Review Article

Blood transfusion practices in neuroanaesthesia

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ABSTRACT

Neuroanaesthesia practice is associated with risk of significant blood loss resulting in anaemia in the intraoperative and postoperative period. The transfusion triggers in a neurologically injured brain are not clearly defined. Both a low haematocrit and a high haematocrit have not shown any improvement in the outcome. Transfusion of red blood cells may improve the cerebral oxygenation on neurophysiological monitors. However, these benefits have not been translated into clinical practice. Transfusion in subarachnoid haemorrhage leads to increased incidence of vasospasm and a poor outcome. Restrictive transfusion strategy is seen to have a lower incidence of pneumonia, urinary tract infection, bacteremia and septic shock in severe head injury. Current evidence suggests that a haemoglobin (Hb) level of <7 g/dl may be deleterious to the neurosurgical population. Target Hb of 8-9 g/dl may be desirable intraoperatively. Different transfusion triggers may hold true for different neurosurgical pathologies.

Key words: Blood transfusion, head injury, neuroanaesthesia, stroke, transfusion trigger

INTRODUCTION

Anaemia is defined as a decrease in the oxygen carrying capacity of blood. The oxygen carrying capacity of blood depends on the total volume of circulating red blood cells (RBCs). The volume of RBCs is measured based on chromium-tagged erythrocytes. This is not possible in a clinical setting; so alternative definitions of anaemia have been based on the haematocrit (Hct) and haemoglobin (Hb) concentrations in blood.

Acute haemodilution down to 5 g/dl of Hb in healthy volunteers does not decrease subcutaneous tissue oxygen tension. Hence severe anaemia (Hb <6 g/dl) *per se* may not impair wound healing. However, reduction of Hb levels to 5-6 g/dl alters cognitive function in healthy human volunteers producing subtle, reversible increases in reaction time and impaired immediate and delayed memory. These cognitive dysfunctions are reversible by erythrocyte transfusion or alternately by administration of oxygen.[1]

The minimal acceptable Hb thresholds are not well established for patients with cerebral injury undergoing neurosurgical procedures. It is believed that the high metabolic requirements of the brain may render the brain susceptible to injury at a low Hb concentration or a low Hct.[2] Brain injury can worsen even above the clinically accepted Hb threshold of 7.0 g/dl.[3] The current transfusion strategies in neurological injury are not well defined and the available evidence is scanty. Clinicians from different centres vary in their transfusion practice. This review will try to analyse the available evidence that may be helpful when decisions are being taken about transfusion to a neurosurgical population in the preoperative, intraoperative and postoperative periods.

TRAUMATIC BRAIN INJURY

Primary traumatic brain injury (TBI) injury consists of concussion, contusion, laceration, and haematoma. The systemic secondary insults that contribute to brain damage include hypoxaemia, hypotension, anaemia,

hypocarbia, hypercarbia, pyrexia, hyponatremia, hypoglycaemia and hyperglycaemia. Under these circumstances a higher Hb level may augment the oxygen delivery (DO2) resulting in a better outcome. However, this has not been translated into clinical practice. In a multicenteric trial[4] comprising patients with moderate to severe head injury, no significant improvements in mortality was seen when a liberal transfusion strategy was compared to a restrictive strategy. Restrictive transfusion strategy was found to have a lower incidence of pneumonia, urinary tract infection, deep venous thrombosis, bacteremia and septic shock in severe head injury.[5] In a recent study of 200 patients with traumatic brain injury, neither the administration of erythropoietin nor maintaining haemoglobin concentration of greater than 10 g/dL resulted in improved neurological outcome at 6 months.[6] The rate of favourable neurological outcome (difference 0.1 [-0.06 to 0.25]; $P = 0.28$) was similar in patients receiving blood at a transfusion trigger 7 or 10 gm/dl. The transfusion threshold of 10 g/dL was associated with a higher incidence of thromboembolic events (Odds ratio 0.32 [0.12 to 0.79]; $P = 0.009$].[6] In contrast to clinical outcome, studies have shown an improvement in neurophysiological monitors with an apparent improvement in cerebral well-being. Erythrocyte transfusion increased the cerebral tissue oxygenation in anaemic patients with severe TBI with a low baseline brain tissue oxygen (PtiO$_2$) levels (<15 mmHg).[7] Zygun *et al.* showed similar results with an increase in brain tissue oxygen (PtiO$_2$) but no appreciable improvement on cerebral metabolism (on microdialysis) as measured by lactate pyruvate ratio and brain pH after transfusion of packed RBCs.[8] A recent study by Sekhon *et al.*[9] showed that a mean 7 days Hb level of <90 g/L was associated with a three-fold increase in hospital mortality.

Currently, no well-defined transfusion triggers based on evidence guide the transfusion practices in head injury patients. A systemic review protocol[10] is on way and may answer some of the controversial issues.

ANEURYSMAL SUBARACHNOID HAEMORRHAGE

Delayed cerebral ischemia (DCI) is the principal cause of secondary brain injury after aneurysmal subarachnoid haemorrhage (SAH). Anaemia (Hb <10 g/dl), quite common after SAH, is associated with worse outcome leading to cerebral infarction.[11] Higher Hb levels are believed to increase the blood viscosity and

associated autoregulatory vasoconstriction due to increased arterial oxygen content (CaO$_2$). There is no net beneficial effect in cerebral DO2. The traditional management of DCI attempted to augment cerebral blood flow (CBF) with triple H therapy defined by hypertension, hypervolemia and haemodilution. Because the fundamental objective in managing DCI is maximizing DO2 and not CBF, haemodilution by reducing CaO$_2$ may actually be detrimental. Although avoiding hypovolemia reduces the risk of DCI after SAH, prophylactic hypervolemia has not been seen to offer any benefit with the incidence of symptomatic cerebral vasospasm similar in hypervolemic and normovolemic groups.[12] In contrast a significant rise in cerebral DO2 without lowering of global CBF was seen on positron emission tomography by Dhar *et al*[13] by transfusion of one unit RBCs in anaemic patients in SAH. The rise in DO2 was found to be greater in oligemic regions but was attenuated within territories exhibiting angiographic vasospasm.

Blood transfusion may lead to an increased incidence of vasospasm, leading to a poor outcome in SAH patients.[14] Intraoperative transfusion has not been found to influence the angiographically confirmed vasospasm; however, postoperative transfusion has been associated with a worse outcome.[14]

The optimal target Hb in SAH remains unknown. A lower mean Hb during the acute phase of aneurysmal SAH-induced cerebral vasospasm has been found to be an independent predictor of intra-arterial vasospasm.[15] Evidence[16] suggests that with a Hb of <9 g/dl or Hct of 0.27, there may be an increased incidence of cerebral hypoxia and cell energy dysfunction as observed by cerebral microdialysis and brain oxygen monitoring.

INTRACEREBRAL HAEMORRHAGE

Intracerebral haemorrhage, one of the most devastating forms of stroke carries 40% mortality within a span of 30 days. Rest of the survivors are left with severe disability. Haematoma growth occurs in 70% of these patients and is an independent determinant of death and disability.[17] The phase III results of Factor seven for acute haemorrhagic stroke (FAST) trial, showed that recombinant activated factor VII (rFVIIa) given within 4 h after the onset of symptoms of intracerebral haemorrhage significantly reduced growth of the haematoma but failed to improve survival or functional outcome at 90 days.[18] Anaemia (Hb <10 g/dl) usually

develops in most patients with intracranial haemorrhage during hospitalisation. It was seen that transfusion of packed RBCs improves the outcome in these patients.[19]

INTRACRANIAL TUMOUR SURGERY

Intracranial tumours are supposed to be associated with major blood loss and large volumes transfusion of blood products. Recent advances in neurosurgical techniques and acceptability of low transfusion triggers have decreased the need for intraoperative transfusions. The amount of transfusion requirements depend on age, tumour type and the surgical access. Low grade gliomas, transsphenoidal resection of pituitary tumours or astrocytomas do not usually need blood transfusion. However, transfusion requirements are high in infants, in highly vascular tumours such as meningiomas and cerebellopontine tumours.[20] Brain tissue, being rich in thromboplastin, causes its release during tumour surgery trigerring the extrinsic pathway. Necrotic and tumorous tissues may also produce tissue factors initiating the coagulation cascade. This may lead to development of disseminated intravascular coagulation (DIC). Intraoperatively bleeding due to DIC is controlled by direct pressure, fresh frozen plasma (FFP) and platelets. rFVIIa has been used in paediatric cases[21] to control microvascular bleeding during brain tumor surgery. It may have an emerging role on the intraoperative blood coagulation after failure of conventional therapy with FFP and platelet concentrates.

Blood transfusion may be an independent risk factor for cancer progression[22] as a result of the immunomodulatory effects. The relevance of these findings in neurological tumours is uncertain. Allogenic leukocytes are major mediating agents for cancer progression after blood transfusion. Hence leukodepletion is a common prophylactic procedure. RBCs may also be responsible for the cancer promoting effects of blood transfusion. These effects of RBCs critically depend on the duration of blood storage, irrespective of donors histocompatibility. Storage may result in the deterioration of RBC, which may be responsible for carcinogenic effects.

ACUTE ISCHEMIC STROKE

Patients with an abnormal haemostasis at the stroke onset, with an international normalized ratio (INR) >1.7, elevated partial-thromboplastin time (PTT), or platelet count <100,000/µL, are not considered candidates for thrombolysis with intravenous recombinant tissue plasminogen activator. However, in a pooled analysis of MERCI and multi MERCI trials,[23] it was seen that patients with abnormal haemostasis who underwent thrombectomy did not have a higher incidence of symptomatic intracranial haemorrhage. However, patients with abnormal haemostasis had lower rates of good outcomes probably as a result of lower prestroke health status.

Optimal Hb levels in embolic stroke have not been defined. Both haemodilution and increased haematocrit have not showed any beneficial effects. Tanne *et al*.[24] observed an increased risk for death at both extremes of Hb in patients with acute stroke.

NEUROSURGICAL PATIENT RECEIVING ANTICOAGULANTS

Patients receiving long-term treatment with warfarin for atrial fibrillation or a mechanical heart valve are put off warfarin for elective neurosurgical procedures. Bridging anticoagulation by low molecular weight heparin reduces their risk for developing blood clots, such as stroke, but may increase the risk for developing bleeding complications after surgery. Recently, Siegal *et al*. observed that Vitamin K antagonist treated patients receiving periprocedural heparin bridging had an increased risk of major bleeding.[25] At the same time the risks of thromboembolic events were similar when compared to nonbridged patients.[25] This data comprises of a combination general surgical, gynaecological, orthopaedic cardiothoracic and neurosurgical population. The relevance of this data separately to neurosurgical population needs to be revalidated.

In emergency neurosurgical procedures, conventional methods of warfarin reversal involve the use of Vitamin K and FFP. However, they are slow and ineffective and may not prevent progression of intracranial haemorrhage. For patients with life-threatening bleeding or intracranial haemorrhage, the American College of chest physicians recommends the use of prothrombin complex concentrates (PCCs) or rFVIIa to immediately reverse the INR.[26] However, there is no available evidence that has shown that neurosurgical patients have a better outcome with PCC when compared with plasma.

SPINAL SURGERIES

A great variation exists in the blood loss and transfusion requirements of patients undergoing

spinal surgeries. A simple one or two level discectomy usually does not need any blood transfusion. However, fusions with instrumentation are associated with blood loss and require large volumes of blood replacement.[20] Surgical groups which require a significant transfusions of >2 units of RBCs include deformity surgery, tumor surgery, trauma surgery and multilevel disc surgery (>3 levels).[27] Tumors of the vertebral column are highly vascular leading to major intraoperative blood loss. This is complicated by the lack of intraoperative autotransfusion due to concerns over tumor metastasis.

PAEDIATRIC NEUROSURGERY

Paediatric patients undergoing tumour resection and correction procedures for craniosynostosis may bleed excessively compared to their blood volume and require transfusion. However, surgical procedures for ventriculoperitoneal shunt for hydrocephalus and repair of meningoencephalocele do not usually require any transfusion unless the defect is very large and associated with significant blood loss. Surgical stages where sudden and extensive blood loss occurs are usually the initial scalp dissection and raising of the periosteum.[28] In children during periods of rapid blood loss, transfusion may be guided by haemodynamic trends of arterial and central venous pressures. During periods of haemodynamic stability

absolute transfusion triggers around Hb level of 7-8 g/dl may be taken as a guide for transfusion.[28] When the blood volume loss approaches 1.5 times the total blood volumes, haemostatic blood products may be used empirically (such as FFP and platelets) in the absence of supporting laboratory results to correct anticipated dilutional coagulopathy.[28,29] In the presence of definitive laboratory criteria of a prothrombin time or activated PTT values >1.5 times normal, fibrinogen <0.8-1 g/L, and a platelet count <50-80,000/μL) are used for administration of FFP and platelets.[28,29]

In patients undergoing surgery for cranioplasty, Cortellazzi *et al.*[30] advocated the early transfusion strategy. The authors gave a transfusion of 20% of estimated red cell volume combined with a third of this volume of FFP just after coronal opening in addition to a crystalloid infusion of 8 ml/kg/h. With this strategy a better outcome in terms of intensive care unit stay and hospital stay was observed.

BLOOD CONSERVATION STRATEGIES

Blood conservation strategies in neurosurgical practice have utilised predonation of autologous blood before surgery, acute normovolaemic haemodilution, preoperative administration of erythropoietin, induced hypotension and intraoperative cell

Table 1: Advantages and disadvantages of blood transfusion in neuroanaesthesia practice			
	Advantages	**Disadvantages**	**Suggested target Hb**
TBI	Improved brain tissue oxygenation	Higher incidence of pneumonia, bacteremia and septic shock	>9 g/dl[9]
	Better survival with a mean 7 days Hb>90 g/L	No improvement in cerebral metabolism on cerebral microdialysis	
Aneurysmal SAH	Hb>9 g/dl, decreases incidence of cerebral hypoxia and cell energy dysfunction	Increased viscosity thus decreasing the CBF	>9 g/dl[16]
	Rise in cerebral oxygen delivery without lowering of global CBF (seen on PET)		
Intracranial tumour surgery	Used for volume replacement during MBL	Independent risk factor for cancer progression due to immunomodulatory effects	During periods of MBL, transfusion is guided by haemodynamic trends of arterial and CVP[28]
Spinal surgery	Improves oxygen carrying capacity after 24-48 h	Massive blood transfusion leads to DIC	During periods of haemodynamic stability absolute transfusion triggers around Hb of 7-8 g/dl may be taken as a guide for transfusion[28,29]
Pediatric neurosurgery	rFVIIa helpful to control microvascular bleeding during brain tumor surgery	Autologous blood transfusion from cell saver may lead to deposition of tumour seedlings	
Acute ischemic stroke	Increases cerebral oxygen delivery	Elevated Hct may also be a potential physiologic determinant of reduced penumbral salvage	Hb target for intervention in acute embolic stroke is unknown
		Higher Hct values have a significant association with reduced reperfusion and greater infarct size after ischemic stroke	Hb<13 g/dl in males, <12 g/dl in women may be undesirable[24]

Hb – Haemoglobin; MBL – Major blood loss; Hct – Haematocrit; PET – Positron emission tomography; CVP – Central venous pressure; SAH – Subarachnoid haemorrhage; rFVIIa – Recombinant activated factor VII; DIC – Disseminated intravascular coagulation; CBF – Cerebral blood flow

Table 2: A summary of major studies in the last decade that influenced the transfusion practice in neuroanaesthesiology	
Study	**Conclusion**
TBI	
McIntyre *et al*. 2006[4]	No difference in liberal (Hb between 10.0 and 12.0 g/dl) and restrictive transfusion (Hb 7.0 and 9.0 g/dl)
Leal-Noval *et al*. 2006[7]	Erythrocyte transfusion leads to better cerebral oxygenation in TBI. Low baseline $PtiO_2$ levels (<15 mmHg) benefit the most
George *et al*. 2008[5]	Restrictive transfusion is safe for head-injured patients with lower incidence of pneumonia, bacteremia, septic shock
Zygun *et al*. 2009[8]	Transfusion of RBCs leads to better $PtiO_2$ without effect on markers of cerebral metabolism (LPR and brain pH)
Sekhon *et al*. 2012[9]	Mean 7 days Hb concentration of<90 g/L is associated with increased hospital mortality in patients with severe TBI
Robertson CS *et al*. 2014 [6]	Neither the administration of erythropoietin nor maintaining haemoglobin concentration of greater than 10 g/dL resulted in improved neurological outcome at 6 months.[6]
	Transfusion threshold of 10 g/dL was associated with a higher incidence of thromboembolic events[6]
Aneurysmal SAH	
Lennihan *et al*. 2000[12]	Hypervolemia resulted in increased cardiac filling pressures but did not increase CBF when compared with normovolemia
Smith *et al*. 2004[14]	Vasospasm is seen with postoperative RBC transfusion and worse outcome is seen with intraoperative RBC transfusion
Kramer *et al*. 2008[11]	Anaemia (Hb<10 g/dl) is predictive of adverse outcomes. But this observation is not a justification for liberal transfusion
Dhar *et al*. 2009[13]	Transfusion of RBCs in SAH increases cerebral oxygen delivery without lowering global CBF
Oddo *et al*. 2009[16]	Hb<9 g/dl is associated with an increased incidence of brain hypoxia and cell energy dysfunction in poor grade SAH
Bell *et al*. 2014[15]	Low mean Hb in acute phase of SAH-induced cerebral vasospasm is an independent predictor of IAVT and poor discharge mRS
ICH	
Mayer *et al*. 2008[18]	Haemostatic therapy with rFVIIa reduces growth of hematoma but does improve survival after ICH
Sheth *et al*. 2011[19]	Anaemia (Hb<10 g/dl) develops in majority of patients with ICH during hospitalization. PRBC transfusion improves the outcome
Acute ischemic stroke	
Nogueira *et al*. 2009[23]	Patients with abnormal haemostasis undergoing thrombectomy do not have a higher risk for spontaneous ICH
Tanne *et al*. 2010[24]	Both extremes of Hb increase the mortality in stroke patients
Neurosurgical patient receiving anticoagulants	
Ansell *et al*. 2008[26]	For intracranial haemorrhage use PCC or rFVIIa to immediately reverse the INR (Grade 1C)
Siegal *et al*. 2012[25]	Vitamin K antagonist-treated patients receiving periprocedural heparin bridging have an increased risk of major bleeding and at similar risk of thromboembolic events compared to nonbridged patients

Hb – Haemoglobin; TBI – Traumatic brain injury; $PtiO_2$ – Brain tissue oxygen; LPR – Lactate pyruvate ratio; RBCs – Red blood cells; ICH – Intracerebral haemorrhage; SAH – Subarachnoid haemorrhage; CBF – Cerebral blood flow; IAVT – Intra-arterial vasospasm therapy; mRS – Modified Rankin scale; PCC – Prothrombin complex concentrate; rFVIIa – Recombinant activated factor VII; PRBC – Packed red blood cell; INR – International normalized ratio

salvage. Autologous blood transfusions have been found to be safe in patients undergoing intracranial surgery and appear to be more cost effective. In spinal surgery, in the prone position, hypotension may decrease the perfusion pressure in the optic nerve. This may lead to ischemic injury either because of anatomic variation in the circulation or because of abnormal autoregulation.[31] However, the American Society of Anesthesiologists task force on perioperative visual loss found out that the use of deliberate hypotensive techniques during spine surgery has not been associated with development of perioperative visual loss.[31] A transfusion threshold that would eliminate the risk of perioperative visual loss related to anaemia cannot be established at this time.[32]

The preoperative administration of erythropoietin in spinal surgery at 80 centres[33] showed a high incidence of deep vein thrombosis and other clinically relevant thrombovascular events. However, use of erythropoietin in craniostenosis

patients along with intraoperative use of a cell saver by Krajewski *et al.*[34] showed that children who received recombinant human erythropoietin at 3 weeks, 2 weeks, and 1 week preoperatively had lower transfusions rates (5% vs. 100% control group) and received lower volumes of blood than in the control group (0.05 pediatric units vs. 1.74 pediatric units). In SAH the use of antifibrinolytics such such as epsilon-aminocaproic acid and tranexamic acid were seen to be responsible for increased risk of vasospasm and hydrocephalus. However, a re-evaluation of the use of these agents during early surgical clipping has shown a reduction in the rebleeding rates without any increased incidence of cerebral vasospam.[35]

USE OF BLOOD PRODUCTS

Loss of one blood volume and replacement with RBCs alone results in a fall of the clotting factor levels to approximately 30% of the basal levels. This is the minimal level thought to be required for adequate haemostasis. FFP transfusion to replace clotting factors is often recommended for these patients. In trauma, recent studies showed that early and aggressive use of FFP at a 1:1 ratio with RBCs improved survival in cases of massive haemorrhage.[36] This strategy, called as, haemostatic damage control or formula-driven resuscitation is receiving substantial attention worldwide. However, it requires immediate access to large volumes of thawed universal donor FFP. Early formula-driven haemostatic resuscitation use is expanding and is gradually being used in nontraumatic bleedings in critical care. Similar to recently published military data on FFPs, transfusion of platelet: RBC ratios of 1:1 has been seen to be associated with a better early and late survival, decreased haemorrhagic death and a concomitant increase in multiple organ failure-related mortality.[37] Similar studies in a neurosurgical population are not available till date. Areas of potential research in future include determination of optimal Hb values in the preoperative period, if any, to improve the outcome. Table 1 summarises the advantages and disadvantages of blood transfusion in neuroanaesthesia practice while Table 2 summarises the main studies in last decade that have influenced the transfusion practices in neuroanaesthesiology. Studies may be designed to identify the optimal blood conservation strategies and transfusion triggers for various conditions.

SUMMARY

The current evidence shows that anaemia is deleterious to a neurologically injured brain. Higher Hb levels improve the cerebral oxygenation as measured by brain oxygen tensions, near infra red spectroscopy, cerebral microdialysis and jugular venous oximetry. However, this has not been translated into better clinical outcomes. Further studies are needed to address the missing links. In neurosurgical patients, Hb levels below 7 g/dl may be deleterious to cerebral oxygenation. Higher Hb values may be targeted in the presence of cardiac and respiratory comorbidities.

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