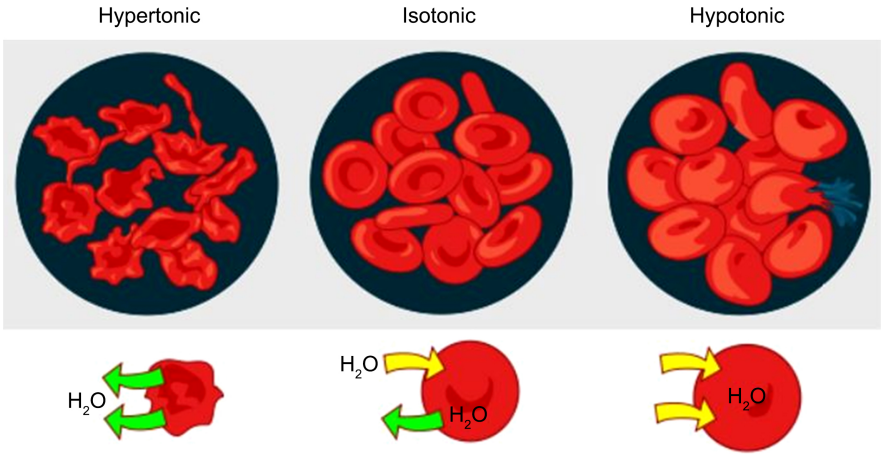

Figure 1. Possible mechanism of hemoglobinuria with resulting of hypophosphatemia (https://en.wikipedia.org/wiki/File).

[16]. However, hemoglobinuria is the first clinical sign before the onset of anemia, depression, in-appetence and decrease in the milk yield. Other clinical signs include slightly pale mucous membrane, heart rate 98 per minute is it less or more than normal, bit difficulty in the respiratory, constipation [1], decrease in the capillary refill time (1 - 2 per sec), enlarged lymph nodes, weak pulse, mild salivation and panting [17]. According to findings by Resum *et al.*, [10] higher level of creatinine and urea is also detected in PPH animals which might be due to the damage to the kidney resulting from anemic hypoxia due to acute hemolysis. Affected animals are normally weak and often recumbent, which by the time, a forced exercise can be fatal [7].

7. Clinical Pathology

Affected animals in a herd with low level of phosphorous (2 - 3 mg/dL) with limb paralysis as a clinical sign or some of them may have moderately low values of phosphorous below 4 mg/dL without any clinical sign [10] [17]. Macwilliams *et al.* [7] reported that the hematological features of post-parturient hemoglobinuria in bovine have the feature of an acute intravascular hemolytic anemia. The Pocket Cell Volume (PCV) or hematocrit falls rapidly to its lowest level within 4 - 9 days after the onset of hemoglobinuria. Some researchers are proposing that phosphorous deficiency is the leading mechanism of hypophosphatemia, in PPH and related syndrome of hemoglobinuria by decreasing red cells glycolysis and resulting ATP synthesis [8] [33]. According to Saed Albayati *et al.* [14] in the affected animals a significant reduction in RBC concentration, Hb, and PCV shows a positive relationship between the total RBC count and both Hb and PCV leading to sever anemia. The intravascular hemolysis happens due to destruction of glycolytic pathway and evacuation of ATP in RBC that resulting in phosphorous deficiency. However, anemia is also observed due to lysis of erythrocytes and dysfunction of liver. Disabled liver function is impeded with metabolism of minerals, vitamins, and proteins which are essential for the synthesis of erythrocytes and hemoglobin [34]. Some researchers reported that the creatinine, bilirubin, blood sugar and serum ALKP were increased in the affected animals [17] [35] which is proposing jaundice due to intravascular hemolysis [12]. However, serum phosphorous, copper and selenium were significantly ($P < 0.001$) decreased, while molybdenum ($P < 0.001$) were increased in the affected animal in compare to the healthy animals [9]. Furthermore, Zhang *et al.* [5] reported that reduction of inorganic phosphorous in feed is directly affecting RBC function which results in significant decrease in the number of RBC and the level of mean corpuscular hemoglobin [MCH], and an increase in mean corpuscular volume [MCV].

8. Diagnosis

PPH diagnosis is made on the basis of affected animal history, clinical signs such as coffee-colored urine, pale mucous membrane, straining during defecation

[17] and laboratory findings such as measuring the activity of lecithin cholesterol acyltransferase (LCAT) [10]. Measuring the phosphorous level in the affected animals that are normally low (around 2.2 mg/dL) is another valuable tool for diagnoses [7] [8] [16]. The existence of Hb in urine can be check by using commercially available stick strips or Benzidine test [13]. Diagnostic confirmation of PPH includes low serum phosphorous, low PCV and hemoglobinuria have been reported by [2]. Low PCV, erythrocytes, and hemoglobin and serum inorganic phosphorous, whereas increase in TLC (Total Leucocytes), percentage of granulocyte and serum total bilirubin [36].

8.1. Differential Diagnosis

PPH should be differentially diagnosed from other factors of hemolytic anemia that are not limited to the postpartum [7] [10] [17] [35]. To confirm the diagnosis and to remove hematuria as a cause of discoloration of the urine, laboratory examinations are usually necessary [2].

8.2. Mortality Rate

The mortality rates of PPH affected animals have been reported from 12% - 15% [9] [17], but unusually high mortality rate of 53.5% - 63.4% also have been reported from the fatality rate of PPH is related upon to the time of the beginning of therapy. By receiving early therapy in buffaloes and dairy cattle, the mortality rate is also low. Death in the affected animals is usually occurring due to anoxic anoxia [2].

8.3. Necropsy Finding

Necropsy findings of the dead animals are including icterus, pale mucous membranes, hepatomegaly, and red urine in bladder [2], along with the pale and enlarged. In affected animals liver and kidney are pale enlarged and congested with hemosiderin. Liver and kidneys are congested with hemosiderin. Liver is swollen, and degeneration and fatty infiltration are also evidence. The urine appears discolored in bladder and widespread of icterus is seen, throughout the body of affected animals [37].

8.4. Urine Analysis

The urine analysis and hematology are the most commonly accepted diagnostic tools for PPH [10]. The color of urine in affected animals are varying from red; dark red to coffee color [9]. The urine of PPH affected animals are 100% positive for hemoglobinuria and 95% positive for albuminuria [35]. Some researchers [10] [36] [38] have been reported the presence of protein, and high PH (pH of 8.0 - 9.0) in the PPH affected animals. Akhtar *et al.* [35] and Soren *et al.* [23] reported that the microscopic examinations have been confirmed the presence of erythrocyte in urine with uniformly radish brown color [10]. Moreover, the urine analysis reveals the presence of protein, hemoglobin, sometimes ketones

and bile pigments [17]. However, the urine of affected animals also contains blood, glucose, nitrates, protein, ketone and leukocytes [32] [35] [36].

9. Treatment

There are many methods for treatment of PPH that can be helped to save the life of affected animals and prevent the condition and degree of anemia. Wakayo *et al.* [39] reported that the initial diagnosis and indicated successful treatment the clinical condition. Hence, parenteral phosphorus supplementation and periodic hematological evaluation can be valuable in conforming diagnosis, assessing prognosis and success of treatment in case post-parturient hemoglobinuria. Seven days of parenteral phosphorus supplementation and supportive therapy significantly improved the clinical condition (temperament, food intake and urine color) in case of post-parturient hemoglobinuria. Senthil Kumar *et al.* [13] observed that supplementation of acid inorganic phosphorous can be successfully used for the therapeutic management of PPH in a cross bred dairy animals. Radostits *et al.* [2] reported that the suitable treatment of PPH in dairy cattle and buffaloes is whole blood transfusion, sodium acid phosphate IV and administration of Di-calcium phosphate orally. A group of researchers successfully treated buffaloes with phosphorus supplementation and supportive therapy in form of IV administration. Administration of sodium acid phosphate 40.3% solution for 7 days and injection of sodium salt twice a day for 3 days have high efficacy. Moreover, some researchers reported the treatment of PPH in buffaloes by IV infusion of copper glycinate and oral administration of di-calcium phosphate that obtained a good result [40]. The great effects with toldimfos sodium (85%) followed by tea leaves (56%) while the low effects were discovered with sodium acid phosphate (18%) [41]. Some researchers reported that the approval treatment for PPH in North American includes intravenous administration of sodium acid phosphate (60 g in 300 mL of sterile water IV) (Bradford [12] should be followed by oral phosphorous supplementation, transmission of fresh blood also recommended, 102 g of bone meal administrated as a drench twice a day, and administration of fluids to maintenance of dehydration is necessary for affected animals [41] [42]. Treatment with sodium acid phosphate along with ascorbic acid was found to be highly effective as compared to sodium acid phosphate alone [43]. Treatment with buffered phosphorous preparation showed early recovery about (2 - 3 days) minimum dose and without reaction [44].

The best treatment for severely affected cows in PPH is transfusion of large quantity of whole blood suggested by [10]. In PPH affected animals about 4 litter blood to a 400 kg cow is recommended. If the animal is incapable and mucous membrane colorless, on that time the amount of blood will usually enough for up to two days by which time an additional transfusion may be necessary. After the blood transfusion, fluid therapy is necessary as both supportive therapy and to reduce the danger of hemoglobinuric nephrosis [2].

Supportive therapy: Some researchers [1] [17] have been reported that sup-

portive therapy also an important thing for treatment of PPH affected animals and they are including on the basis of the following method:

1) Liver tropic (Thiamin hydrochloride 30 mg, Pyrinidone hydrochloride 13.75 mg and Cyanocobalamin 50 mg), 10 ml, IM, once a day for 5 days.

2) Anti-inflammatory (Dexamethasone 4.4 mg/ml), 10 ml, IM, once a day for 3 days.

3) Calcium borogluconate together with Magnesium and Phosphorous in organic combination and Dextrose (Mifex), 300 ml slow IV and reset subcutaneously.

4) Nicinamide, Folic acid, Vit. B_{12} and B_6 Glycinated iron copper and cobalt, vitamin E. (RBCrakt). Fluid therapy, Rumenotoric-BiovetYcgoold.

10. Prevention

The prevention of post-parturient hemoglobinuria particularly during late gestation and early lactation, According to requirements for maintenance and milk production, an adequate intake of phosphorus should be ensured [17]. Most researchers observed that the etiology of PPH is still unresolved, so this problem can be multifactorial. The control and prevention of this disorder include using of phosphorous and other mineral and vitamin supplementation [1] [45]. While the serum inorganic phosphorous is below 5 g/100ml, supplementing a source of phosphorous in ration or in water is recommended [45]. **Table 1** gives phosphorous contents and amount of various phosphatic supplements for maintenance of cow and sheep.

When a large number of dairy cattle are to be affected with phosphorous deficiency, it is maybe comfortable to administer a water soluble salt of phosphorous in drinking water [45]. An optimal intake of other minerals and Vitamins (Particularly Ca, Zn, Cu, Iodine, Mn and Mg; Vit D, E, and etc.) should be recommended by supplementing diet. Monthly parenteral administration of Vitamin D (Vit.AD_3E 10 ml for adult cattle and buffaloes). Parenteral administration of Vitamin D can increase the absorption of both phosphorous and calcium from the small intestine. Removing the intake of cruciferous plants, Lucerne, berseem

Table 1. Comparative value of various phosphatic supplements for maintenance [5].

Products	Phosphorous %	Amount for requirement (g)		Amount of deficiency (g)	
		cattle	sheep	cattle	sheep
Di-calcium phosphate	17	56	8	28	4
Tri-calcium phosphate	14	68	10	34	5
Bone meal	9.5	100	15	50	7
Bone ash	15	64	10	32	5
Degelatinised bone meal	13	70	12	35	6

and sugar beets from the ration of pregnant and dairy cattle and buffaloes [17] [45]. Radostits *et al.* [2] reported that the suitable control of PPH affected animals is ensuring adequate intake of dietary phosphorous and copper. After copper supplementation of animals in copper deficient areas, a decrease in the occurrence of the PPH is reported.

11. Conclusion

According to the finding of most researchers, hypophosphatemia in the body could be answerable for PPH in dairy animals. Phosphorous deficiency plays an important role in causing PPH which is recognized by acute intravascular hemolysis, anemia, hemoglobinuria, and phosphatemia. Most commonly affected high producing dairy cattle and buffaloes in their third to the sixth lactation. The etiologies of this problem are phosphorous deficiency or ration containing cruciferous plant or beet products. The diagnosis of PPH can be done on the basis of the anamnesis, clinical signs, and laboratory findings and after removing other causes of intravascular hemolysis. The prevention of post-parturient hemoglobinuria particularly during late pregnancy and early lactation, using phosphorous and other mineral and vitamin supplementation could be helpful.

12. Problem Statement

Afghanistan is a country that is currently faced with lots of internal and external problems, including poverty. There are not enough funds for researchers to conduct researches; hence, the researcher activity on conducting research is closed to the zero levels. Therefore, there is no researches have been done about the diseases in cattle, including PPH (as you may not be able to find any report about the mentioned diseases that have been done in Afghanistan, on the internet). Therefore, conducting researches in any aspect of metabolic diseases would be concluded as a good achievement for the future of my country, as well as, for the future of higher education, in Afghanistan.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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