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Review Article

"Bloodless Surgery" In Jehovah's Witness-A Critical Review

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Abstract

Jehovah's Witness refuse blood and blood product support even in critical situation due to their religious beliefs. However they do accept any form of medical intervention, including organ transplantation as long as blood or blood products are not used in the procedure. Jehovah's Witness can tolerate acute blood loss because of physiological changes, including compensatory increase of respiratory rate, hyper-dynamic circulation, increasing heart rate, acidosis, increase of 2.3 DPG that shifts oxygen saturation curve to the right with increased release of oxygen to anoxic tissue. But this compensatory mechanism fails if there is more than one fourth of blood loss, especially in an acute situation. This happens during trauma, burns, general surgery or gastrointestinal hemorrhage. Techniques used to minimize blood loss include: perioperative blood salvage using Cell Saver, surgical techniques to prevent intra-operative blood loss, use of anti-fibrinolytics, induced hypotension during surgical procedure, minimizing phlebotomy and iatrogenic blood loss, oxygen while nasal cannula, use of volume expanders, erythropoietin, IV iron and blood substitutes (Table 1).

- Reducing iatrogenic anemia and intra-operative hemorrhage loss
- Maximize blood production by administration of erythropoietin & IV iron
- Maximize cardiac output by alternatives to blood transfusions as crystalloids
- Increase oxygen via nasal cannula
- Decrease metabolic rate
- Blood substitutes (PEGylated bovine carboxy-hemoglobin)
- Use of Hydroxyethyl starch

Table 1: Reducing surgical mortality in Jehovah's Witness

Management of Jehovah's Witness has medical, ethical, social and psychological issues, not only related to the patient and the family but also the medical team involved in the management of these patients. We will review some of these issues in the perioperative management of Jehovah's Witness.

Introduction

The Jehovah's Witness is a Christian religions movement with approximately 7.8 million members worldwide [1]. Their fundamental belief is that blood transfusion is equated with the "eating of blood" and if blood is transfused, it could lead to elimination of any hope for eternal life [2]. Most of the Jehovah's Witness accept crystalloids, colloids, erythropoietin, recombinant coagulation factors and artificial red cell substitutes. Some accept autologous blood transfusion, fresh frozen plasma and blood retrieved through the Cell saver [3]. There are medical, social and ethical issues with Jehovah's Witness, when they require intervention during surgery and in emergency situations including trauma (Table 2).

Ethical issues	Respect autonomy Beneficence - the principle of goodness in action Non-Maleficence – avoiding harmful effect Justice
Medical issues	Ethics of intervention by medical professional Nursing/ancillary personnel unable to perform duties according to their training Patient's conflict of interest between life and their religious beliefs
Social issues	Criminal/ civil based on religious objection Protection of children and adolescents from the religious beliefs Inadvertent use of blood products in unconscious patients

Table 2: Ethical, medical and legal issues in Jehovah's Witness

Because Jehovah's Witness do not accept allogenic blood products, autologous blood transfusion, retrieval of intraoperative cell salvage, hemodilution, hypothermia, a proteinin, DDAVP, antifibrinolytic therapy and hematinic therapy are used in dealing with Jehovah's Witness needing surgical procedures [4-6]. Sometimes to avoid excessive bleeding peri-operatively recombinant factor VIIa has been used with success [7]. The postoperative course of a patient with Jehovah's Witness is better if the patient does have long-standing history of anemia as pre-existing compensatory mechanisms will help the patient to recover from acute blood loss. Patients refusing blood transfusion for various reasons do not appear to have increased incidence of morbidity or mortality following trauma or surgery induced hemorrhage [8]. The exact minimal level of hemoglobin sustaining human brain function is not known, but there are reports wherein patients have recovered completely with their brain function with hemoglobin less than 2 g. following surgical bleed [9]. Following active blood loss there is increase in morbidity and mortality secondary to myocardial ischemia and congestive heart failure [10]. There is conflicting evidence regarding the use of recombinant erythropoietin in morbidity or mortality after surgery [11,12]. Most of the published series with reference to Jehovah's Witness are either limited number of case series or retrospective studies. No prospective controlled trial of surgical management of Jehovah's Witness using recombinant erythropoietin is available. We aim to review the available data in the use of recombinant erythropoietin in surgical management of Jehovah's Witness.

Tolerance of anemia in acute blood loss

Acute reduction of hemoglobin concentration to 7 g/dl does not produce detectable changes in human cognitive function. Further reduction of hemoglobin level to 6 and 5 g/dl produces subtle, reversible increases in reaction time and impaired immediate and delayed memory [13]. Without transfusion, it is possible to survive at low hemoglobin concentrations, while mortality with an unknown incidence is encountered at hemoglobin concentrations below 5 g [14]. Multiple independent factors influence outcome in the severely anemic patient. The relationship between outcome and hemoglobin (Hgb), oxygen extraction ratio (ER), history of cardiac, renal, pulmonary, and/or hepatic disease, diabetes, malignancy, sepsis, hypertension, and active bleeding was analyzed in severe anemia (Hgb less than 7.0 gm/dl, mean = 4.6 +/- .2 gm/dl) to evaluate the effect of Hgb on survival and to look for other predictors of outcome. Active bleeding was a predictor for levels of Hgb below 4.0 gm/dl. Hgb level alone was a significant predictor only at levels below 3 gm/d the strongest being sepsis and active bleeding [15]. Additionally, there is evidence to suggest transfusions in critically ill patients' diminished organ function as well as a higher mortality rate [16].

Recombinant erythropoietin and hemoglobin concentration

Recombinant erythropoietin is a growth factor that stimulates proliferation and differentiation of erythroid precursors, accelerated increase of red cell production and improving hemoglobin from the patient's baseline. There is a timeline between administration of recombinant erythropoietin and increase in the reticulocyte response which takes about 7-10 days [17]. In acute distress states (trauma/surgery) there is transient erythropoietin deficiency and negative feedback to the erythroid precursors and decreased erythropoiesis [18]. Clinical trials have demonstrated a dose-response relationship between erythropoietin and red blood cell expansion [19]. The range in response (erythropoiesis) to dose (erythropoietin) is not related to patient gender or age [20]. There are at least two receptor binding sites for exogenous erythropoietin. High-affinity sites mediate the growth function of erythroid colony forming unit during the first eight hours and low-affinity receptors may mediate some unrecognized erythropoietin function [21].The biologic response is, therefore, maximal at lower levels than the erythropoietin concentration required to saturate all erythropoietin-binding sites [22]. A 72 hour interval between erythropoietin administrations is superior to a 24-hour interval [22]. Erythropoietin therapy stimulates the gradual expansion of erythroid mass [23]. Expansion and maturation of erythroid precursor cells are, therefore, limiting factors in the erythropoietic response to acute blood loss anemia and in treatment strategies using larger erythropoietin dosages. In a study of escalating (400%) erythropoietin dose administered to patients undergoing aggressive phlebotomy, the marrow erythropoietic index increased from 2.9 times (with endogenous erythropoietin stimulation) to 3.6 times over basal rates of erythropoiesis, representing only a 5.8%

increase in erythropoiesis [24].

Discussion

Management during cardiac surgery

Treatment with recombinant human erythropoietin remains unapproved in the US for patients undergoing cardiac or vascular surgery, but it is a valuable adjunct in Jehovah's Witness patients, for whom blood is unacceptable [25].The bloodless surgery strategy involved preoperative hematopoiesis with recombinant human erythropoietin and iron, intraoperative acute normovolemic hemodilution, the use of a cell-saver system, administration of high-dose tranexamic acid, controlled hypotension, avoidance of low body temperature, simplification of the surgery, and lower blood dilution during cardiopulmonary bypass [26]. The three main aims in treatment of Jehovah's Witness are: the volume of red blood cells should be increased before surgery, the volume of blood loss should be minimized during surgery and finally bleeding should be prevented after surgery [27]. Ratcliff et al reported successful outcome in Jehovah's Witness achieved by preoperative erythropoietin, preoperative iron administration, selection of a cardiopulmonary bypass circuit specific to the patient's height and weight, acute normovolemic hemodilution, retrograde autologous prime and venous autologous prime, tranexamic acid administration, zerobalance ultra-filtration, flushing of the pump suckers post- cardiopulmonary bypass, modified ultra-filtration, and cell salvage. Successful outcome of cardiac surgery even in neonates has been recorded using this method [28]. Major progress to maintain stability in cardiac surgery were multifactorial: preoperative erythropoietin in order to reach an hemoglobin minimal value of 14 g., warm blood cardioplegia, ultra-early extubation to achieve the with an equivalent risk to that of classical surgery, despite an operative risk aggravation, due to the association of recent conservative techniques [29]. Complex open heart operations were performed without homologous transfusion by optimally applying currently available blood conservation techniques including the use of (l) aprotinin (full Hammersmith regimen), (2) high-dose erythropoietin, (3) 'maximal'-volume intraoperative autologous blood donation, (4) low-prime cardiopulmonary bypass, (5) exclusive use of intraoperative cell salvage, and (6) continuous reinfusion of shed mediastinal blood [30]. Hematocrit recovery shows a 1-week lag in severely anemic postsurgical patients treated without recombinant erythropoietin. Exogenous recombinant erythropoietin appears to accelerate hematocrit recovery in the first week. Use of recombinant erythropoietin in the immediate postoperative period may help avoid or reduce homologous blood transfusion [31]. Erythropoietin made surgery for aortic coarctation possible in a Jehovah's witness patient [32]. Erythropoietin therapy contributed substantially to the successful outcome of in skull-base surgery [33]. Successful surgery is a reported in massive descending thoracic aneurysm in a Jehovah's witness treated with thromboexclusion with preoperative erythropoietin therapy was used [34]. Twenty-four patients survived and are alive and well after open-heart surgery using preoperative erythropoietin [35]. A total of 322 Jehovah's Witness patients and 87 453 controls (non-Jehovah's Witness) underwent cardiac surgery. Jehovah's Witness patients do not appear to be at increased risk for surgical complications or long-term mortality when comparisons are properly made by transfusion status. Thus, current extreme blood management strategies do not appear to place patients at heightened risk for reduced long-term survival [36]. As the practice of cardiothoracic surgery continues to evolve in the face of an aging population and increasing comorbidities, patients are being offered options that once may have been considered off limits, often without guidelines or consensus available to guide the surgeon or the Jehovah's Witness patients [37]. Out of 35 Jehovah's Witness patients 18 underwent coronary artery bypass graft with the mean decrease of hematocrit serum levels was 12.5±5.4% and 4 patients died in the perioperative phase [38]. Key points that contributed to success in surgery were optimal preoperative hematopoietic conditioning using erythropoietin and iron, a miniaturized cardiopulmonary bypass circuit including a low prime volume oxygenator and crystalloid cardioplegia, and a well-coordinated multidisciplinary team [39]. Successful allograft root re-replacement for prosthetic valve endocarditis with improvement of renal function in a Jehovah's Witness patient without the use of blood products [40]. Total aortic arch replacement for the treatment of kommerell's diverticulum in a jehovah's witness [41].

Management in non-cardiac surgery

Treatment with recombinant erythropoietin increases preoperative Hb levels to a point making it possible to compensate for operative blood loss. Recombinant erythropoietin combined with daily iron substitution may be useful in patients who refuse transfusion based on religious convictions [42]. There is a case report of acute blood loss following surgery with an extremely low hematocrit (despite her Hb levels (2.8 g/dL). Patient remained lucid and later when the patient lost consciousness (Hb, 1.4 g/dL), was promptly sedated, curarized, and put onto mechanical controlled ventilation. Aggressive erythropoietin therapy increased the patient's Hb level by 240% in 10 days, and patient recovered. This demonstrates that critical levels of oxygen delivery may be lower than previously thought possible [43]. Successful craniomaxillofacial surgery in the Jehovah's Witness patient was performed with a management protocol developed utilizing preoperative erythropoietin and ferrous sulfate therapy, intraoperative in-line normo-

volemi chemodilution, and meticulous intraoperative hemostasis which allows us to perform major craniomaxillofacial reconstructions in Jehovah's Witness patients without the use of homologous or predonated autologous blood transfusions [44]. According to Hableret al. the cornerstones of treatment include: 1) education of the patient about blood conservation techniques generally accepted by Jehovah's Witnesses, 2) preoperative optimization of the cardiopulmonary status and correction of preoperative anemia without blood product support, 3) perioperative collection of autologous blood, 4) minimization of perioperative blood loss and 5) utilization of the organism's natural anemia tolerance and its acute accentuation in the case of life-threatening anemia [45]. Despite a preoperative hemoglobin level of 5.1 g, curative pancreaticoduodenectomy was successfully performed using preoperative erythropoietin [46]. The use of rFIX, rFVIIa, erythropoetin, iron, and tranexamic acid before, during and after scoliosis surgery may be a viable and safe option for hemophilia patients with inhibitors, who refuse blood products [47]. Recombinant erythropoietin enables use of haemodilution to minimise red cell loss during the explant procedure, and auto transfusion to raise the haematocrit after haemostasis is secure in Jehovah Witness patients who had successful liver transplantation without blood transfusion [48]. The duration and extent of acute hemodilution that the human body can withstand remains unclear. Many consider 184 mL/m/min to be the oxygen delivery (Do2) threshold below which oxygen consumption (Vo2) begins to decrease. There is a case report of a critically ill Jehovah's Witness patient who tolerated a much lower level of Do2, coupled with severe acute anemia that persisted for >10 days without any sequelae [49]. Successful management of severe blood loss after tumor resection is reported in a Jehovah's Witness who recovered under a therapy regimen of recombinant human erythropoietin and parenteral iron [50]. Erythropoietin therapy contributed substantially to the successful outcome of in skull-base surgery [33]. The use of rFIX, rFVIIa, erythropoetin, iron, and tranexamic acid before, during and after scoliosis surgery may be a viable and safe option for hemophilia patients with inhibitors, who refuse blood products [47]. Successful use of temporary balloon occlusion to minimize blood loss during an open reduction internal fixation of a both-column acetabulum fracture in a Jehovah's Witness patient [51]. The authors of this report describe a transfusion-free protocol with acceptable morbidity and mortality in noncardiac surgery in 48 Jehovah's Witnesses. Infectious complications due to transfusion are avoided; anemia is managed mainly with prophylactic erythropoietin, IV iron therapy, and volume support; and thrombocytopenia is managed solely with the use of hemostatic agents, vitamin K, and oprelvekin [52]. Post-operative recombinant human erythropoietin, along with parenteral iron and adequate nutrition, may be useful in patients who refuse transfusion or cannot be transfused because of difficult cross-reacting antibodies in a Jehovah's Witness [53]. Erythropoietin was used successfully in a Jehovah's Witness infant for left upper lobectomy because of congenital lobar emphysema [54]. The efficacy of erythropoietin and IV iron in salvaging patients from life-threatening anemia following surgery [55]. Recombinant human erythropoietin was used successfully in a Jehovah's Witness requiring major reconstructive surgery requiring a major operation in preoperative and perioperative period [56]. Despite significant anemia, a child successfully underwent hemi-spherectomy with the child's hematocrit sufficiently increased by the use of erythropoietin, so that a two-stage could be performed without blood transfusion [57]. In rapidly progressing primary biliary cirrhosis liver transplantation was done with the use of preoperative recombinant human erythropoietin [58].

Conclusion

Use of recombinant erythropoietin in cardiac and noncardiac surgeries appears to be valuable. In most of the studies recombinant erythropoietin is used along with other agents including a Aprotinin, Tranexamic acid, DDAVP, IV iron and blood salvage measures including autologous blood collection and Cell Saver system. There are many case series where successful outcome is reported after surgical intervention with and without erythropoietin. There are no published prospective controlled studies in surgical procedures with and without recombinant erythropoietin therapy. Erythropoietin has a lag period of about 7-10 days; this agent may not be of great value in massive blood loss following surgery. We need prospective controlled trials for recombinant erythropoietin to be approved by regulatory agencies in US and Europe for this indication

Future direction

Blood substitutes including PEGylated bovine carboxyhemoglobin has been found efficacious in salvaging patients from acute blood loss. Other agents including recombinant factor VII concentrate, anti-fibrinolytic therapy and hyperbaric oxygen have been used in critical care units with reasonable success. Non-surgical treatment of malignant tumors include stereotactic radio-surgery, radiofrequency ablation, biologicals (vascular endothelial growth factor inhibitor), targeted therapy (use epidermal growth factor therapy, EML4 alk inhibitor, checkpoint inhibitors whenever appropriate for the treatment of lung cancer, renal cell carcinoma and melanoma), anti-fibrinolytics and PEGylated erythropoietin have been valuable in selected situations. However IV iron, erythropoietin and uses Cell Saver with other blood conservation techniques appears to be backbone in the management of Jehovah's Witness in the perioperative period.

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