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Non-Pharmacological Interventions For Anemia: A Systematic Review

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Abstract

Global prevalence of anemia in non-pregnant women of childbearing age is estimated at 29.0% and often occurs in low- and middle-income countries, belonging to low socioeconomic strata. Iron deficiency can cause direct or risky disability. The research determined the effectiveness of Non-pharmacological Interventions for Anemia. The method used was with the help of electronic base data from journals published on PubMed, Proquest, EBSCOhost, and Science Direct, about 6 out of 1186 articles were reviewed. The study found 6 articles with varied respondents using patients, male rats, nurses, Sprague-Dawley (SD) Rattus norvegicus domestica, bovine serum, premature neonates. Non-pharmacological interventions that were developed in overcoming anemia in both human and animal samples and the development of treatment and laboratory examinations in the treatment of anemia were hepcidin expression, HM10760A.

Keywords: Intervention, Non-Pharmacological, Anemia

Introduction

The global prevalence of anemia in non-pregnant women of childbearing age is estimated at 29.0% (WHO, 2012). It commonly occurs in low- and middle-income countries or women with low socioeconomic strata (Zhu et al., 2021). Anemia has multiple direct causes that always coexist: it can be caused by infectious parasites (Kumar et al., 2020), inflammatory disorders (De-Regil et al., 2015), congenital abnormalities of hemoglobin structure, oxidative stress (an imbalance between free radicals and antioxidants), and

deficiencies of vitamins and minerals (vitamins A and B12, and folate, and especially iron) which account for half of the anemia cases (WHO, 2011). Iron deficiency from the long-term imbalance caused by inadequate iron intake, poor absorption or utilization of iron, increased iron requirements, or chronic blood loss (Alleyne et al., 2008).

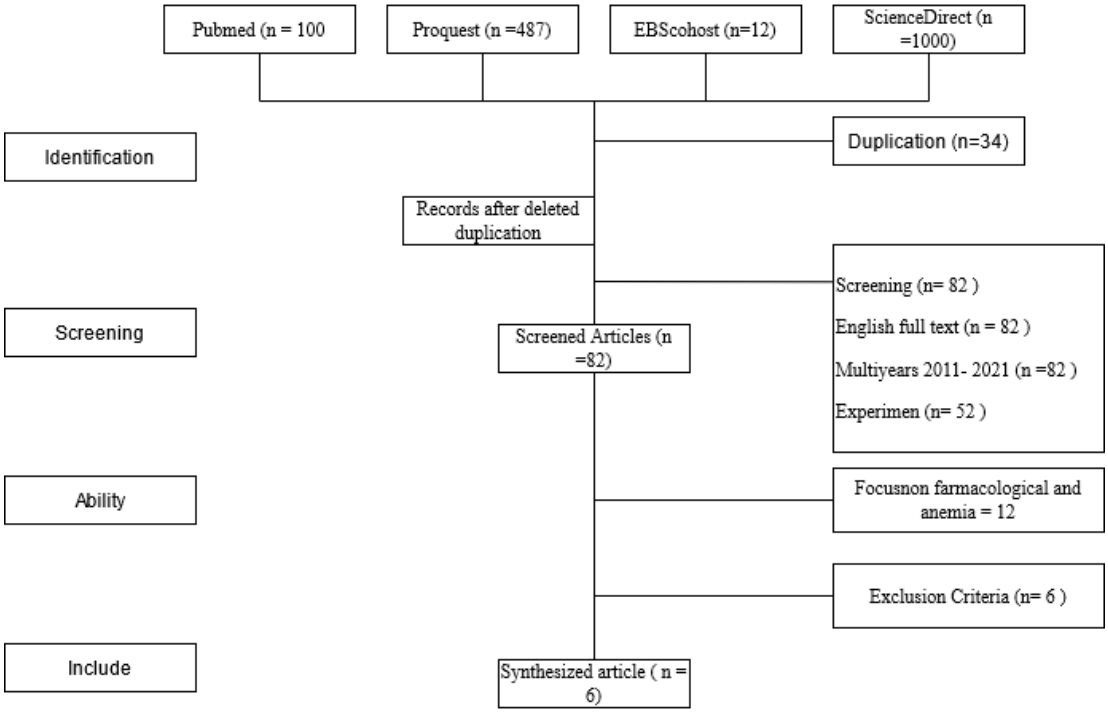
Anemia in women of childbearing age is diagnosed when the hemoglobin concentration in the blood is below 120 g/L, an example that varies with residence, altitude above sea level (altitude), and smoking (Wegmüller et al., 2020). Iron deficiency anemia is diagnosed by the combined presence of anemia and iron deficiency, measured by ferritin (<15 Og/L) or other indicators of iron status such as serum transferrin receptors or zinc protoporphyrin (Wegmüller et al., 2020). Efforts to overcome anemia can be made with pharmacological or non-pharmacological therapy. Pharmacologically, it can be done by consuming iron supplements, vitamin B12, folic acid, and blood transfusions. Also, There are non-pharmacological therapies, such as consuming fruits, dates, vegetables, rosella tea, and Moringa leaf extract, which can be made into juices, puddings, or in the form of tea (Avista, 2019).

Many studies have been carried out to overcome anemia, both in young women and childbearing age women. Indeed, the condition of anemia must be resolved immediately considering the dangerous effects if anemia is just ignored. This situation is a factor in compiling a Systematic Review related to non-pharmacological therapies used to improve anemia (Resmi&Setiani, 2020).The purpose of this study was to determine the effectiveness of Non-pharmacological Interventions for the treatment of anemia.

Materials and Methods

Theprocess in compilingthepublishedjournalarticles in thissystematicreviewreferredto PRISMA forallstages of thereview on 4 electronicbase data, namelyPubmed, Proquest, EBSCOhost, andScience Direct. Thefindingwasbykeywords in English, including "nurse AND nonpharmacologictherapy OR non-pharmacological AND anemia" werethe main searchkeywordthatyielded 1186 articles. Journalswerethenspecifiedbased on theinclusioncriteria, namely(1). Articlespublished in fulltextand English; (2). Articlespublished in thelast 10 years (2011 – 2021); (3). Full article; (4). Type of research Experiment; (5). Duplicate. Afterbeingdeterminedbased on theinclusioncriteria, theremaining 82 articleswereselectedfromthefoursearchdatabaseswiththecontent "NonpharmacologicalandAnemia" anddeterminedbased on theinclusioncriteria, andthenthe rest were 12 articles. Furthermore, it wasselectedagainbased on thepurposeinto 6 articlesandreviewed, as shown in Figure 1.

Figure 1. Prisma Flowchart



Results and Discussion

Nursing Delirium Screening Scale

Nursing Delirium Screening Scale (Nu-DESC) twice daily for the first 3 days after surgery. Further outcome variables were somatic laboratory parameters and variables related to surgery, anesthesia, and postoperative recovery. 10 l of venous or arterial blood was drawn. AChE and BChE were determined with the ChE check mobile from Securetec. Results: Of the 217 patients, 60 (27.6%) developed postoperative delirium (POD). Patients with POD were older (p =0.005), had anemia (p =0.01), and had worsening renal function (p = 0.006). Subsequently, these patients had decreased intraoperative cerebral saturation (NIRS) (p <0.001) and higher intraoperative catecholamine requirements (p =0.03). Delirious patients showed more inflammatory response (p <0.001). AChE and BChE values are mostly in the norm file. Patients with values outside the norm did not have POD more frequently than others. Regarding AChE and BChE patients did not differ in having delirium or not (p > 0.10) (John et al., 2017).

The secondary outcome variables indicated that patients with moderate delirium were older, had anemia, had poorer kidney function, had lower brain saturation during surgery, and had a higher need for noradrenaline. Furthermore, these patients have a higher inflammatory response. The main outcome was that the AChE and BChE values were mainly within the norm and did not differ in patients experiencing postoperative delirium or not. Due to recent studies that considered the important role of AChE and BChE in delirious critically ill patients, this study focused on AChE and BChE in patients No after cardiac surgery and their impact on postoperative delirium. The results did not show any difference in AChE and BChE in patients with delirium compared to those without (John et al., 2017).

Hepcidin Expression

Important to the hepcidin-ferroportin axis in regulating hepcidin expression, controlled by various factors, mainly related to iron abundance and utilization, inflammation, hypoxia erythropoietic activity (Wang et al., 2017). Two main pathways are known to be responsible for hepcidin expression. The iron-mediated

pathway involves the BMP/SMAD signaling pathway, where BMP6 is systemic iron-sensing, capable of inducing hepatic hepcidin expression. It interacts with its receptor, a complex formed by dimerization of type-II and type-I BMP receptors and the co-receptor Hemojuvelin (HJV), with subsequent phosphorylation of SMAD1/5/8, association with SMAD4, and translocation to the nucleus (Poli et al., 2014). The second pathway involves the inflammatory cytokine IL-6 and the JAK/STAT3 pathway (Schmidt, 2015), which cooperates with the BMP/SMAD pathway to stimulate hepcidin expression under inflammatory conditions (Campelo et al., 2018). Hepcidin dysregulation is common in many pathologies related to iron imbalance. Hereditary hemochromatosis is characterized by low levels of hepcidin with consequent iron overload due to genetic mutations in iron-related genes (Brissot et al., 2018) "Refreshing Iron Deficiency Anemia" (IRIDA), a genetic form of anemia, characterized by high levels of hepcidin and consequent iron deficiency anemia severe mutations in Tmprss6 (a serine protease acting on the HJV co-receptor as a negative controller of the BMP/SMAD pathway) (Guillem et al., 2012) and Anemia of Chronic Disease (ACD) or Anemia of inflammation (AI), a common form of anemia caused by chronic disease, infection and/or inflammation, and is characterized by high hepcidin levels and iron deficiency (Poli et al., 2014). Chronic Disease or Inflammatory Anemia and in the form of genetic anemia called IRIDA; Pharmacological downregulation of hepcidin in this disorder may improve anemia. Commercial heparin is a potent inhibitor of hepcidin expression by interfering with the BMP6/SMAD pathway. The non-anticoagulant heparin, modified to remove the anti-thrombin binding site, is equally potent and can improve iron status. Heparin requires 2O- and 6O-sulfation average molecular weight (MW) of up to 4000–8000 Daltons, depending on the degree of sulfation, to perform its anti-hepcidin activity. Pentosane polysulfate (PPS), which shares high sulfate level heparin, is a compound with low anticoagulant activity already used for pharmaceutical treatments (Asperti et al., 2020). Maturing this disease's relevance, many groups studied different pharmacological approaches to modulate hepcidin and restore proper iron homeostasis (Ginzburg, 2019). In particular, we found that heparin is a compound that suppresses hepcidin expression induced by BMP6 and IL6, in vitro and in vivo (Poli et al., 2014).

Pain Identification

Interviewed nurses recognized that children with SCD used verbal or non-verbal communication and identified their crying and complaining as the most common manifestations. Moreover, for young children, the methods for assessing pain are observation of facial expressions, irritation, and moaning; for older children, verbal reports and anxiety. Nurses recognize a child's pain and use pharmacological and non-pharmacological methods to control it but have difficulty assessing (Campelo et al., 2018). The identification of these painful events is based on each child's cognitive development. Until the age of two y.o, the adopted valuation criteria are physiological and behavioral aspects. From this age, the reports about their experiences could evaluate the intensity or severity of the crisis pain. The use of appropriate instruments, such as pain scales, is also possible (Afedi&Aqcsi, 2021). In addition to drug therapy, non-pharmacological strategies (such as emotional support and promotion of comfort) are also helpful in controlling, caring for, and helping children recover. Thus, the attention paid to children with SCD during their painful experience requires skills from the nurse to recognize, evaluate and control pain, always to keep in mind the age and subjectivity of each child when dealing with their behavioral reactions, for integral and humane care. Based on repeated dose toxicity studies for 13 weeks, 2.61 g/kg and 22.03 g/kg can be considered NOAELs (no observed side effect level) in rats and monkeys, respectively. Most of the observations recorded at low and medium dose levels were typical of the pharmacological effects of EPO and were not uniquely associated with HM10760A toxicity. The safety of HM10760A needs to be further confirmed in future clinical studies to elucidate the differences between human and animal physiology (Lim

et al., 2020). Declaration of Competition of Interests The author declares that there is no conflict of interest.

HM10760A

The single-dose and repeated-dose toxicity profiles of HM10760A were characterized after single and repeated i.v doses for a duration of up to 13 weeks in rats and monkeys. Although acute toxicity studies are not mandatory, the more sensitive sex (female) mice in small sizes were used to determine lethal dose before the main toxicity study (13 weeks). As a result, confirmation can be made of the expected pharmacological effect of HM10760A, namely an increase in erythropoiesis. In the main 13-week repeat toxicity study, treatment with HM10760A led to increased erythropoiesis in all testis of the treated group documented with increases in erythrocyte count, Hb level, HCT, and reticulocyte count. Significant increase in absolute and relative spleen weight in moderate-dose males and both sexes in the high-dose group and spleen enlargement in high-dose males correlated with histological changes consisting of minimal to moderate extramedullary hematopoiesis. The increase in bilirubin levels recorded in both sexes reflects increased turnover and degradation of erythrocytes (Lim et al., 2020).

Macroscopically, generalized reddish discoloration or single organ discoloration in some animals treated with moderate doses of HM10760A. Most animals of both sexes treated with high doses of HM10760A were associated with congestion due to polycythemia and an associated increase in HCT values. Cardiac myocardial hypertrophy and increased cardiac weight in animals treated with moderate and high doses of HM10760A were thought to be due to increased cardiac muscle workload. Some of the noted inflammatory and degenerative lesions were mainly associated with thrombosis or vascular lesions. The latter may be a consequence of technically related lesions after repeated venipuncture. Elevated leukocyte and lymphocyte levels in mid- and high- dose females may be associated with these inflammatory lesions and peritonitis, as well as in the kidney comprising an increased incidence and/or severity of tubular basophilia in animals treated with moderate and high doses of HM10760A both sexes, which was still found in convalescent males and correlated with increased kidney weight. In addition, increased interstitial inflammation in males treated with high-dose HM10760A increased pyelitis in convalescent men, chronic necrosis and/or infarction in males treated with high-dose HM10760A, and a single case of periarteritis were found (Lim et al., 2020).

An increased incidence and/or severity of fat changes concomitant with centrilobular hypertrophy was noted in the livers of females treated with medium-dose HM10760A and in animals of both sexes treated with high-dose HM10760A, which is considered adaptive in the absence of other lesions, e.g., apoptosis, necrosis, fibrosis, and others. The increased incidence of reactive alveolar macrophages in men's lungs treated with the combination of medium and high doses of HM10760A with a dose-related increase in lung weight cannot be ruled out with certainty to be a treatment effect. However, the low severity of these lesions is in the background, and the significance is still unclear. The primary test item-associated lesions due to the pharmacological action of the test item were noted in the spleen and bone marrow. They consisted of an increased incidence and/or severity of extramedullary hematopoiesis, particularly erythropoiesis in the spleen of females treated with moderate-dose HM10760A and animals of both sexes with high-dose HM10760A. The increase in granulopoiesis with the M:E Ratio to 70%: 30% may be a secondary consequence of the inflammatory lesion, and therefore reactive or due to the direct action of the test item. These changes were accompanied by bone marrow hypercellularity in animals of both sexes treated with high doses of HM10760A.

In conclusion, the lesions are mainly related to the pharmacological action consisting of changes in the M:E ratio leading to an increase in the RBC count and HCT leading to hemodynamic changes. Inflammatory changes (thrombosis, inflammation, and necrosis) in some organs that cause morbidity are secondary to excessive pharmacological action. EPO is a factor that regulates the production of red blood cells produced in the kidneys according to the concentration of oxygen in the body. Anemia can be corrected by giving EPO to relieve the symptoms of anemia. To compare the in vivo effectiveness of HM10760A with Aranesp or Mircera in an anemia model system, we created a cisplatin-induced anemia rat model (CIA). Following a single administration of Aranesp, Mircera, or HM10760A in CIA mice, the response was characterized by a rapid increase in reticulocyte count that peaked 7 days after dosing, followed by a decrease and return to values close to baseline 10–30 days post-dose. The dose at 52.85 g/kg HM10760A (once) induced the most significant increase in reticulocyte count.

Moreover, reticulocyte stimulation induced by 30 g/kg Mircera was similar to that of 5.27 g/kg HM10760A. In CIA mice, a single i.v administration of 52.85 µg/kg HM10760A increased reticulocyte count, Hb levels, and HCT levels above baseline than 30 g/kg Mircera (data not shown). HM10760A has reduced binding to the receptor relative to EPO, driven mainly by its slower association rate. This slow association may result in a more sustained stimulation of the EPO receptor. Furthermore, the slow rate of association may contribute to clearance mediated receptor avoidance. HM10760A has a novel long-acting mechanism to avoid vascular endothelial mediated clearance through its FcRn-binding property. In addition, the half-life of HM10760A may be increased by conjugation to PEG. Thus, the development of M10760A with prolonged survival in circulation offers the advantages of more precise dosing and may improve adherence and clinical effectiveness compared to the original EPO. HM10760A is a highly purified chemical conjugate of rhEPO, and a 3.4 kDa non-peptidyl PEG linker links HMC001. A rhEPO was first produced by transformed CHO cells in a serum-free medium and then purified. In addition, HMC001 was produced by fermentation converting Escherichia coli as inclusion bodies, followed by sequential refolding and purification. The promotion of erythropoiesis by administering HM10760A can be confirmed by an increase in the reticulocyte level at first. Despite the differences with concentrations, after repeated administration of HM10760A, reticulocyte levels increased to the highest between 6 days and 2 weeks and then returned to levels comparable to those of controls. In addition, an increase in HCT and Hb was observed along with an increase in reticulocyte levels (Lim et al., 2020).

Divalent metal transporter DMT1/SLC11A2

Divalent metal transporter-1 (SLC11A2 / DMT1), also known as DCT1 and Nramp2, uses the H electrochemical gradient, MN as the driving force to transport divalent metal ions as Fe2+ 2+2+, and other metals across the cell membrane. DMT1 I A 62-kDa protein with 12 predictable spanning membrane domains with intracellular N and C termini and I are ubiquitously expressed, most notably in the proximal duodenum, in immature erythroid cells from the bone marrow, brain, and kidney. Enterocytes take up the diet, unbound heme iron in Fe, CD2+ (iron) across the apical membrane via DMT1. This transporter is also involved in iron transport from the endocytic vesicle to the cytosol as part of the transferrin receptor (TfR)-mediated cellular uptake. Kinetic analysis has shown that DMT1 mediates the transport of Fe in a coupled manner with a stoichiometry of 1:1. DMT1 displays a high affinity for Fe2++ and H2++ and H with apparent affinities of 1–5 mM and 1 mM, respectively (Montalbetti et al., 2015). The dysfunction of human T1DM is associated with iron deficiency anemia, iron overload disorders, neurodegenerative diseases (e.g., Parkinson's and Alzheimer's disease), and cancers (colorectal and esophageal adenocarcinoma).

The involvement of DMT1 in this disorder makes this protein a promising target for drug discovery. A specific modulator of DMT1 transport activity could be used as a tool to study the structure and transport mechanism of this transporter and the regulatory authority in iron homeostasis in health and disease. Over the past few years, significant efforts have been devoted to the findings of The new DMT1 modulator. Emerging technologies such as chemical genetic screening have led to the discovery of small molecule compounds that differentiate between non-transferrin bound iron uptake and transferrin-mediated iron uptake. Two small molecules of the compound were reported to block DMT1-mediated iron uptake specifically. More recently, a series of benzylisothiourea and pyrazole derivative compounds were shown to act as potent DMT1 inhibitors. However, there is scarce information about the mechanism of action of this small molecule compound in DMT1 transporting activity. The extended finding was conducted for new small-molecule compounds that specifically block human DMT1-mediated iron uptake. A new compound, pyrimidine 8, mediates a reversible linear noncompetitive inhibition of hDMT1 transport activity. This compound did not affect hDMT1 cell surface expression and showed no dependence with its extracellular pH. To our knowledge, this is the first experimental evidence that DMT1 can be allosterically regulated by pharmacological agents (Wegmüller et al., 2020).

It showed that the noncompetitive inhibition of hDMT1-mediated Fe transport by pyrimidine 8 did not exhibit any dependence on extracellular pH at the measured pH values. In summary, we found that the pyrimidine compound 8 mediates a linear noncompetitive inhibition of hDMT1-mediated Fe2+ 2+ transport activity. This inhibition was reversible, did not affect the transporter's cell surface expression, and showed no dependence on extracellular pH. That is the discovery of pyrimidine.

Conservative Management

The substantial ongoing heterogeneity in clinical practice regarding PDA management was recently highlighted by the European Population-Based Cohort Study (EPICE). It reported that PDA treatment varied from 10% to 39% between regions, and differences in perinatal characteristics could not explain this difference. There is increasing consensus that shunt volume, rather than periodic estimates of transductive diameter, represents a more holistic and accurate measurement of the hemodynamic impact of PDA. The physiology of channel impact is governed by Poiseuille's law, which states that "At constant driving pressure, the fluid flow rate through the tube is directly proportional to the fourth power of the tube radius and inversely proportional to the length and viscosity of the tube. "Management of preterm neonates with PDA remains contentious. The justification for a conservative approach to PDA management arises from the large body of evidence that no benefit of ductal closure is found in prophylactic treatment studies. The conservative approach recommends active management of PDA shunts without administering drugs promoting PDA closure, including fluid restriction, avoidance of anemia, ventilation strategies, and diuretic therapy. It is important to clarify that the conservative approach should not be construed as "avoidance" of PDA assessment, monitoring, or management.

It is also important to recognize that the Conservatives' strategy does not have a strong evidence base in the population of interest, may have potentially harmful side effects, and may expose infants with high volume shunts to significant consequences of ductal patency. The ideal approach to the management of PDA is still unclear. Weld; widely used strategies include universal or targeted prophylaxis, medical and surgical strategies to close a PDA that may be early or late, and finally, a conservative approach to a PDA shunt (14). Trials are ongoing progress to investigate the impact of the conservative approach and investigate the effect of initial targeted therapy based on the PDA risk score. In the meantime, clinicians should use the best available evidence to guide treatment approaches. A comprehensive assessment of the

PDA shunt volume can help delineate the patient with the most significant physiologic disturbances secondary to the volume shunt. This strategy should limit the use of medication, which is potentially harmful, to infants where the benefits outweigh any risks. Thus, a risk-based approach to patient selection for PDA treatment is an emerging area of interest that requires further study (Smith et al., 2018)

Conclusion

Based on the research results from the 6 articles, patients with anemia were given non-pharmacological therapeutic interventions. That was including (1) Nursing Delirium Screening Scale (Nu-DESC) twice a day for the first 3 days after surgery. Further outcome variables were somatic laboratory parameters and variables related to surgery, anesthesia, and postoperative recovery. (2) Regulating the expression of hepcidin, Chronic Disease or Inflammatory Anemia and in the form of genetic anemia called IRIDA; Pharmacological downregulation of hepcidin in this disorder may improve anemia. Commercial heparin is a potent inhibitor of hepcidin expression by interfering with the BMP6/SMAD pathway. The non-anticoagulant heparin, modified to remove the anti-thrombin binding site. It is equally potent and can improve iron status. (3) Identification of pain (emotional support and promotion of comfort). Nurses recognize the child's pain and use pharmacological and non-pharmacological methods to control it but difficult in assessing. (4) Treatment with HM10760A causes increased erythropoiesis. (5) Divalent Metal transporter1 (DMT1) mediates iron absorption through the intestinal mucosa. It facilitates peripheral delivery of iron released by transferrin in the endosome. (6) A comprehensive assessment of the PDA shunt volume can help delineate the patients with the greatest physiologic disturbances secondary to the volume shunt. This strategy should limit the use of medication, which is potentially harmful, to infants where the benefits outweigh any risks.

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