Submitted July 2019; Accepted December 2019

CASE REPORT

How low can your haemoglobin concentration go?

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Keywords - **haemorrhagic shock, severe anaemia, uterine leiomyoma, cardiac ischaemia, organ dysfunction**

Abstract

A 48-year-old female presented to the emergency department in severe haemorrhagic shock with associated altered mental status. She had suffered severe vaginal blood loss for the past two days. A CT scan did not show any signs of active bleeding, but revealed a large uterine leiomyoma, likely to have caused the severe vaginal blood loss. She was admitted to the intensive care unit for resuscitation with multiple transfusions. The first haemoglobin concentration was 0.9 mmol/l. She developed major cardiac ischaemia and severe acidosis due to the haemorrhagic shock, but survived. Severe anaemia, especially in acute onset due to major haemorrhage, is associated with high mortality and morbidity. In our medical practice to date, we have never encountered such an extreme case of anaemia compatible with life.

Introduction

Severe anaemia, especially in acute onset due to major haemorrhage, is associated with high mortality and morbidity such as cardiac ischaemia and multi-organ dysfunction, as presented in this case.

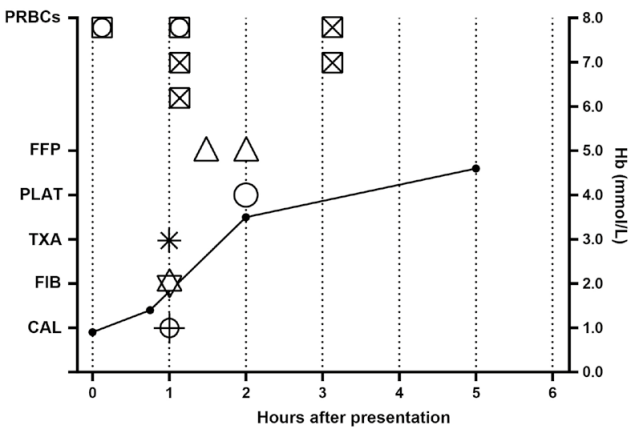

Figure 1. Timeline (X-axis) of the administration of blood components and procoagulant medication (left Y-axis), and the haemoglobin concentration (right Y-axis). PRBCs = packed red blood cells (two O-negative and four typed and cross-matched), FFP = fresh frozen plasma, PLAT = platelets, TXA = tranexamic acid, FIB = fibrinogen, CAL = calcium gluconate, Hb = haemoglobin concentration

Case report

A 48-year-old female presented to the emergency department in severe haemorrhagic shock with associated altered mental status. She had suffered major vaginal blood loss with large clots for the past two days but did not consult the general practitioner or emergency services until the time of presentation. She is para 2 with no medical history and reported no use of medication. Physical examination on presentation showed extreme pallor, anxiety and restlessness, tachypnoea (respiratory rate of 23/min), hypoxaemia ($SatO_2$ of 92% with 15 l/min oxygen on a non-rebreather-mask), hypotension (70/35 mmHg) with a weak pulse (heart rate 90/min) and no capillary refill, and hypothermia (33.0 ˚C). Although she was disorientated and anxious she was still able to speak coherently, mentioning feeling cold and thirsty. We suspected major internal haemorrhage with hypovolaemic shock and started resuscitation with infusion of crystalloid fluids (500 ml Ringer's lactate solution, on top of the 1000 ml administered by the ambulance personnel in the prehospital setting) and norepinephrine. We aimed at permissive hypotension with a target systolic blood pressure (SBP) of 100 mmHg, in order to minimise blood loss and limit infusion of crystalloid fluids to prevent further haemodilution and coagulopathy. The patient was gradually warmed up using a Bair Hugger™. Concomitantly, we activated our major haemorrhage protocol and started resuscitation with transfusion of O-negative packed red blood

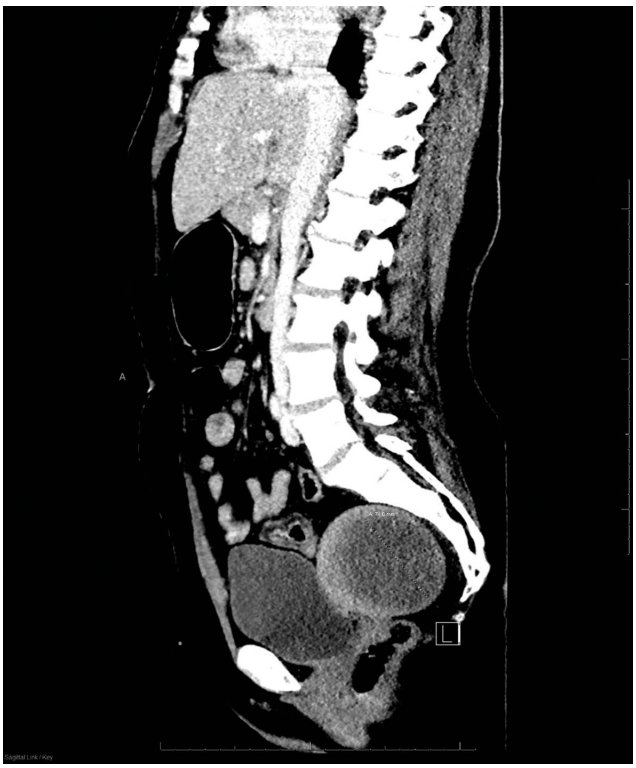

Figure 2. CT scan of the abdomen: image of uterine leiomyoma, no signs of active bleeding

cells (PRBCs), pending blood group typed and cross-matched PRBCs (*figure 1*).

A CT scan of the chest and abdomen did not show extravasation of contrast fluid and ruled out aortic dissection, ruptured abdominal aneurysm, intestinal bleeding, extra-uterine pregnancy and active bleeding in utero. It did reveal uterine leiomyoma (*figure 2*). In the absence of active haemorrhage that would require surgical intervention, the patient was admitted to the intensive care unit (ICU) for further resuscitation and transfusion. While inserting venous and arterial lines we observed backflow of extremely diluted blood. The first laboratory results (*table 1*) showed a haemoglobin concentration of 0.9 mmol/l, haematocrit of 0.06 l/l and thrombocytopenia with a platelet count of 110 x 10^9/l. After one unit of PRBCs was administered, the haemoglobin concentration increased to 1.4 mmol/l with a haematocrit 0.09 l/l. Further blood analysis revealed severe lactic acidosis (pH 7.07, serum lactate 20.6 mmol/l), acute renal failure and elevated cardiac enzymes (*table 1*). An electrocardiogram (ECG) showed signs of subendocardial pan-ischaemia (*figure 3*).

In total six units of PRBCs (two O-negative), two of fresh frozen plasma, one unit of platelets, two grams of fibrinogen, two grams of calcium gluconate and one gram of tranexamic acid were administered. This resulted in a stable haemoglobin concentration of 4.6 mmol/l (*figure 1*). Since the pH was still above 7.00 we decided not to actively correct the metabolic/lactic acidosis with sodium bicarbonate. Our patient gradually improved. We diagnosed a severe uterine haemorrhage due to uterine leiomyoma. Secondary to the extreme anaemia she not only developed lactic acidosis as a sign of disturbed oxygen delivery and tissue oxygenation, but also massive subendocardial demand ischaemia with elevated cardiac enzymes (*table 1*) and signs of subendocardial ischaemia on the ECG (*figure 3*). She rapidly recovered, with normalisation of the ECG, and was discharged to the gynaecological ward within 24 hours after presentation. Echocardiography showed normal function and dimensions of the heart, and ultimately there was complete recovery of cerebral, renal and liver function. Analysis by the haematologist ruled out coagulation disorders (e.g. Von Willebrand Factor activity 140%). Histological analysis of the endometrium confirmed the diagnosis of uterine leiomyoma with ischaemic changes. She was treated with lynestrenol (Orgametril®) and scheduled for hysterectomy.

Discussion

Severe anaemia, especially due to acute major haemorrhage, is associated with high morbidity (such as myocardial infarction, arrhythmia, congestive heart failure, infections) and mortality. Case reports of extreme anaemia in surgical and trauma patients and perioperative reports of anaemia in Jehovah's Witnesses showed increased mortality and morbidity when haemoglobin concentrations dropped below 3.1 mmol/l.[1-4]

Patients with acute major haemorrhage are at risk of severe cardiovascular deterioration as a result of hypovolaemic shock and compromised oxygen transport. If not treated in time, irreversible damage to vital organs may occur, subsequently leading to multiple organ failure and death. We present a case of a 48-year-old woman with severe anaemia (haemoglobin concentration 0.9 mmol/l) due to severe haemorrhage from uterine leiomyoma, resulting in anaemia and hypovolaemia, coagulopathy, tissue malperfusion, severe acidosis, further progression of bleeding and finally cardiac, cerebral, renal and liver dysfunction. Menorrhagia is a known complication of uterine leiomyoma and can lead to anaemia. Although extremely rare, spontaneous rupture of vessels overlying uterine leiomyoma causing severe vaginal blood loss or haemoperitoneum and hypovolaemic shock has been documented.[5-9]

In our case, the first haemoglobin concentration of 0.9 mmol/l (haematocrit 0.06 l/l) was followed by 1.4 mmol/l (haematocrit 0.09 l/l) after one unit of PRBCs was administered, suggesting the first sample analysis was accurate. To eliminate potential erroneous results, in our hospital all haemoglobin concentrations <4.0 mmol/l are routinely executed twice (XN-analyser). These routine control samples confirmed the low first haemoglobin concentration of 0.9 mmol/l and subsequently 1.4 mmol/l.

We assume our patient gradually developed chronic anaemia due to menorrhagia, leading to physiological adaptation enabling her to still circulate, oxygenate and retain consciousness after two days of extensive blood loss,

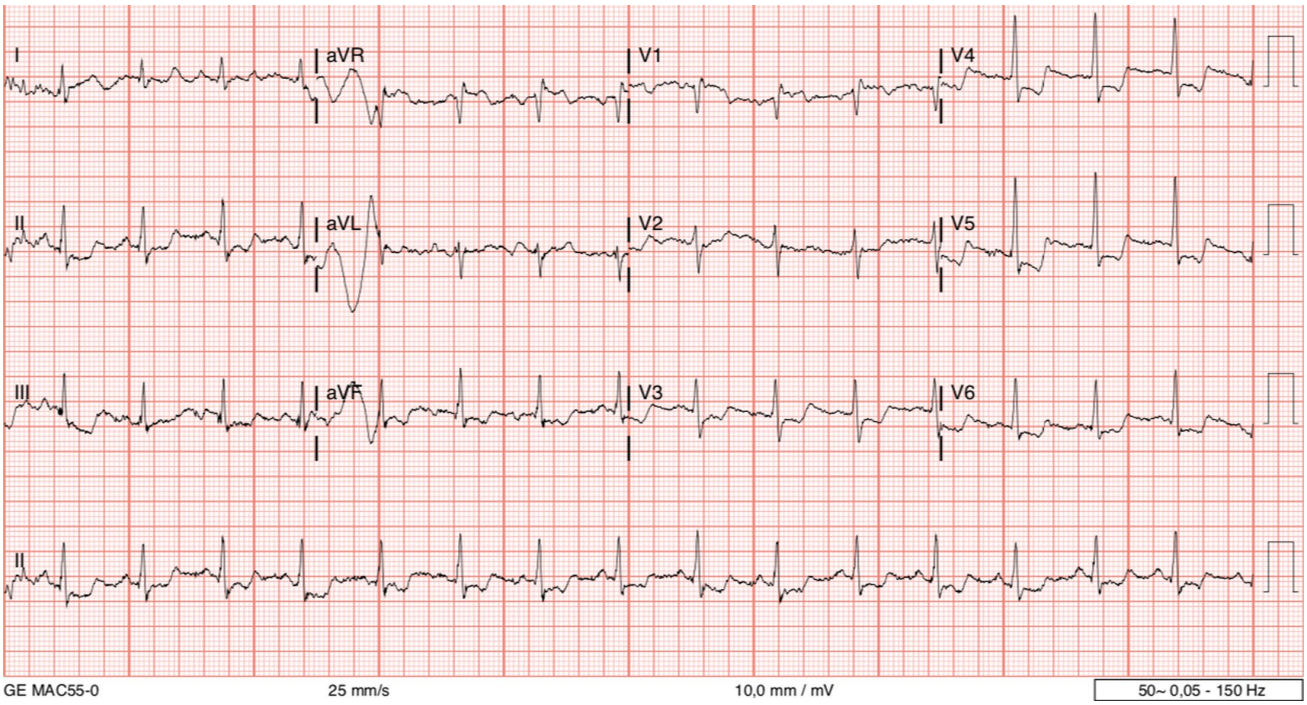

Figure 3. ECG on ICU admission, showing diffuse ST-segment depression and ST-segment elevation in aVR, suspect for subendocardial pan-ischaemia

ultimately resulting in this severe anaemia. Haemodilution due to the initial resuscitation with crystalloid fluids probably also played a role in this severe anaemia. Adaptation to chronic anaemia consists of several different processes: 1) activation of oxygen-sensing mechanisms, resulting in an increase of renal erythropoietin production to restore haemoglobin concentration and an increase in cardiac output; 2) respiratory adaptation with increased minute ventilation, ensuring optimal $SatO_2$ is maintained with a reduced haemoglobin to maximise blood oxygen content; 3) hypoxia-sensing cells activating the sympathetic nervous system, increasing cardiac output and reducing systemic vascular resistance; 4) increased tissue oxygen extraction; 5) metabolic cellular adaptations, resulting in reduced tissue oxygen consumption by several organs to maintain maximum global oxygen utilisation to the vital organs such as the heart and the brain.[10,11]

Despite these possible adaptive mechanisms, our patient not only developed severe acidosis with a raised lactate level as a sign of disturbed oxygen delivery and tissue oxygenation, but also massive subendocardial demand ischaemia with elevated cardiac enzymes (*table 1*) and an abnormal ECG (*figure 3*). We hypothesise that the adaptive processes fell short due to major haemorrhage resulting in this severe anaemia with a haemoglobin concentration well below the critical limit of 3.1 mmol/l as mentioned in previous reports.[3,4,10]

We assume 'only' six units of PRBCs were necessary during resuscitation to accomplish a stable haemoglobin concentration of 4.6 mmol/l because of spontaneous cessation of ongoing active bleeding at the time of presentation and during resuscitation.

Acute coagulopathy in severe haemorrhage is a well-known phenomenon, especially in traumatology.[12] Causal factors are acidosis, hypothermia, resuscitation-associated dilutional coagulopathy and severe depletion of red blood cells, platelets and coagulation factors. Rapid intravenous infusion of crystalloid or colloid fluids is generally applied during ongoing haemorrhage to establish haemodynamic stability, restore adequate intravascular volume and improve oxygen tissue delivery.[13] When given in large volumes, however, crystalloid or colloid fluids initiate dilution of clotting factors resulting in coagulopathy.[14-16] Furthermore, the use of colloid fluids has proven to negatively influence coagulation capacity and endothelial function.[17,18] Caution should be exercised with aggressive fluid resuscitation. Additionally, rapid consumption of fibrinogen, clotting factors and platelets as a result of persistent blood loss, aggravates coagulopathy.[15] These findings have led to less aggressive fluid resuscitation in patients with traumatic and postpartum haemorrhagic shock.[19,20] In light of this, we initially aimed at maintaining permissive hypotension with infusion of crystalloid fluids and norepinephrine, starting transfusion with O-negative PRBCs as soon as possible to prevent further worsening of the coagulopathy and bleeding.

The goal of permissive hypotension is to maintain the minimal blood pressure necessary to perfuse the vital organs. The rationale is that elevations in blood pressure before adequate haemostasis is achieved may compromise a tenuous clot and exacerbate blood loss.[19] Although most research has been

Table 1. Laboratory results on presentation and during/after resuscitation and transfusion, with reference values and time points

Laboratory results	On presentation	+ 45 minutes	+ 1 hour and 45 minutes	+ 2 hours	+5 hours	+ 5 hours and 30 minutes	+ 6 hours	+ 9 hours and 30 minutes	+ 10 hours	+ 13 hours	Reference values
Haemoglobin	0.9	1.4		3.5	4.6	4.6		4.6			7.5-10.0 mmol/l
Haematocrit	0.06	0.09		0.19	0.23	0.23		0.22			0.35-0.45 l/l
Platelets	110	107		81	95	85		74			150-450 x10^9/l
INR		1.5									
PT				14.0				13.8			9.9-11.8 sec
APTT				17				23			22-28 sec
Fibrinogen				2.8							2.0-4.0 g/l
Lactate		20.6		13.6		4.0					<2.2 mmol/l
Sodium		133	135		135		136		136		133-142 mmol/l
Potassium		5.2	5.3		4.6		4.4		4.0		3.5-5.0 mmol/l
Chloride		99									98-107 mmol/l
Calcium ion		1.08									1.10-1.30 mmol/l
Phosphate				3.39				1.40			0.74-1.52 mmol/l
Magnesium				1.11				0.91			0.70-1.00 mmol/l
Urea		10.0						10.0			2.5-6.7 mmol/l
Creatinine		195						110			50-95 µmol/l
Bilirubin		<5						17			5-20 µmol/l
AF		60				72		74			30-120 U/l
GGT		8				15		10			<27 U/l
ASAT		2237				3596		4384			<30 U/l
ALAT		1821				2412		2884			<35 U/l
LD		4245				7057		>7500			<250 U/l
CK		241				828				1529	<122 U/l
CK-MB		97				115				94	<25 U/l
CK-MB % total CK						14				6	<4%
Troponin-I (HS)		313				9056				7608	<26 ng/ml
pH		7.07	7.16		7.39		7.42		7.47		7.36-7.44
Bicarbonate (arterial)		4.0	7.1		16.0		18.8		21.6		23-27 mmol/l
Base excess		-23.7	-19.9		-8.1		-5.0		-1.7		-3.0-3.0 mmol/l
PaCO2		1.8	2.7		3.6		3.9		3.9		4.5-6.1 kPa
PaO2		37.6	12.1		7.2		7.7		8.6		10.0-13.5 kPa
SatO2		1.00	0.98		0.92		0.93		0.95		0.95-0.98
Anion gap		31.30	26.40		15.60		13.50		10.20		

conducted in animal models, a few studies in trauma patients show that delayed fluid resuscitation (versus immediate fluid resuscitation) and resuscitation with permissive hypotension with systolic blood pressure (SBP) goals down to 70 mmHg (versus non-limited SBP) resulted in no difference in mortality and even improved survival in both intervention groups compared with the control groups.[21-23] In trauma patients it has been shown that aggressive volume administration, often initiated in the pre-hospital setting, increased the incidence of secondary compartment syndrome, damage-control laparotomy, coagulopathy, multi-organ failure, nosocomial infections, the number of blood component transfusions as well as the number of massively transfused patients and prolonged the length of ICU and hospital stays.[24] Therefore, the recent 2019 'European guideline on management of major bleeding and coagulopathy following trauma' advocates the concept of

'damage-control resuscitation' for initial treatment of trauma-induced hypotension, with restricted volume replacement and permissive hypotension with a target systolic blood pressure of 80-90 mmHg (mean arterial pressure 50-60 mmHg) until major bleeding has been stopped in the initial phase following trauma without brain injury.[24]

Although our patient was not a trauma patient, we assume that the pathophysiological mechanisms of acute haemorrhage and resuscitation are comparable, and that these findings may also be applied to patients with non-traumatic types of haemorrhagic shock. In our case we achieved clinical stability retaining consciousness of the patient with permissive hypotension with a target SBP of 100 mmHg and therefore refrained from further lowering the blood pressure.

Conclusion

Severe anaemia, especially in acute haemorrhage with haemoglobin concentrations dropping to 3.1 mmol/l, is associated with high mortality and morbidity. These patients are at risk of severe cardiovascular complications due to hypovolaemic shock and compromised oxygen transport and delivery resulting in acute organ dysfunction. As in our patient, they are at increased risk of cardiac ischaemia (and possible cardiac arrest), cerebral hypoxia, kidney and liver dysfunction and severe acidosis. Limiting infusion of crystalloid or colloid fluids during resuscitation should be considered to prevent further worsening of the coagulopathy and bleeding. Permissive hypotension with target SBP 80-90 mmHg is recommended.

In our medical practice to date, we have not encountered a case of such severe anaemia with a haemoglobin concentration of 0.9 mmol/l without concomitant mortality.

Disclosures

All authors declare no conflict of interest. No funding or financial support was received.

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