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Post parturient hemoglobinuria

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Abstract
Post parturient hemoglobinuria is the metabolic disease of bovine characterized by hemoglobinuria, intravascular hemolysis and anemia. It mainly affects mature cows, basically high yielding animals. The predisposing time is the third to sixth lactation. The disease is mainly caused by feeding cruciferous plants and low phosphorus diet. Arid and semi-arid zone is most susceptible region in India. Hypophosphatemia in this disease leads to RBC lysis and reduction in ATP generation. Inorganic phosphorus (Sodium acid phosphate) is recommended for treatment.

Keywords: Hemoglobinuria, phosphorus, inorganic, cruciferous

Introduction:

Post parturient hemoglobinuria is a stochastic condition that affects high producing dairy cows and buffaloes that are at a significant risk of contracting the disease throughout the period from calving until 3-4 weeks after parturition, which is the transition from late pregnancy to early lactation. It is marked by anemia, haemoglobinuria and intravascular hemolysis.

Incidence and Occurrence:

The typical hemolytic condition only affects mature cows, and it typically appears 2–4 weeks after calving (*Blood et al, 1989).* The most frequently impacted dairy cows are high-yielding animals in their third to sixth lactation. Beef cattle do not frequently contract this disease. It is believed that phosphorus-deficient soils and dry weather are predisposing factors, and the illness is frequently a concern on specific farms. The disease can occur at pasture in locations with severe phosphorus shortage, but it is more common during extended periods of habitation in Europe and North America. The disease has a very low incidence in the overall cattle population and a case fatality rate range from 10% to 50%.
Two unique kinds have been observed in New Zealand. In one case, young calf of around 2 years of age have subclinical anemia of the Heinz body type, with no evidence of hypophosphatemia. Other cases of the disease are reported in North America, where older mature high producing cows are affected, and hypophosphatemia is widespread in both affected animals and healthy herd mates. (*Ellison, R.S.et all. 1986)*
Cu deficiency is regarded as a significant contributor to PPH in New Zealand, however most cases of PPH in other nations lack abnormalities in copper status. (Smith, B. et.al.1975). Post-parturient hemoglobinuria tends to occur during the winter months, especially when preceded by a dry growing season. (McWilliams et al.1982). Similar symptoms accompanied by hypophosphatemia have been seen in postpartum periods in Indian buffalo (*Kurukandkar, V.D. et.al 1981)* and late pregnancy in Egyptian buffalo. The list of feeds connected to PPH include.
a) the roots and leaves of sugar beets (mangles).
b) field crops such green oats, perennial ryegrass, Egyptian clover, and alfalfa.
c) plants in the genus Brassica, also known as cruciferous plants.
Some foods, such rape and kale, have low phosphorus content (0.4% dry matter) or a high calcium to phosphorus ratio (> 2:1). A low serum phosphorus concentration may interact with hemolytic saponins from sugar beets or alfalfa to predispose PPH. It has also been suggested that feeding cruciferous plants caused the hemolytic crisis and that phosphorus deficiency was a "necessary predisposing factor."

Etio-pathogenesis:

In India's arid and semi-arid regions are more susceptible. PPH affects buffaloes in a big way. Extensive studies have been done and are currently being done in this regard to determine the precise reason for intravascular hemolysis, the condition that leads to hemoglobinuria in this illness. Even though the precise pathophysiology of this issue is not entirely understood, linked risk factors include consumption of:

1. Cruciferous vegetables, berseem saponin.
2. A lack of phosphorus in the diet.
3. Drop in serum copper and selenium levels, and an increase in molybdenum have all been linked to increased molybdenum (Neto et al., 2007; Brechbuhl et al., 2008).

Hypophosphatemia is one of these causes that is frequently mentioned (Chugh et al., 1996; Khan and Akhtar, 2007). Hypophosphatemia is thought to lead to a reduction in red blood cells, glycolysis, and ATP generation. Oxidative stress, a crucial component of aerobic metabolism, has been related to hypophosphatemia in the per parturient period of bovine dairy animals. It is described as a disruption of the per oxidant-antioxidant balance in the favor of former.

Reduced ATP generation and decreased glucose uptake by erythrocytes result in decreased synthesis and reduced levels of glutathione make erythrocytes more vulnerable to the damaging effects of oxidants, which causes oxidative stress, lipid peroxidation of the red cell membrane, and ultimately intravascular hemolysis, which causes haemoglobinuria and haemoglobinuria (Yadav et al., 2014). (Fig. 2) (Khan and Akhtar, 2007).

Copper and Selenium may also provide some protection against the effects of orally acquired hemolytic agents in cruciferous plants. (*Mcwilliams, P.S. et al.1985).* Copper shortage would probably reduce superoxide dismutase activity, impair the erythrocyte's ability to resist oxidative damage, and result in the formation of Heinz bodies. Death in fatal cases is due to anemic anoxia.

Decreased Phosphorous
|
Inhibit the glycolytic pathway of RBCs.
|
Decrease glycolysis and ATP synthesis.
|
Altered structural and functional changes, and increased fragility of RBCs.
|
Hemolysis and Hemoglobinuria

Clinical findings:

The premonitory indicator before anemia is frequently red, dark red, or coffee-colored urine depending on the length and severity of the disease (Soren et al., 2014).

Mucous membranes may become icteric as the anemia worsens (*Bhikane et al., 2004; Radostits et al., 2007)* Further symptoms include tachycardia, quick and shallow breathing, depression, normal appetite initially followed by gradual inappetence and anorexia after 1-2 days, decreased milk production. Variable symptoms of the disease in its early stages are an elevated temperature and intense thirst (*Nagpal et al. 2006, Soren et al. 2014).* Affected cows are weak and often recumbent and show exercise intolerance. Buffaloes with PPH have normal body temperatures unlike cows that show moderate fever up to 103.5°F, elevated heart rates, Dyspnoea, impaired rumen motility and characteristic straining while defecation inspite of normal consistency of faeces. (*Soren et al. 2014 & Reddy et al. 2014)*. Faeces may vary from normal to constipated or dry. Labored breathing and jugular pulsation can be observed during the terminal stage of disease (*Soren et al., 2014).* Acute stage of the disease usually lasts upto 3-5 days and can terminate in death or followed by protracted period of recovery of 2-8 weeks. During recuperation, Ketonuria and anorexia could occur. Buffaloes usually die if left untreated.

Clinical pathology:

PPH has the hematological characteristics of acute intravascular hemolytic anemia. 4 - 9 days following the commencement of hemoglobinuria, the packed cell volume rapidly decreases to its lowest level. The plasma, which was initially hemoglobinemic, turns icteric as the erythrocytes are gradually destroyed. Anemia is characterized morphologically by indications of intensified erythrogenesis. On stained blood films, it's typical to notice polychromasia, anisocytosis, macrocytosis, basophilic stippling, reticulocytotic, and an increase in metarubricytes. The echinocytes in the current nomenclature may be comparable to the swollen erythrocytes with dimpled centers and thorn-apple shaped erythrocytes that were characterized back in 1940.

Erythrocyte osmotic fragility research has produced mixed results. Neutrophilic leukocytosis is often observed during hemolytic crises. Typical non-lactating animals in an impacted herd may have serum inorganic phosphorous levels in the typical range of 4.0-7.0mg/dl in marginally phosphorous deficient locations. afflicted animals have extremely low levels, i.e., 0.4-1.5mg/dl, while lactating cows in an afflicted herd may have relatively low levels of 2-3mg/dl. Serum calcium level decreases (normal 8-12 mg%). Ca: P ratio increases up to 5:1 (Normal 2:1).
In addition to Cu-Mo imbalance, Heinz bodies have been found consistently in erythrocytes of New Zealand cattle with PPH. It is uncertain how a copper shortage led to the development of Heinz bodies. When hemoglobin that has undergone denaturation precipitates due to irreversible oxidation, Heinz bodies are created. The erythrocyte's defense system against oxidative stress includes the copper metalloenzyme superoxide dismutase. Copper shortage would probably reduce superoxide dismutase activity, impair the erythrocyte's ability to resist oxidative damage, and result in Heinz body formation.

Diagnosis:

The history of the animal's advanced pregnancy or recently calved animal is used to make the diagnosis. Its diagnosis is aided by clinical symptoms.
Clinical pathology and blood tests help with diagnosis determining the serum inorganic phosphorous levels with other parameters as stated above under Clinical Pathology. Haemoglobin levels as low as 3–4 g/dl are seen in advanced buffalo cases.
Urinalysis is helpful in PPH diagnosis. The most notable clinical indicator of PPH is haemoglobinuria. Depending on how the disease is progressing, Rothra's test (ketone bodies), Roberts (protein), Benzidine test (Hb) comes out to be positive. Microscopic analysis of the urine reveals absence of erythrocytes, ruling out hematuria.
Response to Phosphorous therapy/treatment can also be a definite criterion to diagnose PPH.

Differential diagnosis:

It is important to differentiate the disease from other disease in which hemoglobinuria is a clinical symptom.
✓Babesiosis can be distinguished based on a blood smear analysis.
✓Bacillary haemoglobinuria causes a strong systemic reaction, including fever and stomachache.
✓ To distinguish it from leptospirosis, a systemic reaction and dark field microscopy of urine or blood for thread-like organisms are necessary.
✓ No haemoglobinuria occur in Anaplasmosis and theileriosis.
✓There is a history of snake bites, and fang marks are visible in case of snake bite.
✓There have been previous instances of lighting stroke and severe burns to differentiate it from PPH.

Treatment:

PPH treatment is dependent on the underlying etiological causes.

I. A wide variety of medications have been tested in hypophosphatemic patients (buffalo), with varying degrees of efficacy. Sodium dihydrogen orthophosphate (also known as sodium acid phosphate) is administered in acutely ill animals @60g in 300 ml of distilled water (as 20% solution) and a similar dose subcutaneously, followed by additional subcutaneous injections at 12-hour intervals on three occasions, and similar daily doses orally. (Blood *et al., 2010)*. Due to the risk of acidic indigestion during oral treatment, parenteral administration is preferred. Up to 85% efficiency has been attained with it.
II. If there is hypocupraemia, administering copper salts is useful, especially in cows. Copper sulphate is administered intravenously in doses @5g dissolved in normal saline.
III. In certain cases, molybdenosis needs to be addressed as well. Recently, copper glycinate (1.5 mg/kg with a maximum of 500 mg dissolved in Ns IV, single dose) has also been successfully attempted.
IV. Injecting ascorbic acid at a dose of 15-20 mg/kg i/v every day for 2-4 days is another option. Since ascorbic acid is an antioxidant, it lowers the oxidative stress on RBCs.
V. Antifibrinolytic drugs as in affected buffaloes, there has been an increase in fibrinolytic activity and an accumulation of fibrinogen breakdown products.
VI. Using Botropase in the following dosage: 10 ml in 20 ml of normal saline, injected intravenously twice day for 1-3 days. For 3–4 days, inject 300 mg of PAMBA (para-amino-methyl benzoic acid) in 500 ml of D5.Administer Epsilon-Amino Caproic Acid (EACA) by injecting 20 gm of powdered EACA diluted in 500 cc of D5 once daily for three to four days.
VII. Supportive therapy is to be indicated to increase recovery and prevent relapse in such cases. 500–1000 ml of 20% dextrose intravenously is injected once daily for two–three days.
VIII. 5 ml of Vit"B" complex daily for 5-7 days together with liver extract is injected parenterally.

IX. To treat anaemia, Jaggery is fed orally for seven to ten days. Hematinic drugs to be given once haemoglobinuria is stopped as iron is known to enhance oxidative stress.
X. Large quantities of Whole Blood transfusion may be the only treatment in serious circumstances. A minimum of 5 litres of Blood to a 450kg cow is recommended.
XI. To maintain serum Pi levels, use a mineral mixture of 50 gm everyday orally. Ascorbic acid @7.5 g dissolved in NSS (500ml) IV along with 60g mineral mixture (with good amount of inorganic phosphorous) orally once daily till recovery has been reported to be highly efficacious in buffalo.

Prevention & Control:

Following the manifestation of clinical indications, therapy should be initiated as soon as feasible. When an animal develops anorectic symptoms, the response to therapy is delayed, and the cases are frequently difficult to treat. The treatment must be continued until the urine test for benzedine is negative. It implies that haemolysis has ceased and that only haemoglobin from previously haemolyzed cells is flowing through the urine.
During pregnancy, animals should be fed a balanced diet rich in minerals, notably phosphorus. Pregnant buffaloes should be given a good quality mineral mixture at a rate of 25g/day for at least three months before the predicted date of parturition.
The recently calved or advanced pregnant cattle need to be protected from cold stress and provisions of adequate quantity of concentrates and green ad lib.

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