นิพนธ์ต้นฉบับ – Original Article

การประเมินประสิทธิภาพและความปลอดภัยของการให้ธาตุเหล็กทางหลอดเลือดดำ เพื่อเป็นทางเลือกและหรือใช้เสริมการให้เลือดทดแทนในผู้ป่วยทางสูติศาสตร์และนรีเวชวิทยาของโรงพยาบาลศรีนครินทร์ :รายงานเบื้องต้น

ยุทธพงศ์ วีระวัฒนตระกูล, โกวิท คำพิทักษ์, สงวนโชค ล้วนรัตนากร
ภาควิชาสูติศาสตร์และนรีเวชวิทยา คณะแพทยศาสตร์ มหาวิทยาลัยขอนแก่น ขอนแก่น ประเทศไทย

Evaluation of Efficacy and Safety of Intravenous Iron Therapy as an Alternative/Adjunct to Allogeneic Blood Transfusion in Obstetric and Gynecological Cases at Srinagarind Hospital : Preliminary Report

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วัตถุประสงค์ : การศึกษานี้มีวัตถุประสงค์ 4 อย่าง คือ 1.หาอัตราการหลีกเลี่ยงการให้เลือดได้ของผู้ป่วยสูติศาสตร์และนรีเวชวิทยาที่โรงพยาบาลศรีนครินทร์ 2.วิเคราะห์หาปัจจัยสำคัญที่มีผลต่อความสำเร็จในการหลีกเลี่ยงการให้เลือด 3.หาอาการและผลข้างเคียงจากการให้ธาตุเหล็กทางหลอดเลือดดำในการใช้ทางคลินิก 4.เปรียบเทียบความเสี่ยงและประโยชน์ของการให้ธาตุเหล็กทางหลอดเลือดดำชนิด iron-sucrose ในการใช้เป็นทางเลือกทดแทนและหรือเสริมการให้เลือดทดแทน

วิธีการศึกษา : 1.ค้นหาผู้ป่วยสูติศาสตร์และนรีเวชวิทยาที่ได้รับการให้ธาตุเหล็กทางหลอดเลือดดำชนิด iron-sucrose ตั้งแต่มกราคม 2550-กรกฎาคม 2552 2.รวบรวมข้อมูลพื้นฐานของผู้ป่วยเหล่านี้ได้แก่อายุ ความเข้มข้นของเลือดก่อนและหลังการให้ iron-sucrose ปริมาณเลือดที่ออก การให้เลือดทดแทนอาการและอาการข้างเคียงจากการให้ธาตุเหล็กทางหลอดเลือดดำ

ผลการศึกษา : ผู้ป่วย 13 รายจาก 15 ราย ที่ให้ธาตุเหล็กทางหลอดเลือดดำสามารถหลีกเลี่ยงการให้เลือดทดแทน (ร้อยละ 86.7) โดยแยกเป็นผู้ป่วยทางสูติศาสตร์ 5 รายจาก 6 ราย (ร้อยละ 83.3) และเป็นผู้ป่วยทางนรีเวชวิทยา 8 รายจาก 9 ราย (ร้อยละ 88.9) ปัจจัยที่มีผลต่อความสำเร็จในการหลีกเลี่ยงการให้เลือดทดแทน ในผู้ป่วยทางสูติศาสตร์ ได้แก่ ความเข้มข้นของเลือดก่อนการรักษา ปริมาณเลือดที่ออกและความเข้มข้นของเลือดภายหลังการให้ธาตุเหล็กทางหลอดเลือดดำสำหรับในผู้ป่วยทางนรีเวชวิทยา ได้แก่

Objectives: To determine the ratio of obstetric and gynecological (Ob-Gyn) cases at Srinagarind Hospital that can omit a blood transfusion; To analyse the factors effecting the success in omitting blood transfusion; To review the symptoms and side-effects of iron-sucrose in clinical use; and, to compare the risk/benefit of iron-sucrose as an alternative/adjunct to allogeneic blood transfusion.

Methods: We retrieved the records of OBGYN cases between January 2007 and July 2009 that received iron-sucrose (Venofer) as an intervention; and, analysed the data on age, hematocrit before and after intervention with iron-sucrose, estimated blood loss, intervention with blood transfusion, symptoms and side-effects of the iron-sucrose.

Results: Fifteen cases received intravenous iron therapy, 13 of which did not need a blood transfusion (86.7%). Five of 6 obstetric cases (83.3%) and 8 of 9 gynecological cases (88.9%) did not need a blood transfusion. The factors associated with omitting blood transfusion in the obstetric cases included: initial hematocrit, amount of blood loss and hematocrit post-intravenous iron therapy. In the gynecological cases, they were: initial hematocrit, amount of blood loss and type of operation. Only one case in these 15 cases had an adverse

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ความเข้มข้นของเลือดก่อนการรักษา ปริมาณเลือดที่ออก และชนิดของการผ่าตัดในผู้ป่วยที่รับธาตุเหล็กทางหลอดเลือดดำ 15 รายนั้น พบรายงานผลข้างเคียงเพียง 1 ราย คือ รู้สึกออกร้อน หน้าแดง โดยอาการหายไปเมื่อให้ยาในอัตราที่ช้าลงจาก 1 ชั่วโมงเป็น 4 ชั่วโมง หากพิจารณาความเสี่ยงจากการรับเลือดการให้ธาตุเหล็กทางหลอดเลือดดำนับเป็นทางเลือกที่มีคุณค่า แทนการให้เลือด

สรุป : การให้ธาตุเหล็กทางหลอดเลือดดำชนิด iron-sucrose ในผู้ป่วยทางสูติศาสตร์และนรีเวชวิทยาจัดเป็นวิธีที่ปลอดภัยและเป็นทางเลือกที่มีคุณค่า การเลือกใช้อย่างเหมาะสมในผู้ป่วยสามารถหลีกเลี่ยงการให้เลือดทดแทนได้ในร้อยละที่สูง อย่างไรก็ตามยังต้องมีการศึกษาเพิ่มเติมในจำนวนผู้ป่วยที่มากขึ้นเพื่อยืนยันผลการศึกษาต่อไป

คำสำคัญ : ประสิทธิภาพและความปลอดภัย, การให้ธาตุเหล็กทางหลอดเลือดดำ, การใช้เลือดทดแทน, ผู้ป่วยทางสูติศาสตร์และนรีเวชวิทยา

reaction (i.e., feeling hot and flush). These reactions disappeared when the infusion rate was extended from 1 hour to 4 hours. Considering the risk from blood transfusion, intravenous iron therapy represents a valuable alternative.

Conclusions: Intravenous iron therapy with iron-sucrose in Ob-Gyn cases was a safe and valuable procedure. Appropriately selected cases had a high percentage of success in omitting blood transfusion; nevertheless, more cases are needed for confirmation.

Keywords: Efficacy and safety, Intravenous iron therapy, Blood transfusion, Obstetric and gynecological cases.

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Introduction

Obstetric cases, especially the complicated ones, are at high risk of bleeding, and massive bleeding is one of the 4 leading causes of maternal death (*i.e.,* hypertension, embolism, hemorrhage and infection).[1,2] Such bleeding may occur in the first half of pregnancy due to abortion, ectopic pregnancy or molar pregnancy.[3] In late pregnancy, massive bleeding may occur from placenta previa and abruptio placentae. During the intrapartum period, excessive blood loss could be from: dystocia, cesarean section in certain conditions (*i.e.,* placenta previa, uterine atony). In the postpartum period, massive bleeding may occur because of: uterine atony, retained placental fragments, infection or coagulopathy.[1] Among gynecological cases with anticipated blood loss before surgery (*i.e.,* uterine leiomyoma, abnormal uterine bleeding, gynecological cancer) further surgical blood loss may be harmful.[4-6]

Acute blood loss with anemia may occur, making a transfusion inevitable.[7,8] In mild to moderate anemia, without further blood loss, a transfusion may be omitted.[9] Oral iron supplementation about 1 wk will be needed to improve the hemoglobin level compared to only 2-3 days of parenteral iron-sucrose supplementation.[10] Intravenous iron therapy is an alternative/ adjunct to allogeneic blood transfusion in obstetric and gynecological cases at high risk for hemorrhage. When blood transfusion can be omitted, the risks of blood donor transfusion are avoided and the blood supply is conserved[11].

Since 2007, parenteral iron-sucrose has been offered at Srinagarind Hospital in obstetric cases once bleeding has ceased and if the degree of anemia warrants a transfusion. For this research, only the cases that chose the iron-sucrose were recruited. After the intervention, the hematocrit level and clinical symptoms were re-evaluated, and only if necessary, a blood transfusion was given.

Objectives

This study was done to determine (a) the ratio of success vs. non success in omitting blood transfusion (b) the factors affecting, symptoms and side effects of iron-sucrose in clinical use, and risk-benefit of iron-sucrose as an alternative/adjunct to allogeneic blood transfusion.

Methods

This study was reviewed and approved by the Ethics Committee of Khon Kaen University (HE 510707). We conducted a retrospective evaluation (for efficacy and safety) of medical records and laboratory reports of Ob-Gyn cases who received intravenous iron therapy between January 2007 and July 2009 at Srinagarind Hospital.

Results

During the period studied, 15 cases received iron-sucrose instead of blood transfusion: 1 in 6 obstetric cases and 1 in 9 gynecological cases needed a blood transfusion after the iron-sucrose intervention. The ratio of Ob-Gyn cases at Srinagarind Hospital that can omit blood transfusion was 13:15 (86.7%).

The 6 obstetric cases had (a) intervention with iron-sucrose after the bleeding ceased (b) mild to moderate anemia and (c) normal hemodynamics. There was: 1 case of missed abortion; 1 case of massive bleeding from placenta previa that required an emergency cesarean section; 2 cases of normal labor with postpartum hemorrhage; and, 2 cases of cesarean section with intraoperative heavy blood loss. Only 1 case of the 6 needed a blood transfusion (2 units) despite the intervention: this case had massive antepartum hemorrhage from placenta previa and intraoperative blood loss of 1,200 ml. The other 5 obstetric cases, that had had the iron-sucrose intervention, avoided needing a blood transfusion: all 5 felt better, had reduced dizziness and malaise and were satisfied with the treatment. The ratio of obstetric cases that can omit a blood transfusion was 5:6 (83.3%) (Table 1).

Nine gynecological cases received iron-sucrose at hospital before elective surgery; 6 of whom had a hematocrit < 30 vol% (or hemoglobin < 10 g/dL for those who did not meet the criteria for elective surgery). Three of these cases had a hematocrit level just above the criteria. All 9 gynecological cases received 200 mg of iron-sucrose 1–2 days before surgery and their hematocrit level rose to > 30 vol% in the morning of the surgery. Eight cases were able to omit a blood transfusion and had a good hematocrit level without anemic symptoms.

One case, however, could not avoid a blood transfusion. This case was an elderly 67-year-old with a huge ovarian mass. A total abdominal hysterectomy with bilateral salpingo-oophorectomy and omentectomy was performed. The ratio of gynecological cases that was able to omit a blood transfusion was 8:9 (88.9%). (Table 2).

Success in omitting a blood transfusion in obstetric cases depended on the (a) initial hematocrit (b) amount of blood loss and (c) hematocrit post-intervention with iron-sucrose. The lowest hematocrit after intervention with iron-sucrose in obstetric cases that could omit blood transfusion was 21.3 vol%. This patient felt much better and could look after her infant without anemic symptoms. The only obstetric case that needed 2 units of blood transfusion had antepartum hemorrhage with placenta previa totalis and heavy bleeding, before and during cesarean section. This case still had anemic symptoms after intervention with iron-sucrose and the hematocrit level was 20.5 vol% before the transfusion was given.

The success in omitting blood transfusion in gynecological cases depended on the: initial hematocrit, intra-operative blood loss and type of operations. Six of the 9 gynecological cases in the study had a blood concentration that did not meet the criteria for elective surgery.

These 6 gynecological cases had a hematocrit level < 30 vol% on admission. Intervention with iron-sucrose was given after admission and all six then had a hematocrit level > 30 vol% and so met the criteria for elective surgery as scheduled. These 6 gynecological cases were operated for simple hysterectomy and laparoscopic assisted vaginal hysterectomy (LAVH). None of them had a hematocrit < 25 vol%, after their respective surgery, so a blood transfusion was omitted. Three of the 9 gynecological cases had a hematocrit > 30 vol% on admission and all received full supplementation with oral iron tablets before admission. Iron-sucrose was given immediately after admission which was

Table 1 Details of the six obstetric cases

Condition	Age	Initial hematocrit	Procedure	Cause & Estimated blood Loss	Hematocrit before an dafter intervention	Intervention1	Intervention2	Discharge hematocrit
1. Missed Abortion (uterus size 14 wks of gestation)	34	35	Misoprostol vaginal suppositories	Incomplete abortion with 800 ml blood loss curettage performed	24	Iron-sucrose 100 mg and 100 mg in 2 consecutive days	No	26
2. G1P1 36 wks PROM with spontaneous labor	27	32	Normal labor with episiotomy (3100 gm)	PPH at postpartum ward 500 ml	26	Iron-sucrose 200 mg	No	24
3. G1P1 40 wks with spontaneous labor	24	36	Normal labor with episiotomy (3270 gm)	PPH 500 ml at labor room and PPH at postpartum ward 300 ml	25.1	Iron-sucrose 200 mg	No	21.3
4. G1P1 39 wks Infertile	29	34.2	LTC/S	Heavy bleeding 1400 ml	26	Iron-sucrose 200 mg	No	24
5. G3P3 36 wks placenta previa totalis (2nd episode bleeding)	38	32	Emergency LTC/S due to APH 400 ml	LT C/S heavy bleeding 1200 ml	28,20.5	Iron-sucrose 200 mg	Blood transfusion 2 units	30
6. G2P2 38+ wks Induction of labor	23	32	Emergency LTC/S due to cervical dystocia	LT C/S heavy bleeding 1000 ml	26.5	Iron-sucrose 200 mg and 200 mg in 2 consecutive days	No	23

G = Gravida P = Parity PROM = Premature rupture of the membranes PPH = Postpartum hemorrhage

LTC/S = low transverse cesarean section APH = Antepartum hemorrhage

Table 2 Details of the nine gynecological cases

Condition	Age	Admission hematocrit	Intervention1	Hematocrit just before operation	Type of operation	Intervention2	Discharge hematocrit
1. Myoma uteri 16-wk size with hypermenorrhea	44	28.5	Iron-sucrose 200 mg	32	TAH with BSO	No	31
2. Myoma uteri with menorrhagia and anemia	41	29.4	Iron-sucrose 200 mg	31	TAH with Rt SO (myoma with adenomyosis and pelvic endometriosis)	No	31
3. Pelvic mass	67	31	Iron-sucrose 200 mg	33	TAH with BSO omentectomy	Postoperative hematocrit 24% and blood transfusion 1 unit was given	30
4. Myoma 14-wk size with hypermenorrhea	49	28	Iron-sucrose 200 mg	31	TAH with BSO	No	30
5. Subserous myoma	41	28.7	Iron-sucrose 200 mg	31.5	TAH	No	30
6. Myoma 12-wk size with hypermenorrhea	48	32.3	Iron-sucrose 200 mg	35	TAH with BSO	No	33
7. Myoma 10-wk size with hypermenorrhea	50	29.8	Iron-sucrose 200 mg	31	LAVH with Lt SO	No	28
8. Adenomyosis 12 wks sized with hypermenorrhea and anemia	42	29.9	Iron-sucrose 200 mg	31	TAH	No	29
9. Prolapsed submucous myoma 4x5 cm	38	31	Iron-sucrose 200 mg	33	Transvaginal myomectomy	No	31

TAH with BSO = total abdominal hysterectomy with bilateral salpingo-oophorectomy

LAVH = laparoscopic assisted vaginal hysterectomy

Lt SO = left salpingo-oophorectomy

Rt SO = right salpingo-oophorectomy

1–2 days before their respective surgery. All of them had an improved hematocrit; except one elderly patient with a huge pelvic mass who needed a total abdominal hysterectomy with bilateral salpingo-oophorectomy and omentectomy plus 1 unit of blood at ward. The patient was anemic and her post-operative hematocrit was 24 vol%. She might have needed more units of blood if the iron-sucrose intervention had not been provided before her surgery.

Symptoms and side-effects of iron-sucrose were found in 1 of 15 cases. This sole patient was a 41 -year-old with subserous myoma uteri and the side-effect she reported was feeling hot and flushed. After careful evaluation of her symptoms, it was determined beyond these side-effects she was not experiencing any serious adverse effects. Her symptoms might have been from rapid infusion of the iron-sucrose. Because of this case, we later prolonged the infusion time from 1 to 4 hours, with close observation of the patient.

Discussion

Obstetric cases eligible for intravenous iron therapy should be (a) stable (b) without further blood loss (c) have but moderate anemia and (d) be in good hemodynamic condition. Adverse side-effects from intravenous iron-sucrose are relatively rare and not serious as compared with other forms of intravenous iron.[12,13] Intravenous iron-sucrose in cases of scheduled gynecological surgeries—whose hematocrit does not meet, or is just above, the criteria for elective surgery are used for the purpose of omitting blood transfusion. The iron-sucrose intervention can allow the omission of blood transfusion and/or reduce the units of blood should a transfusion be needed. In this study, intravenous iron therapy was on an in-patient basis and the significant rise of blood concentration was between 3 and 5 days after the treatment.[14]

The rising of the blood concentration from this intravenous iron therapy is faster than oral iron supplements which is helpful for cases with limited gastrointestinal absorption.[13] Clinical observation revealed that patients so treated experience a rapid improvement of the well-being.[13]

Some physicians become aware of serious adverse effects of intravenous iron therapy including anaphylaxis and anaphylactoid reaction.[15] These serious side-effects were due to the iron-dextran, (> 100,000 Da, a large molecule)[15]. Iron-sucrose is in the form of an iron hydroxide-saccharate complex (34,000-60,000 Da), and no biological polymers are formed, so anaphylactic reactions are extremely rare.[11,15] The eneral side-effects of iron-sucrose include: metallic taste, feeling hot, nausea, local irritation and dizziness. [11,15] Positron emission tomography (PET scan) studies show an immediate accumulation in the bone marrow. The half-life is 5.5 h and the plasma levels of iron-sucrose return to pre-treatment values within 24 h of administration. Iron-sucrose is rapidly taken up for erythropoiesis.[11]

Since the early 1990s, iron-sucrose (venofer®) has been used during pregnancy and the puerperium at the Zurich University Hospital Obstetric Clinics. The prerequisites for its use are:[11] (1) anemia, Hb < 10 g/dL (2) confirmed iron deficiency (ferritin < 15 mg/L) (3) completion of the first trimester (4) failure of a 14-day course of oral iron therapy (5) no hemoglobinopathy (6) no liver disease (7) no acute or chronic bacterial infection and (8) no known iron overload (e.g., hemochromatosis).

At the Zurich University Hospital, the iron saccharate complex is administered through a venous butterfly cannula. Once correct positioning in the vein has been tested with normal saline, iron saccharate can be administered undiluted as a bolus or diluted (e.g., to 100-200 ml with normal saline) as a short infusion. Administration of a test dose (1 ml) is required in some countries. The subsequent bolus injection is given over 5-10 min, the short infusion over ~20 min. The maximum single dose is 200 mg. Zurich University Hospital generally gives 2 doses/week on an outpatient basis, to achieve a target Hb value of 11.0 g/dL.[11]

In our experience, however, the treatment is given on an in-patient basis. For the first case in our study, we used iron-sucrose (venofer®) 100 mg diluted in 250 ml with normal saline as a slow infusion in 2-4 h under close observation. For the other cases, we used

iron-sucrose 200 mg diluted in 250 ml or 100 ml with normal saline as a slow infusion in 1-2 h. Only in one case was there any reaction—feeling hot and flushed. After careful evaluation, a slower infusion rate of iron-sucrose (over 4 h) alleviated the symptoms.

The overall efficacy and safety of intravenous iron therapy in obstetric and gynecological cases at Srinagarind Hospital are good, such that blood transfusion could be omitted in 86.7% of the cases we studied. Importantly, even the cases requiring blood transfusion after these intervention needed less units of blood transfusion. The factors that affected success were (a) initial hematocrit (b) amount of blood loss (c) type of operation (d) blood concentration after iron-sucrose therapy and (e) patient symptoms. Most obstetric cases are younger than gynecological ones. Three of our 6 obstetric cases had a hematocrit < 25% after intravenous iron-sucrose therapy (21.3, 23 and 24%, respectively). All of them, however, had good clinical symptoms, well-being and a normal postpartum check up without anemia. Likewise all of the gynecological cases had no complications at the 1 month follow up visit.

The infection risks of blood transfusion include parasites, bacteria, viruses and prions that depend on the efficacy of the blood bank. The general incidence of risks of: HIV infection from blood transfusion is 1:1-1:12 million; hepatitis B virus 1:50,000-1:5 million; hepatitis C virus 1:100,000-1:5 million; bacteria 1:2000, CMV, EBV, parasite (e.g., malaria) and prions undefined.[11,16]

The immunological risks of blood products can have either an acute or chronic course: acute hemolytic reaction, late-type reactions, allergies, transfusion-related acute lung injury, transfusion-related graft vs. host disease, post-transfusion purpura, de novo antibodies to blood groups or HLA.[11,16]

Erythrocyte damage caused by storage, increasing storage periods have detectable negative effects on the quality of erythrocytes, and these can result in adverse effects in transfusion recipients. The effect of storage on the properties of erythrocytes include: membrane defects (increased rigidity), reduced 2,3-DPG content, reduced survival, hemolysis, acidosis, hyperglycemia, cytokine accumulation, histamine and kinin accumulation, microaggregation, increased agglutination tendency.[11]

Blood transfusion is necessary to treat acute massive hemorrhage.[7,16] In cases where bleeding has stopped and the hemodynamics are stable with mild to moderate anemia, intravenous iron therapy can be used as an alternative/adjunct to blood transfusion. It is moreover a good way to reduce units of transfusion and obviate the risks of blood transfusion. A further larger study will be needed for confirmation.

Conflict of interest

The authors have no competing interests.

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