911! It’s a bleeding tonsil...with Hemophilia A!

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Objectives:

1. Discuss the preoperative considerations for a patient with a post operative bleeding tonsil.
2. Discuss the anesthetic management of the patient with a post operative bleeding tonsil and hemophilia.
3. Understand the pathophysiology of hemophilia A and the options for hemostatic management.
4. Describe the pathophysiology of malignant hyperthermia and the risk for having this condition with a positive family history.

Stem:
As the anesthesiologist on call, you receive a page from the ENT surgeon to inform you that a young boy just presented in the emergency department who had his tonsils out last week and is now bleeding. Oh, and by the way, he has hemophilia...

You arrive in the emergency department (ED) to find a 4 year old boy who is awake and alert, but pale, tachycardic and in mild distress. Pulse 143 | Temp 98.1 | Resp 20 | Wt 16.9 kg | SaO2 98%. Per the parents, he had an episode of hematemesis approximately 1 hour prior to arrival in the ED and vomited about ½ cup of blood with clots. Since his arrival in the ED, he has had 4 more episodes of large frank and dark bloody emesis. His PICC line is accessed and he is receiving a NS bolus of 20ml/kg. You are told labs have been drawn and sent, and hematology has been paged.

Questions:

1. How do you assess this patient’s volume status? What are your priorities for resuscitating this patient? What further information would you want concerning this patient’s hemophilia? What labs do you want to see?
2. Assuming the patient is relatively stable, what further information and preparation do you want before taking this child urgently to the operating room? What equipment do you want available? What types of fluid do you want available? What if the patient is unstable and needs to go emergently?
Following the fluid bolus of 20ml/kg NS, the patient’s HR is 120 and the rest of his vital signs remain the same. His lab results come back including WBC 17.1/Hgb 7.6/Hct 24/plt 680. CBC following his tonsillectomy 10 days prior was WBC 13.3/Hb 8.6/Hct 26.7/Plt 407. Factor VIII level is still pending.

3. **Is this patient adequately resuscitated? In light of his lab results, how would you recommend proceeding with resuscitation?**

The parents tell you he is post operative day #10 from a tonsillectomy performed secondary to worsening recurrent bleeding episodes in the face of chronic tonsillitis. These episodes have required factor administration multiple times in the past. His initial surgery went without incident and he was discharged after overnight observation on a regimen of factor VIII and amicar. The PICC line was placed prior to his discharge so he could receive the factor VIII and amicar at home. Just then, the nurse walks in with 2 units of O negative blood and the patient vomits a large amount of frank blood with clots. The Factor VIII level is still pending and hematology has not yet returned the page.

4. **Is this patient actively bleeding? Would you give O negative blood or await crossmatch?**

5. **What is the deficiency in hemophilia A? What is the appropriate management of the hemophiliac for elective surgery? Does this differ for an urgent/emergent procedure? How do you replace factor deficiency in hemophilia A?**

As you are wheeling the patient out of the door on the way to the operating room, Mom tells you that her brother had a reaction to anesthesia where he became very hot and had to stay in the ICU for a few days after his surgery. She was told to mention this if she or her children ever needed anesthesia. Her son did fine with the anesthesia to have his tonsillectomy.

6. **What is your plan for induction and intubation in this patient? Would you avoid succinylcholine and inhalational agents in this patient? If so, how would you induce and maintain anesthesia? Do you wait 20 minutes to flush your anesthesia machine?**

7. **Would you use a cuffed endotracheal tube? What would you pick for maintenance? Pain control? Would you suction the stomach prior to extubation? Would you extubate deep to avoid bucking on emergence and potential for recurrent bleeding?**

You perform a RSI induction and maintain the patient on TIVA with propofol. The surgeon discovers a right tonsillar fossa blood clot and bleeding vessel. The vessel is ligated, but continued oozing is noted in the tonsillar bed despite adequate surgical hemostasis. The factor VIII level comes back at 36.4%

8. **How will you treat this patient in light of his factor VIII level of 36.4%? What are other options if the factor VIII level is adequate and surgical hemostasis achieved, but the patient is still bleeding? Is recombinant factor VII of value at this point? What other strategies are there for hemostasis?**
Discussion:

1. **How do you assess this patient's volume status? What are your priorities for resuscitating this patient? (Access, fluids, factors, antifibrinolytics, blood?) What further information would you want concerning this patient’s hemophilia? What labs do you want to see? (hb/hct, plt, coags, lytes, type and cross?)**

Post-tonsillectomy bleeding can be categorized as primary (occurring within 24 hours of surgery) or secondary (occurring around a week or so after surgery when the eschar covering the tonsillar bed sloughs). Primary bleeding is usually more brisk and profuse than secondary bleeding, but it can be difficult to assess the amount of bleeding since large amounts of blood may be swallowed.

The bleeding post-tonsillectomy patient will be hypovolemic from several factors including emesis, ongoing blood loss, and potential decreased oral intake due to post-operative pain. An estimation of volume status can be made by a quick history and physical. Reviewing the anesthetic record is helpful to determine medications used, intraoperative blood loss and fluid replacement the patient has received. Clinical assessment of volume status includes investigating:

- Blood pressure – hypotension is a late sign of hypovolemic shock in children. An acute volume loss of 30% may occur before changes in blood pressure are seen
- Heart rate – tachycardia occurs due to catecholamine release to maintain cardiac output in the face of hypovolemia
- Perfusion - capillary refill time >2sec, mottling, pallor, cyanosis are indicators of poor perfusion
- Respiratory rate - tachypnea occurs in response to acidosis which develops with severe anemia and poor perfusion
- Skin temperature – is decreased in hypovolemic shock due to peripheral vasoconstriction
- Urine output - <1ml/kg indicates inadequate renal perfusion
- Mental status - presence of irritability or lethargy is a late sign of hypovolemic shock

Reports of dizziness or orthostatic hypotension may indicate a greater than 20% loss of circulating blood volume and the need for aggressive resuscitation.

The patient should be resuscitated and adequate IV access obtained before inducing anesthesia. Fluid resuscitation should proceed with 20ml/kg of an isotonic crystalloid solution, colloid or blood, depending on the hematocrit and medical history. A hematology consult is warranted to discuss the best strategy for management and hemostasis, but if not immediately available, factor administration should be started in the face of an acute bleeding episode.

Pertinent information to obtain regarding this patient’s disease includes the severity of his disease, his history of factor administration and his home regimen after discharge from his operation. Disease severity for hemophilia A is based on the level of factor VIII as seen in the table below. Approximately 2/3 of patients with hemophilia have severe disease and transfusion of factors with severe disease creates a higher prevalence of factor inhibitors in these patients (1).
Table 1: Disease severity in hemophilia A (1-3)

<table>
<thead>
<tr>
<th>Severity</th>
<th>Factor VIII level (% activity)</th>
<th>Prevalence</th>
<th>Presence of Inhibitors</th>
<th>Age at first bleeding episode</th>
<th>Bleeding Episodes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Severe</td>
<td>&lt;2%</td>
<td>66%</td>
<td>15%-20%</td>
<td>&lt;1yo</td>
<td>Spontaneous, predominantly in joints and muscles</td>
</tr>
<tr>
<td>Moderate</td>
<td>2%-10%</td>
<td>15%</td>
<td>&lt;3%</td>
<td>&lt;2yo</td>
<td>Occasional spontaneous bleeding. Severe bleeding with trauma or surgery</td>
</tr>
<tr>
<td>Mild</td>
<td>&gt;10%</td>
<td>20%</td>
<td>rare</td>
<td>3-14yo or older</td>
<td>Severe bleeding with major trauma or surgery</td>
</tr>
</tbody>
</table>

Labs to obtain at this time should include CBC, factor 8 level and type and cross. The patient already comes in with a diagnosis of Hemophilia A, so coagulation studies are not useful at this time. For patients with hemophilia A, prothrombin time (PT) and bleeding time will be normal while partial thromboplastin time (aPTT) will be prolonged.

A CBC and factor VIII levels will help to guide resuscitation management and factor replacement. In light of the potential for severe, continued bleeding, adequate units of packed red cells should be made available, remembering that approximately 4ml/kg with raise Hgb by 1g/dL. Factor replacement should be started immediately and therapy adjusted accordingly with the results of factor VIII levels.

2. **Assuming the patient is relatively stable, what further information and preparation do you want before taking this child urgently to the operating room? Should further IV access be obtained? Would you place a foley? A-line? What equipment do you want available? What types of fluid do you want available? What if the patient is unstable and needs to go emergently?**

Assuming the patient is relatively stable, appropriate resuscitation should proceed prior to induction of anesthesia. Vital signs and results of hematocrit will help guide fluid replacement. Giving 20ml/kg boluses of an isotonic crystalloid and/or colloid solution will help replete hypovolemia. But, if hematocrit is low, further crystalloid/colloid resuscitation will only make this worse and packed red cell transfusion may be required. Ultimately, the imperative is adequate volume resuscitation prior to anesthetic induction in the operating room (3).
While considering adequacy of resuscitation, the adequacy of IV access should also be considered. This patient has a functioning PICC line, but if vigorous bleeding is present or anticipated, this will not be adequate for infusing large volumes of fluids quickly. Placing an additional IV is ideal, but can be challenging in a frightened, volume depleted child. If emergency access is needed, placement of an intraosseous needle may be appropriate.

Problems specific to anesthetic induction include hypovolemia from bleeding, potentially difficult airway due to blood/clots in the oropharynx, and risk of aspiration due to a stomach full of blood and food. Prior to arrival in the operating room, preparations should include:

- Multiple laryngoscopes with a variety of blades
- Styletted endotracheal tubes – multiple tubes of the same size may be warranted in case the first tube is clogged by clot
- Multiple large bore suction devices
- Drugs to perform rapid sequence induction of anesthesia
- Type and crossmatch for 2 or more units of blood
- Blood warming device

The room should be prepared with the equipment above prior to induction of anesthesia. If the patient is unstable and needs to go to the operating room prior to the availability of crossmatched blood, O negative blood may be needed.

3. **Is this patient adequately resuscitated? In light of his lab results, how would you recommend proceeding with resuscitation?**

This patient is still not adequately resuscitated. Normal vital signs for a child of this age are:

<table>
<thead>
<tr>
<th>AGE</th>
<th>HEART RATE (beats/min)</th>
<th>BLOOD PRESSURE (mm Hg)</th>
<th>RESPIRATORY RATE (breaths/min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Premature</td>
<td>120-170</td>
<td>55-75/35-45</td>
<td>40-70</td>
</tr>
<tr>
<td>0-3 mo</td>
<td>100-150</td>
<td>65-85/45-55</td>
<td>35-55</td>
</tr>
<tr>
<td>3-6 mo</td>
<td>90-120</td>
<td>70-90/50-65</td>
<td>30-45</td>
</tr>
<tr>
<td>6-12 mo</td>
<td>80-120</td>
<td>80-100/55-65</td>
<td>25-40</td>
</tr>
<tr>
<td>1-3 yr</td>
<td>70-110</td>
<td>90-105/55-70</td>
<td>20-30</td>
</tr>
<tr>
<td>3-6 yr</td>
<td>65-110</td>
<td>95-110/60-75</td>
<td>20-25</td>
</tr>
<tr>
<td>6-12 yr</td>
<td>60-95</td>
<td>100-120/60-75</td>
<td>14-22</td>
</tr>
<tr>
<td>12+yr</td>
<td>55-85</td>
<td>110-135/65-85</td>
<td>12-18</td>
</tr>
</tbody>
</table>

Another fluid bolus is indicated. Since the Hct has fallen from 26.7 10 days prior to 24 on presentation to the emergency department, blood transfusion may be most appropriate at this time to prevent further hemodilution and drop in Hct with large crystalloid bolus administration. If crossmatched blood is not yet available, a colloid bolus may be better than crystalloid if the
patient is stable enough to wait for the crossmatched blood. If not, O negative blood is most appropriate.

4. **Is this patient actively bleeding? Would you give O negative blood or await crossmatch?**

It is difficult to tell where blood may be coming from in the patient with a post-tonsillectomy bleed. Blood might be coming directly from the tonsillar bed, or more likely, has been slowly oozing and swallowed and is now being regurgitated from the stomach. In the patient with hemophilia, it may be even more difficult to discern. Administration of O negative blood should be guided by the patient’s clinical picture. Hemodynamic improvement with crystalloid fluid boluses and an acceptable hematocrit may indicate the patient is stable enough to wait for crossmatched blood. Hemodynamic instability and unacceptably low or continually falling hematocrit may necessitate transfusion of O negative blood. In any case, factor replacement is indicated and should not be delayed in post-tonsillectomy bleeding in the hemophiliac.

5. **What is the deficiency in hemophilia A? What is the appropriate management of the hemophiliac for elective surgery? Does this differ for an urgent/emergent procedure? How do you replace factor deficiency in hemophilia A?**

Hemophilia A is an x-linked recessive disorder where there is a deficient or defective factor VIII protein. The prevalence of this disorder is approximately 1 in 10,000 live births with males most commonly affected. Daughters of affected fathers are obligate carriers of the gene, and may be affected if their mothers are also carriers or in cases of extreme lionization (3, 5). Clinically, soft tissue and bleeding into joints is characteristic of the disease, but the severity of these symptoms is variable and generally correlates with the degree of factor deficiency. For patients with severe disease (Table 1), factor activity is usually less than 2% and spontaneous hemorrhages are more common.

The mainstay of therapy is replacement of the deficient/defective factor VIII. In the past, treatment of hemorrhage with fresh frozen plasma (FFP) or cryoprecipitate (cryo) was used to replace factor VIII levels. Use of FFP was limited by concurrent volume administration that occurs with this product and it also had a limited rise in factor VIII levels (FFP will only raise factor VIII levels up to 20%). Both FFP and cryo also carry the risk of exposure to infectious agents. Recombinant forms of factor VIII are preferred as they do not carry infectious risks, but they are expensive and unavailable in some parts of the world. [and are associated with the formation of inhibitors to factor VII. (2, Lee)] Appropriate management of the patient with hemophilia A for surgery depends on the nature of the procedure. Consultation with a hematologist to discuss the appropriate perioperative management of these patients should be sought since the optimal levels and duration of factor replacement during the perioperative period to prevent bleeding complications is not conclusively established. For tonsillectomy, preoperative factor VIII levels are generally recommended to be brought to 100%.

Recommendations for factor replacement beyond the immediate post-operative period are more variable, but should generally be maintained at appropriate levels (30-100%) for up to 14 days following major surgery such as tonsillectomy (2, 6). This should not differ whether it is an elective or urgent/emergent surgery.
The plan for replacement of factor VIII levels should be done in consultation with a hematologist. If one is not available and therapy must proceed as in this case, I believe a target factor VIII level of 80-100% is appropriate. To achieve this with recombinant factor VIII administration, the dose of factor VIII is calculated as follows:

- Each unit of factor VIII/kg body weight infused will raise plasma factor VIII activity levels by 2%.
- Units of factor VIII to infuse = (body weight in kg)(% activity level desired)(0.5)

For this patient to achieve 100% factor VIII levels, he would need:

\[(16.9 \text{ kg})(100\%)(0.5) = 845 \text{ units}\]

Replacement therapy should begin even before assessment of this patient is complete, or lab values are back since this is a severe bleeding episode that is potentially life-threatening (2).

6. **What is your plan for induction and intubation in this patient? Would you avoid succinylcholine and inhalational agents in this patient? If so, how would you induce and maintain anesthesia? Do you wait 20 minutes to flush your anesthesia machine?**

The patient with post-tonsillectomy bleeding is considered to have a full stomach and should undergo a rapid sequence induction. Unfortunately, the mother relates a last minute story that is suspicious for an episode of malignant hyperthermia (MH) in this patient’s uncle. If time allows, more history into the specific reaction, family history, and any testing in family members would help plan your anesthetic. Testing via caffeine halothane contracture testing (CHCT) or genetic testing for MH. If testing was performed in the uncle or the mom and they were found to be negative for MH susceptibility, you are free to plan your anesthetic using succinylcholine and inhalational agents. If testing was not performed, there may be a chance the patient is MH susceptible (MHS). MH is inherited in an autosomal dominant fashion, so there is a 50% chance the mother could be MHS and a 25% chance the patient could be MHS. Without family testing affirming the mother is not MHS, and especially if time does not permit to investigate this episode more completely, it is best to treat this patient as MHS and avoid any triggering agents.

Rapid sequence induction should be performed in this patient and maintenance via TIVA is more appropriate. Since succinylcholine and inhalational agents should be avoided, induction can proceed with propofol, ketamine or etomidate depending on the patient’s hemodynamic status. Use of succinylcholine is contraindicated, but rapid relaxation may be provided by rocuronium 1.2mg/kg or remifentanil 0.3-0.5mcg/kg. Prolonged paralysis may be experienced for short cases with the high dose of rocuronium needed for rapid onset of relaxation. Remifentanil bolus for relaxation may produce profound bradycardia and should probably be preceded by an adequate dose of atropine.

Running a total intravenous anesthetic (TIVA) with a modified rapid sequence induction can be done with fairly minimal preoperative notice. A complicating factor in this instance is the short notice given about the possibility of MHS and what to do about use of the anesthesia machine. Ideally a dedicated MH anesthesia machine would be available to quickly move into the room for use. This is usually not the case and anesthetic vapors may be retained in the anesthesia machine long after the vaporizer is turned off. Current recommendations for clearing the
residual inhalation agent involve removing all vaporizers from the machine, flushing the
machine for anywhere from 20-104 minutes using fresh gas flow rates of greater than 10
liters/min with the ventilator on, and then replacing the fresh gas outlet hose, carbon dioxide
absorbent and circuit (7). This should be done, but takes time. This process should be initiated,
but if time does not permit completion due to the emergent condition of the patient, it may be
possible to proceed using a standard ventilator (ICU) or an alternate oxygen source with an
ambu-bag for the anesthetic until the machine is properly flushed.

7. Would you use a cuffed endotracheal tube? What would you pick for maintenance?
Pain control? Would you suction the stomach prior to extubation? Would you
extubate deep to avoid bucking on emergence and potential for recurrent bleeding?

Patients with post-tonsillectomy hemorrhage are considered to have a full stomach. This is not
only from possible recent food ingestion, but also because unknown and potentially large
amounts of blood may have been swallowed. A cuffed endotracheal tube is advantageous in this
case to minimize the possibility of incorrect tube size placement and need for repeat intubations
in a difficult airway situation. It may also help to minimize the chance of aspirating blood.

With the history of MHS in the family, this patient should be maintained with TIVA to avoid
exposure to triggering agents and risk of an MH episode. Pain control with narcotic medications
is appropriate, but medications that alter platelet function such as nonsteroidal anti-inflammatory
drugs (NSAIDS) should be avoided.

Blind suctioning of the oropharynx or stomach should be avoided. Suctioning of the stomach at
the end of the case can be done by the surgeon under direct visualization to avoid trauma to the
tonsillar beds. This does not assure an empty stomach, however, and it is important to extubate
these patients when they are fully awake and in control of airway reflexes. Placing the child in
the lateral position and extubating when purposeful responses are elicited will help to avoid
aspiration events during extubation (8).

8. How will you treat this patient in light of his factor VIII level of 36.4%? What are
other options if the factor VIII level is adequate and surgical hemostasis achieved, but
the patient is still bleeding? Is recombinant factor VII of value at this point? What
other strategies are there for hemostasis?

As a consequence of factor VIII therapy, those with severe disease are most at risk of developing
inhibitory IgG antibodies (inhibitors) for factor VIII. A factor VIII level of 36.4% should raise
concern for the presence of inhibitors in this patient. If the factor level of 36.4% was drawn prior
to factor VIII administration, the levels should theoretically be sufficient if an infusion with a
target of 100% activity was given. Inadequate clinical response to this infusion suggests
inhibitors may be present. Likewise, if 36.4% is the factor level following factor VIII
administration, the shortened half-life of the molecule is concerning for inhibitor formation. In
either case, further administration of factor VIII may be ineffective to achieve hemostasis.
Management of this patient in terms of further therapy should ideally be done in consultation
with a hematologist.

If inhibitors develop, patients may no longer respond to factor VIII therapy. In these instances,
recombinant factor VII (rfVIIa) is considered the first-line option for controlling bleeding in
hemophilia patients (9, 10). rfVIIa is currently approved for use in the treatment of bleeding episodes and for prevention of hemorrhage during surgery or invasive procedures in patients with hemophilia and inhibitors. It works by activating factor X directly on the platelet surface leading to increased thrombin production and enhanced platelet aggregation (11). If inhibitors to factor VIII are present, or if bleeding continues despite adequate factor levels and surgical hemostasis without the presence of inhibitors, rfVIIa can be given in a dose of 90mcg/kg every 2 hours until hemostasis is achieved. Unfortunately, no good clinical studies exist to guide testing of factor levels to tailor dosing and timing of administration. As such, treatment endpoints are usually based on clinical outcomes.

FEIBA ® is another option for treatment of bleeding in patients who develop inhibitors. FIEBA ® is a concentrate of plasma-derived vitamin K-dependent clotting factors (factors II, VII, IX and X). An effective dose is 50-100units/kg every 12 hours, not to exceed 200units/kg/day. As with rfVIIa administration, clinical outcomes are used to guide treatment.

Other pharmacologic treatment options for hemophiliac patients with inhibitors include antifibrinolytic agents such as tranexamic acid or epsilon aminocaproic acid. These agents should not be used in combination with FEIBA therapy as this increases the risk of thromboembolic adverse events. Desmopressin (DDAVP) causes endothelial release of factor VIII and von Willebrand factor and has been useful in patients with mild disease, but is ineffective in patients with severe hemophilia A.

Selected References: