Focused Update: Perioperative Management of Jehovah’s Witness Patients in Relation to Their Refusal of Allogeneic Blood Transfusion

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1. GENERAL CONSIDERATIONS

The religious organization of Jehovah’s Witnesses (JW) numbers approximately 7.6 million members worldwide. The most important particularity of surgical JW patients consists in their strict refusal of allogeneic blood transfusion (red blood cells [RBC], plasma and platelets), even in the presence of life-threatening anemia and/or coagulopathy. However, today JW patients can undergo major surgical procedures without facing an excessive risk of death1-3 – provided that a prospectively conceived and structured perioperative management is applied.

This perioperative management focuses on the prevention of lethal anemia and coagulopathy. The cornerstones are (1) the preoperative optimization of cardiopulmonary status and the correction of preoperative anemia and coagulopathy, (2) the perioperative collection of autologous blood, (3) the minimization of perioperative blood loss and (4) the utilization of the organism’s natural tolerance to anemia and its acute accentuation in the case of life-threatening anemia. Concurrently, it is essential to evaluate as early as possible the JW patient’s acceptance of the different blood conservation techniques and, if necessary, to update the patient on the techniques generally accepted by the JW community4, 5.

2. PREOPERATIVE MANAGEMENT

2.1. DIAGNOSIS AND TREATMENT OF CARDIOPULMONARY MORBIDITY

In the presence of major blood loss and subsequent severe dilutional anemia, the heart is simultaneously the main compensatory organ for anemia (increased cardiac output) as well as the organ at highest risk for anemic hypoxia. Preoperative restriction of cardiac performance should be identified early, evaluated, and improved maximally until the day of surgery. The same applies to the pulmonary status. With worsening anemia, the role of physically dissolved plasma oxygen (O₂) in preserving tissue oxygenation increases. Maximal use of supranormal inspiratory O₂ fractions (hyperoxic ventilation, see below 6.3) requires optimal pulmonary function.
2.2. IDENTIFICATION AND CORRECTION OF PREOPERATIVE ANEMIA AND COAGULOPATHY

In a retrospective analysis of JW patients undergoing non-cardiac surgery, a preoperative hemoglobin (Hb) concentration <10 g/dL significantly correlated with increased postoperative mortality, particularly in patients at elevated cardiac risk and with a perioperative drop of Hb ≥4 g/dL. In the optimal situation, the JW patient should enter surgery with a normal Hb level. Straightforward algorithms (e.g. Figure 1) allow general practitioners to differentiate between the major causes of anemia (iron deficiency, renal anemia and anemia of chronic disease) and to start the appropriate corrective treatment ahead of an operation.

In analogy to preoperative anemia, preoperative coagulopathy should be identified and likewise cor-

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Algorithm for the identification, differentiation and therapy of preoperative anemia
Adapted from Goodnough et al.

1. **Hb** < 12 g/dL for females
   - Evaluation necessary
   - **Iron status?**

2. **Iron deficiency**
   - Consider referral to gastroenterologist to rule out malignancy

3. **Iron therapy**
   - 1) Oral iron in divided doses
   - 2) IV iron if intolerance to oral iron, gastrointestinal uptake problems (hepcidin), or short timeline before surgery

4. **Serum creatinine Glomerular filtration rate**
   - Abnormal
   - Normal

5. **Suspected renal anemia**
   - Consider referral to nephrologist

6. **Anemia of chronic disease**
   - No response

7. **Recombinant human erythropoietin**
   - Folic acid and/or vitamin B12 therapy

**Abbreviations:** Hb, hemoglobin concentration; SF, serum ferritin; TSAT, transferrin saturation; IV, intravenous.
rected. Specific attention should be focused on the reasonable interruption of any pharmacological treatment impairing plasmatic coagulation and/or platelet function.

2.3. ACCEPTANCE OF BLOOD CONSERVATION TECHNIQUES

It is essential to clarify as early as possible the JW patient’s acceptance or refusal of blood conservation techniques prior to surgery and to document each decision in writing (Table 1). Necessary education of the patient is supported by members of the local or regional JW Hospital Liaison Committee.

ANH and CS are individually accepted. Some JW patients may require that the patient, collection system, processing unit and blood bag are continuously connected and form a constantly closed system (“closed circuit”). Irradiation of CS blood is individually accepted despite short-term separation between the patient and blood bag.

3. PERIOPERATIVE COLLECTION OF AUTOLOGOUS BLOOD

3.1. ACUTE NORMOVOLEMIC HEMODILUTION

ANH consists of the isovolemic exchange of whole blood with a cell-free crystalloid (3:1 exchange) or colloid solution (1:1 exchange) directly prior to surgery. Depending on the targeted hematocrit (Hct) value (usually 21–30%), a variable amount of fresh autologous whole blood, including platelets and coagulation factors, is withdrawn from the patient.

Acceptance and refusal of blood conservation techniques by JW patients

<table>
<thead>
<tr>
<th>BLOOD CONSERVATION TECHNIQUE</th>
<th>ACCEPTANCE BY JEHOVAH’S WITNESSES</th>
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<tbody>
<tr>
<td>Preoperative autologous donation (PAD)</td>
<td>No</td>
</tr>
<tr>
<td>Acute normovolemic hemodilution (ANH)</td>
<td>(Yes) — Precondition: closed circuit</td>
</tr>
<tr>
<td>Intra- and postoperative cell salvage (CS)</td>
<td>(Yes) — Precondition: closed circuit</td>
</tr>
<tr>
<td>Irradiation of CS blood in case of malignant tumor surgery</td>
<td>(Yes) — Individual decision</td>
</tr>
<tr>
<td>Recombinant human erythropoietin (rHuEPO)</td>
<td>(Yes) — Precondition: albumin-free preparation</td>
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<tr>
<td>Fibrinogen concentrate, prothrombin complex concentrate (PCC), factor XIII concentrate, cryoprecipitate</td>
<td>(Yes) — Individual decision</td>
</tr>
<tr>
<td>Recombinant activated factor VII (rFVIIa)</td>
<td>Yes</td>
</tr>
<tr>
<td>Antifibrinolytics, desmopressin</td>
<td>Yes</td>
</tr>
<tr>
<td>Isolated hemoglobin solutions (human/bovine)</td>
<td>(Yes) — Individual decision</td>
</tr>
<tr>
<td>Perfluorocarbon emulsions</td>
<td>Yes</td>
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</table>

Table 1
The presence of a tumor does not contraindicate ANH. Monitoring of the intravascular volume status in the presence of extreme ANH (Hct <21%) is difficult and requires at least the continuous measurement of central venous pressure (CVP). Superior monitoring modalities include the continuous monitoring of ventricular stroke volume variation, the intermittent measurement of intrathoracic blood volume, or the evaluation of ventricular filling with transthoracic or transesophageal echocardiography.

3.2. INTRAOPERATIVE RED CELL SALVAGE
ICS consists of the collection, washing and retransfusion of autologous blood directly aspirated from the surgical field. The technique produces an autologous packed red blood cell (pRBC) unit with a hematocrit ranging from 60 to 70% that is devoid of any coagulation components and platelets. In tumor surgery, ICS is possible if the processed pRBC concentrate is gamma irradiated (50 Gray).

4. MINIMIZATION OF INTRAOPERATIVE BLOOD LOSS
Several measures allow surgeons and anesthesiologists to control the amount of blood loss should intraoperative hemorrhagic complications arise (Table 2).

4.1. SURGICAL TECHNIQUE, PATIENT POSITIONING AND CHOICE OF ANESTHESIA
The most effective measure to control bleeding and to avoid allogeneic transfusions consists in an experienced, rapid and skilful surgical technique. Besides the problem-oriented planning of the type of surgery (e.g. preference for minimally invasive techniques), the choice of anesthesia (preference for regional rather than general anesthesia), positioning of the surgical site at or even above heart level (e.g. 20° Trendelenburg or lateral position) to reduce hydrostatic venous engorgement, atraumatic tissue dissection (e.g. water-jet or ultrasound dissection), as well as application of technical and pharmacological adjuvants (e.g. argon beam coagulator, fibrin glue, local hemostatics) to effectively control small sources of bleeding early are essential. Anticipation by the surgeon and—in the presence of an imminent severe bleeding problem—a strategic change towards interruption of an unfinished operation require close communication between the surgeon and the anesthesiologist, both of whom should be experienced in the treatment of JW patients.

4.2. MANAGEMENT OF TEMPERATURE, PH AND CENTRAL VENOUS PRESSURE
The activity of coagulation factors as well as platelet function are temperature and pH dependent. Thus, normothermia should be maintained by effective

<table>
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<th>Possibilities to minimize intraoperative blood loss</th>
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<tr>
<td>Skilful surgical technique</td>
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<td>Positioning of the surgical field above heart level</td>
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<td>Regional anesthesia</td>
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<tr>
<td>Maintenance of normothermia</td>
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<tr>
<td>Maintenance of a physiologic pH</td>
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<tr>
<td>CVP management</td>
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<tr>
<td>Deliberate hypotension</td>
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<tr>
<td>Choice of infusion solutions that have no effect on coagulation</td>
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<tr>
<td>Early onset of coagulation management: administration of fibrinogen concentrate, cryoprecipitate, prothrombin complex concentrate (PCC), antifibrinolytics, desmopressin, factor XIII concentrate, recombinant activated factor VII (rFVIIa)</td>
</tr>
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</table>

Table 2
warming of the patient and infusion solutions. An improvement of coagulation by the correction of acidosis has not been demonstrated so far. During liver resection, the reduction of CVP (anti-Trendelenburg positioning, reduction of positive end-expiratory pressure) significantly reduces blood loss. Special attention should be paid to the risk of air embolism in the presence of iatrogenic CVP reduction.

4.3. DELIBERATE HYPOTENSION

Deliberate hypotension (DH) consists of the intentional, pharmacological reduction of the systolic arterial pressure to 80 mmHg or of the mean arterial pressure to 50 mmHg with a view to reducing arterial BL in the surgical field. Due to the risk of tissue hypoperfusion and organ dysfunction, ‘classic’ DH should be reserved for patients without coexisting cardiopulmonary morbidity.

4.4 FLUID MANAGEMENT

To prevent direct impairment of coagulation during blood loss by the fluid therapy itself, infusion solutions devoid of effects on coagulation (electrolyte-balanced crystalloids, low-molecular-weight hydroxyethyl starch [HES] solutions with a low degree of substitution—not exceeding 50 mL/kg BW/day—gelatin or human albumin solution) should be preferred.
4.5 COAGULATION MANAGEMENT

Fluid therapy for blood loss causes dilution of all components of the coagulation and fibrinolytic systems and finally results in “dilutional coagulopathy”. The first coagulation factor that falls below a level requiring substitution is fibrinogen (i.e. <150 mg/dL), followed by coagulation factors of the prothrombin complex and, finally, platelets. While moderate dynamics of blood loss allow a differentiated coagulation management on the basis of the results obtained with thromboelastography, the lack of this analytic measure and/or the presence of more severe blood loss require the early and calculated administration of procoagulant factors such as fibrinogen concentrate and prothrombin complex concentrate (PCC) and/or antifibrinolytic agents such as tranexamic acid.

The therapeutic administration of desmopressin mobilizes available factor VIII, increases the activity of von Willebrand factor and stimulates platelet aggregation. Clot stability may additionally be increased by the administration of factor XIII concentrate. In case of massive bleeding, the “off-label” early administration of recombinant factor VIIa (rFVIIa) may be considered (Figure 2, Table 3). However, the maximum effectiveness of this coagulation factor depends on stable general conditions for coagulation, particularly normothermia, normal pH and adequate platelet count.

5. TOLERANCE OF DILUTIONAL ANEMIA

Should intraoperative BL occur, the JW patient benefits from the fact that normal tissue oxygenation does not depend on a physiologic Hb level. In surgical patients operated under general anesthesia, extreme normovolemic dilutional anemia, with Hb as low as 1.1–3 g/dL, has been survived without organ dysfunction. This reflects the large natural tolerance to anemia when cardiopulmonary function is normal. The situation is different for the compromised heart with restricted coronary reserve where signs of myocardial ischemia and/or functional deterioration already appear at higher Hb levels (7–10 g/dL).

The importance of perioperative dilutional anemia on vital outcomes can be estimated on the basis of

<table>
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<th>Dosage of procoagulant drugs in massive blood loss</th>
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<tr>
<td><strong>Fibrinogen concentrate</strong></td>
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<tr>
<td>Target: plasma fibrinogen concentration &gt;150 mg/dL</td>
</tr>
<tr>
<td><strong>Prothrombin complex concentrate (PCC)</strong></td>
</tr>
<tr>
<td>Target: Prothrombin time (PT) &gt;30–40%</td>
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<tr>
<td><strong>Tranexamic acid</strong></td>
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<td></td>
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<tr>
<td><strong>Desmopressin</strong></td>
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<tr>
<td><strong>Factor XIII concentrate</strong></td>
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<tr>
<td><strong>Recombinant factor VIIa</strong></td>
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Table 3
the results of large clinical studies (generally performed in JWs) investigating the relationship between postoperative anemia and mortality. Down to a postoperative Hb of 8 g/dL, no statistical relationship between anemia and mortality could be detected, even in elderly patients with preexisting cardiopulmonary disease and in intensive care patients with multiple morbidities. In anemic patients (Hb <8 g/dL), whose death was causally related to anemia, Hb was always below 5 g/dL.

6. THERAPEUTIC INCREASE OF TOLERANCE TO ANEMIA

In case of unexpected massive blood loss, the tolerance to anemia of the JW patient can be rapidly and effectively increased via the following measures (Table 4).

Since hypothermia impairs coagulation (see 4.2), it should only be used in non-bleeding patients (e.g. in the intensive care unit setting).

6.1. RESTORATION AND/OR MAINTENANCE OF NORMOVOLEMIA

The basic prerequisite for the effective compensation of dilutional anemia is normovolemia.

6.2. MYOCARDIAL FUNCTION

Situations accompanied by an increase of myocardial O2 demand (tachycardia, increase of ventricular wall tension, increase of myocardial contractility) must be avoided. The early continuous infusion of norepinephrine compensates for the dilutional decrease of systemic vascular resistance and thus stabilizes the coronary perfusion pressure (experimental data).

6.3. INSPIRATORY O2 FRACTION (FiO2)

Ventilation with a supranormal FiO2 (hyperoxic ventilation) increases the physically dissolved fraction of arterial O2 content. Physically dissolved plasma O2 is biologically highly available and covers up to 75% of total O2 demand in conditions of extreme dilutional anemia (experimental data).

6.4. MUSCULAR RELAXATION

Striated skeletal muscles count for approximately 30% of the total body mass. Muscular relaxation significantly reduces total O2 demand and increases tolerance to anemia (experimental data).

6.5. HYPOTHERMIA

Hypothermia reduces total O2 demand. Due to the negative impact of hypothermia on coagulation, the intentional induction of hypothermia in bleeding patients in order to increase tolerance to anemia cannot, however, be recommended.

6.6. ADEQUATE DEPTH OF ANESTHESIA

Given that almost all anesthetic drugs investigated suppress the cardiac output response to dilutional anemia and thus reduce tolerance to anemia, overly deep anesthesia should be avoided to the same extent as anesthesia that is too light (increased sympathetic tone and O2 demand).

<table>
<thead>
<tr>
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<tr>
<td>Restoration and/or maintenance of normovolemia</td>
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<tr>
<td>Hyperoxic ventilation (FiO2 1.0)</td>
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<tr>
<td>Adequate depth of anesthesia</td>
</tr>
<tr>
<td>Continuous infusion of norepinephrine</td>
</tr>
<tr>
<td>Muscular relaxation</td>
</tr>
<tr>
<td>Hypothermia</td>
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</table>
6.7. CHOICE OF THE INFUSION SOLUTION
While 3% gelatin and 6% HES 200.000/0.5 did not affect anemia tolerance in animals, an advantage of 6% HES 130.000/0.4 could be demonstrated over 3.5% gelatin, 6% HES 450.000/0.7 and Ringer’s lactate solutions. The administration of fluids with intrinsic O₂ transport capacity (artificial O₂ carriers containing isolated human or bovine Hb; perfluorocarbons) increases the tolerance to anemia in animals and humans. To date no artificial O₂ carrier is approved for clinical use in the USA or in Europe.

7. POSTOPERATIVE MANAGEMENT
JW patients with severe postoperative anemia (Hb <5–6 g/dL in young healthy patients, Hb <8 g/dL in elderly patients with cardiopulmonary comorbidity) should be kept under observation in an intensive care unit. If anemia worsens, the indication for a surgical reintervention must be confirmed immediately. Induction of general anesthesia, intubation and hyperoxic ventilation as well as muscular relaxation should be considered early. Optimal basic conditions for coagulation must be ensured and antifibrinolytic treatment should be initiated early. If possible, postoperative cell salvage of drainage blood should be performed. Laboratory tests should be reduced to a minimum and, if necessary, should be performed with low volume (e.g. pediatric) blood sampling systems. Erythropoiesis should be stimulated by the administration of intravenous (IV) iron (e.g. ferric carboxymaltose 1000 mg weekly), vitamin B₁₂ (1 mg IV daily) and folic acid (20 mg IV on alternate days), as well as recombinant human erythropoietin (40,000 IU SC weekly).”

REFERENCES