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Controlling Iron Deficiency Anaemia (IDA) in Newborn Piglets through Iron Supplementation

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Abstract

Iron deficiency is the most common nutrient deficiency occurs not only in humans but also in animals that lead to anemia, a condition where circulating red blood cells are lower in numbers or hemoglobin level in blood is low. Microcytic - hypochromic anemia can lead to Iron Deficiency Anaemia (IDA), a condition where red blood cells are fewer in number than normal level with smaller in size and decreased red color. In, rapidly growing piglets this is the major cause of death. Newborn contains almost 50 mg of iron during birth which gets exhausted very quickly and require 7-15 mg of iron daily. Sow milk contain minimal amount of iron which is insufficient for the newborn piglets. Rearing in confinement worsen the condition. Iron supplementations are administered to the new born so as to overcome and recover from the negative aspects of anemia.

Keywords: Iron deficiency; anemia; iron metabolism; pig; iron; hemoglobin.

Introduction

Iron is the most essential mineral that our body needs for physiological functions such as for cellular and neurological development of any organism (Wessling-Resnick, 2014). Heme and non heme are the two forms of iron available in dietery form. Plants contain nonheme iron only whereas seafoods and meat contains both heme and non heme iron. Heme present in electron transfer chain proteins as a part of varies co-factors (Iron-Sulfur cluster) and heme groups which help to produce ATP in mitochondrial cristae. The heme groups are part of hemoglobin (Hb), a protein that constitutes one-third of the red blood cells (RBC) which transports oxygen from lungs to tissues. In Blood, iron constitutes red pigment as hemoglobin and in muscles as myoglobin (Murray-Kolbe and Beard, 2010).

Anaemia in piglets is caused by the lower levels of iron in hemoglobin. Newborns piglets need an adequate amount of iron levels. For example, newborn infants have sufficient amounts of iron stored which are required for their development during the first six months as compared to piglets that are born with 50 mg of iron which is lowest among newborn mammals (Rao and Georgieff, 2007; Svoboda & Drabek, 2005). Iron levels in sows' milk is found to be very low that is only 1 mg per day but the daily requirement is at least 7 to 16 mg of iron per day. In the 19th century, ferrous sulfate was introduced by Pierre Blaud who formulated the standard treatment for IDA for the to cure of chlorosis (Blaud, 1832). Ferrous and ferric iron salts are iron supplements in the form of ferrous sulfate, ferrous fumarate, ferrous gluconate, ferric sulfate and ferric citrate. Ferrous iron is mostly used than ferric iron because of its higher solubility (De Maeyer et al, 1989).

During birth, an adequate amount of iron is required for the growth, but due to a lack of iron resources, piglets become anemic. The piglets cannot synthesize an adequate amount of Hb and oxygen-carrying capacity is reduced drastically (Colombo *et al*, 2014). On observation of blood samples from the iron-deficient anaemic pigs, their red blood cells appear to be smaller and lighter in color when compared to normal cells. This condition is called microcytic hypochromic anaemia (Mc Glone & Pond, 2003). Thus, if piglets do not obtain adequate iron supply during the first few weeks, the oxygen carrying capacity of red blood cells will decrease and this will lead to anaemia, which causes low immunity, low weight gains and in drastic cases death of the piglets, which in turn is an economic loss to the farmers or breeders (Osborne & Davis, 1968). Further, Luke & Gordon (1950) reported that anemic pigs are more susceptible to diseases like pneumonia, influenza and disorders of the alimentary tract. Therefore, an exogenous source of iron is essential to prevent the reduction in the RBC hemoglobin level.

In swine production, iron supplementation of piglets is a routine and mandatory practice performed with the use of various iron supplements, at differential doses and various time schedules. One day old piglets are generally not anemic showing Hgb concentration above 8 g/dL but the concentration gradually decrease after a few days of birth and iron supplementation has to be administered (Egeli *et al,* 1998). Most of the iron supplementation starts on the 2nd or 3rd day after birth. Generally on the 3rd day, Hgb levels in non-supplemented piglets drop to the level of 6–7 g/dL and at weaning is drastically decreased even below to 4–5 g/dL, which indicates a state of extreme anemia (Lipi *et al,* 2010). Therefore, the Hb value is a convenient way in finding out the necessity of iron supplementation. Because of the importance of iron, this article reviews the role of iron in pig industry, its supplementation to prevent IDA as the anemic piglets still constitute a very important reference group for research purpose.

Iron metabolism in the body

Ferrous (Fe^{2+}) and ferric (Fe^{3+}) forms of iron are used in various biochemical reactions such as oxygen transport, oxidative phosphorylation and DNA synthesis (Pierre & Fontecave, 1999). The most important mechanism to regulate iron homeostasis in the body is the intestinal absorption of iron that happens in the duodenum (Richardson & Ponka, 1997). Regulating iron levels at the systemic and cellular levels is critically important. In mammals, a system of proteins are involved in iron transport, storage and maintaining iron balance in the whole body, which regulates iron redox status through signaling and feedback mechanism (Fig. 1) (Harrison & Arosio, 1996; Ponka & Lok 1999, Kikuchi *et al,* 2005). Cells that help in the systemic iron homeostasis include duodenum enterocytes, erythroblasts in bone marrow, macrophages in liver and spleen and hepatocytes (Sukhbaatar & Weichhart, 2018).

Duodenal enterocytes are absorptive polarized cells, which have two protein tandems (iron reductase or oxidase and a transporter) in the section of the cell membrane that comes into contact with the intestinal lumen and in the section directed towards blood vessels. They supply iron to the whole body by absorbing it from food in the inorganic iron (ionic form) and the form of organic iron that is haem. Ferric ions are being reduced to ferrous iron by duodenal cytochrome b (DcytB) which is located on the apical membrane side of the enterocyte are then transported to its interior by a divalent metal transporter1 (DMT1) (Mims and Prchal, 2005). From enterocytes, iron is released into the bloodstream by ferroportin with the use of hephaestin – a transmembrane copper-dependent ferroxidase which transports iron from enterocytes in the circulation (Petrak & Vyoral, 2005). Ferroportin is found on the cell membrane of both enterocytes and macrophages (Nemeth *et al,* 2004).

The ferrous iron gets oxidized back to ferric iron and is stored as ferritin, an iron storage compound. The ferrous iron gets transported to the other cells of the liver, spleen and bone marrow. Serum ferritin levels reflect the other body stores of iron such as hemoglobin and packed cell volume. Since, serum ferritin is low in iron deficiency and high in iron overload, which theoretically estimates the levels of iron in pigs (Daru et al, 2017). Iron leaves the cell through the basal surface through a transporter called ferroportin (Ireg- 1) and must be converted to ferric iron to be transported with the help of hepastin which converts Fe^{2+} to Fe^{3+} form.

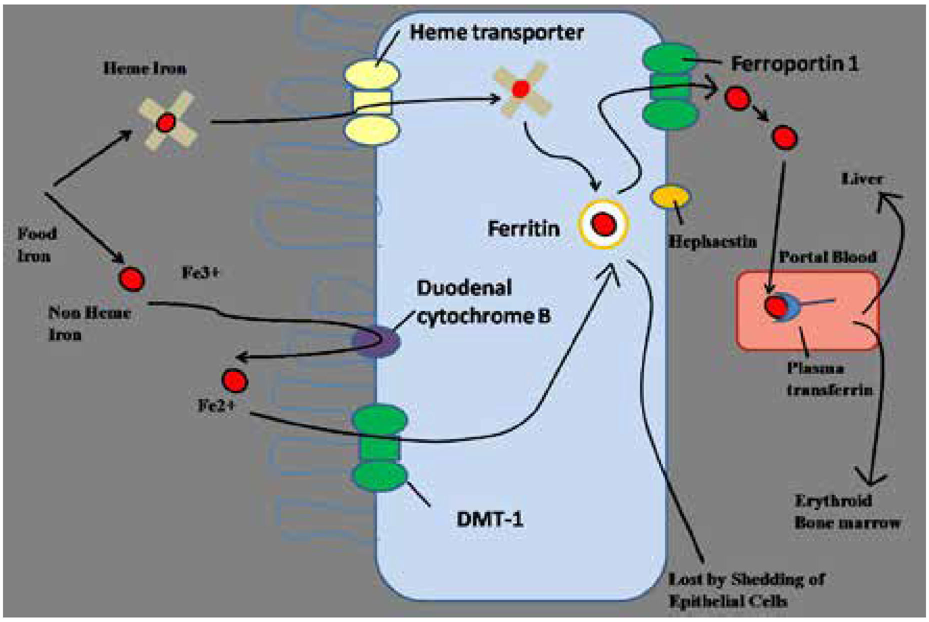

Fig. 1 Iron metabolism in mammals

Erythroblasts cells need iron for the synthesis of haem, which then gets integrated in hemoglobin molecules. Transferrin receptor 1 (TfR1) on erythroblast membranes, help these cells to absorb iron bound to serum transferrin (Johnson *et al*, 2007). In the erythropoiesis process, increased haem synthesis in erythroblasts is higher than in nonerythroid cells (Ponka, 1999). Also, the process of recovery of iron ions present in the Hb of old and damaged red cells takes place by a process called phagocytosis by macrophages. Iron for haem synthesis is reutilized in erythroblasts of the bone barrow by haem oxygenase 1 to maintain the systemic iron homeostasis in mammals. So, iron is delivered from macrophages into the circulatory system by ferroportin, which works along with caeruloplasmin - a ferroxidase subject to copper particles (Abboud & Haile, 2000; Anderson & Frazer, 2005).

Hepatocytes controls the systemic iron metabolism by secreting Hepcidin, a peptide circulating hormone made up of 25 amino acid into the blood (Pietrangelo, 2011). This is a feedback mechanism induced when the iron levels are high in liver and high saturation of transferrin with iron. That is hepcidin binds to ferroportin, which is found on the cell membrane of both enterocytes and macrophages (Nemeth *et al*, 2004). During interaction, ferroportin move to the cytoplasm followed by its degradation in lysosomes. Due to this, iron gets collected in the enterocytes and constantly exfoliating into the intestinal lumen and thereby stopping the iron flow from macrophages into the blood as high amount of iron gets recycled daily by this route, otherwise it may lead to hypoferremia, which is an iron deficiency in the blood. This feedback mechanism inhibits iron absorption and recirculation, decreased serum iron levels, and reduced transport to hepatocyes (Viatte & Vaulont, 2009).

Signs of iron deficiency Anaemia in pigs

The primary sign of iron-deficient anaemia in pigs are roughness of hair coat and loss of pigmentation in the mucus membrane and loss of in characteristic pink ears and snout in 2-3 weeks old pigs. Anaemic pig will have low resistance to fight against diseases, respiratory problems and diarrhea. In chronically ill pigs, reduced growth, wrinkled skin, appetite loss, diarrhea and reduce weight along with drooping of the head and ears gain were also noted. In acute anaemia, difficult breathing or a spasmodic movement of the diaphragm muscles following exercise which is referred to as “thumps”. In some cases, the enlargement of the heart and spleen, fluid in the chest and abdomen and thin watery blood was also observed (Zimmerman et al, 2019).

Diagnosis of iron deficiency anaemia in piglets in laboratory

Iron Deficiency is detected using haemoglobin concentration. A system was set where pigs were categorized for anemia based on their Hb concentration (grams /deciliter). If the Hb level is 10 or above, it is considered normal. If Hb level is below 9g/100 ml, then its borderline anemia and iron supplementation is needed bu hen Hb levels drops below 8g/100 ml then its becoming anaemic. When Hb levels drops to 7g/100 ml then anaemia affects the growth rate and Hb level at 6 is considered severe anaemia and 4 with increase mortality (Zimmerman *et al*, 2019)

The use of advanced technology such as haematology analyzers combined with cytometry also provides us the information of blood determinations (Chhabra, 2018). In the cyanmethemoglobin method, lysis of RBCs and the release of haemoglobin occur from the blood samples when mixed with the haemoglobin reagent which is measured colorimetrically. This is the best method for estimation of Hb levels quantitatively (Moritz & Becker, 2010). Iron metabolism is also helpful in the assessment of anemia. Biochemical tests were carried out to check the levels of ferritin, serum iron, transferrin in blood serum and transferrin saturation, as well as total iron binding capacity (TIBC) which are the indicators anemia in piglets (Wish, 2006)

In case of iron deficiency, low levels of ferritin and iron in blood serum whereas high levels of transferrin and TIBC were recorded. Serum iron levels were measured colorimetrically based on the formation of a coloured iron-chromogen complex. Hepcidin levels are measured quantitatively using Mass Spectrometry and Immunochemical parameters. Pig plasma and pig urine helps in determining the Hepcidin levels during iron treatment in piglets (Staroń *et al*, 2015).

Causes of Iron Deficiency Anaemia in Piglets

Iron deficiency is seen mostly in nursing pigs which is a potential problem because the swine producers farrowed litters in concrete confinement that breaks the contact of nursing pig with soil. The causes of IDA are due to the following reasons:

- Very low iron content in the liver of newly born piglets

The baby pigs are born with a total of about 40mg of iron in their body in the form of hemoglobin in blood and storage forms in the liver. They need a daily iron requirement of about 7mg to maintain blood hemoglobin levels in the growing baby pig. Attempts have been made to increase the body iron by administering large amounts of iron to the sow during late gestation by injection or in feed, but have not proven to be successful (Zimmerman *et al*, 2019).

- Low levels of iron content in sow's colostrum and milk

Sow's colostrum and milk contain all nutrients which the piglets require during the growth except iron. The iron concentration in colostrum is not more than 2ppm, and in milk is lower about 1ppm. Due to the low concentration of iron in sows milk, baby pigs cannot obtain more than 1mg of daily iron which is less than the daily requirement of iron 7mg. To increase the iron concentration in milk, sows during late gestation are given with high levels of various forms of iron or by injecting a large amount of iron-dextran.

- Removal of contact with soil and placement in concrete floor

When placed in confinement or concrete floor, pigs cannot obtain their daily requirement of iron from the soil through their snout which is used for digging the soil and obtaining iron from it.

- The fast growth rate of the nursing pigs compared to other species

Nursing piglets have a tremendous ability to grow during the first 6 weeks after birth as compared to other domestic mammals. The fast growth rate of the nursing pig demands high iron intake to maintain the Hb content in the blood.

Status of Iron Deficiency Anaemia

Supplementation of the diet of piglets with hemoglobin efficiently prevented the deterioration of their hematological indices and plasma iron levels, and rescued them from the severe anemia observed in non-supplemented animals. The pig model works aa major mammalian model for human studies because of its similarities in size, physiology, sleep-wake rhythms, organ development, and disease progression, allows for deliberately timed studies and collection of repeated peripheral samples and tissues (Lunney, 2007). Thus, in the present study, we evaluated whether iron content in the plasma and liver displayed diurnal variations in piglets and assessed changes in the diurnal expression patterns of genes related to the regulation of iron uptake and homeostasis.

After birth, Piglets develop anaemia within 10-14 days without additional iron supplementation (Framstad & Sjaastad, 1991). Pig farmers rarely allow for the development of such serious health consequences of irondeficiency in piglets, preventing them from iron supplementation, mainly based on iron dextran administration (Egeli & Framstad, 1999). After intramuscular injection irondextran reaches the lymphatic system, and then blood. There, it is taken up by macrophages (mainly hepatic), whose enzymatic activity leads to the release of iron ions. With the help of ferroportin and ceruloplasmin, iron is transferred from macrophages to blood, where it is bound to transferrin and together with this protein transported to body cells (Svoboda & Drabek 2005). The total amount of iron administered as iron dextran varies from 200 to 400 mg Fe per piglet, which effectively corrects anaemia and prevents its development. Apart from intramuscular injections, per os supplementation is also used. The most frequently orally supplementation is performed by the application of ironfumarate or iron lactate preparations with bivalent iron (Svoboda & Drábek, 2002; Svoboda *et al*, 2004).

Intramuscular administration of large amounts of iron dextran (FeDex) on days 3 to 6 postpartum is current practice in the swine industry (Svoboda & Drabek, 2005; Egeli & Framstad, 1999) and have been proven to rectify the hematological status of piglets. However, it seems unlikely that 100 to 200 mg of iron (a commonly applied dose) is given in a single injection to a piglet with only about 40 to 50 mg of iron in its body at birth (Mahan & Shields, 1998) is efficiently metabolized and detoxified.

Iron supplementation used in treating iron deficiency anemia in piglets

• Iron dextran

Iron dextran is a high molecular compound that can be given orally or intramuscularly (Svoboda & Drábek, 2005). In newborn piglets, iron dextran is utilized routinely for parenteral administration. To attain maximal efficiency, it must be given as soon as possible after birth to avoid a decrease in absorption later due to intestinal closure (Iben, 1998). A study conducted showed that oral administration of 115 mg Fe in form of iron dextran, by giving the first dose of 8–12 h *postpartum* and the second at the age of 12 days, prevented anemia in piglets (Witchi & Heinritzi, 2001). Oral iron dextran showed higher weight gains than piglets given iron by other methods. Also, a single dose of oral administration of 230 mg iron dextran prevented anaemia in piglets and resulted in growth comparable to parenterally treated piglets when given have free access to creep feed containing enough iron (Svoboda & Drábek, 2002).

• Iron salts supplementation

Iron salts contain iron in the bivalent form of Fe^{2+} that is iron sulphate, iron fumarate, and iron lactate. As bivalent iron has almost 16 times better absorption than trivalent iron (Szudzik et al, 2018). Egeli & Framstad (1999) stated that iron given orally is available for haemoglobin synthesis quicker than parenteral iron dextran. The oral administration of iron in the form of salts is considered to be safer than iron injection. Mucosal blockage of iron absorption occurs in the small intestine, when an excess of iron is present in mucosal cells it will get deposited in the form of ferritin to prevent oxidative damage by ionic iron. But a high dose of iron can overcome this blocking mechanism resulting in toxicity (Smith, 1997). Oral fumarate achieved even better efficiency in the preventing of piglet anaemia when administrated on 3 to 8 h following birth compared to 3 days after birth (Kallela & Karlsson, 1972).

Iron salts can bemixed with sphagnum or peat moss, or mixed in a meal or as pellet form. Iron blocks are designed to be secured to the dividing wall between nearby farrowing pens and sometimes iron solutions are also kept in special dispensers. Iron pills, liquid and paste preparations are also given to pigs to prevent anaemia. They are designed to be placed in the creep area of the pen and are effective in preventing anaemia when placed properly in creep area.

- **Iron Chelates**

They very well absorbed as an amino acid complex or small peptides due to their high stability to remain intact in the gastrointestinal tract. Adding 120 mg Fe/ kg in the form of an amino acid complex in the diet of sows improved the iron condition of piglets by placental and mammary transfer of iron but was not successful in replacing parenteral iron administration (Faa & Crisponi, 1999).

Carbonyl Iron

Carbonyl iron powder is made up of elemental uncharged iron which gets absorbed for haemoglobin synthesis in humans and less toxic compared to iron salts (Gordeuk *et al*, 1990). The conversion of carbonyl iron into soluble ionized iron is essential for absorption which is influenced by gastric pH because it's less soluble at a higher pH (Swain *et al*, 2003). A double dose of 230 mg carbonyl iron on days 3 and 9 of life resulted in a increase in Hb but did not prevent the development of anaemia, due to the comparatively high pH of the gastric content in suckling piglets which have a negative effect on its absorption (Svoboda *et al*, 2007).

- **Iron polymaltose complex**

It is a complex of iron and carbohydrate used for anaemia prevention. Iron is released and absorbed gradually from the complex. It's efficient, non-toxic and safe on humans. This complex can be used for the prevention of anaemia in suckling piglets (Svoboda *et al*, 2008).

- **Iron microparticles**

Encapsulation can improve the bioavailability of oral iron. In this, microparticles are used made from iron sulphate and porcine erythrocytes to fight against anemia in suckling piglets under controlled doses (Antileo *et al*, 2016).

Conclusion

In young piglets, iron deficiency anemia was known from several decades, which can lower the growth and development of piglets. Several best methods are available for the diagnosis and prevention of anemia but still the piglets anemia occurs due to the methods followed by farmers and breeders by keeping the sows in confinement zones. Iron treatment to sows will somewhat improve the blood parameters in sow but for the farrowing piglets it would not change much. Iron supplementations are provided to the piglets once the anemia has been diagnosed. Haematological and biochemical parameters are reliable and important for the treatment. There is a huge need to include the advanced methods for diagnosing and treating iron deficiency anemia in the piglets.

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