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Studies on hemodynamics and coagulation in neuroanesthesia

Teemu Luostarinen

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TABLE OF CONTENTS

LIST OF ORIGINAL PUBLICATIONS

This thesis is based on the following original articles, which are referred to in the text by their Roman numerals:

I. Luostarinen T, Lehto H, Skrifvars MB, Kivisaari R, Niemelä M, Hernesniemi J, Randell T, Niemi T. Transfusion frequency of red blood cells, fresh frozen plasma and platelets during ruptured cerebral aneurysm surgery. World Neurosurg 2015;84:446-50.

II. Luostarinen T, Takala RS, Niemi T, Katila AJ, Niemelä M, Hernesniemi J, Randell T. Adenosine-induced cardiac arrest during intraoperative cerebral aneurysm rupture. World Neurosurg 2010;73:79-83.

III. Luostarinen T, Silvasti-Lundell M, Mederois T, Romani R, Hernesniemi J, Niemi T. Thromboelastometry during intraoperative transfusion of fresh frozen plasma in pediatric neurosurgery. J Anesth 2012;26:770–774.

IV. Luostarinen T, Niiya T, Schramko A, Rosenberg P, Niemi T. Comparison of hypertonic saline and mannitol on whole blood coagulation in vitro assessed by thromboelastometry. Neurocrit Care 2011;14:238-243.

V. Luostarinen T, Dilmen OK, Niiya T, Niemi T. Effect of arterial blood pressure on the arterial to end-tidal carbon dioxide difference during anesthesia induction in patients scheduled for craniotomy. J Neurosurg Anesthesiol 2010;22:303-308.

VI. Luostarinen T, Lindroos A-C, Niiya T, Silvasti-Lundell M, Schramko A, Hernesniemi J, Randell T, Niemi T. Prone versus sitting position in neurosurgery – differences in patient hemodynamics and in stroke volume – directed fluid administration. Submitted.

ABBREVIATIONS

BBB	blood-brain barrier
BSA	body surface area
CBF	cerebral blood flow
CFT	clot formation time
CI	cardiac index
CO	cardiac output
CO_2	carbon dioxide
CPP	cerebral perfusion pressure
CT	clotting time
$EtCO_2$	end-tidal concentration of carbon dioxide
FFP	fresh frozen plasma
FiO_2	fraction of inspired oxygen
GDT	goal-directed therapy
GOS	Glasgow outcome scale
HES	hydroxyethyl starch
HH	Hunt & Hess
HS	hypertonic saline
ICP	intracranial pressure
ICU	intensive care unit
MAP	mean arterial pressure
MCF	maximum clot firmness
MRI	magnetic resonance imaging
NaCl	sodium chloride
$PaCO_2$	arterial carbon dioxide partial pressure
PaO_2	arterial oxygen partial pressure
P/F	PaO_2/FiO_2 ratio
PT	prothrombin time
PTT	thromboplastin time
RAC	Ringer's acetate
RBC	red blood cell
RBCT	red blood cell transfusion
SAH	subarachnoid hemorrhage
SV	stroke volume
SVI	stroke volume index
SVV	stroke volume variation
TBI	traumatic brain injury
VAE	venous air embolism
WFNS	World Federation of Neurological Surgeons

ABSTRACT

Introduction

By understanding the effect that anesthesiological interventions, patient positioning, and neurosurgical pathologies have on regulatory mechanics of cerebral blood flow and oxygen consumption, it is possible to guarantee sufficient blood flow and oxygenation of the brain and to provide good surgical conditions for a neurosurgeon. Perioperative fluid administration should have a minimal effect on blood coagulation in neurosurgery. Optimal hemoglobin level in the neurosurgical patient population is unknown. Transfusion of blood products itself may be associated with worse outcome. Good hemodynamic control and well-planned patient positioning are important to ensure sufficient cerebral perfusion pressure (CPP) and to minimize intraoperative bleeding.

The objective of this thesis was to examine clinically important aspects of neuroanesthesia regarding cerebral blood flow and perfusion pressure, blood coagulation, and transfusion of blood products in neurosurgical patients.

Patients and methods

This study consists of 130 adult and two pediatric neurosurgical patients and 10 healthy volunteers (Studies III-VI). In addition, Studies I and II include a retrospective review of 1014 plus 488 patients' (partly the same patients) medical records.

Data on patients operated on for ruptured cerebral arterial aneurysm at Helsinki University Hospital between 2006 and 2009 (Study I) and at Helsinki University Hospital and Turku University Hospital between 2003 and 2008 (Study II) were reviewed to calculate the transfusion rates of blood products (Study I) and the incidence of adenosine use (Study II). Possible risk factors for red blood cell (RBC) transfusion (RBCT) and its effect on outcome were also investigated.

Rotational thromboelastometry (Rotem®) analysis was used to evaluate the ability of fresh frozen plasma (FFP) and RBCT to maintain adequate coagulation capacity in two pediatric neurosurgical patients suffering from massive bleeding during craniotomy (Study III) and to compare the effect of equimolar and equivolemic solutions of mannitol and hypertonic saline on blood coagulation in vitro (Study IV).

Effect of change in mean arterial pressure (MAP) on the difference between arterial carbon dioxide partial pressure ($PaCO_2$) and end-tidal concentration of carbon dioxide ($EtCO_2$) was measured from patients anesthetized for craniotomy to test reliability of $EtCO_2$ as an estimate of $PaCO_2$ (Study V). After data combination from two previously conducted, separate prospective trials comparing stroke volume (SV)-directed administration of hydroxyethyl starch (HES 130/0.4) and Ringer's acetate (RAC) in prone and sitting positions during neurosurgery, the differences in SV-directed fluid administration between the two different positions were measured with the purpose of determining whether one of the fluids would be more beneficial than the other in achieving stable hemodynamics (Study VI).

Results

Intraoperative transfusion rates for RBC, FFP, and platelet transfusion intraoperatively were 7.6%, 3.1%, and 1.2%, respectively. RBCT was associated with intraoperative rupture of an aneurysm. Lower preoperative hemoglobin value, worse Fisher grade, and intraoperative rupture of an aneurysm independently increased the likelihood of intraoperative RBCT. Intraoperative RBCT increases the patient's risk for worse neurological outcome, even when controlled with other variables, such as the World Federation of Neurological Surgeons (WFNS) classification and Fisher grade. With early perioperative transfusion of RBC and FFP, it is possible to preserve normal coagulation capacity when massive bleeding during surgery is expected.

A total of 16 of 1014 patients operated on for ruptured cerebral arterial aneurysm received adenosine during surgery. All but one adenosine administration was related to intraoperative rupture of an aneurysm. The median single dose for adenosine was 12 (range 6-18) mg and the median cumulative dose 27 (18-89) mg. After 10 min of adenosine administration, patients had stable hemodynamics and no adverse effects were reported.

A 15% mannitol solution in 10 vol% and 20 vol% dilutions impaired coagulation more than an equiosmolar 2.5% saline in vitro. Overall, mannitol disturbed coagulation more than any other study solution. An increment in the concentration of saline solution resulted in a weaker clot.

The percentage change in MAP had a positive correlation with measured $PaCO_2$-$EtCO_2$ difference after anesthesia induction in the craniotomy patient population.

Study fluid consumption did not differ between the two surgery positions. The cumulative dose of RAC (prone and sitting position combined) to optimize fluid filling at 30 min after surgery was higher than the dose of HES (ratio 1.5:1). Patients in a sitting position had a lower MAP over time and higher cardiac and stroke volume indices than patients in a prone position.

Conclusion

Intraoperative RBCT may itself worsen SAH patients' neurological outcome. In the event of sudden intraoperative rupture of an aneurysm, adenosine-induced asystole can be used to stop the bleeding and facilitate clipping of the aneurysm. Early infusion of FFP instead of crystalloids should be considered to compensate for expected excess bleeding in neurosurgery to preserve normal coagulation capacity. Moreover, hypertonic saline might be a more favorable solution than mannitol in treating elevated intracranial pressure due to its less harmful effect on blood coagulation.

Hemodynamic changes make $EtCO_2$ unreliable in estimating $PaCO_2$. Therefore, optimal ventilation before neurosurgery should be confirmed by arterial blood gas analysis. Preemptive goal-directed fluid administration with either RAC or HES solutions before positioning enables a stable hemodynamic state during neurosurgery in both prone and sitting positions. Fluid requirement did not differ between the two surgery positions, and the ratio of HES:RAC to achieve comparable hemodynamics is 1:1.5.

1. INTRODUCTION

The main goal of neuroanesthesia is to maintain adequate cerebral perfusion pressure (CPP) and, consequently, cerebral blood flow (CBF) to guarantee sufficient oxygenation of the brain. Moreover, neuroanesthesia aims to provide good surgical conditions for the neurosurgeon and to use available tools such as drug therapy for neuroprotection in situations where there is a risk of decreased oxygen delivery to the brain [1]. To succeed in these goals, the anesthesiologist must have adequate knowledge of the effect that anesthetics, intravenous fluids, other anesthesiological interventions, and neurosurgical pathologies have on CBF, CPP, autoregulation, carbon dioxide reactivity, brain metabolism, and flow-metabolic coupling. Autoregulation of CBF is often, at least partially, disturbed in neurosurgical patients [2]. Therefore, good hemodynamic control of the patient during neurosurgery is essential to maintain adequate CPP and to prevent intraoperative blood loss. As intracranial pressure (ICP) monitoring is not always feasible in the perioperative phase, MAP alone provides a CPP approximation.

No specific guidelines exist for fluid therapy in neurosurgical patients. To prevent sudden changes in plasma osmolarity, hypotonic fluids should be avoided [3]. Normal coagulation capacity is essential in neurosurgery, and therefore, perioperative fluid administration should be planned in a way that does not jeopardize coagulation [4]. Artificial colloids are known to have a negative effect on blood coagulation [5-7]. Regarding intraoperative fluid administration, colloids have been thought to be superior to crystalloids in increasing hypovolemic patients' intravascular volume and cardiac stroke volume, but recent findings indicate that the difference might be notably smaller than earlier believed [8-10]. Recent controversies regarding colloid safety have, however, diminished their use [11,12].

Optimal hemoglobin level in the neurosurgical patient population is unknown, and transfusion of blood products itself may be associated with worse outcome [13]. On the other hand, early transfusion of blood products might be needed during neurosurgery in order to maintain normal coagulation capacity. Stable hemodynamics and treatment of hypertension in the perioperative phase are essential in preventing bleeding complications [14,15]. Controlled hypotensive anesthesia especially in cerebral arterial aneurysm surgery was previously used to prevent bleeding and intraoperative rupture of an aneurysm, but this practice is no longer supported due to complications associated with hypotensive anesthesia [16]. However, adenosine-induced cardioplegia is a relatively novel method to facilitate temporary clipping in the event of intraoperative rupture of an aneurysm, potentially also decreasing the risk of red blood cell transfusion (RBCT) [17].

Osmotherapy plays an important role in neuroanesthesia. As water movement between an intact blood-brain barrier (BBB) is guided by the osmotic gradient between plasma and the brain, both mannitol and hypertonic saline (HS) can be used to reduce ICP by increasing plasma osmolarity [18]. They are equally effective in reducing ICP and also carry a risk of certain clinically important side-effects [19-21]. Although BBB is practically impermeable to HS and mannitol, an impaired BBB can cause leakage of both sodium and mannitol into the cerebrospinal fluid [22]. Mannitol and HS may interfere with blood coagulation, but data comparing these two solutions do not exist [6,23,24].

CBF is strongly regulated by arterial CO_2 partial pressure ($PaCO_2$). Hypoventilation

causes vasodilation in cerebral arteries and increases CBF and potentially ICP, whereas hyperventilation causes vasoconstriction and a decrease in CBF [2]. An increase in $PaCO_2$ may cause a marked increase in ICP in situations where other compensatory mechanics have already been exhausted. Therefore, it is of the utmost importance to prevent hypoventilation in neurosurgical patients during anesthesia induction, bearing in mind that CO_2 reactivity is disturbed in hypotension [25,26].

Some neurosurgical procedures can be performed in either the sitting or prone position. Both of these positions in general anesthesia expose the patient to hemodynamic alternations, i.e. hypotension and changes in cardiac function [27,28]. Whether there is a difference between sitting and prone positions in patients' hemodynamic profiles and in requirements of intravenous fluid administration is not known.

The objective of this thesis was to examine clinically important aspects of neuroanesthesia regarding management of perioperative hemodynamics in securing sufficient CPP, transfusion practice without compromising blood coagulation, and transfusion of blood products in neurosurgical patients.

2. REVIEW OF THE LITERATURE

2.1 Cerebral blood flow and anesthesia

2.1.1 Cerebral blood flow and its regulation

The human brain, despite its relatively small proportion of body size, has high metabolic activity, requiring 20% of total basal oxygen consumption. Constant CBF is required to satisfy the brain's oxygen needs. The brain receives 15% of resting cardiac output in adults. The average cerebral blood flow is 50 ml/100 g/min, however, there is a great variation between white and gray matter of the brain [29]. A decrease in CBF to 20-25 ml/100 g/min exposes the brain tissue to ischemia. CBF of less than 10 ml/100 g/min will result in infarction within a few minutes [30-32]. CBF is partly regulated by the brain's complex intrinsic mechanism called flow-metabolic coupling, which optimally matches oxygen delivery and consumption. An increase in local metabolic activity will result in higher CBF in that area [29,33,34].

In normal circumstances, CBF autoregulation describes the ability of the brain to maintain a stable CBF despite fluctuations in cerebral perfusion pressure (CPP). CPP is calculated as mean arterial pressure (MAP) minus intracranial pressure (ICP), or central venous pressure if higher [2]. A change in MAP, and consequently in CPP, results in changes in cerebrovascular resistance (vasodilatation or –constriction in cerebral arteries). It is believed that autoregulation works when systemic mean arterial blood pressure varies between 50 and 150 mmHg. More recent findings suggest, however, that the lower threshold might actually be higher. There are variations between individuals, and, for example, hypertonia shifts the autoregulation curve to the right. Outside these thresholds, CBF is directly related to CPP [29,35,36]. Autoregulation is further divided into dynamic and static autoregulation. Dynamic autoregulation acts as a rapid response to pressure pulsations in systemic blood pressure, whereas static autoregulation reflects long-term changes in MAP [29,37,38]. Traumatic brain injury (TBI), subarachnoid hemorrhage (SAH), brain tumors, and various other neurosurgical conditions may alter the regulatory mechanics of CBF [39-41].

$PaCO_2$ is a strong regulator of CBF and a linear-like correlation exists between CBF and $PaCO_2$. Hyperventilation results in lower $PaCO_2$ and vasoconstriction in cerebral arteries, thus reducing blood flow, whereas higher $PaCO_2$ increases CBF by vasodilation of the cerebral arteries [42,43]. Low $PaCO_2$ value caused by hyperventilation may result in brain tissue hypoxemia due to intense vasoconstriction [44]. For this reason, current neuroanesthesia practice targets normoventilation. When treating increased ICP, hyperventilation may be used for short time periods, but in this case the treatment should include appropriate monitoring of brain tissue oxygenation [45]. Carbon dioxide (CO_2) reactivity is disturbed in hypotension [25,26].

Capnometry is routinely used to monitor end-tidal concentration of carbon dioxide ($EtCO_2$) with patients under controlled ventilation to assess alveolar ventilation and $PaCO_2$ [46]. $PaCO_2$ is a strong regulator of CBF and even small changes in CBF can produce a drastic change in ICP. Therefore, the accuracy of $EtCO_2$ to predict $PaCO_2$ is not sufficient in neurosurgical patients. Repeated arterial blood gas analyses are needed to secure optimal ventilation during the perioperative phase and also in ICU [47,48]. The $PaCO_2$-$EtCO_2$ difference is affected by both alveolar ventilation and systemic blood circulation. An intrapulmonary shunt results in ventilation

perfusion mismatch, which increases the $PaCO_2$-$EtCO_2$ difference [49]. The reason behind this phenomenon maybe underlying pulmonary disease, atelectasis formation, or even volatile anesthetics [49-52]. The believed negative effect of volatile anesthetics on hypoxic pulmonary vasoconstriction is not, however, unanimously supported [53]. The impact of systemic circulation on the $PaCO_2$-$EtCO_2$ difference is not clear. A linear relation has been shown between systemic blood pressure and $PaCO_2$-$EtCO_2$ difference in ICU patients but results in the perioperative phase with surgical patients are conflicting [48,54]. A positive correlation between changes in cardiac output and $EtCO_2$ has been reported with surgical patients [55,56].

2.1.2 Intracranial pressure

According to the historic Monro-Kellie doctrine, the intracranial space is a fixed volume comprising brain tissue, cerebrospinal fluid, and blood. If the volume of any of these components were to increase, it must be compensated by a decrease in volume of another component [57,58]. As brain tissue consists mainly of incompressible fluid, compensatory mechanics are very limited, including drainage of CBF to the spinal compartment and, to a lesser extent, a decrease in intracranial volume of venous blood. As indicated by the pressure-volume curve, which is not linear but exponential, these compensatory mechanisms are able to maintain a normal ICP for any change in volume less than approximately 100–120 ml, but beyond this the ICP will increase abruptly and there is a risk of brain tissue herniation [59,60].

2.1.3 Anesthetics and cerebral blood flow

The effects of volatile and intravenous anesthetics on CBF and cerebral metabolism are well-described in the literature [61-63]. Volatile anesthetics, although reducing the cerebral metabolic rate, is known to cause vasodilation in cerebral arteries and also to impair autoregulation and flow-metabolic coupling. The severity of the disturbance varies between anesthetics and is dose-related. Sevoflurane is often considered the best volatile anesthetic because it has the least effect on vasodilation and autoregulation [61]. Propofol, while interfering little with autoregulation and CO_2 reactivity, is a vasoconstrictor, and therefore, with its reducing effect on brain metabolism, is usually the most suitable anesthetic for patients with elevated ICP [63]. Animal models suggest that both volatile anesthetics and propofol also possess neuroprotective properties [64-66].

2.2 Perioperative fluid therapy and hemodynamic management

2.2.1 Fluid management

In the general surgery population, discussion about optimal perioperative fluid application is ongoing [67,68]. Historically, a liberal fluid regimen has been applied to guarantee adequate tissue perfusion with sufficient circulating intravascular volume. Substitution of possible fluid losses from fasting, evaporation, and fluid shifts to a third space due to surgery have been ensured with liberal administration of fluids. However, recent concerns about potential tissue edema, particularly in the intestine, due to fluid overflow, and questions regarding the existence of a third space have increased the popularity of a more restrictive fluid administration [67,69,70]. Controversy remains since the terms “liberal” and “restricted” are not well-established in the literature, and most of the studies involve only abdominal surgery patients [71]. It has been suggested that fluid therapy guided by the patient’s fluid responsiveness could improve patient outcome [72]. This individual

goal-directed therapy (GDT) for fluid administration is based on the physiological principle of the Frank-Starling law, where stroke volume of the heart increases in curvilinear response to an increase in preload of the heart until the plateau phase is reached [73,74]. Earlier, pulmonary artery catheter was required for GDT, but today less invasive methods measuring flow-based hemodynamic parameters are available. These include transesophageal ultrasound, arterial waveform analysis, and pulse contour analysis (Vigileo®, Picco®, and Lidco® systems). A recent meta-analysis of 29 previously conducted studies concludes that preemptive hemodynamic monitoring-guided therapy improves the outcome of high-risk surgical patients [75].

No specific guidelines exist for perioperative fluid administration in neurosurgical patients. The goal ought to be in preserving adequate perfusion and oxygen delivery to the brain and normal coagulation capacity. GDT has been adopted in neurosurgery as well, and stoke volume variation (SVV) has been reported to be a good predictor of fluid responsiveness [76,77].

2.2.2 Crystalloids and colloids

Crystalloids may vary in osmolarity, but have an oncotic pressure of zero, whereas colloids, such as albumin and hydroxyethyl starch (HES) solutions, contain high molecular compounds that create oncotic forces and add overall colloid osmotic pressure [67]. Crystalloids may vary in osmolarity, but have an oncotic pressure of zero, whereas colloids, such as albumin and hydroxyethyl starch (HES) solutions, contain high molecular compounds that create oncotic forces and add overall colloid osmotic pressure [67].

Crystalloids' ability to increase intravascular volume is limited because these solutions will distribute evenly within the extracellular space. A reported 20% of normal saline and 17% of lactated Ringer's solution remain in the intravascular space [67,78]England. In addition, 0.9% saline, or "normal saline" as it is often called, has an equal concentration of sodium and chloride ions (154 mmol/l), making it slightly hypertonic compared with physiological plasma sodium levels. Saline solutions are associated with a risk of hyperchloremic acidosis [79-81]. Chloride concentration has been reduced in buffered solutions, such as Ringer's acetate (RAC), where chloride concentration is 103 mmol/l, thus decreasing the risk of hyperchloremic acidosis. RAC resembles extracellular fluid in terms of ion concentrations [82]. If RAC solutions are used in neurosurgical patients, their relatively low sodium concentration must be considered. Plasma osmolarity affects water movement through BBB, and reduction in plasma osmolarity may lead to increased brain edema [3].

Colloids, including human-derived albumin and synthetic solutions such as gelatin, dextran, and hydroxyethyl starch (HES), have been used to increase intravascular volume more efficiently than crystalloids [83]. Oncotic force and duration of volume expanding effect depend on molecular size of the solutions [83]. HES solutions have developed from earlier high molecular weight and molar substitution to more rapidly degradable lower molecular weight and low degree of substitution solutions such as HES 130/0.4 [84].

Regarding intraoperative fluid administration, there has been an ongoing vigorous debate about whether colloids are more effective than crystalloids in increasing hypovolemic patients' intravascular volume and stroke volume (SV) of the heart [8-10,85-87]. Recent findings with ICU and surgical patients show that the difference between the two solution types is notably smaller than earlier believed [10,88,89], being 1.3- to 1.6-

fold in favor of colloid solutions. However, in situations where acute bleeding occurs a five-fold amount of crystalloids compared with colloids has been recommended to replace blood loss [78].

Crystalloids and artificial colloids as well as albumin have all historically been used to treat neurosurgical patients. When lactated Ringer and HES solutions were compared regarding their effect on brain relaxation and brain metabolism, no evidence was found that one solution type would be more beneficial than the other [90].

Dilution caused by administration of normal saline induces a hypercoagulable state, and thus, is not associated with decreased blood coagulation [91]. Data concerning the effect of RAC solution on blood coagulation are limited, but an experiment in vivo shows that a dilution of over 50% is needed to impair coagulation [92].

All artificial colloids may interfere negatively with blood coagulation [5-7,93-95]. The effect of HES solutions on blood coagulation depends on the molecular weight and substitution degree of the solutions, with third-generation HES 130/0.4 having the smallest effect [96]. Albumin has been considered to have a minimal effect on blood coagulation, but when administered in large doses can interfere with coagulation. The effect might be partly explained by dilution [7,97].

Use of hydroxyethyl starch solutions has been questioned since the publication of two large randomized trials comparing HES solution with crystalloids in fluid resuscitation [11,12]. Increased mortality and likelihood of renal replacement therapy among severe sepsis patients were associated in the 6S-trial with the use of HES solutions compared with RAC solution [11]. One study concluded that in a heterogeneous ICU patient population no difference in mortality existed, but patients who received fluid resuscitation with HES needed renal replacement therapy more often than patients receiving saline [12]. Another multicenter trial repeated the result of an association between increased risk of kidney failure and HES with ICU patients, but no difference in mortality was found [98].

Safety of HES in perioperative care remains partly unclear due to the lack of large randomized trials. However, two meta-analyses of HES use in surgical patients found no association between increased risk of kidney failure and use of HES [99,100] or between increased mortality and use of HES [100].

Albumin is not associated with increased risk of adverse events in ICU and septic patient populations [88,101]. However, the post-hoc analysis of the SAFE study revealed that patients with traumatic brain injury (TBI) had higher mortality if they had been treated with albumin and saline instead of only saline [102].

The consensus statement of the European Society of Intensive Care Medicine task force does not recommend the use of low molecular weight HES and gelatin solutions in patients with severe sepsis or kidney injury or colloids in general in patients with TBI [103].

2.2.3 Mannitol and hypertonic saline

Osmotherapy is often used in treatment of elevated ICP in patients suffering from TBI, brain tumor, SAH, or other intracranial volume-occupying lesions [104]. Traditionally, mannitol has been the agent of choice, but HS has proved to be a worthy alternative [105-108]. HS is equally effective or even better than mannitol in reducing brain swelling, and consequently ICP, in patients undergoing craniotomy [19-22,109,110]. A recent retrospective review evaluating HS and mannitol during ICU stay concluded that HS was more effective in cumulative and daily ICP burdens after severe TBI [111]. However, due to the heterogeneity of the studies regarding osmolarity and volumes

of the solutions and the lack of randomized controlled trials, no definite conclusions about the superiority of HS to mannitol in treating ICP can be made.

Earlier in vitro reports indicate that both mannitol and HS possess features that may jeopardize blood coagulation [6,23,24,112]. Mannitol alone reduces clot strength and when combined with hydroxyethyl starch the effect is even more profound [6]. HS at different concentrations (3–7.5%) impairs coagulation process by inhibiting fibrin formation and platelet function [23,24,112]

Both solutions have clinically important side-effects. Contrary to HS, mannitol is associated, particularly after repeated doses, with acute renal failure [113-116]. As mannitol has a strong diuretic effect, it may also cause disturbances in a patient's fluid balance and electrolyte levels, consequently requiring adjustments in general fluid administration [117]. Moreover, the osmotic response to mannitol treatment is not entirely predictable, and there is a risk of unwanted rebound increase in ICP, especially after repeated doses. This phenomenon is believed to result from intact BBB allowing leakage of mannitol into brain tissue [118-120]. Variations in plasma sodium levels are evident when using mannitol or HS. While mannitol causes hyponatremia, the use of HS increases plasma sodium levels and can result in hyperchloremic acidosis [22].

2.2.4 Red blood cells, platelets, and fresh frozen plasma

A recent review evaluating studies that have tried to establish hemoglobin level thresholds for red blood cell (RBC) transfusion in neurosurgical patients concluded that the optimal hemoglobin level remains unclear [13]. Challenges are posed by the vast variety of neurosurgical conditions and the requirement possibly not being the same perioperatively as during intensive care [13]. It is currently believed that neurointensive care patient populations would benefit from slightly higher hemoglobin levels than general ICU patients because the brains' strict oxygen requirements in the former group make it vulnerable to hypoperfusion and hypoxia [121].

SAH patients with a higher hemoglobin level may have a better outcome, but the optimal hemoglobin level remains unknown. Adding to the complexity of the issue, red blood cell transfusion itself seems to be associated with worse neurological outcome and increased risk of vasospasm in SAH patients, although conflicting results have also been reported [122-128]. RBCT during ICU stay of SAH patients is also associated with other medical complications such as pneumonia [129]. The age of transfused RBCs has recently received increased interest, although thus far RBC age has not been shown to have an effect on outcome of SAH patients receiving RBCT [123,130]. The transfusion rate for RBCs during surgery for ruptured arterial aneurysm varies between 5.6% and 27.2% [131-133].

No specific thresholds for transfusion of platelets or fresh frozen plasma (FFP) are available due to insufficient evidence.

Massive bleeding during neurosurgery can occur abruptly. Guidelines are lacking for the treatment of neurosurgical patients, both adult and pediatric patients, during massive bleeding. However, current guidelines for trauma patients recommend early use of RBC, FFP, and platelets [134-136]. Historically, RBCs were administered first together with crystalloids, but today it is suggested that FFP and platelets be given together with RBCs in a volume ratio of 1:1:1 [137]. Decreased fibrinogen concentration is an important factor in impaired coagulation capacity [138].

Recommendations for blood product use in pediatric ICU patients are conservative, and blood product transfusion is advised only after coagulation deficit is confirmed

by laboratory testing [139]. This treatment approach is not suitable for pediatric neurosurgical patients, in whom abrupt bleeding during surgery is possible and can quickly result in severe hypovolemia. In this situation, any laboratory test would be too slow to guide fluid administration.

2.2.5 Perioperative hemodynamic control

In general, stable hemodynamics is required during the perioperative phase in neurosurgery to guarantee sufficient CPP pressure and to minimize intraoperative bleeding [15]. The blood pressure target must be adjusted according to the underlying pathology. In TBI, patients often have an increased ICP, thus requiring higher CPP for optimal oxygen delivery. After surgical opening of the dura, the often associated decrease in blood pressure should be monitored to prevent an excessive decrease in blood pressure [140].

Patients with SAH due to ruptured arterial aneurysm are at high risk of re-bleeding [141]. Therefore, good hemodynamic control is essential and any peaks in blood pressure should be avoided throughout the perioperative period until the aneurysm is safely occluded from the circulation [142,143]. Again, if ICP is increased, blood pressure should be adjusted accordingly. Opening of the dura will decrease the transmural pressure difference of the aneurysm wall and may lead the a rupture of an aneurysm if systemic blood pressure is too high [143]. During temporary clipping an increase of systemic blood pressure may be considered to optimize oxygen supply through collateral blood flow [142,143].

2.2.6 Adenosine

Adenosine is an endogenously occurring nucleoside. It has a very short negative effect on cardiac sinoatrial and atrioventricular nodes, resulting in decreased heart rate and prolonged conductance. Adenosine acts on cardiac A1 receptors, causing hyperpolarization by increased outward flux of potassium, and reduces intracellular cyclic adenosine monophosphate. This further inhibits calcium entry into the cell. When administered intravenously, adenosine has a quick onset of action and a short half-life [144-146]. The duration of the occurring asystole is dose-dependent [147].

Adenosine has been traditionally used in cardiology for treatment of supraventricular tachyarrhythmia [146]. In the surgical field, adenosine-induced asystole was first applied in cardiac bypass surgery and also in thoracic surgery to facilitate precise deployment of stent grafts [148,149].

In the field of neurosurgery, adenosine-induced transient asystole was first described in endovascular embolization of cerebral arteriovenous malformation. Soon after, the first report of adenosine use in surgery for cerebral arterial aneurysm was described in a case where repeated dosing of adenosine was used to facilitate clipping of a basilar arterial aneurysm [17,150]. Clinical experience has

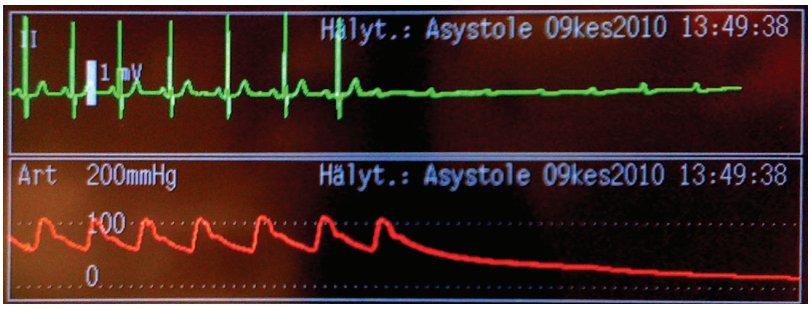


Figure 1 Example of adenosine-induced cardiac arrest seen in electrocardiography (figure used with the permission of the copyright holder Hanna Tuominen).

shown that adenosine-induced cardiac arrest is a valuable tool in facilitating clipping of an aneurysm, especially in situations where proximal occlusion of the feeding artery by temporary clipping is not possible or in the event of intraoperative rupture of an aneurysm (Figure 1).

2.3 Perioperative coagulation

2.3.1 Measurement of coagulation

A postoperative hematoma is a potential life-threatening complication after intracranial surgery and is frequently associated with a poor outcome and even death of neurosurgical patients [4].

Postoperative bleeding complications are often related to perioperative coagulation disturbance, and therefore, it is essential to detect pre-existing hemostatic problems and to preserve normal coagulation capacity throughout neurosurgical procedures. The reason for underlying disturbance is often multifactorial and can be related to medications interfering with the coagulation system or platelet function or to a deficiency in endogenic coagulation factor production [151]. Patients can develop an acute coagulation disturbance perioperatively due to blood loss, dilution, and consumption of coagulation factors or, in rare cases, disseminated coagulopathy. On the other hand, hypercoagulopathy is often detected in patients undergoing craniotomy, and risk of postoperative thromboembolic complications is increased [151-153].

Although important to screen, normal preoperative laboratory data do not guarantee that the patient's coagulation capacity is normal. For example, factor VIII deficiency, which has been shown to contribute to postoperative bleeding problems, might go unnoticed because it is not detected by partial thromboplastin time (PTT) or prothrombin time (PT) [151]. Also, platelet count remains normal even if platelets are dysfunctional due to antiplatelet drugs. Careful preoperative evaluation and risk assessment for bleeding are important, as is additional coagulation testing when indicated [151].

2.3.2 Thromboelastometry

In the perioperative setting, traditional coagulation tests are often too slow to guide transfusion of fluids and blood products [154]. Contrary to these traditional laboratory tests, visco-elastic whole-blood point-of-care testing allows quick and dynamic evaluation of the entire coagulation process and also enables intrinsic and extrinsic coagulation pathways to be distinguished from pure fibrin formation [155,156].

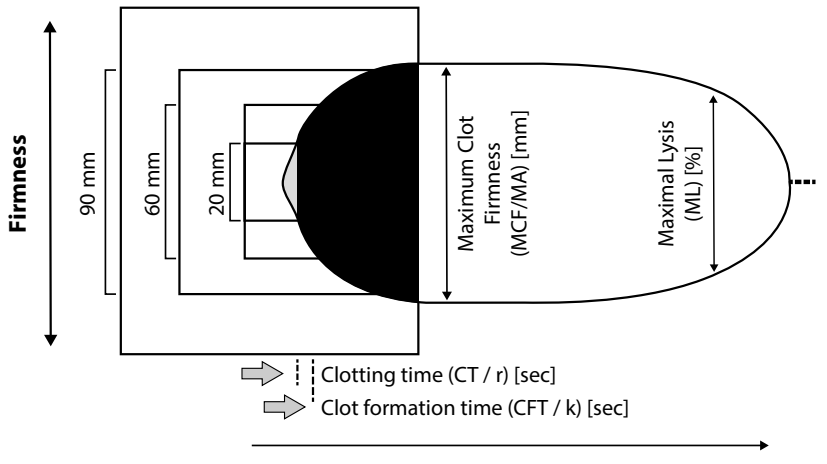


Figure 2 Sample of thromboelastometry tracing and parameters (reprinted and modified from www.practical-haemostasis.com with permission of the website owner David Perry).

Thromboelastography was developed already in 1948, but the first clinical report of its use came in the 1980s [156,157]. Development from the original thromboelastometry has led to commercially available visco-elastic whole-blood analyzers: thromboelastography (TEG®), thromboelastometry (RoTEM®), and Sonoclot® [158].

In thromboelastometry analysis (RoTEM®), citrated blood is combined with the desired reagent in a cup to start the coagulation test. The cup is then placed under a slowly oscillating pin.

The analyzer measures the changes in elasticity of the developing clot. Usually 30 minutes is enough for the analysis, but the coagulation process can be investigated at all times during the analysis, as the development of the forming clot is graphically displayed and the start of clot formation can occur within minutes. Besides the visual estimation of the graphic display of the coagulation process, several numeric values can be obtained and normal reference ranges have been established [156] (Figure 2).

- Clotting time (CT) describes the time from start of analysis until start of clot formation. Heparin effect or lack of coagulation factors can be the reason behind increased CT. In hypercoagulable state, CT is decreased.
- Clot formation time (CFT) and alpha angel describes the velocity of the forming clot. Decreased values can be seen in platelet or fibrinogen deficiency.
- Maximum clot firmness (MCF) is the strength of the developed clot until the start of potential fibrinolysis.
- Maximum lysis (ML) shows the decrease in clot strength after MCF is reached. Increased lysis is an indication of hyperfibrinolysis.

Different reagents are used in RoTEM® analysis. ExTEM® includes tissue thromboplastin and screens the extrinsic pathway [158]. FibTEM® is similar to ExTEM®, but has cytochalasin added to inhibit platelet function, thus allowing estimation of fibrinogen contribution to clot strength [158]. ApTEM® includes aprotinin to detect possible increased fibrinolysis relative to ExTEM® [158]. InTEM® is added with contact activator and screens the intrinsic pathway [158].

A limitation of thromboelastometry in perioperative settings is that it is unable to detect platelet dysfunction caused by platelet aggregation inhibitors such as acetylsalicylic acid and clopidogrel or von Willebrand's disease [159,160]. Other testing methods designed for measuring platelet function should be used in these cases [160].

A meta-analysis that evaluated the use of RoTEM® or TEG® in a bleeding trauma patient population stated that they might be useful in detecting early coagulopathy [161]. Whether they have impact on blood product consumption or mortality remains unclear [161]. In the perioperative phase, thromboelastometry-guided treatment has reduced blood product use in cardiac surgery and bleeding burn patients [162,163].

Reports concerning the use of thromboelastometry in neurosurgical patients have concentrated on hypercoagulability, which is often associated with patients undergoing craniotomy [152,153], or on underlying coagulation abnormality [164].

2.4 Patient positioning in neurosurgery

To achieve an optimal surgical approach, different patient positions have been used in neurosurgery. Patient can be operated on in supine or prone position, but also in lateral or sitting or semi-sitting position [165].

Neurosurgery in sitting position was more popular in the 1970s and 1980s than it is today. Still now, there is a great variation

in which centers and in which countries sitting position is used, often depending on tradition and the experience of the individual neurosurgeon [166]. Sitting position offers advantages in certain types of neurosurgery and is often preferred when operating on lesions in the posterior cranial fossa [167]. When the patient is in the sitting position, ICP is decreased and the operating field is clearer due to gravity forcing blood and cerebrospinal fluid downwards. With the anatomical approach, surgery in a sitting position is associated with lesser risk of cranial nerve damage [168]. A major concern, posing challenges for both the neurosurgeon and anesthesiologist, is venous air embolism (VAE). Reported incidence varies between 1.6% and 50%, the incidence being lower in the semi-sitting position [85,169-171]. VAE is best detected with precordial Doppler ultrasound, but also decrease in $EtCO_2$ will reveal 80% of the VAEs detected by ultrasound [172].

The prone position provides good surgical access to the posterior head, neck, and spinal column, and it is therefore used for spinal surgery. The prone position is also possible for some parietal, occipital, and suboccipital craniotomies [28]. Some operations can be performed in both prone and sitting positions, in which case the decision is made according to the neurosurgeon's preference. Anesthesiological aspects should also be taken into consideration [27].

Neurosurgery in general anesthesia both in prone and sitting positions exposes the patient to hemodynamic alterations, i.e. hypotension and changes in cardiac function, compared with the supine position [27,173-177].

The sitting position causes hypotension and a decrease in cardiac function, posing a challenge in providing sufficient CPP and oxygen delivery to the brain [173,174,178]. Hemodynamic changes can partly be explained by pooling of venous blood to the lower extremities. [173]. Carefully planned position, preemptive fluid optimization, and use of an anti-gravity suit may diminish changes in patients' hemodynamics. CI, SVI, and SVV before positioning may have a predictive value for hypotension occurring after positioning [179]. A decrease in cardiac function is also associated with surgery in the prone position. Decreased cardiac function is believed to result from reduced venous return and ventricular compliance of the heart [176,177]. Hemodynamic changes may be prevented by adequate fluid replacement prior to positioning [176].

3. AIMS OF THE STUDY

This study examines clinically relevant aspects of neuroanesthesia regarding cerebral blood flow and perfusion pressure, blood coagulation, and transfusion of blood products in neurosurgical patients.

Specific aims were as follows:

1. To evaluate perioperative transfusion rates of RBC, platelets, and FFP in patients operated on for ruptured cerebral arterial aneurysm.

2. To identify potential risk factors for RBCT and its effect on patient outcome.

3. To investigate the incidence of cardioplegia caused by intraoperative use of adenosine during surgery of ruptured cerebral arterial aneurysm.

4. To examine coagulation during replacement of blood loss with FFP and RBCs.

5. To compare in vitro the effect that equimolar and equivolemic solutions of mannitol and HS have on blood coagulation.

6. To characterize the impact of arterial blood pressure change on PaCO2-EtCO2 in patients anesthetized for craniotomy.

7. To compare the intraoperative requirement of HES 130/0.4 and RAC to achieve stable hemodynamics guided by stroke volume measurement between neurosurgery in the prone and sitting positions.

4. MATERIALS AND METHODS

This study was carried out at the Department of Anesthesiology and Intensive Care and the Department of Neurosurgery of Helsinki University Hospital, Finland. Seventy-two neurosurgical adult and 2 neurosurgical pediatric patients and 10 healthy volunteers participated in Studies III-V. Study VI included 58 patients previously recruited for two earlier studies [10,85]. Additionally, Studies I and II included a retrospective review of the medical records of 488 plus 1014 patients (partly the same patients) (Table 1).

The Helsinki University Central Hospital Scientific board approved all studies. In addition, the Ethics Committee of the hospital district approved Studies IV-VI. All patients and volunteers in Studies IV-VI gave their informed consent to participate.

Table 1 Study characteristics.

	N	Subjects	Study design	Intervention	Primary end-point
I	488	Neurosurgical patients	Retrospective	None	Incidence of perioperative transfusion of blood products in patients operated on for ruptured cerebral arterial aneurysm
II	1014	Neurosurgical patients	Retrospective	None	Incidence of perioperative use of adenosine in patients operated on for ruptured cerebral arterial aneurysm
III	2	Pediatric patients	Clinical report	None	Coagulation assessed with thromboelastometry (Rotem®)
IV	10	Healthy volunteers	In vitro experiment	10 and 20 vol% dilution of blood with mannitol 15%, NaCl0.9%, 2.5%, and 3.5%	Coagulation assessed with thromboelastometry (Rotem®)
V	72	Neurosurgical patients	Prospective	None	Effect of systemic blood pressure changes on $PaCO_2$-$EtCO_2$ difference
VI	30+28	Neurosurgical patients	Post-hoc analysis of two separate prospective trials	SV-directed administration of RAC and HES 130/0.4	Volumes of RAC and HES in prone vs sitting position

$PaCO_2$ = arterial carbon dioxide partial pressure
$EtCO_2$ = end-tidal concentration of carbon dioxide
RAC = Ringer's acetate
HES = hydroxyethyl starch

4.1 Studies I and II

Anesthesia reports of the patients operated on for ruptured cerebral arterial aneurysm at the Department of Neurosurgery of Helsinki University Hospital between 2006 and 2009 (Study I) and at the neurosurgical departments of Helsinki University Hospital and Turku University Hospital between 2003 and 2008 (Study II) were reviewed to identify patients who had received blood products (Study I) or adenosine (Study II) intraoperatively.

After identifying patients (Study I) who had received RBC, platelets, or FFP during preparation for surgery, intraoperatively, or during the immediate postoperative period (within 24 hours of surgery), transfusion rates of RBC, platelets, and FFP were calculated. These patients were then compared with patients listed in the general Helsinki database of aneurysmal SAH. A multiple regression model was created to identify explanatory factors for RBCT and outcome where GOS was divided into two categories: good outcome (GOS 4-5) and poor outcome (GOS 1-3).

In Study II, the dose of adenosine, hemodynamics before and after its administration, and length of stay in intensive care unit (ICU) and hospital were recorded. In addition, the patients were grouped according to discharge status from hospital (dead or alive) and according to outcome (good outcome, GOS 4-5; poor outcome, GOS 1-3).

4.2 Study III

This clinical report included two previously healthy children scheduled for craniotomy due to brain tumor. A 10-month-old boy had been diagnosed with a richly vascularized tumor extending to the mesencephalon and hypothalamus (Figure 3). Similarly, in a 5-month-old boy, magnetic resonance imaging (MRI) had revealed a massive tumor in the left pontocerebellar area causing pressure to the brainstem (Figure 4). Massive intraoperative bleeding was anticipated due to the nature of the brain tumor in both patients.

In addition to crystalloid solution, FFP infusion was started after the induction of anesthesia. RBCs were administered according to intraoperative bleeding. Besides traditional laboratory tests (hemoglobin, hematocrit, platelet count, and PT%), a four-channel thromboelastometry device (Rotem®, Pentafarm AG, Basle, Switzerland) was used for coagulation analysis. Four different thromboelastometry tracings were used: Intem® (intrinsic pathway), Extem® (extrinsic pathway), Fibtem® (platelet function inhibition by cytochalasin D), and Aptem® (added aprotinin to detect hyperfibrinolysis). These tests were carried out pre-, intra-, and postoperatively and on the morning of the first postoperative day.

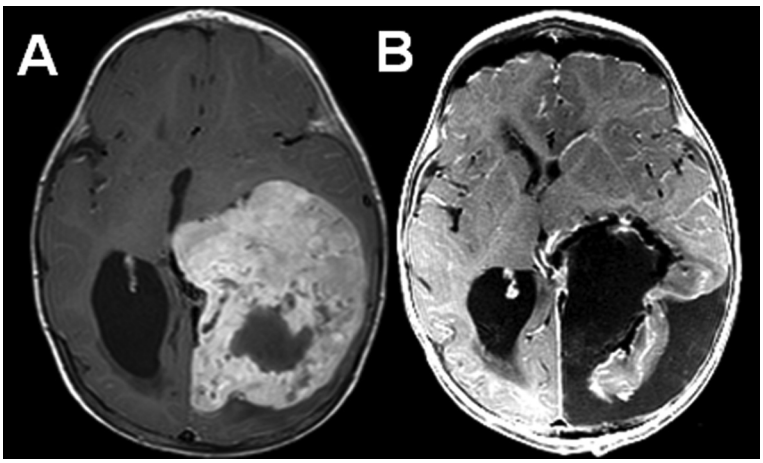


Figure 3 MRI before (A) and after (B) surgery.

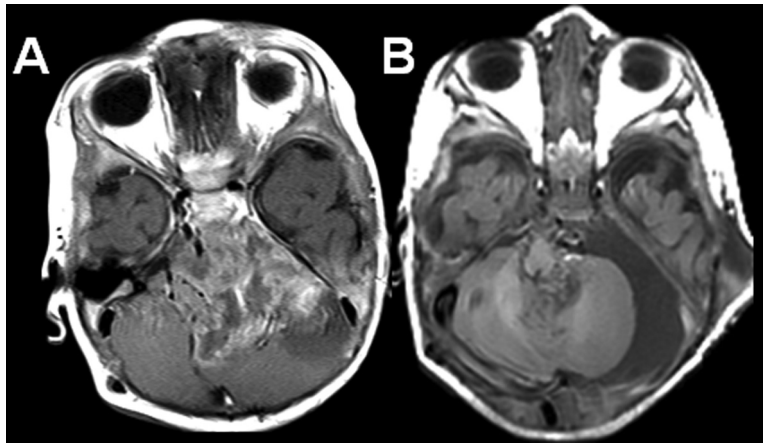


Figure 4 MRI before (A) and after (B) surgery.

4.3 Study IV

Venous blood samples taken from 10 previously healthy volunteers were diluted with the study solutions to make 0, 10, and 20 vol% final concentrations. The study solutions were 0.9% saline (Natriumklorid Braun® 9 mg/ml, reported osmolarity 300 mOsm/l), 2.5% saline (1 part Natriumklorid Braun® 234 mg/ml + 13.1 parts Natriumklorid Braun® 9 mg/ml), 3.5% saline (1 part Natriumklorid Braun® 234 mg/ml + 7.6 parts Natriumklorid Braun® 9 mg/ml), and 15% mannitol (Mannitol Braun® 150 mg/ml infusion fluid). The manufacturer of Mannitol Braun® 150 mg/ml infusion fluid reports that theoretical osmolarity of the fluid is 825 mOsm/l. Calculated osmolarity for 2.5% saline is 830 mOsm/l and for 3.5% saline 1160 mOsm/l.

Two four-channel thromboelastometry devices (Rotem®, Pentafarm AG, Basel, Switzerland) were used for the coagulation analysis of the diluted samples and a control sample. Extrinsic ROTEM (tissue coagulation activator, EXTEM®) and fibrinogen ROTEM (FIBTEM®) were used for the analysis. Developments in the coagulation process were recorded over a 30-min period. Measured coagulation parameters for ExTEM® were clotting time (CT), clot formation time (CFT), maximum clot firmness (MCF), and alpha angle (clot formation rate). Only MCF was measured in FibTEM® analysis.

4.4 Study V

Seventy-two adult patients scheduled for craniotomy at the Department of Neurosurgery, Helsinki University Hospital, were enrolled in this study. Patients with a history of pulmonary or cardiac valve disease, a decreased state of consciousness, or who already had an endotracheal tube or had required emergency surgery were excluded from the trial.

The change of MAP between intubation and attachment of the patient's head to a head frame (measured at 5-min intervals and prior to attachment) was calculated. The measured difference between $PaCO_2$ and $EtCO_2$ at the time of pinning of the head was compared with the calculated difference in MAP.

4.5 Study VI

Study VI consisted of 58 patients (30+28) from two previously conducted, separate prospective trials comparing stroke volume-directed administration of hydroxyethyl starch (HES 130/0.4) and Ringer's acetate in prone [10] and sitting [85] positions during neurosurgery. The results of differences between the study fluids in achieving stable hemodynamics within one surgery position and also the effect that these two fluids have on patient blood coagulation measured by Rotem® analysis have been reported earlier [10,85].

Patients younger than 18 years with body mass index (BMI) > 36 kg/m^2 in the

prone position or > 40 kg/m^2 in the sitting position, congestive heart failure, other than sinus rhythm on electrocardiography (ECG), renal failure (plasma creatinine > 120 μmol/l), hepatic failure, anemia (hemoglobin < 100 g/l), and thrombocytopenia (platelet count < 100x10^9/l) were excluded. Additionally, expected use of mannitol in the sitting position resulted in exclusion.

Before anesthesia induction, a basal Ringer's acetate (RAC) infusion was initiated at a rate of 3 ml/kg/h (an additional 40 mmol/l of NaCl was added to RAC basal infusion of patients in sitting position).

Both study sequences (prone and sitting position) had the same protocol for the study fluid administration. Patients were randomly assigned (using closed envelopes drawn in sequential order by the primary investigators) in blocks of three to receive one of the following study solutions:

1. 6% HES solution (Voluven®; 60 mg/ml, average molecular weight 130 kDa, molar substitution ratio 0.4, pH 4.0–5.5, contents Na^+ 154 mmol/l, Cl^- 154 mmol/l; Fresenius Kabi, Bad Homburg, Germany) (HES group, n = 15 in prone position + 15 in sitting position).
2. Ringer's acetate solution (Ringer-acetate®, pH 6.0, contents Na^+ 131 mmol/l, Cl^- 112 mmol/l, K^+ 4 mmol/l, Ca^{++} 2 mmol/l, Mg^{++} 1 mmol/l, $CH3COO^-$ 30 mmol/l; Fresenius Kabi) (RAC group, n = 15 in prone position + 15 in sitting position).

After anesthesia induction, while lying supine, all patients received an initial 200 ml bolus of the study fluid over 2–4 min, and hemodynamic measurements were performed before and 3 min after the administration of study fluid. A new bolus of 100 ml over 2–4 min was given immediately after the hemodynamic measurements, until stroke volume (SV) did not increase more than 10%. The hemodynamic measurements were performed 3 min after each bolus.

Thereafter, patients were positioned for surgery. Registration of hemodynamic parameters took place at 5-min intervals during surgery. If SV decreased more than 10% from the value obtained in the supine position, further study fluid boluses of 100 ml were administered. If the SV did not increase with three consecutive boluses, the volume expansion was stopped and the patient was considered a non-responder. Hemodynamic parameters were registered also at the end of surgery and after the patient was placed in the supine position.

The target MAP was 60 mmHg or higher at the brain level. Boluses of phenylephrine (0.05–0.1 mg) or ephedrine (5–10 mg) were given if MAP was below 60 mmHg despite the study fluid administration. A phenylephrine infusion was started whenever MAP remained below 60 mmHg for more than 5 min.

Basal infusion of RAC (with NaCl supplement if required) continued at a rate of 1 ml/kg/h until the first postoperative morning. Registration of urine output and fluid balance took place at pre-determined intervals.

After data combination, two-way ANOVA was used to test differences in stroke volume-directed fluid administration between the two different positions (surgery in prone vs. sitting position) and to determine whether one of the study fluids was more beneficial than the other.

4.6 Anesthesia and monitoring (Studies V and VI)

Anesthesia was induced in the supine position with fentanyl and either thiopental or propofol. Endotracheal intubation was facilitated by either suxamethonium or rocuronium. Anesthesia was maintained with

sevoflurane with or without nitrous oxygen (N_2O) and air and additional fentanyl boluses or a continuous infusion of propofol and remifentanil in patients operated on in prone position and with a continuous infusion of propofol in patients in sitting position with the permission to use sevoflurane to treat severe hypertension. After tracheal intubation, volume-controlled mechanical ventilation without positive end-expiratory pressure (PEEP) was initiated. In Study V, tidal volume was set to 8-10 ml/kg body weight and rate of ventilation to 10-15/min, targeting normoventilation ($PaCO_2$ 4.5-5.0 kPa). In Study IV, ventilator settings were determined by the attending anesthesiologist.

Monitoring of anesthesia prior to intubation included noninvasive arterial blood pressure, ECG (lead II), and arterial saturation of oxygen (SpO_2). After tracheal intubation, monitors of nasopharyngeal temperature, side-stream spirometry (Side stream®, Datex-Ohmeda Inc., GE Healthcare, Madison, WI, USA), and end-tidal concentration of carbon dioxide were applied. Additionally, a 20G arterial catheter (Becton Dickinson, Temse, Belgium or 20 BD Arterial Cannula, Singapore) was inserted into the radial artery for invasive monitoring of arterial pressures and to obtain blood samples.

To continuously monitor cardiac output (CO), cardiac index (CI), stroke volume (SV), stroke volume index (SVI), and stroke volume variation (SVV) in Study VI, the Vigileo System (Edwards Lifesciences, Irvine, CA, USA) with software version 3.02 was applied by connecting it into an arterial line with a pressure transducer set (FloTrac; Edwards Lifesciences) zeroed at the heart level. For patients operated on in sitting position, an additional set was applied and zeroed at the level of the foramen Monroi for measurement of systolic, diastolic, and mean arterial pressure.

4.7 Patient positioning (Study VI)

In prone position, bilateral chest supports were used and the patient's head was placed on a headrest (Prone View Protective Helmet System; Dupaco, Oceanside, CA, USA), or fixed with the Sugita pin head-holder device (Sugita Head Frames; Mizuho America, Union City, CA, USA). In sitting position, patients were dressed in an antigravity suit, the patient's upper body was elevated 50–100° and the head was attached to a head-holder device (Mayfield; Integra Life Sciences, Plainsboro, NJ, USA) and tilted forward 20–30° with the patient sitting with knees slightly flexed on a pillow.

4.8 Statistical analyses

The statistical analyses for all data were done with the following statistical software: SYSTAT 10.2 statistical package (SYSTAT Software, Inc., San Jose, CA, USA), IBM SPSS Statistics®, version 21, StatView PowerPC version 5.0 (SAS Institute Inc., Cary, NC, USA), or the statistician's personal non-commercial software.

The descriptive statistics are shown as mean ± SD, as median (range), or as numbers (percentage). The differences between the groups were analyzed by t-test (Study II) or ANOVA (Studies IV-VI followed by t-test or Tukey–Kramer for paired comparisons if needed). Fisher's exact test was used for categorical variables and Mann-Whitney U-test for continuous variables for group comparison (Study I).

Linear regression was used to detect a possible correlation between change in MAP and $PaCO_2$-$EtCO_2$ difference (Study V). Logistic regression and odd ratios were used for assessment relationships between the two outcome variables and each main study variable (Study I). Tested variables of risk factors for RBCT were hemoglobin

concentration, platelet count, plasma prothrombin time value (P-PT, %), WFNS and Fisher grades, aneurysm location, intraoperative aneurysm rupture, aneurysm size, and gender. For outcome analysis, variables were intraoperative rupture of an aneurysm, RBCT, WFNS and Fisher grades, age, preoperative hemoglobin, and aneurysm size. Variables independently associated with study outcomes with a p-value of less than 0.1 in univariate analysis were included in multivariable logistic regression analysis. Additionally, a propensity score was calculated using covariates that were associated with intraoperative red blood cell transfusion, and this was added to the multivariate analysis assessing the outcome as a covariate. Variance inflation factor was calculated in order to detect possible multicollinearity between the covariates (Study I).

The number of volunteers in Study IV was based on the calculation that in a cross-over study setting eight volunteers would be needed to discover a greater than 1 standard deviation (SD) difference in MCF between the equiosmolar HS and mannitol groups of similar vol% dilution (alpha error 0.05).

P-value less than 0.05 was considered significant in all analyses.

5. RESULTS

All patients initially included in Studies III and IV completed the study. Study V consisted of patients enrolled earlier for two separately conducted studies [10,85].

5.1 RBC, FFP, and platelet transfusion

Seventy of 488 patients operated on for ruptured cerebral arterial aneurysm received blood products during the perioperative phase (I). Transfusion rates for RBC, FFP, and platelet transfusion intraoperatively were 7.6% (37/488), 3.1% (15/488), and 1.2% (6/488), and postoperatively 3.5% (17/488), 1.6% (8/488), and 0.9% (4/488), respectively. Five patients received RBCs both intra- and postoperatively (Figure 5).

Hemoglobin concentration was 107±18 g/l before and 117±14 g/l after the transfusion of RBC. Thromboplastin time (P-TT, %) was 63±16 before and 82±39 after transfusion of FFP, and platelet count was 98±15 10^9/l before and 181±62 10^9/l after transfusion of platelets. Individual hemoglobin concentration, platelet count, or P-TT was outside the normal laboratory reference range in 38.6% of these patients preoperatively and in 29.2% of those who had intraoperative RBCT. Among the 70 patients who received blood products, 7 were on acetylsalicylic acid, 3 on warfarin, and one on clopidogrel prior to the surgery.

Twenty-six of 37 patients who received RBCs during surgery had suffered from intraoperative rupture of an aneurysm.

Total volume of RBC, FFP, and platelet concentrates transfused were 730±503 ml, 560±283 ml, and 500±199 ml, respectively. One patient with a large (diameter 20 mm, base 8 mm) ruptured basilar aneurysm suffered from a massive bleeding of 10520 ml during surgery and received 2400 ml of RBCs, 800 ml of platelets, and 1000 ml of FFP intraoperatively. Mean blood loss for patients who received RBCT during surgery was 1470 (±1890) ml.

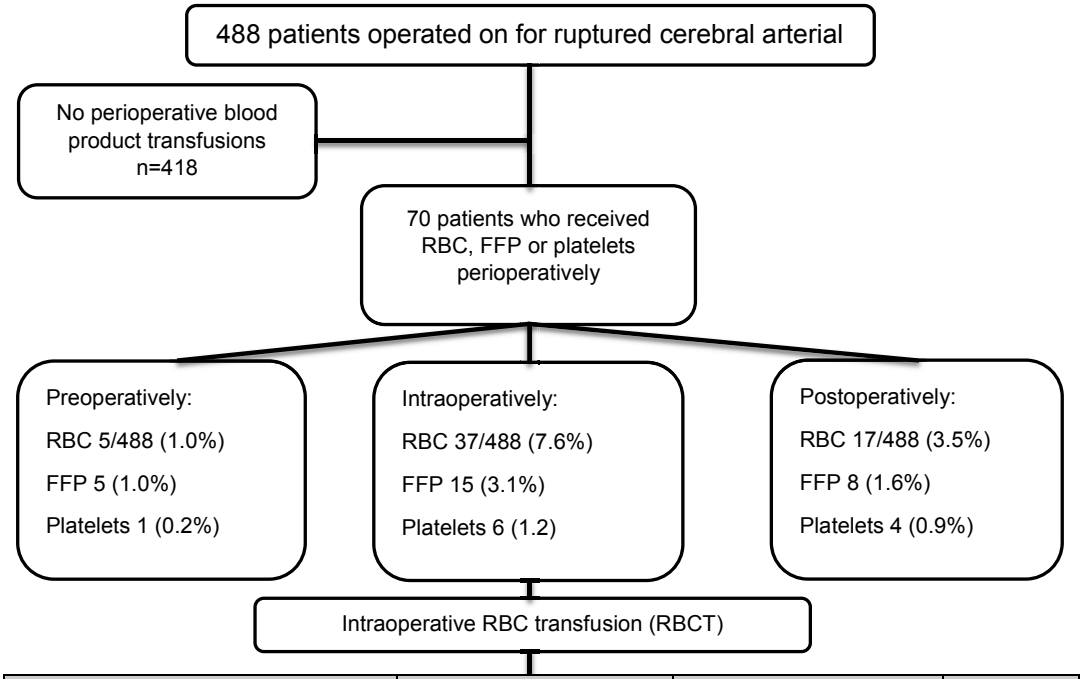
5.2 Intraoperative RBCT, risk factors, and outcome

When divided into two groups, indexed by the need for intraoperative RBCT (yes or no), preoperative hemoglobin concentration was lower in patients who received intraoperative RBCT. A significant difference was also found in preoperative WFNS and Fisher grades between the two groups. Additionally, GOS at three months was lower among patients who received RBCs during surgery (Figure 5). No statistical difference was present in aneurysm location between the two groups (Table 2).

In multivariate analysis, intraoperative rupture of an aneurysm, lower preoperative hemoglobin value, and worse WFNS grade independently increased the likelihood of intraoperative RBCT (OR 10.86; CI 4.74-24.89, 0.98; 0.93-0.96, and 1.81; 0.91-1.53, respectively). The risk for unfavorable outcome was significantly increased with patients who received RBCs during surgery (OR 5.13; CI 1.53-17.15). Other independent factors associated with worse neurological outcome were worse preoperative WFNS grade, worse Fisher grade, and older age (1.97; 1.64-2.36, 1.89; 1.23-2.92, and 1.07; 1.04-1.10, respectively). These findings remained essentially unchanged after including a propensity score of intraoperative RBC transfusion in the outcome model.

5.3 Adenosine

Twelve of 825 patients (1.5%) at Helsinki University Hospital and 4 of 189 patients (2.1%) at Turku University Hospital, thus



	RBCT during surgery: yes n=37	RBCT during surgery: no n=451	P
Female	28 (9.4%)	269 (90.6%)	
Male	9 (4.7%)	182 (95.3%)	0.55
Age (years)	56(±13)	54(±12)	0.44
Hemoglobin (g/l)	117(±16)	128(±18)	0.001
Thromboplastin time P-TT%	97(±23)	92(±29)	0.30
Thrombocyte count (10^9/l)	233(±79)	226(±61)	0.52
WFNS (1-5)	2 (1-5)	4 (1-5)	<0.001
WFNS 1	6 (16.2%)	211 (46.8%)	
WFNS 2	2 (5.4%)	51 (11.3%)	
WFNS 3	1 (2.7%)	19 (4.2%)	
WFNS 4	14 (37.8%)	73 (16.2%)	
WFNS 5	14 (37.8%)	97 (21.5%)	
Fisher grade (1-4)	4(2-4)	4(1-4)	0.005
Fisher grade 1	0	15 (3.3%)	
Fisher grade 2	1 (2.7%)	61(13.5%)	
Fisher grade 3	6 (16.2%)	140 (31.0%)	
Fisher grade 4	30 (81.1%)	222 (49.2%)	
Fisher grade not available	0	13 (2.9%)	
GOS at 3 months	3(1-5)	4(1-5)	<0.001
Intraoperative aneurysm rupture	28 (75.7%)	103 (22.8%)	<0.001

Figure 5 Flow chart of intraoperative transfusion rates of blood products and patient characteristics when divided according to the intraoperative red blood cell transfusion.

Data are presented as numbers of patients (percentage) or mean (±SD), P-value < 0.05 considered signifigant
WFNS=World Federation of Neurological Surgeons, GOS=Glasgow outcome scale

Table 2 Aneurysm location in Studies I and II.

Study	I	II*	
Aneurysm location	**Adenosine**	**RBCT during surgery: yes**	**RBCT during surgery: no**
ICA	2 (12.5%)	7 (18.9%)	84 (18.6%)
MCA	4 (25%)	16 (43.2%)	154 (34.1%)
AComm+A1	3 (18.75%)	5 (13.5%)	138 (30.6%)
Pericallosal artery	1 (6.25%)	0	24 (5.3%)
VA	0	1 (2.7%)	2 (0.4%)
PICA	0	3 (8.1%)	21 (4.7%)
PCA	1 (6.25%)	0	3 (0.7%)
Basilar artery	5 (31.25%)	5 (13.5%)	25 (15.5%)

Data are presented as number of patients (percentage). *P=0.06 (aneurysm location between study groups)

AComm+A1=Anterior communicating artery + Anterior cerebral artery, part A1, ICA=Internal carotid artery MCA=Middle cerebral artery, PICA=Posterior inferior cerebellar artery, PCA= Posterior cerebral artery, RBCT= red blood cell transfusion, VA=Vertebral artery

16 of altogether 1014 patients (1.6%), who underwent surgery for cerebral arterial aneurysm received adenosine during the operation (Study II). All but one adenosine administration was related to intraoperative rupture of an aneurysm. Median single dose for adenosine was 12 (range 6-18) mg, and when multiple boluses of adenosine were required the median cumulative dose was 27 (18-89) mg. After 10 min of adenosine administration, patients had stable hemodynamics. Mean systolic and diastolic blood pressure was 113 ± 14 and 57 ± 9 mmHg, respectively, and mean heart rate 74 ± 15 per minute. The distribution of aneurysm locations of patients receiving adenosine is shown in Table 2.

5.4 Coagulation during replacement of blood loss with FFP and RBCs

Intraoperative blood loss and fluid replacement for the two patients are shown in Table 3. While coagulation time (CT), clot formation time (CFT), alpha angle, and maximum clot firmness (MCF) were within normal reference ranges (ExTEM® and InTEM® analysis) before surgery, both patients had increased fibrin MCF preoperatively (FibTEM®). CFT was prolonged and MCF decreased in all samples taken after the beginning of surgery, but all values remained within normal reference ranges. The decrease in MCF in FibTEM® analysis was more

Table 3 Patient characteristics and fluid administration in Study III.

	Patient 1	Patient 2
Age (months)	10	5
Height (cm)/Weight (kg)	78/9.9	67/7.0
Blood loss, ml	750	380
Total amount of fluids (ml)	1504	870
Total amount of fresh frozen plasma (ml)	400	240
Total amount of red blood cells (ml)	500 (OR)/60 (ICU)	250 (OR)/60 (ICU)

profound in Patient 2 than in Patient 1 and reached the critical value of 8 mm at the end of surgery (Figure 6).

RoTEM® analyses on the first postoperative morning were comparable with the preoperative values. MCF in FibTEM® was increased in both patients, i.e., showing a trend towards hypercoagulopathy. Maximum lyses (ML) were within normal reference ranges in both patients.

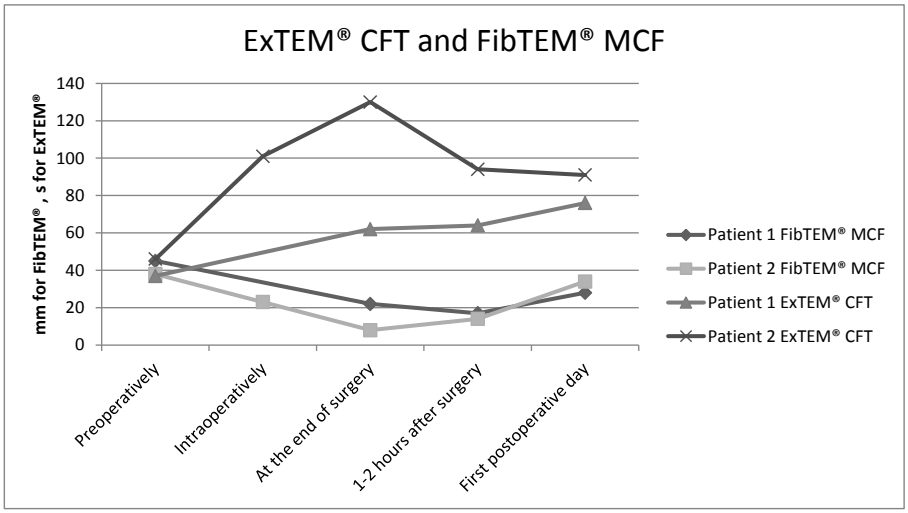


Figure 6 Results of ExTEM® and FibTEM® analyses in Study III.

CFT=clot formation time, normal reference range 34–159 s, MCF=maximum clot firmness, normal reference range 9-25 mm
Mm=millimeters, S=seconds

5.5 Coagulation in vitro

Mannitol in 10 vol% and 20 vol% dilutions impairs coagulation more than equiosmolar 2.5% NaCl in vitro. This is reflected in the weaker maximum clot firmness (MCF) in FibTEM® analysis in the mannitol group than in the 2.5% NaCl group after both dilutions. Additionally, ExTEM® analysis revealed weaker MCF and longer clot formation time (CFT) in the mannitol group than in the 2.5% NaCl group after 20 vol% dilution. Overall, the coagulation profile of mannitol was more disturbed than that of other study solutions. An increment in the concentration of the NaCl solution resulted in a weaker clot (Table 4).

Table 4 RoTEM® results after 10 vol% and 20 vol% dilutions with study solutions and the control without dilution.

		Mannitol	0.9% HS	2.5% HS	3.5% HS	P*	Control
ExTEM®	10%	87.6(14.5)[1,3]	63.1(15.4)	73.7(25.6)	76.8(47.9)	0.30	58.7(9.8)
CT	20%	89.8(22.9)[3]	77.2(33.0)	56.0(7.9)	84.8(44.9)	0.20	
ExTEM®	10%	172.5(103.3)	123.4(86.1)	137.4(82.1)	129.2(62.0)	0.03	119.6(59.7)
CFT	20%	341.4(241.6)[2,3]	134.0(89.6)	167.2(94.9)[1]	216.9(97.8)[3]	<0.001	
ExTEM®	10%	49.0(7.9)[3]	47.3(6.4)[3]	50.7(7.6)[3]	49.3(5.5)[3]	0.36	54.8(8.3)
MCF	20%	42.3(7.9)[2,3]	51.2(6.5)	48.2(6.4)[3]	47.8(6.9)[3]	<0.001	
ExTEM®	10%	62.2(10.1)[3]	67.5(10.3)	65.4(10.0)	66.5(7.9)	0.005	67.9(8.6)
Alpha	20%	44.0(13.8)[2,3]	65.5(10.3)	61.8(10.4)[3]	57.3(8.5)[3]	<0.001	
FibTEM®	10%	86.6(20.1)	58.9(11.7)[3]	64.7(16.2)	84.6(89.1)	0.43	69.1(21.0)
CT	20%	171.9(197.3)	75.4(15.0)	63.8(30.2)	83.5(31.0)	0.09	
FibTEM®	10%	10.2(3.0)	11.8(3.0)	12.3(4.1)	10.6(3.3)	0.01	13.6(6.0)
MCF	20%	6.8(2.5)[2,3]	9.6(3.0)	11.5(3.3)	10.8(2.9)	<0.001	

Values are mean (SD); analyzed by repeated measures ANOVA, **P* = overall value between study solutions excluding control.

Comparison of each dilution group with Tukey-Kramer's post-hoc test. Combinations with p<0.05: [1]Mannintol compared with 0.9% HS, [2] Mannitol compared with 0.9% HS, 2.5% HS, and 3.5% HS

[3]Compared with control p<0.05 (t-test).

CT=clotting time, CFT=clot formation time, MCF=maximum clot firmness

5.6 Blood pressure and $PaCO_2$-$EtCO_2$ difference

The percentage change in MAP had a positive correlation between measured $PaCO_2$-$EtCO_2$ differences after anesthesia induction in a heterogeneous craniotomy patient population. The greater the percentage change in MAP, the greater the PaCO2-EtCO2 difference (p=0.0008, r=0.388). The time period from intubation to head pinning lasted 12.2 (5.6) min. The duration of the study period did not correlate with $PaCO_2$-$EtCO_2$ difference.

Patients were subgrouped after study completion according to the difference between MAP awake and MAP during $PaCO_2$ determination into four groups: MAP decrease of <20% (n=17), 20-29% (n=24), 30-35% (n=16), and >35% (n=15). $PaCO_2$ was higher and $PaCO_2$-$EtCO_2$ difference greater in patients with MAP decrease of over 35% or 30-35% than in patients with MAP decrease of less than 20%: 0.96 (0.43) kPa or 0.85 (0.31) kPa versus 0.55 (0.24) kPa, respectively (p<0.05 between groups).

Increase in fraction of inspired oxygen (FiO_2) correlated negatively with $PaCO_2$-$EtCO_2$ difference (p=0.01). No correlation between decrease in MAP and change in PaO_2/FiO_2 ratio (P/F) was found.

5.7 Prone versus sitting position

Data from 58 patients (30 in prone position, 28 in sitting position) were analyzed after the assessment of the eligibility of 72 patients. Exclusion flow charts have been reported in conjunction with the original reports of both individual studies [10,85].

When combined data were divided in two groups according to the study fluid (RAC vs. HES), patients in the RAC group had

higher weight, height, and body surface area (BSA). Cumulative mean dose of basal RAC was similar between the study groups. When divided according to the surgery position, the groups were comparable, with the exception that patients in the sitting position were younger ($p<0.01$) and had higher ASA classification ($p<0.001$).

A significant difference emerged between mean cumulative doses of RAC and HES (prone and sitting positions combined) in optimizing the fluid filling at 30 min and at the end of surgery (452±155 ml vs. 341±109 ml and 678±390 ml vs. 455±253 ml, respectively). After adjusting RAC and HES doses according to patients' weight, the mean doses of RAC at 30 min and at the end of surgery remained higher than those of HES (5.5±1.6 ml/kg vs. 4.8±1.7 and 8.2±4.2 ml/kg vs. 6.4±3.6 ml/kg, respectively), but statistical significance was lost. There was no difference between RAC and HES doses before positioning in either position. Six patients receiving RAC (2 in sitting and 4 in prone position) and one patient receiving HES (prone position) were considered non-responders.

Patients in the sitting position had lower MAP over time and higher CI and SVI than patients in the prone position. No difference was present in study fluid consumption between the two groups during surgery.

6. DISCUSSION

6.1 Transfusion of RBC, FFP, and platelets and risk factors associated with RBCT

The rate of intraoperative RBCT in our material of 488 patients was 7.6%. Previously reported intraoperative transfusion rates of RBCs in ruptured cerebral aneurysm surgery populations have varied between 5.6% and 27.2%. In a study conducted by Coutere and coworkers, the transfusion rate was 5.6%. This study consisted of a larger entity of cerebrovascular surgery patients, including those with ruptured (n=77) and unruptured aneurysms, arteriovenous malformations, and carotid artery stenosis [132]. Two other larger studies of 441 and 101 (of which 5 had aneurysm coiled) patients have reported significantly higher incidences (27.2% and 19.8%, respectively) of RBCT [131,133]. Intraoperative thrombocyte and FFP transfusion rates, 1.2% and 3.6%, respectively, can be considered low, although no comparative data exist.

In aneurysm surgery, a stable surgery can abruptly turn into a catastrophic situation due to the rupture of an aneurysm. In these situations, anesthesiologists are likely to give RBCT preemptively to prevent the situation from escalating further. This conclusion can be drawn from our results, where 68% of the intraoperative RBCTs were administered after a rupture of an aneurysm. Moreover, when identifying variables that might predict risk of intraoperative RBCT, intraoperative rupture of an aneurysm independently increased the risk of intraoperative RBCT. Higher Fisher grade and lower preoperative hemoglobin value emerged from multivariate analysis as independent risk factors for intraoperative RBCT, suggesting that, overall, patients needing RBCT are those who are more seriously ill before surgery.

Patients who had intraoperative RBCT were in worse neurological condition three months after surgery. This finding is in line with earlier reports indicating that RBCT is associated with increased risk of vasospasm and worse neurological outcome [123,180]. Although intraoperative RBCT in our study increased patient's risk for worse neurological outcome, even when controlled with other variables, such as intraoperative rupture of an aneurysm, WFNS grade, and Fisher grade, it is debatable whether a true relationship exists between intraoperative RBCT and patient outcome. RBCT may only reflect the severity of the disease, especially as in our material the frequency of intraoperative rupture of an aneurysm among patients receiving RBCT was relatively high. On the other hand, high OR for intraoperative RBCT in outcome analysis remained even when propensity score for RBCT was added to the analysis. This suggests that in our material there is a true relation between RBCT and worse neurological outcome. For our patients, the age of transfused RBCs was not known, but according to recent findings, the age of RBCs does not affect patient's outcome or development of organ dysfunction [181,182].

6.2 Adenosine

In the event of sudden intraoperative rupture of an aneurysm, adenosine-induced cardioplegia is a relatively novel method to stop the bleeding, thus facilitating temporary clipping of an aneurysm. After a few single patient case studies of adenosine-induced transient asystole in cerebral arterial aneurysm surgery, we were the first to describe a series of patients who had received adenosine for this indication intraoperatively after identifying 16 patients of 1014

operated on for cerebral arterial aneurysm [17,183,184]. The median single dose of adenosine in our study was 12 mg, in line with the recommended dose for supraventricular tachycardia [185,186]. Subsequently, adenosine dose to achieve asystole in our clinic has increased according to the dose recommendation of 0.2-0.4 mg per ideal body weight of Bebawy and coworkers [147]. With that dosing, a profound hypotension (systolic blood pressure < 60 mmHg) was achieved for a period of 45 seconds and duration of hypotension had a positive correlation with adenosine dosing. Bebawy and coworkers reported an in-depth analysis of adenosine use (using partly the same patients as in the previous publications) and concluded that short-term morbidity associated with adenosine use is minimal [187].

Adenosine is now considered a useful tool in aneurysm surgery, not only when bleeding occurs from ruptured aneurysm and visibility is lost, but also in situations where temporary clipping of a feeding artery is not feasible. Historically, these patients have been treated with extracranial artery occlusion, hypotensive anesthesia, and even hypothermic circulatory flow arrest [188]. As intraoperative asystole is not an official indication of adenosine, some concerns of its safety have been raised. In our retrospective review, patients had stable hemodynamics 10 minutes after administration of adenosine, and no adverse effects were reported. Furthermore, three relatively large retrospective reviews concluded that use of adenosine in intracranial aneurysm surgery is not associated with worse neurological outcome or increased cardiac complications or mortality [189-191]. Prospective randomized trials would provide more information about the safety profile of adenosine in aneurysm surgery.

6.3 Blood coagulation – effect of mannitol, HS, and FFP

In an in vitro environment, 15% mannitol solution decreases blood coagulation more than equimolar and equivolemic 2.5% hypertonic saline solution. In thromboelastometry tracing, not only is the coagulation process slower, but the forming clot is weaker. Impairment in FibTEM® analysis suggests that the weaker clot is, at least partly, the result of fibrin deficiency. An increment in HS concentration may also increase coagulation impairment, so it remains speculative how HS, with a higher concentration and a lower volume, compares with 15% mannitol. Historically, mannitol has been the primary solution in osmotherapy to decrease elevated intracranial pressure (ICP), but HS has gained popularity as an alternative method. HS seems to be equally if not more effective in reducing ICP and is also associated with less severe side-effects.

In our case report of two pediatric neurosurgical patients, we could see that by applying early transfusion of FFP the coagulation capacity remained almost normal throughout the surgery even when patients suffered from massive bleeding. Noteworthy is that even with FFP early infusion a marked decrease in PT% was evident (25-29% during surgery). More notably, the fibrinogen-dependent clot weakened, reaching abnormal levels. One of the patients received tranexamic acid during surgery. Administration of tranexamic acid has been reported to decrease need for blood product transfusion in pediatric craniofacial surgery [192]. However, a relatively large amount of colloids was then needed for fluid replacement, which is a questionable solution with today's knowledge of the harms associated with colloid use. A recent review addressing perioperative transfusion of blood products with pediatric patients during craniotomy recommends a fairly restricted use of blood

products due to their possible side-effects, but at the same time acknowledges the great challenge of finding an optimal transfusion regimen when abrupt sudden bleeding occurs. Thromboelastometry is offered as one solution to guide maintenance of normal coagulation capacity [193].

The avoidance of perioperative bleeding and postoperative hematomas in neurosurgery is essential to prevent worse outcome. Patients with a brain tumor often have various coagulation abnormalities, posing a challenge for perioperative treatment of these patients [4,194]. Both patients in our report were in a hypercoagulable state prior to surgery. Had the coagulation capacity been normal before operation, the fibrinogen-dependent clot weakness would probably have been more profound even with early transfusion of FFP. Both patients received also mannitol at the beginning of surgery, potentially interfering with blood coagulation. Close monitoring of coagulation status postoperatively is important to detect possible hypercoagulability and increased risk of thrombosis.

Our results, which should be verified in vivo, indicate that from the viewpoint of blood coagulation HS might be less harmful than mannitol in treatment of elevated ICP. Especially in situations where the neurosurgical patient suffers from massive bleeding, mannitol should be avoided and early infusion of FFP should be considered to maintain the required coagulation capacity. It must be noted, however, that efficacy of FFP to correct a fibrinogen deficit is limited.

Thromboelastometry (RoTEM®) offers a more dynamic evaluation of the coagulation process compared with traditional laboratory tests and was used in our studies to evaluate coagulation disturbance caused by bleeding and dilution. Thromboelastometry is a well-established method in coagulation analysis of patients suffering from bleeding [161]. Thromboelastometry may, however, lack consistency in results from the same sample if different analyzers are used. MCF value shows the highest consistency [195].

6.4 Impact of change in MAP on $PaCO_2$-$EtCO_2$ difference

The noted significant positive correlation between the MAP decrease and the $EtCO_2$-$PaCO_2$ difference immediately after induction of anesthesia in this heterogeneous craniotomy patient population indicates that monitoring of $EtCO_2$ as an estimate of $PaCO_2$ is misleading and optimal ventilation should be confirmed by arterial blood gas analysis in patients undergoing neurosurgery. This is essential because in neurosurgical patients with an occupying intracranial lesion any increase in CBF due to elevated $PaCO_2$ may result in a sudden increase in ICP. In hypotension, carbon dioxide reactivity becomes impaired, and the combined effect on CBF is even more profound [25,26].

Reliability of $EtCO_2$ as an estimate of $PaCO_2$ has been questioned before and our results are in line with earlier reports. Although we showed a linear correlation between MAP change and $EtCO_2$-$PaCO_2$ difference, conflicting data exist, especially when evaluating different surgery positions [47,48,196]. This diminishes the usefulness of $EtCO_2$ measurement as a surrogate marker of $PaCO_2$ and supports the direct measurement of $PaCO_2$. When patients in our study were divided into groups according to the decrease in MAP after induction (decrease of <20%, 20-29%, 30-35%, and > 35%), $EtCO_2$ remained similar, but $PaCO_2$-$EtCO_2$ was greater in patients with a MAP decrease of over 30% than in patients with a MAP decrease of less than 20%. Additionally, minute ventilation values were slightly lower (although not statistically significant) when MAP decreased over 30%. This perhaps indicates that

adjustment of mechanical ventilation was guided exclusively by the $EtCO_2$ value. In fact, the patients were similarly ventilated according to the $EtCO_2$ in the study groups, even though $PaCO_2$ was increased in patients with a pronounced decrease in MAP.

An increment of FiO_2 has been reported to marginally increase the $EtCO_2$-$PaCO_2$ difference [197]. Our results show the opposite, as we found a negative correlation between FiO_2 and $EtCO_2$-$PaCO_2$ difference. Moreover, 100% inspired oxygen leads to the formation of atelectasis and increases intrapulmonary shunt, but its effect on $EtCO_2$-$PaCO_2$ is unknown [50,198]. We observed no correlation between P/F ratio change and MAP decrease. This may indicate that MAP affects $EtCO_2$-$PaCO_2$ independently of atelectasis.

6.5 Hemodynamics in prone and sitting positions

Goal-directed fluid administration to achieve stable hemodynamics did not differ between surgery in sitting and prone positions. HES was more effective than RAC in achieving comparable hemodynamics, as according to our results, requirement of RAC was 1.5-fold that of HES. Clinically, this might be an overestimation, because when fluid doses were adjusted with patients' weight, a difference between HES and RAC doses was maintained (1:1.3), but significance was lost. This finding supports other recent reports suggesting that the ratio between colloids and crystalloids is more equal than earlier thought [9,10,85,199]. The clinical evaluation revealed that patients in our study were normovolemic prior to surgery. With hypovolemic patients, volume-expanding capabilities of HES and RAC might be different.

According to our results, the previously reported decrease in cardiac function [176,177,200] in the prone position can be prevented with stroke volume-directed fluid administration and moderate use of vasoactive drugs. Moreover, we demonstrated that with similar fluid administration, patients in the sitting position maintained good cardiac function after positioning and a decrease in cardiac function did not occur [173]. Although MAP remained adequate throughout the surgery, it was lower in the sitting position, confirming a tendency towards hypotension in this position. Patients in the sitting position in our study wore antigravity suits, which in part prevents pooling of the blood to the lower extremities, thus helping to stabilize patient hemodynamics.

No universally accepted method of measuring CPP in neurosurgical patients exists. The standard in our department during craniotomy is to measure the MAP at the level of the foramen Monroi, giving us a more accurate estimate of CPP. When measuring MAP at the level of the heart, the values are 15-25 mmHg higher, better reflecting the systemic blood pressure [201,202].

The Vigileo Flotrac System (version 3.02) was used in Study VI for cardiac output monitoring, following the normal practice of our department when perioperative cardiac output monitoring is required. The studies done with older versions of Vigileo have shown an underestimation of CO in a low vascular resistance state compared with the intermittent bolus thermodilution technique [203,204]. Compared with the previous versions, the newer third-generation system has shown an improvement, with accuracy even in the low vascular resistance state, e.g. in septic shock [205,206]. Acute changes in peripheral vascular resistance caused by vasopressor may, however, reduce the reliability of CO measurement [207,208].

7. CONCLUSIONS

This thesis aimed to examine critical aspects of neuroanesthesia with regard to CBF, CPP, blood coagulation, and transfusion of blood products.

In our material, transfusion frequencies of RBCs, FFP, and platelets during ruptured cerebral aneurysm surgery were low. Intraoperative RBCT seems to be preemptive in nature according to the hemoglobin levels prior to transfusion. RBCT is strongly associated with intraoperative rupture of an aneurysm. Lower hemoglobin value, larger aneurysm size, and more severe bleeding (higher Fisher grade) also increased the likelihood of intraoperative RBCT.

Intraoperative RBCT may itself worsen SAH patients' neurological outcome, even when controlled with other variables such as WFNS grade, Fisher grade, and patients' age. In the event that sudden intraoperative rupture of an aneurysm occurs, adenosine-induced transient asystole can be used to stop the bleeding and facilitate clipping of the aneurysm without compromising patient hemodynamics afterwards.

During a massive bleeding early infusion of FFP together with RBCT should be considered to preserve the normal coagulation capacity required for neurosurgery. Based on our in vitro observation, HS might be more favorable solution than mannitol due to its less harmful effect on blood coagulation. An increment in HS concentration may have a negative effect on coagulation.

Reliability of $EtCO_2$ as an estimate of $PaCO_2$ after anesthesia induction is not adequate, as seen in the correlation between a decrease in MAP and $EtCO_2$-$PaCO_2$ difference. Optimal ventilation after induction of anesthesia should be confirmed by arterial blood gas analysis in patients undergoing neurosurgery to prevent a potentially harmful increase in $PaCO_2$, and consequently, in CBF.

Anesthesia in both sitting and prone positions is associated with changes in blood pressure and cardiac function. However, preemptive GDT with either RAC or HES solutions before positioning enables a stable hemodynamic state during neurosurgery in both positions. The fluid requirement was not different between the two positions, and the ratio between HES and RAC to achieve comparable hemodynamics was 1:1.5.

8. CLINICAL IMPLICATIONS AND SUGGESTIONS FOR FURTHER STUDIES

With modern microsurgical techniques and well-executed neuroanesthesia, the requirement of intraoperative blood product transfusion is low during surgery for ruptured arterial aneurysm. By preventing intraoperative rupture of an aneurysm with good hemodynamic control, the need for potentially harmful RBCT is less probable. Adenosine-induced transient asystole is a feasible method, without compromising hemodynamics, in the occurrence of intraoperative rupture of an aneurysm. This enables the neurosurgeon to clear the surgical field, facilitating temporary clipping to stop the bleeding in this potentially life-threatening situation.

Early infusion of FFB should be considered instead of crystalloids in replacement therapy of marked bleeding to preserve normal coagulation capacity. The less harmful effect of HS, relative to mannitol, on blood coagulation may shift the decision towards HS when choosing an optimal solution for treatment of elevated ICP or brain swelling, at least when excess bleeding occurs. However, the clinical relevance of this finding remains unclear and warrants further study.

Neurosurgical patients with an intracranial volume-occupying lesion are extremely vulnerable to changes in CBF. As $PaCO_2$ is a strong regulator of CBF, an uncontrolled increase in $PaCO_2$ should be avoided at all times. Reliability of $EtCO_2$ as an estimate of $PaCO_2$ after anesthesia induction is inadequate. The effect that a possible decrease in arterial blood pressure can have on $PaCO_2$ should be noted, and ventilation ought to be confirmed by arterial blood gas analysis.

Preemptive GDT with either RAC or HES solutions before positioning enables a stable hemodynamic state during neurosurgery in both sitting and prone positions. The fluid requirement did not differ between the two positions. Slightly less HES is needed to achieve comparable hemodynamics, but is it questionable whether this advantage outweighs the recent concerns regarding colloid safety. Stable hemodynamics prevents misleading fluctuation in $EtCO_2$, allowing early detection of VAE should it occur when the patient is operated on in a sitting position.

Optimal fluid administration and transfusion practice of blood products with neurosurgical patients remain unknown despite the increasing number of studies conducted. Whether colloids have a place in fluid administration in the future in neurosurgical patient populations remains speculative, warranting further research.

Debate regarding the optimal hemoglobin level for neurosurgical patients, particularly SAH patients, is ongoing. Prospective controlled randomized studies are needed to clarify the associations between RBCT, anemia, and outcome.

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Transfusion Frequency of Red Blood Cells, Fresh Frozen Plasma, and Platelets During Ruptured Cerebral Aneurysm Surgery

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BACKGROUND: **The use of blood products after subarachnoid hemorrhage (SAH) is common, but not without controversy. The optimal hemoglobin level in patients with SAH is unknown, and data on perioperative need for red blood cell (RBC), fresh frozen plasma (FFP), or platelet transfusions are limited. We studied perioperative administration of RBCs, FFP, and platelets and the impact of red blood cell transfusions (RBCTs) on outcome in patients undergoing surgery for ruptured a cerebral arterial aneurysm.**

METHODS: **A retrospective analysis was performed of 488 patients with aneurysmal SAH during the years 2006–2009 at Helsinki University Central Hospital. Patients who received RBC, FFP, or platelet concentrates perioperatively were compared with a cohort of patients from the Helsinki database of aneurysmal SAH who did not receive transfusions. A multiple regression model was created to identify factors related to transfusion and outcome.**

RESULTS: **RBC, FFP, or platelet concentrates were given in 7.6% (37 of 488), 3.1% (15 of 488), and 1.2% (6 of 488) of patients intraoperatively and in 3.5% (17 of 486), 1.6% (8 of 488), and 0.9% (4 of 488) of patients postoperatively. Of 37 intraoperative RBCTs, 26 were related to intraoperative rupture of the aneurysm. Intraoperative RBCTs were associated with lower preoperative hemoglobin concentration, higher World Federation of Neurosurgical Societies classification, and intraoperative rupture of an aneurysm. In multivariate analysis, intraoperative RBCT (odds ratio = 5.13, 95% confidence interval = 1.53–17.15), worse World Federation of Neurosurgical Societies classification and Fisher grade (odds ratio = 1.97, confidence interval = 1.64–2.36 and odds ratio = 1.89, confidence interval = 1.23–2.92, respectively), and increasing age (odds ratio = 1.07, confidence interval = 1.04–1.10) independently increased the risk of poor neurologic outcome at 3 months.**

CONCLUSIONS: **Transfusion frequencies of RBCs, FFP, and platelets were relatively low. Intraoperative RBCT was strongly related to intraoperative rupture of the aneurysm in patients with poor-grade SAH. The observed association between poor outcome and RBCT in patients with SAH warrants further study.**

INTRODUCTION

While the debate of optimal hemoglobin level for a patient with subarachnoid hemorrhage (SAH) is ongoing, the transfusion rate of red blood cells (RBCs), fresh frozen plasma (FFP), or platelets during surgery for ruptured aneurysm and factors correlating with it has received less attention (4-6, 10, 14). Earlier reports indicated that the frequency of intraoperative red blood cell transfusion (RBCT) was 5.6%–27.2% (2, 7, 8), but the incidence of intraoperative transfusion of FFP or platelets is unknown. The present study was designed to describe blood product use and associated clinical characteristics in patients operated on for ruptured cerebral arterial aneurysm at Helsinki University Central Hospital, Helsinki, Finland, between

Key words
- Fresh frozen plasma
- Intraoperative
- Neurosurgery
- Platelets
- Red blood cell
- Subarachnoid hemorrhage
- Transfusion

Abbreviations and Acronyms
FFP: Fresh frozen plasma
GOS: Glasgow Outcome Scale
P-PT, %: Plasma prothrombin time value
RBC: Red blood cell
RBCT: Red blood cell transfusion
SAH: Subarachnoid hemorrhage
WFNS: World Federation of Neurological Surgeons

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January 2006 and September 2009. The hypothesis was that the need for RBCT in our clinic is low, and FFP and platelet transfusions are used mainly in patients on long-term anticoagulation or antiplatelet therapy.

MATERIALS AND METHODS

After approval of Helsinki University Central Hospital Scientific Board, we identified patients who had undergone surgery for ruptured cerebral arterial aneurysm between January 2006 and September 2009 from the Helsinki aneurysm registry and retrieved demographics of these patients. We collected surgical and intensive care unit data and identified patients who had received RBCs, FFP, or platelets intraoperatively or during the immediate postoperative period (within 24 hours of surgery). We also included patients who had been given transfusions during preparation for surgery.

The retrieved variables included age, sex, localization of the aneurysm, preoperative Glasgow Coma Scale score 3–15, World Federation of Neurological Surgeons (WFNS) classification 1–5, Fisher grade 1–4, occurrence of intraoperative rupture of an aneurysm, comorbidities, medication, preoperative laboratory results, hemoglobin concentration, platelet count and plasma prothrombin time value (P-PT, %) before and after transfusion, the amount of transfused blood products, and blood loss. Glasgow Outcome Scale (GOS) score 1–5 at 3 months was used to evaluate outcome. In the logistic regression analysis, the GOS score was dichotomized into good outcome (GOS score 4–5) and bad outcome (GOS score 1–3) and used as the endpoint. We compared clinical characteristics of patients undergoing surgery for ruptured cerebral arterial aneurysm based on the need for transfusion of any type of blood product.

Statistics

Descriptive statistics are shown as mean ± (SD) or median (range). Fisher exact test was used for categorical variables, and Mann-Whitney U test was used for continuous variables. We used logistic regression and odds ratios to assess relationships between the 2 outcome variables and each main study variable. Variables tested for multivariate analysis of risk factors for RBCT were hemoglobin concentration, platelet count, P-PT, %, WFNS classification, Fisher grade, aneurysm location, intraoperative aneurysm rupture, aneurysm size, and sex. For outcome analysis, variables were intraoperative rupture of an aneurysm, RBCT, WFNS classification, Fisher grade, age, preoperative hemoglobin, and aneurysm location. Variables associated with study outcomes with $P < 0.1$ in univariate analysis were included in multivariable logistic regression analysis. A propensity score was calculated using covariates that were associated with intraoperative RBCT and was added to multivariate analysis assessing outcome as a covariate. Additionally, variance inflation factor was calculated to detect possible multicollinearity between the covariates. All statistical analyses were performed using IBM SPSS Statistics version 21 (IBM Corp., Armonk, New York, USA).

RESULTS

During the study period, 488 patients underwent surgery for a ruptured cerebral arterial aneurysm. RBC, FFP, or platelet transfusions were given to 70 patients either during surgery or in the immediate postoperative period. Intraoperative RBC, FFP, and platelet transfusions were given in 7.6% (37 of 488), 3.1% (15 of 488), and 1.2% (6 of 488) of patients, and postoperative RBC, FFP, and platelet transfusions were given in 3.5% (17 of 486), 1.6% (8 of 488), and 0.9% (4 of 488) of patients. In 5 patients, RBCs were transfused intraoperatively and postoperatively (Table 1).

Hemoglobin concentration was 107 g/L ± 18 before and 117 g/L ± 14 after transfusion of RBCs. P-PT, % was 63 ± 16 before and 82 ± 39 after transfusion of FFP, and platelet count was 98 10^9/L ± 15 before and 181 10^9/L ± 62 after transfusion of platelets. Among the 70 patients who received blood products, 7 were taking acetylsalicylic acid, 3 were taking warfarin, and 1 was taking clopidogrel before surgery. Hemoglobin concentration, platelet count, and P-PT, % were outside the normal laboratory reference ranges in 38.6% of transfused patients preoperatively and in 29.2% of patients with intraoperative RBCT. Tranexamic acid was given to 68.6% of patients on admission to Töölö Hospital before surgery. Of 37 patients who received RBCs during surgery, 26 had experienced intraoperative rupture of the aneurysm. Similarly, 7 of 15 patients who required intraoperative FFP transfusion and 1 of 6 patients who required platelet transfusion had intraoperative rupture of the aneurysm.

Total volumes of RBCs, FFP, and platelet concentrates transfused were 730 mL ± 503, 560 mL ± 283, and 500 mL ± 199. One patient with a large (20 mm diameter, 8 mm base) ruptured basilar aneurysm experienced a massive bleed of 10,520 mL during surgery and received 2400 mL of RBCs, 800 mL of platelets, and 1000 mL of FFP intraoperatively. Mean blood loss for patients who received RBCT during surgery was 1470 (± 1890) mL.

Intraoperative RBCT

Table 2 shows main clinical characteristics of the 488 patients divided into 2 groups based on the need for intraoperative RBCT (yes or no). Preoperative hemoglobin concentration was lower in patients who received intraoperative RBCT. There also was a significant difference in preoperative WFNS classification and Fisher grade between the 2 groups. GOS score at 3 months was lower among patients who received RBCs during surgery. There was no statistical difference in aneurysm location between the 2 groups. In multivariate analysis, lower preoperative hemoglobin value, worse Fisher grade, increase in aneurysm size, and intraoperative rupture of an aneurysm independently increased the likelihood of intraoperative RBCT (Table 3).

Table 1. Transfusion Rates of Perioperative Red Blood Cells, Fresh Frozen Plasma, and Platelets

	Before Surgery	During Surgery	Postoperative	Total
RBCs	5/488 (1.0%)	37/488 (7.6%)*	17/488 (3.5%)	52/488
FFP	5 (1.0%)	15 (3.1%)†	8 (1.6%)	23/488
Platelets	1 (0.2%)	6 (1.2%)‡	4 (0.9%)	9/488

FFP, fresh frozen plasma; RBCs, red blood cells.
*RBCs also were given before surgery in 3 patients and postoperatively in 4 patients.
†FFP was given before surgery in 4 patients and postoperatively in 1 patient.
‡Thrombocytes were given before surgery in 1 patient and postoperatively in 1 patient.

Table 2. Preoperative Demographic Data Divided into 2 Groups Based on Need for Intraoperative Red Blood Cell Transfusion

	RBCT During Surgery: Yes	RBCT During Surgery: No	*P* Value
Female	28 (9.4%)	269 (90.6%)	
Male	9 (4.7%)	182 (95.3%)	0.55
Age (years)	56 (± 13)	54 (± 12)	0.44
Hemoglobin (g/L)	117 (± 16)	128 (± 18)	0.001
P-PT, %	97 (± 23)	92 (± 29)	0.30
Thrombocyte count (10^9/L)	233 (± 79)	226 (± 61)	0.52
WFNS classification	2 (1–5)	4 (1–5)	< 0.001
WFNS 1	6 (16.2%)	211 (46.8%)	
WFNS 2	2 (5.4%)	51 (11.3%)	
WFNS 3	1 (2.7%)	19 (4.2%)	
WFNS 4	14 (37.8%)	73 (16.2%)	
WFNS 5	14 (37.8%)	97 (21.5%)	
Fisher grade 1–4	4 (2–4)	4 (1–4)	0.005
Fisher 1	0	15 (3.3%)	
Fisher 2	1 (2.7%)	61 (13.5%)	
Fisher 3	6 (16.2%)	140 (31.0%)	
Fisher 4	30 (81.1%)	222 (49.2%)	
Fisher grade not available	0	13 (2.9%)	
GOS score at 3 months	3 (1–5)	4 (1–5)	< 0.001
Intraoperative aneurysm rupture	28 (75.7%)	103 (22.8%)	< 0.001
Aneurysm location			
ICA	7 (18.9%)	84 (18.6%)	
MCA	16 (43.2%)	154 (34.1%)	
AComm+A1	5 (13.5%)	138 (30.6%)	
Pericallosal artery	0	24 (5.3%)	
VA	1 (2.7%)	2 (0.4%)	
PICA	3 (8.1%)	21 (4.7%)	
PCA	0	3 (0.7%)	
Basilar artery	5 (13.5%)	25 (15.5%)	0.06

Values are mean (± SD) and median (range) or number (percentage).
AComm+A1, anterior communicating artery + anterior cerebral artery, part A1; GOS, Glasgow Outcome Scale; ICA, internal carotid artery; MCA, middle cerebral artery; PCA, posterior cerebral artery; PICA, posterior inferior cerebellar artery; P-PT, %, plasma prothrombin time value; RBCT, red blood cell transfusion; VA, vertebral artery; WFNS, World Federation of Neurological Surgeons.

Outcome

The risk for unfavorable outcome was significantly increased with patients who received RBCs during surgery (odds ratio = 5.13, confidence interval = 1.53–17.15). Other independent factors associated with worse neurologic outcome were older age and worse WNFS classification and Fisher grade preoperatively. These findings remained similar after including a propensity score of intraoperative RBCT in the outcome model (Table 4).

Table 3. Multivariable Analysis of Factors Associated with Increased Risk of Intraoperative Red Blood Cell Transfusion

Preoperative Factor	OR	95% CI	*P* Value
Preoperative hemoglobin (increase by 1 g/L)	0.98	0.93–0.96	0.04
WFNS classification (increase)	1.81	0.91–1.53	0.22
Fisher grade (increase)	2.19	1.03–4.70	0.04
Intraoperative aneurysm rupture (yes)	10.86	4.74–24.89	< 0.001
Aneurysm size (increase by 1 mm)	1.07	1.01–1.41	0.03

CI, confidence interval; OR, odds ratio; WFNS, World Federation of Neurological Surgeons.

DISCUSSION

In the present study, we aimed to characterize the incidence of RBC, FFP, and platelet transfusion, and we found a low rate of intraoperative transfusions in patients undergoing clipping of a ruptured cerebral aneurysm. Most RBCTs were related to intraoperative aneurysm rupture, and FFP and platelet transfusions were related to the preemptive reversal of anticoagulant or antiplatelet therapy. We noted an association between RBCT and poor outcome after 3 months, and this finding warrants further study. This observation is clinically important in view of earlier reports of higher rate of RBCTs during aneurysm surgery (7, 8), which may influence patient outcome and treatment costs. Furthermore, it appears that need for intraoperative RBCT is strongly related to the sudden rupture of an aneurysm during surgery, although almost 40% of the patients had coagulation disturbance preoperatively.

Transfusion of FFP and platelets seemed to be preemptive and related to patient use of anticoagulant or antiplatelet therapy. FFP and platelet transfusions were used to correct evident coagulation disturbances before surgery, such as in patients on long-term anticoagulation or antiplatelet therapy. Transfusion of platelets was so scarce in this patient population that it is impossible to draw definite conclusions of the reasons behind transfusions.

In 2 other larger studies including 441 and 101 (of which 5 had aneurysm coiled) patients, respectively, significantly higher use (27.2% and 19.8%, respectively) of RBCs was reported (7, 8). The low incidence of intraoperative RBCT (7.6%) in our report including 488 patients undergoing aneurysm surgery is in line with the incidence of 5.6% reported earlier by Couture et al. (2) in a series of 77 patients with ruptured aneurysms. However, their result is part of a larger entity of cerebrovascular surgery cases (ruptured and unruptured aneurysms, arteriovenous malformations, and carotid artery stenosis) and the number of patients with ruptured aneurysm was small (n = 77).

The hemoglobin level before RBCT was not abnormally low (i.e., hemoglobin concentration was within normal laboratory reference range). This finding reflects the nature of aneurysm

Table 4. Factors Associated with Increased Risk of Unfavorable Outcome at 3 Months

	Logistic Regression			Propensity Score Adjusted		
Factor	**OR**	**95% CI**	***P* Value**	**OR**	**95% CI**	***P* Value**
Intraoperative RBCT (yes)	5.13	1.53–17.15	0.008	5.12	1.51–17.41	0.009
Intraoperative aneurysm rupture (yes)	1.36	0.73–2.54	0.34	0.96	0.30–3.07	0.96
WNFS classification (increase)	1.97	1.64–2.36	< 0.001	1.94	1.60–2.34	< 0.001
Fisher grade (increase)	1.89	1.23–2.92	0.004	1.76	1.09–2.83	0.02
Preoperative hemoglobin (increase by 1 g/L)	1.01	1.00–1.03	0.20	1.01	1.00–1.03	0.14
Aneurysm size (increase by 1 mm)	1.02	0.96–1.09	0.50	1.01	0.95–1.08	0.74
Age (increase by 1 year)	1.07	1.04–1.10	< 0.001	1.07	1.05–1.10	< 0.001

CI, confidence interval; OR, odds ratio; RBCT, red blood cell transfusion; WFNS, World Federation of Neurological Surgeons.

surgery, where a stable surgery can abruptly turn catastrophic because of the rupture of an aneurysm. In the present study, intraoperative rupture of an aneurysm was strongly associated with intraoperative RBCT, and 68% of the transfusions occurred after a rupture of an aneurysm. Clinicians may be inclined to give RBCT preemptively. The fact that worse Fisher grade together with lower preoperative hemoglobin value was shown by multivariate analysis as an independent risk factor for RBCT suggests that overall patients who need blood product transfusions are the patients with more severe SAH.

Intraoperative RBCT was associated with worse neurologic outcome, even when controlled for other variables, such as intraoperative rupture of an aneurysm, WFNS classification, and Fisher grade. This finding must be seen mainly as hypothesis generating but is in line with findings by Smith et al. (19), who reported that intraoperative RBCs increased the incidence of vasospasm. Whether there is a true relationship between intraoperative RBCT and patient outcome or whether RBCT reflects only the severity of the disease is uncertain, especially as in our study the number of intraoperative ruptures of aneurysms among the patients who received RBCs during surgery was relatively high. Intraoperative rupture of an aneurysm itself was not an independent risk factor for worse neurologic outcome in our analysis; this is probably due to the fact that, in addition to clinically relevant ruptures, even the slightest bleeding from an aneurysm sac is considered an intraoperative rupture in our data.

We limited the postoperative follow-up period for blood product transfusions to 24 hours to keep this study solely related to surgery and its requirements for blood product transfusion. Often postoperative fluid therapy in patients with SAH is guided by partly controversial "HHH" (hypervolemia, hypertension, hemodilution) treatment to prevent vasospasm (13, 20). Although our current practice targets normovolemia, the hemodilution induced by fluid therapy also can require transfusion of blood products regardless of surgery. It is reported that 36%–47% of patients with SAH develop anemia (5, 18, 21). The optimal hemoglobin level in these patients is still debated (9). Higher hemoglobin level may improve patient outcome (5, 14-16), but simultaneously RBCT itself is a risk factor for worse outcome and may increase the risk of extracerebral complications (11, 19). However, our results concerning postoperative RBCT cannot be compared directly with earlier reports because the length of the postoperative period was not clearly defined; Le Roux et al. (7) reported that 46% of patients operated on for ruptured and nonruptured aneurysms received RBCs postoperatively. In that study, high use of RBCs also was associated with poor-grade SAH in patients. Our demonstrated intraoperative FFP and platelet transfusion rates of 3.6% and 1.2%, respectively, can be considered low, but there are limited data for comparison.

Our study confirms that prevention of rebleeding before the aneurysm is secured is the key element to minimize the need for blood product transfusion in patients with SAH. Modern neurosurgical techniques using high magnification of the operating microscope and frequent use of temporary clipping to facilitate safe clipping of the aneurysms together with optimal neuroanesthesia with relatively low systolic blood pressure (systolic blood pressure ~100 mm Hg) are essential to treat these patients successfully (3, 17). Stable hemodynamics, preserved coagulation capacity, and slack brain with the head elevated above the heart level enable neurosurgeon to preserve normal anatomy and to prevent access bleeding during aneurysm clipping. Use of adenosine is a practical tool in the event of sudden intraoperative rupture of an aneurysm (1, 12). Although the need for RBCs can be urgent, we do not routinely crossmatch RBCs for patients before aneurysm surgery. When RBCs are not readily available, the decision to transfuse RBCs is not automated, but is based on the patient's real needs. RBCs can be obtained within 15–20 minutes after the decision to perform RBCT has been made. In the long run, this approach can result in considerable economic savings (8).

CONCLUSIONS

The incidence of perioperative transfusion of blood products in aneurysm surgery is low, and intraoperative RBCT is strongly related to rupture of an aneurysm. The transfusion of FFP and platelets is uncommon and seems to be related to preemptive transfusion in patients on anticoagulation or antiplatelet therapy. Intraoperative RBCT itself may increase a patient's risk of an unfavorable neurologic outcome, but this observed association warrants further study.

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II

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Aneurysms

Adenosine-induced cardiac arrest during intraoperative cerebral aneurysm rupture

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Abstract

Background: Rupture of an intracranial aneurysm during surgical clipping may have devastating consequences. Should this happen all methods ought to be considered to stop the bleeding. A short-term cardiac arrest induced by adenosine could be a feasible method to help the surgeon. We present our experiences in the administration of adenosine during an intraoperative aneurysm rupture.

Methods: Medical records of patients who underwent surgical clipping of a cerebral arterial aneurysm were reviewed from 2 university hospitals' operative database in the years 2003 to 2008. Patients were included in this study if adenosine had been administered during intraoperative rupture of an aneurysm.

Results: Altogether, 16 of 1014 patients were identified with the use of adenosine during an intraoperative rupture of an aneurysm. All of the patients had sinus rhythm and normotension before the rupture of the aneurysm. Twelve patients were administered a single dose of adenosine and 4 multiple boluses for induction of cardiac arrest; the median (range) total dose was 12 (6-18) mg and 27 (18-87) mg, respectively. The clipping of the aneurysm and the recovery of circulation were uneventful in all cases. In a subgroup analysis according to patient outcome as alive/dead, the pre- and postoperative neurologic condition correlated with the outcome, whereas adenosine did not have any effect on the patient outcome.

Conclusion: In a case of a sudden aneurysm rupture, adenosine-induced circulatory arrest could be a safe option to facilitate clipping of an aneurysm. However, if adenosine is used, a very close collaboration between the surgeon and the anesthesiologist is required.

Keywords: Adenosine; Heart arrest; Intracranial aneurysm; Rupture; Spontaneous

1. Introduction

Intraoperative rupture of the cerebral arterial aneurysm can have undesired consequences. Whether it has an effect on patient neurologic outcome remains to be determined. The most recent study suggests, however, that intraoperative aneurysm rupture does not influence patient outcome [1,18]. Stable intraoperative blood pressure, careful microneurosurgical technique, and the application of temporary clips may minimize the risk of rupture of the aneurysm [2,6,9,13]. In a case of an aneurysm rupture, adenosine, a short-acting drug with negative effect on sinoatrial and atrioventricular nodes, has been used successfully to induce transient cardiac arrest to stop the bleeding when suction fails to clear the operative field [10,12,15]. The relatively bloodless field may enable the surgeon to place temporary or permanent clip under visual control.

Abbreviations: ECG, electrocardiography; GCS, Glasgow Coma Scale; GOS, Glasgow Outcome Scale; SAH, subarachnoid hemorrhage

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There are only 3 earlier single-patient case reports with successful use of adenosine in inducing a transient cardiac arrest to facilitate clipping of an aneurysm with or without a rupture [10,12,15]. We analyzed retrospectively the data of the patients who were administered adenosine during the intraoperative rupture of a cerebral arterial aneurysm.

2. Methods

Patients with surgical clipping of an intracranial aneurysm were identified from the operative database and records of Turku and Helsinki University Hospitals over a period of 5.5 years (January 2003-May 2008). These 2 university hospitals serve southern and western Finland with a population of 3 million. Patients were included in the study if there was a rupture of an aneurysm during the surgery and if they had received adenosine after the rupture. As the study is of a retrospective nature, approval by the hospital ethics review committees was not required. The perioperative treatment protocols of patients with SAH, as well as of patients with nonruptured cerebral aneurysm, are similar in both university hospitals [17].

The clinical variables included in the analyses were age, comorbidities, GCS, Fischer scale, Hunt and Hess scale, presence of hydrocephalus, location of the aneurysm, hemodynamics before and after the adenosine, dose of adenosine, use of vasoactive drugs, number of delayed ischemic deficiencies, length of stay in the intensive care unit and in the hospital, patient state at discharge from the hospital, and GOS. Furthermore, the patients were grouped according to discharge from the hospital (dead or alive) and according to outcome (good outcome, GOS 4-5; poor outcome, GOS 1-3).

2.1. Statistics

The descriptive statistics are shown as mean ± SD or as median (range) when the parameters were not distributed normally. The clinical variables and the subgroups (dead/alive and good outcome/poor outcome) were compared by paired t test using the SYSTAT 10.2 statistical package (SYSTAT Software, Inc, San Jose, CA). $P < .05$ was considered statistically significant.

3. Results

Altogether, 16 of 1014 patients (Helsinki, 825; Turku, 189) were identified with the use of adenosine during an intraoperative rupture of an intracranial aneurysm (Table 1). Fifteen of the patients were admitted to the hospital owing to a SAH, and one patient was scheduled for an elective clipping of a basilar aneurysm. Nine of the cerebral aneurysms were located in the anterior and 7 in the posterior cerebral circulation (Table 2). Seven of the patients were previously diagnosed to have hypertension, 2 with coronary artery disease, and 3 with universal atherosclerosis. The comorbidities associated with SAH are presented in Table 3.

Table 1
Demographics of the data, presented as numbers of patients and means ± SD

Sex (male/female)	6/10 (37.5%/62.5%)
Age	53.1 ± 15.5 y
Height	76.0 ± 9.9 kg
Weight	169.9 ± 7.9 cm
SAH/Elective surgery	15/1

Table 2
Locations of the aneurysms

Aneurysms	Numbers (%)
Internal carotid artery	2 (12.5)
Middle cerebral artery	4 (25)
Anterior cerebral artery	1 (6.25)
Anterior communicating artery	2 (12.5)
Posterior cerebral artery	1 (6.25)
Basilar artery	5 (31.25)
Pericallosal artery	1 (6.25)

Fourteen patients had sinus rhythm preoperatively. In one patient, the preoperative ECG was not found. One patient with sinus rhythm had supraventricular extrasystolic beats. Ischemic ECG changes were observed in 4 patients preoperatively. The preoperative plasma potassium level was within normal range in all of the patients.

Anesthesia was maintained with propofol and remifentanil in all patients. Ten minutes before the aneurysm rupture and adenosine bolus, the mean systolic and diastolic blood pressure levels were 119 ± 14 and 59 ± 10 mm Hg, respectively, and the mean heart rate was 70 ± 13 per minute. After intraoperative aneurysm rupture, 12 patients received a single adenosine bolus, whereas 4 patients received repeated boluses of adenosine. The median (range) adenosine dose used for the single bolus was 12 (6-18) mg, whereas the median total dose for multiple boluses was 27 (18-89) mg.

As measured 10 minutes after the adenosine, the hemodynamics of the patients were stabilized. At this stage, the mean systolic and diastolic blood pressure levels were 113 ± 14 and 57 ± 9 mm Hg, respectively, and the mean heart rate was 74 ± 15 per minute. During the surgery, 13 patients needed an infusion of vasoactive drugs to maintain adequate blood pressure. Four patients were administered noradrenalin, 7 patients with phenylephrine, and one patient required both phenylephrine and dobutamine. All vasoactive drugs were commenced after the anesthesia induction and

Table 3
Comorbidities associated with SAH

	Yes	No
Hydrocephalus	5	11
ECG Ischemia	4	12
Neurogenic pulmonary edema	1	15
DIND	2	13

ECG ischemia indicates myocardial ischemia seen on ECG; DIND, delayed ischemic neurologic deficiencies.

infused throughout the surgery. The mean duration of the surgery was 135 ± 27 minutes.

The mean stay in the intensive care unit was 6.3 ± 4.6 days and in the university hospital was 17.9 ± 11.7 days. The median (range) postoperative GCS was 9.5 (3-15). The number of patients discharged alive from the hospital was 12, and 4 died during the hospital stay. Four patients died later in other hospitals owing to complications related to SAH. Two patients experienced delayed ischemic neurologic deficiencies, and one of them died after discharge from the hospital. The median (range) GOS was 2 (1-5). Five patients were discharged with GOS of 5, 2 patients with GOS of 4, one with GOS of 3, and 8 patients with GOS of 1 (died). Table 4 presents the severity of SAH, administered doses of adenosine, and GOS.

In subgroup analysis, there was a significant difference in the median Hunt and Hess score between the patients discharged alive or dead from the hospital, 3.5 (0-5) and 5 (4-5) ($P < .05$), respectively. There was also a significant difference in the median pre- and postoperative GCS between the patients discharged alive or dead, 11.5 (3-15) and 4.5 (3-7) and 14 (4-14) and 4.5 (3-8) ($P < .05$), respectively. The Fischer scale, Hunt and Hess score, GCS on admittance or after the surgery, however, were similar in the good-outcome (GOS 4-5) and in the poor-outcome (GOS 1-3) groups. The total administered dose of adenosine or the hemodynamics were not different between any of these subgroups ($P > .05$).

4. Discussion

In the present study, we analyzed the hospital records of 16 of 1014 patients who had an intraoperative rupture of a cerebral aneurysm with the short-term adenosine-induced circulatory arrest facilitating the clipping. The decision to give adenosine was made in cooperation with the neurosurgeon and the anesthesiologist. The final clipping of the aneurysm as well as the restoration of systemic circulation was successful in all cases. We did not observe any immediate or late adverse events related to the administration of adenosine.

Adenosine has a very short negative dromotropic and chronotropic effect on cardiac sinoatrial and atrioventricular nodes, and it is usually indicated in paroxysmal supraventricular tachyarrhythmia. The administration of adenosine in patients with normal sinus rhythm induces a rapidly reversible cardiac arrest. The intravascular half-life of adenosine at the physiologic level is less than a second. The mechanism of action of adenosine in cardiac muscle is hyperpolarization after its binding to A1 receptors and opening of potassium channels. Adenosine also decreases intracellular cyclic adenosine monophosphate, which inhibits calcium entry into the cell [3,14,16].

In the current study, the majority of the patients presented a cardiac arrest after a single dose of adenosine (median, 12 mg). This median dose is in accordance with the recommended doses of 6 to 12 mg for supraventricular tachyarrhythmias [7,8]. However, 4 of 16 patients were administered adenosine more than once and the median cumulative dose was considerably higher, 27 mg. As assessed retrospectively, there may have been requirements for a prolonged cessation of circulation because of surgical reasons or the ineffectiveness of adenosine to induce cardiac arrest during normal sinus rhythm. Although none of the 16 patients had unstable hemodynamics nor abnormal arrhythmias after the restoration of spontaneous circulation, repeated doses of adenosine might be given only under extremely close collaboration between the surgeon and the anesthesiologist. For instance, Heppner et al [12] reported administration of a high dose of adenosine, that is, 36 mg, in one patient resulting in prolonged cardiac

Table 4
Severity of SAH and outcome of patients receiving adenosine

Patient	GCS	Fischer	Hunt and Hess	Temporary clip	Occlusion time	Adenosine (mg)	GOS
1	13	3	4	No		18	1
2	15	3	2	No		6	5
3	5	3	4	No		18	1
4	6	4	5	Yes	6 min 28 s	9	4
5	5	4	5	Yes	Not known	12	1
6	10	4	4	No		16	1
7	15	1	1	Yes	Not known	12	5
8	3	4	5	Yes	19 min	87	1
9	3	3	5	Yes	Not known	9	3
10	7	4	5	Yes	Not known	12	1
11	15	4	2	Yes	9 min 55 s 3 min 22 s	18	5
12	4	4	5	Yes	Not known	12	1
13	15	Elective	Elective	No		9	5
14	15	3	2	Yes	6 min 18 s	12	5
15	3	4	5	Yes	Not known	36	1
16	10	3	3	Yes	5 min	12	4

Glasgow Outcome Scale: 5 indicates good recovery; 4, moderate disability; 3, severely disabled; 2, vegetative state; 1, death.

arrest up to 52 seconds. Adenosine has also been reported to induce ventricular tachycardia or torsades des pointes [5,11]. Patients in our study received on average significantly smaller doses of adenosine, and cardiac standstills were shorter as well. The fact that most of our patients (n = 13/16) did not have coronary artery disease nor had ischemia in ECG (n = 12/15) preoperatively might have also favored the uneventful restoration of circulation after adenosine.

In the current study, 4 patients with SAH were treated perioperatively with intravenous calcium channel antagonist nimodipine to prevent vasospasm. Calcium channel antagonists and also dipyridamol may inhibit adenosine metabolism and reuptake to cell [11]. Although the adenosine-induced cardiac arrest of the 4 patients with SAH was comparable to that of the patients not on intravenous nimodipine, one should be aware of the possible interaction between nimodipine and adenosine: nimodipine might potentiate the effect of adenosine [4]. The possible interactions of adenosine with propofol, inhaled anesthetics, or opioids are unknown.

Five (31.25%) of 16 patients who were given adenosine underwent surgery of basilar artery aneurysm. This probably refers to the fact that these operations are technically the most challenging ones. This is also supported by other case reports. Groff et al [10] used 3 consequent doses of adenosine to facilitate the placement of a permanent clip to the nonruptured basilar artery aneurysm, whereas the report by Heppner et al [12] describes a case where 3 relatively high and consequent doses of adenosine were used to help the surgeon to place a permanent aneurysm clip on the basilar aneurysm, because the attempt to place a temporary clip had failed. Nussbaum et al [15] gave a single dose of adenosine to control the bleeding of a ruptured anterior communicating artery aneurysm.

The present report has limitations. As all the anesthetic records were hand written, and the study was retrospective, no details of the blood pressure or heart rate immediately after adenosine boluses could be identified. This may be related to the emergency situation with the intraoperative aneurysm rupture. However, we believe if there had been delayed restoration of spontaneous circulation or major hemodynamic instability requiring high doses of vasoactive agents, we could have been able to observe these adverse events in the individual patient's records. We also believe that circulatory arrest facilitated the clipping procedure enabling the neurosurgeon to place a temporary or final clip in a clear field to stop the bleeding, although we lack the neurosurgeon's specific grading of the benefit of the administration of adenosine in single patients. After initial clipping, the clips may be repositioned for optimal occlusion of the aneurysm.

According to our data, there were no differences in any of the measured scales (Hunt and Hess, GCS, Fisher's scale) as the patients were grouped according to good or poor outcome (GOS). However, both the preoperative Hunt and Hess scoring and GCS seemed to be good predictors of in-hospital survival when the patients were grouped at hospital discharge as dead or alive. As the dose of adenosine was comparable in these subgroups, the circulatory arrest induced by adenosine does not seem to have had a deleterious effect on patient outcome. We started to use adenosine soon after it was first introduced in this indication by Groff et al [10] in 1999. Since then, surgical techniques have also changed; especially, the use of temporary clips has become more frequent. Hence, comparison with older material may not be justified in evaluating the effect of adenosine on outcome.

We conclude that adenosine can be safely administered during surgery of a cerebral arterial aneurysm to patients who experience a sudden, uncontrolled bleeding without previous sinoatrial conduction abnormality. Good collaboration between the neurosurgeon and the anesthesiologist is mandatory. The indications of adenosine during intracranial aneurysm surgery are recommended to be discussed preoperatively with the neurosurgeon.

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III

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CLINICAL REPORT

Thromboelastometry during intraoperative transfusion of fresh frozen plasma in pediatric neurosurgery

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Abstract Normal blood coagulation is essential in pediatric neurosurgery because of the risk of abundant bleeding, and therefore it is important to avoid transfusion of fluids that might interfere negatively with the coagulation process. There is a lack of transfusion guidelines in massive bleeding with pediatric neurosurgical patients, and early use of blood compounds is partly controversial. We describe two pediatric patients for whom fresh frozen plasma (FFP) infusion was started at the early phase of brain tumor surgery to prevent intraoperative coagulopathy and hypovolemia. In addition to the traditional laboratory testing, modified thromboelastometry analyses were used to detect possible disturbances in coagulation. Early transfusion of FFP and red blood cells preserved the whole blood coagulation capacity. Even with continuous FFP infusion, fibrin clot firmness was near to critical value at the end of surgery despite increased preoperative values. By using FFP instead of large amounts of crystalloids and colloids when major blood loss is expected, blood coagulation is probably less likely to be impaired. Our results indicate, however, that the capacity of FFP to correct fibrinogen deficit is limited.

Keywords Fluid therapy · Transfusion · Fresh frozen plasma · Red blood cells · Brain tumor · Pediatric neurosurgery

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Introduction

In pediatric brain tumor surgery, the patient is often at risk for abundant bleeding. Normal blood coagulation is essential, and transfusion of fluids must not disturb this homeostasis. All artificial colloids and mannitol, in addition to their dilutional effects, decrease whole blood clot strength, predisposing patients to bleeding [1–3].

Transfusion protocols in massive bleeding are well documented in adult populations [4–6]. Pediatric patient guidelines are, however, scarce, and those for adults are not directly transferable to children [7]. We describe two cases in which an early fresh frozen plasma (FFP) infusion was used in brain tumor surgery to prevent intraoperative coagulopathy and hypovolemia. In addition to traditional laboratory testing, we used modified thromboelastometry analyses to trace possible blood coagulation disturbances.

Case report

Patient 1

A previously healthy 10-month-old boy (height 78 cm, weight 9.9 kg) had a richly vascularized left parieto-occipital tumor. The tumor extended to the mesencephalon and hypothalamus, causing a midline shift and hydrocephalus.

After induction, anesthesia was maintained with propofol and remifentanil infusions. The surgery took place with the patient in a sitting position. After a left paramedian parieto-occipital craniotomy, an occipital interhemispheric fissure was used to approach the tumor. After tumor debulking, the anaplastic meningioma was gradually dissected from the surrounding neurovascular structures and completely removed.

Addition to Ringer acetate solution, FFP infusion at the rate of 20 ml/h was started after anesthesia induction. 50 ml mannitol (150 mg/ml) was administered. Blood loss during surgery was 750 ml (300 ml within 25 min), and the patient received a total of 500 ml red blood cells (RBC) during surgery and another 60 ml in the intensive care unit (ICU), with no need for platelet transfer. The total amount of fluids infused during surgery (blood compounds and crystalloids) was 1,504 ml, and fluid loss (blood and urine) was 1,090 ml. The patient woke up and was extubated without complications 120 min after the operation.

Patient 2

A 5-month-old boy (height 67 cm, weight 7 kg) developed symptoms of increased intracranial pressure. Magnetic resonance imaging (MRI) study revealed a massive tumor in the left pontocerebellar area causing pressure to the brainstem.

Propofol and remifentanil infusions maintained the anesthesia. Surgery took place with the patient in a park bench position with head attached to the Mayfield device.

The neurosurgeon performed a left suboccipital craniotomy. After tumor debulking, he dissected and completely removed the lesion from the surrounding cerebrovascular structures. The tumor was ependymoma gradus II–III.

Together with 0.9 % sodium chloride solution with 5 % glucose (20 ml/h), FFP infusion was started after induction (240 ml in total). 25 ml mannitol (150 mg/ml) was given. Intraoperative blood loss was 380 ml, and the patient received a total of 250 ml RBC during surgery and another 60 ml in the ICU, with no need for platelet transfer. The total amount of fluids infused during surgery (blood compounds and crystalloids) was 870 ml and fluid loss (blood and urine) 960 ml. Two 250-mg boluses of tranexamic acid were given during surgery. The patient was kept sedated in controlled ventilation in the ICU until the first postoperative morning.

Laboratory analyses

The results of laboratory tests are given in Table 1. Both patients had mild anemia and abnormally high platelet count, but thromboplastin time values (PT-%, normal 70–130 %) fell within normal limits.

Four different thromboelastometry tracings were used: Intem® (intrinsic pathway), Extem® (extrinsic pathway), Fibtem® (platelet function inhibition by cytochalasin D), and Aptem® (added aprotinin to detect hyperfibrinolysis).

In Extem® and Fibtem® analyses, coagulation time (CT), clot formation time (CFT), alpha-angle, and maximum clot firmness (MCF) were within normal reference ranges before the surgery, but both patients had increased fibrin MCF preoperatively (Fibtem®). Maximum lysis (ML), indicative of fibrinolytic activity, was 21 % (normal <15 %) in both patients in preoperative Extem® analysis. However, MCF was comparable between Aptem® and Extem® analyses.

Clot formation time was longer in all samples in comparison with the preoperative values (Fig. 1). MCF was slightly decreased in Intem® and Extem® analyses in comparison with preoperative values (Fig. 2). Decrease in MCF in Fibtem® analysis was more profound and reached a critical value of 8 mm at the end of surgery in patient 2 (Fig. 3). Maximum lysis (ML) diminished gradually in both patients, showing least activity at 2 h after the surgery in patient 1 (ML 1 %).

Thromboelastometry analyses in the first postoperative morning were similar to preoperative values. Fibrin clot firmness was increased in both patients, i.e., leaning slightly toward hypercoagulopathy. Maximum lyses (ML) were within normal reference ranges.

Discussion

Both patients were preoperatively considered to have a significant risk of major blood loss during neurosurgery.

Table 1 Results of laboratory and standard coagulation tests

	Hb (g/dl)		Hct (%)		Platelets (E^9/l)		PT (%)	
	P1	P2	P1	P2	P1	P2	P1	P2
Baseline	9.1	10.1	28	31	656	560	122	136
Intraoperative 10.59	8.3	8.5	25	24	633	316		
Intraoperative 12.20	12.3		35		436		93	
End of surgery 13.32	10.7		30		327			93
3 h after operation	9.4		26		292		103	
5 h after operation		12.6		35		220		
9 h after operation	8.5		24		279			
First postoperative day	9.8	11.9	27	34	301	236	120	102

Hb hemoglobin, *Hct* hematocrit, *Eryt* erythrocytes, *PT* prothrombin time, *P1* patient 1, *P2* patient 2

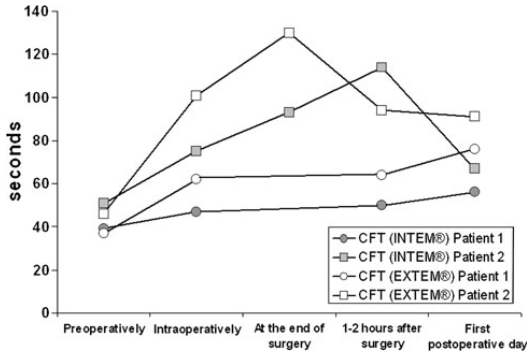

Fig. 1 Clot formation time (*CFT*) in Intem® (normal reference range, 30–110 s) and Extem (34–159 s) analyses

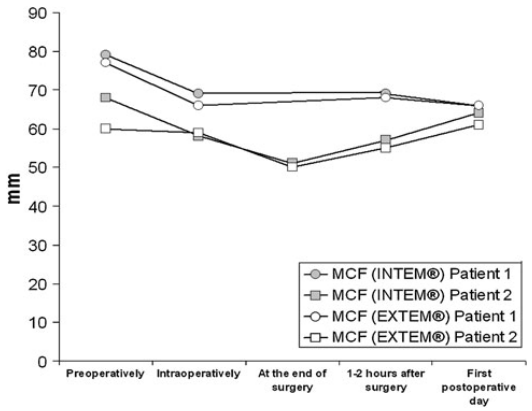

Fig. 2 Maximum clot firmness (*MCF*) in Intem® (normal reference range, 50–72 mm) and Extem (50–72 mm) analyses

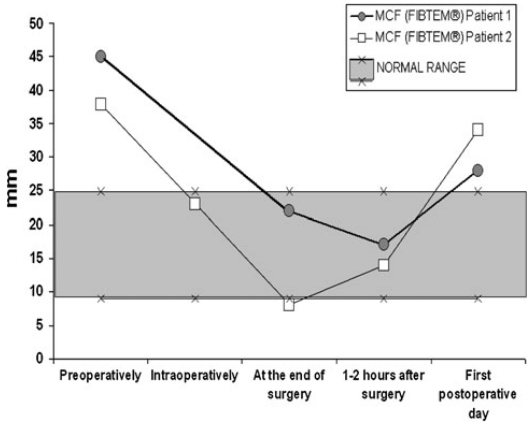

Fig. 3 Maximum clot firmness (*MCF*) in Fibtem® analysis

Thromboelastometry analysis showed that early transfusion therapy with FFP and RBC preserved the whole blood coagulation capacity. Interestingly, fibrin clot firmness was near the critical value at the end of surgery, despite increased preoperative fibrin clot firmness.

Transfusion guidelines concerning pediatric patients address very little intraoperative fluid management during excessive blood loss. The emphasis is more on critically ill patients and patients suffering from a chronic coagulation deficit [8–10]. Although transfusion guidelines for adults in massive bleeding are leaning toward the use of an increased ratio of FFP and platelets in relationship to red blood cells [11], the general view with pediatric patients still is that crystalloids are the first-line solutions and different blood compounds should only be administered when coagulation deficit, revealed by laboratory testing, has developed [8, 9]. This is a challenge when treating pediatric neurosurgical patients. Hypovolemia may develop quickly because of the patient's low blood volume. Second, abrupt massive bleeding is possible, in which situation laboratory testing and thromboelastometry analysis are too slow to guide transfusion of fluids.

To prevent the development of coagulation disturbance and hypovolemia intraoperatively, we started FFP infusion at the beginning of the surgery before major bleeding could occur. Even with continuous FFP infusion, a decrease in PT-% was evident with both patients (25–29 % percentage points during surgery). However, relatively minor changes in CT and CFT values in Intem® and Extem® analysis indicate that a marked deficit of coagulation factors did not developed during surgery. Our results suggest that without an early FFP infusion, or with crystalloid or colloid infusions, a clinically relevant lack of coagulation factors would have occurred during the operations.

Efficacy of FFP to correct fibrinogen deficit is limited. Decrease in clot firmness in Fibtem® analyses was also evident in both our cases, which suggests that our patients would probably have benefited from increment of fibrinogen if surgical hemostasis would not have been satisfactory. Haas and co-workers [12] showed that the administration of fibrinogen during craniosynostosis repair avoided the need for FFP transfusion; instead, colloids were used to compensate blood loss. Use of colloids in massive bleeding, however, is not unambiguously supported, because of their negative interference with blood coagulation [13], especially with mannitol [2]. We gave patient 2 tranexamic acid because of the increased maximum lysis (21 %) preoperatively and positive in vitro effect of aprotinin (Aptem®) on clot strength in the intraoperative analysis. A single bolus of tranexamic acid also reduces bleeding and the need for red blood cell transfusion without extreme fibrinolytic activity in craniosynostosis operations [14].

A postoperative hypercoagulable state is a common finding in children undergoing brain surgery [15], and enhanced coagulation in thromboelastometry analysis is seen after relatively minor blood loss during craniotomy [15]. The specific definition of hypercoagulability and its effect on the risks of either thrombosis, or bleeding, are still unclear in craniotomy patients [16]. Our patients had increased MCF in Fibtem® analyses preoperatively, but in Extem® analyses MCF were within the normal reference range. Hypercoagulability, i.e., increased MCF in Fibtem®, however, decreased during the operations, and the critical values for fibrin clot firmness were almost reached at the end of surgery. A decrease in clot strength is associated with bleeding complications [13].

Thromboelastometry (ROTEM®) allows a dynamic evaluation of the entire coagulation process and distinguishes intrinsic and extrinsic coagulation pathways from pure fibrin formation. The use of thromboelastometry analysis in pediatric surgical patients is well documented [14, 17, 18]. Recent Cochrane analysis states, however, that there is still a lack of evidence that use of ROTEM® would decrease morbidity or mortality [19].

Allergic reactions, transfusion-related acute lung injury (TRALI), and infections are the major concerns related to transfusion of FFP and other blood components [20]. Virus inactivation and reduction of HLA and other antibodies by pooling have led to reduced risks of transfusion-related adverse effects. Instead of traditional FFP, we used Octaplas®, which is a pharmaceutical product that has gone through solvent-detergent treatment and is pooled from approximately 1,000 donors.

Perioperative fluid administration should be planned in advance when treating pediatric neurosurgical patients, and possible detected disturbances in blood coagulation should be handled before surgery. The excessive use of crystalloids and colloids in itself disturbs blood coagulation, and therefore early use of FFP is a noteworthy option when major blood loss is expected. Thromboelastometry offers an additional tool to observe possible disturbances in blood coagulation and to guide administration of fibrinogen or tranexamic acid.

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ORIGINAL ARTICLE

Comparison of Hypertonic Saline and Mannitol on Whole Blood Coagulation In Vitro Assessed by Thromboelastometry

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Abstract
Background Hypertonic saline (HS) is an alternative to mannitol for decreasing intracranial pressure in traumatic brain injury and before craniotomy. Both HS and mannitol may interfere with blood coagulation but their influence on coagulation has not been compared in controlled situations. Therefore, we evaluated different strengths of HS and 15% mannitol on blood coagulation in vitro.
Methods Citrated fresh whole blood, withdrawn from 10 volunteers, was diluted with 0.9%, 2.5%, or 3.5% HS or 15% mannitol to make 10 vol.% and 20 vol.% hemodilution in vitro. The diluted blood and undiluted control samples were analyzed with thromboelastometry (ROTEM®) using two activators, tissue thromboplastin without (ExTEM®) or with cytochalasin (FibTEM®).
Results In the FibTEM® analysis, maximum clot firmness (MCF) was stronger in the 2.5% HS group than in the mannitol group after both dilutions ($P < 0.05$). In the ExTEM® analysis, clot formation time (CFT) was more delayed in the mannitol group than in the 0.9%, 2.5%, or 3.5% HS groups in 20 vol.% hemodilution ($P < 0.05$). MCF was weaker in the mannitol group than in the other groups after 20 vol.% dilution ($P < 0.05$). MCF was also weaker in the 3.5% than in the 0.9% saline group after 20 vol.% dilution ($P < 0.05$).
Conclusions Blood coagulation is disturbed more by 15% mannitol than by equiosmolar 2.5% saline. This disturbance seems to be attributed to overall clot formation and strength but also to pure fibrin clot firmness. This saline solution might be more favorable than mannitol before craniotomy in patients with a high risk of bleeding.

Keywords Hypertonic saline · Mannitol · Coagulation · Traumatic brain injury · Craniotomy · Neurosurgery

Introduction

Mannitol has been the agent of choice in traumatic brain injury when osmotherapy has been needed to decrease intracranial pressure (ICP). It is also widely used in the same indication in neurosurgery with patients having a brain tumor or subarachnoid hemorrhage [1, 2].

Hypertonic saline (HS) can be used in a treatment of increased ICP in traumatic brain injury during neurointensive care. HS also prevents brain swelling during emergency craniotomy and may be an alternative to mannitol. Furthermore, HS is often used to instantly increase intravascular volume in patients with bleeding shock [3–6]. Extensive use of HS can lead to hypernatremia [7]. Earlier studies suggest that HS is equally effective or even better than mannitol in reducing brain swelling in patients undergoing craniotomy [8–15]. However, due to variable study protocols, e.g., regarding osmolarity and administered volumes, definite conclusions about differences in physiological responses or occurrence of untoward effects cannot be drawn.

The results were presented at the ESICM 2010 Meeting, Barcelona, Spain, Oct 9–13, 2010.

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Previous in vitro studies have demonstrated that both mannitol and HS interfere negatively with various components of blood coagulation [16–20]. Mannitol (15%) alone interferes with blood coagulation by reducing clot strength [20]. Mannitol (15%) when combined with hydroxyethyl starch causes a disturbance in fibrin formation and, consequently, in blood coagulation in 10 and 20 vol.% dilution. HS in different concentrations (3–7.5%) disturbs both fibrin formation and platelet function in the coagulation process.

The purpose of the present study was to compare the effect equimolar and equivolemic solutions of HS and mannitol on blood coagulation in vitro. Our hypothesis was that HS with low concentrations of sodium chloride would impair blood coagulation less than 15% mannitol.

Methods

The study protocol was approved by the institutional ethics committee. Written informed consent was obtained for blood donation for the study from 10 (three women, seven men) apparently healthy, non-smoking volunteers aged 21–36 years. No medication was allowed 5 days prior the study day. Fasting of 6 h was required before the blood test.

Thirty milliliter of venous blood was taken from the cubital vein via 20 G needle into three 10-ml glass tubes (Becton–Dickinson, Vacutainer®, Heidelberg, Germany), each containing 3.2% buffered citrate. Citrated whole blood was then diluted with the study solutions to make 0, 10, and 20 vol.% concentrations of the solutions.

The study solutions were 0.9% saline (Natriumklorid Braun® 9 mg/ml, reported osmolarity 300 mOsm/l), 2.5% saline (1 part Natriumklorid Braun® 234 mg/ml + 13.1 parts Natriumklorid Braun® 9 mg/ml), 3.5% saline (1 part Natriumklorid Braun® 234 mg/ml + 7.6 parts Natriumklorid Braun® 9 mg/ml) and 15% mannitol (Mannitol Braun® 150 mg/ml infusion fluid). Manufacturer of Mannitol Braun® 150 mg/ml infusion fluid reports that theoretical osmolarity of the fluid is 825 mOsm/l. Calculated osmolarity for 2.5% saline is 830 mOsm/l and for 3.5% saline 1160 mOsm/l.

Two four channel thrombelastometry devices (Rotem®, Pentafarm AG, Basle, Switzerland) were used to make coagulation analyses within 2 h of blood withdrawal. After re-calcification (Star-TEM®, Pentafarm AG, Basle, Switzerland) of the samples the coagulation process was facilitated by two different activators, tissue thromboplastin without (ExTEM®, Pentafarm AG, Basle, Switzerland) or with cytochalasin (FibTEM®, Pentafarm AG, Basle, Switzerland). The development of coagulation process was registered during 30 min period. The measured coagulation parameters for ExTEM® were clotting time (CT), clot formation time (CFT), maximum clot firmness (MCF), and alpha angle (clot formation rate, denotes the rate of the formation of a solid clot). Only MCF was measured in FibTEM® analysis.

The Rotem® parameters are shown in Fig. 1. CT reflects the time from the start of the measurement until the start of clot formation. CFT refers to the time from the beginning of clot formation until a clot firmness of 20 mm has been reached. Alpha angle is the angle between the central line

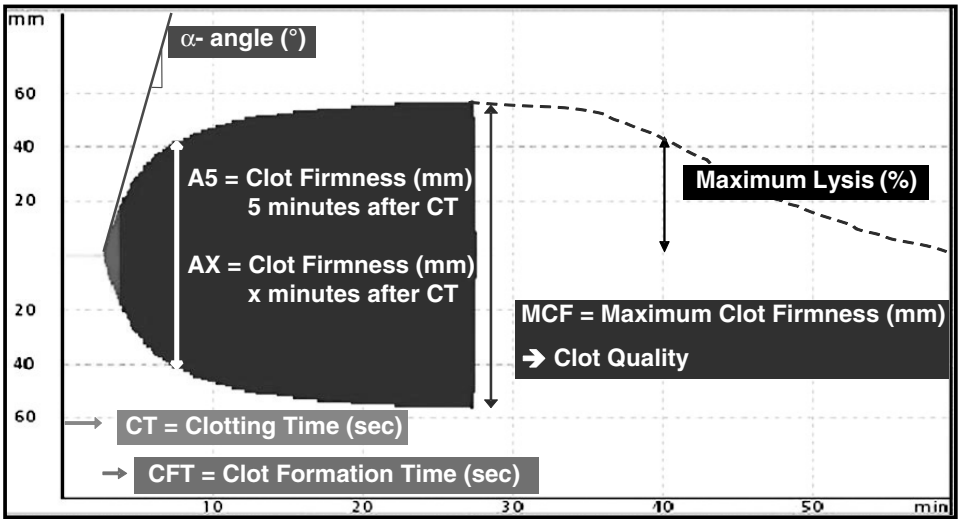

Fig. 1 Rotem® parameters

and the tangent of the curve at the amplitude point of 2 mm. MCF describes the strength of the clot.

Hemoglobin concentration (Hb), hematocrit value (hct), and platelet count were determined in all the study dilutions and the undiluted control samples (Cell-Dyn 610 Haematology Analyser, Seguoia-Turner Corporation, Mountain View, CA, U.S.A).

The number of volunteers was based on our earlier data [21]. In a cross-over study setting, eight volunteers would be needed to discover greater than 1 standard deviation (SD) difference in MCF between the equiosmolar HS and mannitol groups of similar vol.% dilution (alpha error 0.05). The differences between the groups were analyzed by ANOVA followed by *t*-test or Tukey–Kramer for paired comparisons. The results are shown as mean with standard deviations (SD).

Results

All the study solutions with the same vol.% hemodilution induced a comparable decrease in the hematocrit. Platelet count was different between the study solutions in 10 vol.% dilution (Table 1). CT and CFT measurements (ExTEM®) for one 20 vol.% dilution sample were unsuccessful and, therefore it was excluded ($N = 9$ for CT and CFT).

ExTEM® analysis

CT

Clotting time (CT) for mannitol was prolonged in both study dilutions (10 and 20 vol.%) when compared with control ($P < 0.05$), whereas other study solutions (0.9%, 2.5%, and 3.5% saline) showed no difference (Table 2).

Alpha-Angle (Clot Formation Rate)

Alpha-angle was smaller in the 15% mannitol group than in the 0.9% or 3.5% saline group after 10 vol.% dilution ($P < 0.05$). In 20 vol.% hemodilution, alpha-angle was also more decreased in the 15% mannitol group than in the 0.9%, 2.5%, or 3.5% saline groups ($P < 0.05$).

Table 1 Hemodilution data

Laboratory result	Mannitol $n = 10$, each	S0.9% $n = 10$, each	S2.5% $n = 10$, each	S3.5% $n = 10$, each	*P* values	Control $n = 10$
hct (%)						
10%	36.8(3.0)	36.9(3.2)	36.6(3.0)	36.5(2.9)	0.2043	40.9(3.2)
20%	32.6(2.4)	32.8(2.9)	32.7(3.2)	32.4(3.3)	0.4839	
Platelet ($\times 10^3/\mu l$)						
10%	141(71)	138(51)*	166(66)	169(73)	0.0431	145(54)
20%	143(58)	146(61)	143(68)	166(87)	0.2073	

All values are significantly ($P < 0.05$) different from control values (paired *t*-test)

* $P < 0.05$ compared with mannitol, 2.5% HS and 3.5% HS

Table 2 Clotting time (CT) and clot formation time (CFT)

ExTEM®		Mannitol $n = 10$	0.9% HS $n = 10$	2.5% HS $n = 10$	3.5% HS $n = 10$	*P* values	Control $n = 10$
CT (s)							
$n = 10$	10%	87.6(14.5)*	63.1(15.4)	73.7(25.6)	76.8(47.9)	0.3032	58.7(9.8)
$n = 9$	20%	89.8(22.9)*	77.2(33.0)	56.0(7.9)	84.8(44.9)	0.0765	60.8(7.7)
CFT (s)							
$n = 10$	10%	172.5(103.3)#	123.4(86.1)	137.4(82.1)	129.2(62.0)	0.0307	119.6(59.7)
$n = 9$	20%	341.4(241.6)*†	134.0(89.6)	167.2(94.9)*	216.9(97.8)*	0.0002	

* $P < 0.05$ compared with control

# $P < 0.05$ compared with 0.9% HS (CFT)

† $P < 0.05$ compared with 0.9% HS, 2.5% HS and 3.5% HS (CFT)

Values are mean (SD); analyzed by repeated measure ANOVA followed with Tukey–Kramer' post hoc test, within each dilution group

Table 3 Maximum clot firmness (MCF) and alpha angle

ExTEM®	Mannitol $n = 10$	0.9% HS $n = 10$	2.5% HS $n = 10$	3.5% HS $n = 10$	*P* values	Control $n = 10$
MCF (mm)						
10%	49.0(7.9)*	47.3(6.4)*	50.7(7.6)*	49.3(5.5)*	0.3638	54.8(8.3)
20%	42.3(7.9)*#	51.2(6.5)**	48.2(6.4)*	47.8(6.9)*	<0.0001	
Alpha (°)						
10%	62.2(10.1)*†	67.5(10.3)	65.4(10.0)	66.5(7.9)	0.0049	67.9(8.6)
20%	44.0(13.8)*#	65.5(10.3)**	61.8(10.4)*	57.3(8.5)*	<0.0001	

* $P < 0.05$ compared with control

# $P < 0.05$ compared with 0.9% HS, 2.5% HS and 3.5% HS

† $P < 0.05$ compared with 0.9% HS and 3.5% HS

** $P < 0.05$ compared with 3.5% HS

Values are mean (SD). *P* values: analyzed by repeated measure ANOVA followed with Tukey–Kramer' post hoc test, within each dilution group

CFT

Clot formation time (CFT) was more delayed in the 15% mannitol group than in the 0.9%, 2.5%, or 3.5% saline groups in 20 vol.% hemodilution ($P < 0.05$).

MCF

Maximum clot firmness (MCF) was similar with all the study solutions after 10 vol.% dilution, but after 20 vol.% dilution MCF was weaker in the 15% mannitol group than in the other groups ($P < 0.05$). MCF was also weaker in the 3.5% saline than in the 0.9% saline group after 20 vol.% dilution ($P < 0.05$) (Table 3).

FibTEM® Analysis

MCF

There was no difference in MCF between the study solutions in 10 vol.% dilution and the control, but MCF was significantly weaker in the 15% mannitol group in 20 vol.% dilution than in the control group ($P < 0.05$). When comparison was made between each study solution there was a significant difference in MCF between 15% mannitol and 2.5% saline both in 10 vol.% and 20 vol.% dilution 10.2(3.0) vs. 12.3(4.1) and 6.8(2.5) vs. 11.5(3.3), respectively, $P < 0.05$) (Table 4).

Conclusion

Our results indicate that 2.5% saline in 10 vol.% and 20 vol.% dilutions impairs blood coagulation less than equiosmolar 15% mannitol in vitro. An increase in concentration of sodium chloride to 3.5%, however, resulted in weaker coagulation.

Contrary to traditional laboratory coagulation test, thromboelastometry is a method allowing dynamic evaluation of coagulation process [22]. In this study, two different activators (ExTEM® and FibTEM®) were used in thromboelastometry analysis to further evaluate the nature of coagulation disturbance. As FibTEM® analysis inhibits platelet function, it allows the assessment of the fibrinogen component in coagulation process.

Overall, our finding in this study was that 15% mannitol causes more severe disturbance in blood coagulation than any of the other study solutions, including 0.9% saline. This difference between 15% mannitol and other solutions could already be seen when the dilution was 10 vol.%, but was more clear in 20 vol.% dilution. The results showed that not only is the coagulation process slower but the forming clot is weaker as well, when the dilution is made with 15% mannitol. The difference in MCF in FibTEM® analysis between 15% mannitol and other study solutions suggests that coagulation disturbance caused by mannitol is possibly a result from fibrin poor clot formation. Our finding of mannitol deteriorating effect on blood coagulation is in line with an earlier in vitro study [20]. The main focus of that study was to evaluate the effect of mannitol on whole blood coagulation when combined either with Ringer's acetate or hydroxyethyl starch, but the results show that mannitol alone affected blood coagulation in 10 vol.% and 20 vol.% dilution.

As earlier experimental studies have indicated, HS has anticoagulant effects [16–19]. It is unclear, however, at which sodium chloride concentration level the fluid itself starts to impair coagulation. Our results support the previous findings of anticoagulant feature of HS. Furthermore, we discovered that the use of 3.5% saline resulted in weaker clot when compared to 0.9%, but similar difference

Table 4 Clotting time (CT) and maximum clot firmness (MCF)

FibTEM®	Mannitol $n = 10$	0.9% HS $n = 10$	2.5% HS $n = 10$	3.5% HS $n = 10$	*P* values	Control $n = 10$
CT (s)						
10%	86.6(20.1)	58.9(11.7)*	64.7(16.2)	84.6(89.1)	0.4316	69.1(21.0)
20%	171.9(197.3)	75.4(15.0)	63.8(30.2)	83.5(31.0)	0.0921	
MCF (mm)						
10%	10.2(3.0)#	11.8(3.0)	12.3(4.1)	10.6(3.3)	0.0084	13.6(6.0)
20%	6.8(2.5)*†	9.6(3.0)	11.5(3.3)	10.8(2.9)	<0.0001	

* $P < 0.05$ compared with control

# $P < 0.05$ compared with 2.5% HS

† $P < 0.05$ compared with 0.9% HS, 2.5% HS and 3.5% HS

Values are mean (SD); analyzed by repeated measure ANOVA followed with Tukey–Kramer' post hoc test, within each dilution group

was not found between 2.5% saline and 0.9% saline. This indicates that an increment in concentration potentates the negative effect which HS exerts on the coagulation process.

There are several earlier clinical studies comparing the use of mannitol and HS in neurosurgical patients both in the intraoperative setting and in the neurointensive care. However, none of these studies have compared the effects of mannitol and HS on whole blood coagulation. Instead, the focus has been on what effect these two solutions have on ICP, hemodynamics, and acid base balance [8–15]. The results of these studies have been difficult to interpret, and only in one study the osmolarity and the volume have been the same for both solutions [8]. In that particular study, Rozet and coworkers concluded that 20% mannitol and 3% saline had similar effect on brain relaxation during craniotomy. Both solutions caused a similar increase in blood osmolarity lasting for 6 h. Other studies, where either the osmolarity or the volume of the study solutions have been different, have shown that HS is equally effective or even better in reducing ICP or brain swelling.

Apart from the demonstrated differences in the effect on coagulation between mannitol and HS, the risk of certain clinically important side-effects of these solutions may influence the choice of solution in critically ill patients. Mannitol can cause hyponatremia and lactatemia [8]. Mannitol increases urine output which can lead to a negative fluid balance [10, 13]. A more serious complication of mannitol is acute renal failure [23, 24]. The osmotic response to mannitol treatment seems to be variable. Moreover, there is a high risk of a rebound increase in ICP after repeated doses of mannitol if the blood brain barrier (BBB) is damaged [25, 26]. HS boluses or infusions, on the other hand, can result in hypernatremia which often is associated with hyperchloremic metabolic acidosis. However, HS therapy rarely causes acute renal failure [7]. Although BBB is practically impermeable to HS and mannitol, an impaired BBB can cause a leakage of both sodium and mannitol into the cerebrospinal fluid [8].

As normal blood coagulation is essential in neurosurgery, any treatment method that could impair coagulation should be avoided. Our results indicate that from a hemostatic point of view 2.5% saline might be more suitable than equiosmolar 15% mannitol in neurosurgery or neurointensive care when fluid therapy is needed to reduce ICP or brain swelling. Obviously, there is a need to substantiate our in vitro findings clinically in large neurosurgical patient materials.

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V

Effect of Arterial Blood Pressure on the Arterial to End-tidal Carbon Dioxide Difference During Anesthesia Induction in Patients Scheduled for Craniotomy

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Background: Before obtaining results of arterial blood gas analysis in mechanically ventilated patients undergoing neurosurgery, the volume of ventilation is primarily adjusted according to endtidal CO_2 ($EtCO_2$). We characterized the impact of various arterial blood pressure changes on arterial PCO_2 ($PaCO_2$) to $EtCO_2$ differences ($PaCO_2$-$EtCO_2$) in patients anesthetized for craniotomy.

Methods: Seventy-two elective craniotomy patients were enrolled in this prospective study. Noninvasive blood pressure was measured before anesthesia induction. Anesthesia was induced with thiopental, rocuronium or suxamethonium, and fentanyl and was maintained with inhaled anesthetics or propofol and remifentanil. Volume-controlled ventilation was adjusted after intubation according to the clinical judgment. The first arterial blood gas analysis was taken just before the head pinning. Systolic, diastolic, and mean arterial blood pressures (MAP) and heart rate were registered after intubation every 5 minutes until the head pinning.

Results: $PaCO_2$-$EtCO_2$ correlated positively with percentage difference between MAP awake at arrival in operating room and during arterial CO_2 determination ($P = 0.0008$, $r = 0.388$). In analysis according to a MAP decrease of less than 20% (n = 17), 20% to 29% (n = 24), 30% to 35% (n = 16), and more than 35% (n = 15), the mean (SD) $PaCO_2$-$EtCO_2$ was greater in patients with MAP decrease of over 35% or 30% to 35% than in patients with MAP decrease of less than 20%. The mean (SD) absolute values of the $PaCO_2$-$EtCO_2$ were 0.96 (0.43) kPa or 0.85 (0.31) kPa versus 0.55 (0.24) kPa, respectively ($P < 0.05$ between categories). Mean $EtCO_2$ was not different in the various MAP difference categories, but $PaCO_2$ was greatest when MAP decreased more than 35% ($P < 0.05$).

Conclusions: There was a positive correlation between $PaCO_2$-$EtCO_2$ and MAP decrease shortly after induction of anesthesia. $PaCO_2$-$EtCO_2$ is recommended to be interpreted together with change in MAP during early phase of neuroanesthesia to guarantee optimal mechanical ventilation.

Key Words: hemodynamics, blood pressure, end-tidal carbon dioxide, arterial carbon dioxide, neurosurgery

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During general anesthesia, end-tidal CO_2 ($EtCO_2$) is routinely monitored to assess alveolar ventilation and arterial CO_2 partial pressure ($PaCO_2$). Owing to the fact that $PaCO_2$ is a strong regulator of cerebral blood flow, capnography has an important value in intracranial surgery.[1] However, estimation of $PaCO_2$ by monitoring $EtCO_2$ is not invariably reliable in particular during hypotension, and capnography monitoring is recommended to be carried out in association with regular analysis of arterial blood gases during neurosurgery.[2]

The main factors that modulate the $PaCO_2$ to $EtCO_2$ difference ($PaCO_2$-$EtCO_2$) are related to alveolar circulation and ventilation during anesthesia.[3–6] In the clinical setting, arterial blood pressure becomes an important indicator of both systemic and pulmonary perfusion. In experimental circulatory shock changes, which occur in cardiac output are reflected in the exhaled CO_2 concentration.[7] A positive correlation between cardiac output and $EtCO_2$ has also been shown in patients undergoing vascular surgery.[8,9]

The impact of systemic circulation on $PaCO_2$-$EtCO_2$, however, is far more complex. Russell and Graybeal[10] observed a linear correlation between the mean and diastolic arterial pressures with $PaCO_2$-$EtCO_2$ difference in mechanically ventilated neurointensive care patients, but this was not the case in anesthetized nonneurosurgical patients.[11,12] Furthermore, $EtCO_2$ has been reported to be greater than $PaCO_2$ in 4% to 13% of patients during neurosurgery without consistent explanation.[13] Increment

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of fraction of inspired oxygen (FiO_2) enlarges $PaCO_2$-$EtCO_2$.[14] It is also known that coexisting lung disease, the American Society of Anesthesiologists Physical Status classification, or positioning of the patients modulate $PaCO_2$-$EtCO_2$.[12,13]

In this study, our objective was to determine to what extent arterial blood pressure changes affects $PaCO_2$-$EtCO_2$ during the early phase of neuroanesthesia. The secondary aim was to find clinically significant changes in arterial blood pressure that could guide adjustment toward optimal ventilation, before arterial blood gas is analyzed.

METHODS

After the study protocol had been approved by the institutional ethics committee, written informed consent was obtained from 76 patients who were scheduled to undergo craniotomy. Those individuals with a history of pulmonary or cardiac valve decease, decrease state of consciousness or who already were with an endotraceal tube or who had had emergency surgery were excluded from the trial.

On the morning of their operation, the patients were given their prescribed antiepileptic and antihypertensive drugs, excluding ACE inhibitors and diuretics. About 1 hour before being taken to the operating theatre, they received oral diazepam (5 to 15 mg). Upon arrival there, an intravenous drip of acetated Ringer solution was started into which all drugs would be injected. Noninvasive blood pressure was then taken with an automated device, which also measured mean arterial pressure (MAP). In addition, it monitored heart rate, lead II ECG, and peripheral oxygen saturation (ADU or Aisys Integrated Datex-Ohmeda Anesthesia Monitor, Datex-Ohmeda Inc./GE Healthcare, Madison).

When lying supine, the patients were preoxygenated (FiO_2 1.0, 6 L/min) and then after the administration of glycopyrrolate and fentanyl, anesthesia was induced with thiopental. Endotracheal intubation was facilitated by either suxamethonium or rocuronium. Thereafter, anesthesia was maintained with sevoflurane or isoflurane or propofol with or without N_2O and remifentanil. The patients were connected to a ventilator receiving a fresh gas flow of 3 L/min (Datex-Ohmeda ADU- or Aisys General Electric). Positive end-expiratory pressure was set to zero. FiO_2 and other settings would be selected by the anesthesiologist.

A cannula (20 G/1.1 × 45 mm BD Arterial Cannula, Singapore) was inserted into the radial artery for sampling of blood gas and for blood pressure measurement and connected to a disposable transducer set (BD Cabarith PMSET 1DT-XX, Singapore), zeroed at the level of the foramen of Monro.

Immediately before the patients head was pinned, an artery sample for analysis of blood gas was taken and the value of $EtCO_2$ recorded which was to be used for calculation of $PaCO_2$-$EtCO_2$. Hemodynamic parameters were registered at 5 minutes intervals after the intubation and immediately before pinning of the head.

Ventilatory and airway gases were sampled from the breathing circuit by means of a connection piece fitted with a filter (Hygroba "S," Mallinckrodt Dar, Mirandola, Italy), which was attached to a flexible tube (DAR Brathing system, Catheter Mount, Mallinckrodt Dar, Mirandola, Italy) 20 cm from the upper end of the tracheal tube. Inspiratory and expiratory tidal volumes (Vt), minute ventilation (MV), respiration rate, peak and plateau airway pressures, lung compliance, the ratio of the duration of inspiration to the duration of expiration, and airway gas (FiO_2, $EtCO_2$, end-tidal O_2, end-tidal sevoflurane/isoflurane minimum alveolar concentration) parameters were recorded at the beginning of the mechanical ventilation, and before the head pinning without changing patient's position or ventilator settings (Datex-Ohmeda AS/3 AM ADU-Aisys General Electric USA Spirometry). A probe was positioned into the nasopharynx for measurement of temperature (Mona-therm, Tyco Healthcare, Pleasanton). $EtCO_2$ was measured using infrared technology in expired gas sampled through a side-stream spirometry (Side-stream spirometry, Datex-Ohmeda AS/3 AM. The monitors were calibrated at regular intervals during the study using a calibration gas (Quick CAL calibration gas, GE Healthcare Finland Oy, Helsinki, Finland).

PaO_2, $PaCO_2$, and pH, uncorrected for temperature, were measured with a blood gas analyzer (ABL 825, Radiometer Medical A/S, Copenhagen, Denmark). Standard serum bicarbonate concentration and standard base excess (BE) were analyzed using the classical Henderson-Hasselbalch equation and the Siggaard-Andersen nomogram.[15] The total doses of all drugs given during the study were also recorded.

Statistical Analysis

The patient characteristics are shown as mean (± SD) or numbers. Linear regression and analysis of variance (ANOVA) with LSD test were applied as appropriate. $P < 0.05$ was considered significant. The analysis was done by StatView PowerPC Version 5.0, SAS Institute Inc.

RESULTS

Seventy-two out of 76 craniotomy patients that were screened were enrolled in the study. Patient characteristics and indications for craniotomy are presented in Table 1.

The mean (SD) time that lapsed between endotracheal intubation and the initial arterial blood gas sampling was 12.2 (5.6) minutes. A positive correlation was seen between the percentage change in MAP and $PaCO_2$-$EtCO_2$ value. The greater the percentage change in MAP, the greater was the $PaCO_2$-$EtCO_2$ ($P = 0.0008$, $r = 0.388$) (Fig. 1). There was no correlation between the time the patient was ventilated and the $PaCO_2$-$EtCO_2$ ($P > 0.05$). None of the $PaCO_2$-$EtCO_2$ was negative. The mean (SD) minute ventilation and tidal volume were similar during the time of endotracheal intubation and

TABLE 1. Patients' (n = 72) Characteristics and Indications for Surgery and the Subgroup Analysis According to the MAP Difference

	All Patients n = 72	MAP%diff < 20 n = 17	MAP%diff 20-29 n = 24	MAP%diff 30-35 n = 16	MAP%diff > 35 n = 15	*P*
Age (y)	54.7 (12.5)	54.0 (13.3)	50.5 (14.0)	58.3 (10.4)	58.2 (9.6)	0.157
Weight (kg)	76.2 (14.2)	75.5 (14.0)	76.4 (13.1)	77.4 (14.6)	75.3 (16.8)	0.974
Length (cm)	170.2 (9.6)	170.4 (9.3)	169.8 (8.9)	168.3 (10.7)	172.7 (10.3)	0.657
Smoking (n)	16, 22.2%	4, 23.5%	5, 20.8%	3, 18.8%	4, 26.7%	0.955
Coronary disease (n)	6, 8.3%	2, 11.8%	1, 4.2%	2, 12.5%	1, 6.7%	0.747
Hypertension (n)	29, 40.3%	4, 23.5%	7, 29.2%	9, 56.3%	9, 60.0%	0.062
Diabetes mellitus (n)	5, 6.9%	0, 0%	2, 8.3%	0, 0%	3, 20.0%	0.090
Infratentorial tumor (n)	4, 5.6%	0, 0%	1, 4.2%	2, 12.5%	1, 6.7%	0.459
Supratentorial tumor (n)	34, 47.2%	12, 70.6%	12, 50.0%	4, 25.0%	6, 40.0%	0.063
AVM (n)	2, 2.8%	2, 11.8%	0, 0%	0, 0%	0, 0%	0.084
Nonruptured aneurysm (n)	25, 34.7%	2, 11.8%	7, 29.2%	8, 50.0%	8, 53.3%	0.042
Other operations (n)	7, 9.7%	1, 5.9%	4, 16.7%	2, 12.5%	0, 0%	0.339

Values are mean (SD) or number (n). ANOVA or χ^2.
AVM indicates arteriovenous malformation.

pinning of the head, 87.8 (17.5) mL/kg/min and 7.21 (1.24) mL/kg versus 89.8 (16.3) and 7.25 (1.15), respectively ($P > 0.05$). However, the mean (SD) $EtCO_2$ was higher after intubation than before pinning of the head, 4.85 (0.53) kPa versus 4.22 (0.43), respectively ($P < 0.05$).

After completion of the study, the patients were divided into 4 groups according to the difference in MAP between MAP awake at arrival in the operating room and MAP during $PaCO_2$ determination:

1. Group 1 included MAP decrease less than 20% (G-1 group, n = 17),
2. Group 2 included MAP decrease of 20-29% (G-2 group, n = 24),
3. Group 3 included MAP decrease of 30-35% (G-3 group, n = 16) and
4. Group 4 included MAP decrease more than 35% (G-4 group, n = 15).

The $EtCO_2$ remained unchanged between the subgroups ($P = 0.811$) but $PaCO_2$ was found to be greater in G-4 or G-3 groups than in G-2 or G-1 groups ($P = 0.036$). Minute ventilation and tidal volume were similar between the subgroups ($P = 0.248$ and $P = 0.277$, respectively) (Table 2).

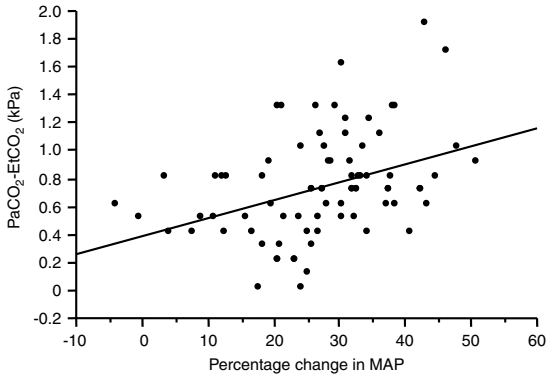

FIGURE 1. Correlation analysis comparing ($PaCO_2$-$EtCO_2$) with (percentage change in mean arterial blood pressures or MAP) ($P = 0.0008$, $r = 0.388$). Pearson correlation coefficient.

$PaCO_2$-$EtCO_2$ in the subgroups is presented in Table 2 and Figure 2. The mean $PaCO_2$-$EtCO_2$ was greater in G-4 group or G-3 group than in G-1 group. The mean (SD) absolute values of $PaCO_2$-$EtCO_2$ were 0.96 (0.43) kPa or 0.85 (0.31) kPa versus 0.55 (0.24) kPa, respectively ($P < 0.05$ between the groups).

Side stream spirometry, airway gas parameters, or arterial partial O_2 pressure (PaO_2) did not differ between the subgroups. Neither did a nasopharyngeal temperature between the subgroups ($P > 0.05$). The mean pH value ranged within normal laboratory reference range, from 7.41 to 7.45, and was statistically different between the subgroups ($P = 0.008$). All measurements were obtained when patients temperature were between 35.0 to 36.7°C. There was a significant ($P = 0.01$) negative correlation between FiO_2 and $PaCO_2$-$EtCO_2$, whereas no correlation between PaO_2/FiO_2 (P/F) ratio change and change in MAP was found.

MAP in the subgroups is presented in Figure 3. The MAP before induction was higher in all groups as compared with MAP values before head pinning ($P < 0.05$). The MAP was higher in group G-4 than in G-2 before induction of anesthesia (MAP awake) whereas the MAP at head pinning was higher in group G-1 than in G-4 ($P < 0.05$) (Fig. 3). The patients' heart rate remained in acceptable clinical limit during the study period.

The doses of drugs used in anesthesia were comparable between the subgroups (Table 3). The cumulative doses of propofol or remifentanil until the time of head pinning did not differ between the subgroups either ($P > 0.05$). Eight patients received phenylephrine (mean dose 0.135 mg) i.v. during the study period. Otherwise no vasoactive agents were administered.

According to the neurologic condition we observed that number of nonruptured aneurysm between the groups was different (Table 1). Other than that, we did not observe statistically significant differences in patient's

TABLE 2. Respiratory Parameters and Subgroup Analysis According to the MAP Difference

	MAP%diff < 20 n = 17	MAP%diff 20-29 n = 24	MAP%diff 30-35 n = 16	MAP%diff > 35 n = 15	*P*
MV/kg (ml/kg/min)	92.0 (11.1)	94.0 (16.7)	85.1 (18.9)	85.7 (17.0)	0.248
TVet/kg (ml/kg)	7.61 (1.04)	7.36 (1.18)	6.93 (1.31)	7.00 (0.97)	0.277
RR (times/min)	11.9 (1.3)	12.3 (1.0)	11.8 (1.3)	11.7 (1.3)	0.481
FiO_2 (0-1.0)	0.50 (0.06)	0.49 (0.06)	0.48 (0.06)	0.48 (0.05)	0.821
EtO_2 (0-1.0)	0.47 (0.06)	0.46 (0.06)	0.45 (0.06)	0.44 (0.05)	0.547
PaO_2 (kPa)	27.1 (7.1)	25.5 (9.2)	22.5 (7.5)	25.1 (8.7)	0.454
$EtCO_2$ (kPa)	4.21 (0.49)	4.17 (0.39)	4.22 (0.49)	4.31 (0.39)	0.811
$PaCO_2$ (kPa)	4.76 (0.60)	4.84 (0.51)	5.07 (0.59)	5.25 (0.37)	0.036
$PaCO_2$-$EtCO_2$ (kPa)	0.55 (0.24)	0.67 (0.41)	0.85 (0.31)	0.96 (0.43)	0.009
Compliance (mL/cmH_2O)	n = 15	n = 21	n = 14	n = 15	0.616
	56.5 (11.8)	62.7 (14.5)	58.1 (13.4)	56.7 (22.7)	
Peak airway pressure (cmH_2O)	17.7 (3.5)	17.5 (3.7)	16.0 (2.0)	17.3 (4.4)	0.508
Plateau airway pressure (cmH_2O)	12.6 (4.2)	12.0 (3.1)	12.4 (1.4)	13.1 (3.9)	0.784
pH (normal 7.35-7.45)	7.45 (0.04)	7.43 (0.03)	7.43 (0.03)	7.41 (0.02)	0.008
BE (normal −2.5-+2.5)	0.94 (1.37)	0.10 (1.84)	1.00 (1.51)	0.39 (1.71)	0.263

Values are mean (SD) or number (n). ANOVA or χ^2.
MV indicates minute ventilation; RR, respiratory ratio; TV, tidal volume.

characteristics in the subgroup analysis according to the MAP difference.

DISCUSSION

A significant positive correlation occurred between the percentage change in MAP and $PaCO_2$-$EtCO_2$ in the immediate period after anesthesia induction in a heterogeneous craniotomy patient population. $PaCO_2$-$EtCO_2$ describes the error in estimating $PaCO_2$ from acute measurement of $EtCO_2$. The results indicate that the decrease in MAP plays a significant role in $PaCO_2$-$EtCO_2$ during the early phase of anesthesia. $PaCO_2$-$EtCO_2$ was greater in patients with a MAP decrease over 30% than in patients with a MAP decrease less than 20%. This suggests that more than 30% decrease in MAP is clinically important and should be taken into account when optimal ventilation is adjusted before arterial blood gas sampling.

Our findings are in accordance with earlier studies in neurosurgical patients.[2,10,13] Monitoring of $EtCO_2$ as an estimate of $PaCO_2$ is misleading, and, thus, optimal ventilation in the start of anesthesia must be confirmed by arterial blood gas analysis. However, the settings of the ventilator have to be adjusted according to the $EtCO_2$ in the early phase of mechanical ventilation. At this stage, anesthesiologist has to take into account the patient's intracranial pathology, method of anesthesia, estimation of systemic and pulmonary circulation, and alveolar ventilation.

The patients' minute ventilation did not differ between the subgroups. Nevertheless, slightly lower minute ventilation values were measured in G-3 and G-4 than in G-2 and G-1 group. This may suggest that the mechanical ventilation was adjusted by the anesthesiologist exclusively according to the $EtCO_2$ value. In fact, the

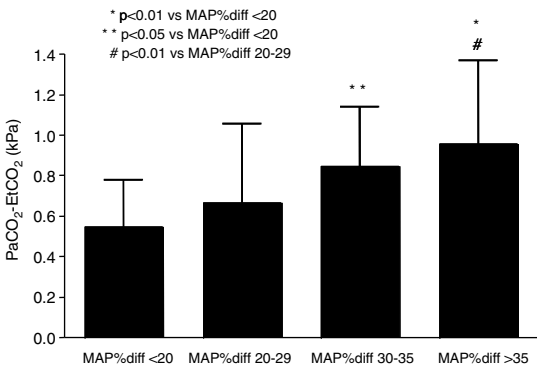

FIGURE 2. Mean (SD) $PaCO_2$-$EtCO_2$ between mean arterial blood pressures MAP%diff groups.

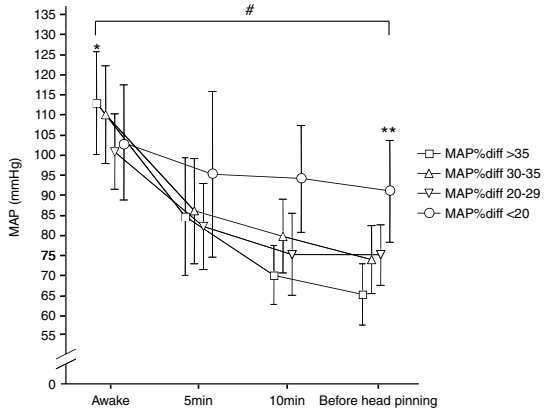

FIGURE 3. Mean arterial blood pressures (MAP) in MAP%diff groups at awake, 5 minutes, 10 minutes, and before head pinning. #$P<0.05$ MAP awake versus MAP before head pinning (within groups). *$P<0.05$ MAP%diff >35 versus MAP%diff 20–29 at awake. **$P<0.05$ MAP%diff >35 versus MAP%diff <20 before head pinning.

TABLE 3. Anesthetics Used and Patients' Temperature in the Subgroup Analysis According to the MAP Difference

	MAP%diff < 20 n = 17	MAP%diff 20-29 n = 24	MAP%diff 30-35 n = 16	MAP%diff > 35 n = 15	*P*
Temperature (°C)	n = 17 36.2 (0.4)	n = 22 36.2 (0.3)	n = 16 36.1 (0.3)	n = 15 36.0 (0.5)	0.315
Propofol (mg/kg)	1.06 (0.80)	0.75 (0.83)	0.48 (0.54)	0.71 (0.82)	0.205
Remifentanyl (μg/kg)	3.18 (4.24)	3.24 (5.78)	3.06 (6.74)	2.73 (4.22)	0.993
Tiopental (mg/kg)	4.76 (1.20)	5.21 (1.39)	4.37 (1.10)	5.14 (1.84)	0.264
Fentanyl (μg/kg)	4.68 (2.11)	5.28 (1.52)	5.58 (1.51)	5.47 (1.53)	0.428
Rocuronium (mg/kg)	n = 16 0.70 (0.11)	n = 21 0.66 (0.13)	n = 16 0.67 (0.15)	n = 15 0.71 (0.12)	0.649
Anesthesia (n)					
Propofol	11	11	7	7	
Propofol + N_2O	4	5	4	3	
Isoflurane or Sevoflurane	2	8	5	5	0.787

Values are mean (SD) or number (n). ANOVA or χ^2.

patients were similarly ventilated according to the $EtCO_2$ in the study groups, even though $PaCO_2$ was increased in patients with pronounced decrease in MAP.

The contribution of MAP on $PaCO_2$-$EtCO_2$ under conditions of this study is furthermore supported by the fact that pulmonary artery pressure is inversely related to the $EtCO_2$ to $PaCO_2$ difference in anesthetized patients.[15] Furthermore, our observation is of clinical importance as cerebral CO_2-reactivity is impaired during hypotension.[1] Therefore, hypercapnia-induced cerebral vasodilatation, or hypocapnia-induced cerebral vasoconstriction may be severely impaired if the patient becomes hypotensive.[1] In clinical practice this indicates that the cerebral blood flow, and thus, the intracranial pressure, cannot be affected by modifying the $PaCO_2$ tension in hypotensive patients. Potential hypoventilation may be avoided in neurosurgical patients with marked decrease of MAP by increasing minute ventilation more than indicated by $EtCO_2$.

Earlier studies indicate that inhalation anesthetics may reduce hypoxic pulmonary vasoconstriction and increase shunt dead space.[16–18] However, there are also studies contradicting this.[19,20] Therefore, the clinical relevance of the effect of inhalation anesthetics have on hypoxic pulmonary vasoconstriction remains controversial. In contrast to inhalation anesthetics, propofol has been shown to have a neutral effect on hypoxic pulmonary vasoconstriction or may even potentiate it[21,22] particularly if compared with the effect of volatile anesthetics.[23] In this study, the method of anesthesia was not standardized. It was chosen according to the patient's clinical condition together with CT or MRI findings. For example, if the patient had elevated intracranial pressure or history of postoperative nausea and vomiting, volatile anesthetics were not used. However, the type of anesthesia used was comparable between the subgroups.

This study has some limitations. The baseline blood pressure was measured noninvasively followed by invasive arterial pressure measurements at level of foramen Monroe. As these 2 different ways of measuring MAP were not done at the same time, we lack the data concerning their comparability. However, this procedure reflects the standard practice in our clinic. Noninvasive blood pressure before anesthesia induction is an important indicator of the patient's circulation and essential in the process of optimization of hemodynamics later during anesthesia. Our observation of the change of MAP may also be slightly exaggerated as in supine position, head slightly elevated, the difference between systolic blood pressure at brain and heart level is approximately 5 to 10 mm Hg. Furthermore, in our study, the patients were preoxygenated with 100% oxygen during induction of anesthesia before intubation and thereafter FiO_2 (mean approximately 0.5) was decided by the anesthesiologist. It is known that the increment of FiO_2 will increase $PaCO_2$-$EtCO_2$.[14] This effect, however, is minimal. Ito et al[14] reported that the change at its maximum was only 0.2 kPa when FiO_2 was increased from 0.21 to 0.97. Moreover, in our study there was significant ($P = 0.01$) negative correlation between FiO_2 and $PaCO_2$-$EtCO_2$. Rusca et al[24] state that 100% oxygen leads to lung atelectasis and, consequently an increase in intrapulmonary shunt. They did not, however, report what effect atelectasis formation had on $PaCO_2$-$EtCO_2$. Our observation of no correlation between P/F ratio change and MAP decrease may indicate that MAP affects CO_2 difference independently of atelectasis.

Cardiac output, pulmonary artery pressure, and pulmonary shunting were not measured in this study. Therefore, the physiologic explanations of our findings remain speculative. However, the results do shed light on the controversial view of the effect of MAP on $PaCO_2$ to $EtCO_2$ difference during early period of neuroanesthesia. The conflicting results of earlier $PaCO_2$-$EtCO_2$ studies may have been biased by the limited cardiovascular monitoring or unreported alterations in hemodynamics.[2,10,13] Furthermore, in contrast to earlier studies, we did not find greater $EtCO_2$ than $PaCO_2$ values, indicating that proper ventilator settings were used, which gives reliability in our findings. Nevertheless, the relationships between hemodynamical alterations and $PaCO_2$ to $EtCO_2$ difference need future research.

In summary, the effect of a possible decrease in arterial blood pressure should be taken into consideration

when mechanical ventilation is optimized before obtaining results of arterial blood gas analysis in the early phase of neuroanesthesia. In this way, potential hypoventilation may be avoided in neurosurgical patients with marked (> 30%) decrease of MAP.

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VI

Prone versus sitting position in neurosurgery – differences in patient hemodynamics and in fluid administration

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Abstract

Background

General anesthesia exposes patient to hemodynamic alternations both in prone and sitting position. As the comparison of the sitting and prone position in neurosurgery is scarce, we aimed to evaluate hemodynamic profile during stroke volume-directed fluid administration in patients undergoing neurosurgery either in sitting or prone position.

Methods

Thirty patients in prone and 28 in sitting position in two separate prospective trials were randomized to receive either Ringer's Acetat (RAC) or hydroxyethyl starch (HES 130 kDa/0.4) for optimization of stroke volume. After combining data from these two trials the two-way analysis of variance was performed to compare patient hemodynamic profile between the two positions and to evaluate differences between RAC and HES consumption.

Results

To achieve comparable hemodynamics during surgery higher mean cumulative dose of RAC than HES was needed (678±390 ml vs 455±253 ml, respectively, $p < 0.05$) However, when fluid consumption was adjusted with weight, statistical difference was lost. Fluid administration was similar weather patient was in prone or sitting position. Mean arterial pressure was lower and cardiac index and stroke volume index was higher overtime when patient was in sitting position.

Conclusion

Sitting position does not require excess fluid treatment compared to prone position. HES is slightly more effective than RAC in achieving comparable hemodynamics, but difference might be explained by patient weight. With goal directed fluid administration and moderate use of vasoactive drugs it is possible to achieve stable hemodynamics in both position.

Introduction

Neurosurgery in general anesthesia exposes patient to hemodynamic alternations, i.e hypotension and changes in cardiac function, both in prone and sitting position [1-4]. Regarding intraoperative fluid administration, it was earlier thought that colloids are superior to crystalloids in increasing hypovolemic patients' intravascular but recent findings show that difference might notably smaller than was earlier believed [5,6]. Similarly, a slightly better capability to improve cardiac stroke volume has been reported with colloids [5]. Recent controversies regarding colloids safety, however, have diminished their use [7,8]. Some neurosurgical procedures can be performed either in sitting or prone position, but comparison of these two positions is scarce [9].

The aim of the current study was to use the prospectively collected data on hemodynamics and fluid volumes in the sitting and prone position and to find out the possible differences between sitting and prone position in patient's hemodynamic profile and stroke volume-directed fluid administration.

Methods

This study consists of two separate patient enrolments. In the first part, adult patients scheduled for elective primary neurosurgery in the prone position at the neurosurgical department of Helsinki University Central Hospital were included in the study. The second phase comprised patients scheduled for elective craniotomy in the sitting position at the same institute. The Ethics Committee for Surgery of the Hospital District of Helsinki and Uusimaa approved both trials (Ethics Committee Numbers 13/13/03/04/09 HUS and 396/E9/2007). Additionally, the National Agency of Medicines in Finland accepted the study protocols (EudraCT Ref. No 2009-009893-28 and EudraCT ref. no. 2007–007106-30). All patients gave their written, informed consent to partake in the study.

Patients younger than 18 years old, with body mass index (BMI) > 36 kg/m^2 in the prone position or > 40 kg/m^2 in the sitting position, congestive heart failure, other than sinus rhythm in electrocardiography (ECG), renal failure (plasma creatinine > 120 μmol/l), hepatic failure, anemia (hemoglobin < 100 g/l), and thrombocytopenia (platelet count < 100x10^9/l) were excluded. Additionally, expected use of mannitol in sitting position resulted in exclusion.

Patients received their antihypertensive mediations excluding the angiotensin-converting enzyme inhibitors preoperatively. Additionally, oral diazepam 5-20 mg served as a premedication.

Before the anesthesia induction a basal Ringer's acetate (RAC) infusion was commenced at the rate of 3 ml/kg/h (an additional 40 mmol/l of NaCl were added to RAC basal infusion of patients in a sitting position). All patients received preoperative antibiotics (cefuroxime or vancomycin).

Anesthesia was induced in the supine position with fentanyl 2–7 μg/kg and either thiopental 2–7 mg/kg or propofol 2–3 mg/kg. All patients received glycopyrrolate 0.2 mg. Rocuronium (0.5–0.9 mg/kg) was used for muscle relaxation. Anesthesia was maintained with sevoflurane (1 MAC) in a mixture of nitrous oxygen and air and additional fentanyl boluses or a continuous infusion of propofol (4–10 mg/kg/h) and remifentanil (0.125–0.25

μg/kg/h) with patients operated on in prone position and with a continuous infusion of propofol (4–12 mg/kg/h) and remifentanil (0.05–0.45 μg/kg/h) with patients in sitting position with the permission the use sevoflurane to treat severe hypertension.

After tracheal intubation, a volume controlled mechanical ventilation without positive end-expiratory pressure (PEEP) was started (tidal volume 8-10 ml/kg body weight and rate of 10-15/min) targeting to a normoventilation ($PaCO_2$ 4.5-5.0 kPa).

Anesthesia monitoring prior intubation included noninvasive arterial blood pressure, ECG (lead II) and arterial saturation of oxygen (SpO_2). After tracheal intubation, monitors of nasopharyngeal temperature, side-stream spirometry (Side stream®, Datex-Ohmeda Inc, GE Healthcare, Madison, WI, USA) and end-tidal concentration of carbon dioxide were applied. Additionally, a 20G arterial catheter (Becton Dickinson, Temse, Belgium) was inserted into the radial artery for invasive monitoring of arterial pressures and to obtain blood samples.

To continuously monitor cardiac output (CO), cardiac index (CI), stroke volume (SV), stroke volume index (SVI), and stroke volume variation (SVV), the Vigileo System (Edwards Lifesciences) with software version 3.02 was applied by connecting it to arterial line with a pressure transducer set (FloTrac; Edwards Lifesciences, Irvine, CA, USA) zeroed at the heart level. For patients operated on in sitting position an additional set was applied and zeroed at the level of foramen Monroi for the measurement of systolic, diastolic, and mean arterial pressure (MAP).

Both study sequences (prone and sitting position) had the same protocol for the study fluid administration. Patients were randomly assigned (using closed envelopes drawn in sequential order by the primary investigators) in blocks of three to receive one of the following study solutions:

1. 6% HES solution (Voluven®; 60 mg/ml, average molecular weight 130 kDa, molar substitution ratio 0.4, pH 4.0–5.5, contents Na^+ 154 mmol/l, Cl^- 154 mmol/l; Fresenius Kabi, Bad Homburg, Germany) (HES group, n = 15 in prone position + 15 in sitting position); and

2. Ringer's acetate solution (Ringer-acetate®, pH 6.0, contents Na^+ 130 mmol/l, Cl^- 112 mmol/l,
K^+ 4 mmol/l, Ca^{++} 2 mmol/l, Mg^{++} 1 mmol/l, $CH3COO^-$ 30 mmol/l; Fresenius Kabi) (RAC group,
n = 15 in prone position + 13 in sitting position).

After anesthesia induction, while lying supine, all patients received an initial 200 ml bolus of the study fluid over 2–4 min, and hemodynamic measurements were performed before and 3 min after the administration of study fluid. A new bolus of 100 ml over 2–4 min was given immediately after the hemodynamic measurements, until SV did not increase more than 10 %. The hemodynamic measurements were performed 3 minutes after each bolus.

Thereafter, patients were positioned for surgery. Patients in sitting position were dressed in an antigravity suit prior positioning. Registration of hemodynamic parameters took place at 5 min intervals during surgery. If SV decreased more than 10% from the value obtained in the supine position, further study fluid boluses of 100 ml were administered. If the SV did not increase with three consecutive boluses, the volume expansion was stopped and the patient was considered as non-responder. Hemodynamic parameters were registered also at the end surgery and after patient positioning back to supine position.

The target for MAP was 60 mmHg or higher at the brain level. Boluses of phenylephrine (0.05–0.1 mg) or ephedrine (5–10 mg) were given if MAP was below 60 mmHg despite the study fluid administration. A phenylephrine or norepinephrine infusion was started whenever MAP remained below 60 mmHg for more than 5 min.

Basal infusion of RAC (with 0,9% NaCl supplement if required) continued at the rate of 1ml/kg/h until the first postoperative morning. Registration of urine output and fluid balance took place at pre-determined intervals.

Patient positioning

In prone position bilateral chest supports were used and patient's head was placed on a headrest (Prone View Protective Helmet System; Dupaco, Oceanside, CA, USA), or fixed

with the Sugita pin head-holder device (Sugita Head Frames; Mizuho America, Union City, CA, USA).

In sitting position the patient's upper body was elevated 50–100 degrees, head attached to a head holder device (Mayfield; Integra Life Sciences, Plainsboro, NJ, USA) and tilted 20–30 degrees forward with the patient sitting with knees slightly flexed on a pillow. For the detection of possible venous air embolism, the probe of pre-cordial Doppler (Versatone D8 Perioperative Doppler; Med-Sonics Inc, Mountain View, CA, USA) was placed over the right fifth intercostal space lateral to sternum.

This study consists of two previously executed trials; stroke volume-directed administration of study fluids with patients operated on in prone position and, another trial in which different group of patients were operated on in sitting position. Results of differences between the study fluids in achieving stable hemodynamics within one surgery position and also the effect these two fluids have on patient blood coagulation measured by Rotem® analysis have been reported earlier in two separate publications [10,11].

Statistics

We performed this analysis *post hoc* by combining the data of the study fluid usage, patient's hemodynamics and basic patient demography from the two previously executed trials.

Two-way variance of analysis (ANOVA) was used to test differences between the study groups (prone vs sitting position; HES vs RAC). When needed, T-test was used to determine differences between two groups. Results are shown as mean and standard deviation (SD). $P < 0.05$ was considered statistically significant.

Hemodynamic data is shown graphically as means at time points from 0 to 230 at 5-minute intervals. If needed, the difference between curves could have been tested using Sign Test. In all cases the P-value would be $P<0,000001$ or less.

Results

Data from 58 patients (30 patients in prone and 28 in sitting position) were analyzed after assessment of 72 patients for eligibility between August 2009 and March 2011. Exclusion flowcharts have been reported in conjunction with the original reports of both individual studies [10,11]

The combined data shows, when divided in two groups according to the study fluid (RAC vs HES) that patients in RAC group had higher weight, height and higher body surface area (BSA). However, the body mass index (BMI) was equal in both groups (table 1). Cumulative mean dose of basal RAC was similar between the study groups. When divided according to the surgery position, the groups were comparable with the exception that patients in the sitting position were younger ($p < 0.01$) and had higher ASA classification ($p<0.001$) (table 2).

The mean cumulative doses of RAC (prone and sitting position combined) to optimize the fluid filling at 30 min and end of surgery was higher than dose of HES (452±155 ml vs 341±109 ml and 678±390 ml vs 455±253 ml, respectively) (table 3). When RAC and HES doses were adjusted with patient's weight the mean doses at 30 min and at the end of surgery for RAC still remained higher than those of HES (5.5±1.6 ml/kg vs 4.8±1.7 and 8.2±4.2 ml/kg vs 6.4±3.6 ml/kg, respectively), but statistical significance was lost. RAC and HES doses before positioning were similar in both positions.

Patients in sitting position had lower MAP overtime and higher CI and SVI than patients in prone position (Figure 1). Regarding the patients position during surgery, there was now difference in study fluid consumption between the two groups (table 3).

Discussion

This study shows that sitting position in neurosurgery does not require excess intravenous fluid administration in comparison with surgery done in prone position. Moreover, the benefit of using HES solutions to optimize patient hemodynamics instead of RAC is only marginal. With goal directed fluid administration and moderate use of vasoactive drugs it is possible to achieve stable hemodynamics in both position.

Neurosurgery in sitting position was more popular in 70's and 80's as it is today. Even today, there is a great variation in its occurrence between the countries where sitting position is used [12]. Sitting position is still often considered preferable when operating on lesions in posterior cranial fossa [9,13]. Advantages of sitting position is decreased intracranial pressure, and a clearer operating field due to gravity forced downward drainage of blood and cerebrospinal fluid. Surgery in a sitting position also decreases the incidence of cranial nerve damage [13]. Sitting position is known to cause hypotension and decrease in cardiac function, setting a challenge to neuroanesthesia in guaranteeing sufficient cerebral blood pressure and oxygen delivery. Another concern of sitting position is venous air embolism (VAE), which has an incidence of 1.6-50%, number being lower in semisitting position [1,3,10,14-17]

Historically, it was believed that colloids capability to increase intravascular volume in hypovolemic patients would be 2-3 fold compared to crystalloids, but recent findings indicates that 1:1 to 1:1.5-1.8 is the more accurate ratio [5,6,18]. Similar ratio was found in elective neurosurgery patients [10,11]. Our result showed a ratio of 1:1.5 between HES and RAC in achieving comparable hemodynamics, which is in line with the earlier findings. Interestingly, even this might be an overestimation, because when adjusted with patients' weight, difference in HES and RAC doses can be seen (1:1.3), but it is not statistically significant anymore.

In this current study, we demonstrated that the previously reported decrease in cardiac function, when prone position is applied, can be prevented with stroke volume-directed fluid administration and moderate use of vasoactive drugs [19-22]. Moreover, with similar fluid and vasoactive drug administration, patients in sitting position maintained good cardiac function after positioning and decrease in cardiac function did not occur [1]. Although MAP

remained adequate throughout the surgery, it was lower in sitting position, confirming tendency of hypotension in this position. Patients in the sitting position in our study were antigravity suits, which in part prevents pooling of the blood in the lower extremities and, thus, help stabilizing patient hemodynamics. Patients in sitting position had higher CI than patients operated on supine. That possible reflects to patients in sitting position being healthier and younger. Noteworthy is that anesthesia was maintained with propofol in sitting position while mainly volatile anesthetics were used in supine position. This adds to the complexity of CI interpretation [23].

As there is great variety in methods of measuring cerebral perfusion pressure (CPP) in neurosurgical patients, it should be noted that we measured the MAP at the level of foramen Monroi giving us more accurate estimate of cerebral perfusion pressure (CPP). If MAP would have been measured at the level of heart, would the values be 15-25 mmHg higher and reflecting more to the systemic blood pressure [24,25].

Discussion about safety of artificial colloids is ongoing. Increased risk of mortality and kidney failure in critically ill patients is associated with the use of hydroxyethyl starch and related consensus statement have decreased use of artificial colloids dramatically [7,8,26] . Recent years have seen plethora of reports trying to determine whether these risk are factual in other patient population as well (i.e. general surgery patients). Possible negative effect colloids have on coagulation is important to bear in mind when treating neurosurgical patients as normal coagulation capacity in this patient population is essential [27]. Although the initial filling dose of study fluids where not enough to stabilize hemodynamics before positioning, the total doses of intraoperative fluids in our study were low and only minor difference in doses was seen between HES and RAC. In that light, it would be difficult to recommend HES use also with patients operated on in sitting position in this patient population.

We conclude, that neurosurgery in sitting position does not require excessive fluid administration compared to prone position in achieving stable hemodynamics. Possible minor benefit gained from using HES to diminish fluid load is counteracted by the possible harms associated with the use of artificial colloids.

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Table 1

Patients characteristics when diveded according to the study fluid (HES or RAC).

	HES	RAC	p
M/F	6/23	15/14	< 0.05
Age (years)	48±16	48±19	ns
Weight (cm)	73.3±12.9	82.0±15.4	< 0.05
Height (kg)	165.8±8.8	171.6±9.3	< 0.05
BSA (m^2)	1.83±0.18	1.97±0.23	< 0.05
ASA I/II/III/IV	2/8/18/1	4/5/18/2	ns
Basal RAC (ml)	783±218	819±309	ns

Data are presented mean ± standard deviation, ns=non significant.
ASA, American Society of Anesthesiologists; BSA, body surface area; HES, hydroxyethylstarch 130/0.4; RAC, Ringer's acetate

Table 2

Patients characteristics when diveded according to the surgery position (prone or sitting).

	Prone	Sitting	p
M/F	13/17	8/20	ns
Age (years)	54±18	42±15	< 0.01
Weight (cm)	79±15	76±14	ns
Height (kg)	170±8	167±9	ns
BSA (m^2)	1.93±0.22	1.88±0,20	ns
ASA I/II/III/IV	6/13/10/1	0/0/26/2	<0.001
Efedrin total dose (mg)	9.2±4.9	4.4±1.3	ns
Neosynphrine tot dose (mg)	1.4±1.7	1.4±2.3	ns

Data are presented mean ± standard deviation, ns=non significant
ASA, American Society of Anesthesiologists; BSA, body surface area;

Table 3

Study fluid (RAC and HES) consumption in two different surgery position and positions combined (prone and sitting).

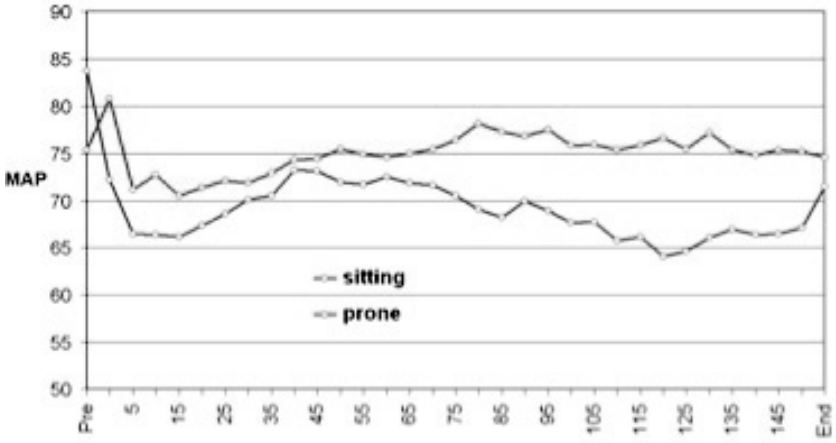
Fluid	Sitting	Prone	Position Combined	P value
HES total ml	464±284	447±229	455±253	
RAC total ml	707±425	653±368	679±390	
Study fluids combined	586±376	550±319	567±345	< 0.05 (between the fluids)
HES start bolus ml	271±47	240±51	255±51	
RAC start bolus ml	264±50	267±62	266±55	
Study fluids combined	268±48	253±57	260±53	ns
HES at 30 min ml	343±94	340±124	341±109	
RAC at 30 min ml	450±156	453±160	452±155	
Study fluids combined	396±137	397±152	397±144	< 0.001 (between the fluids)

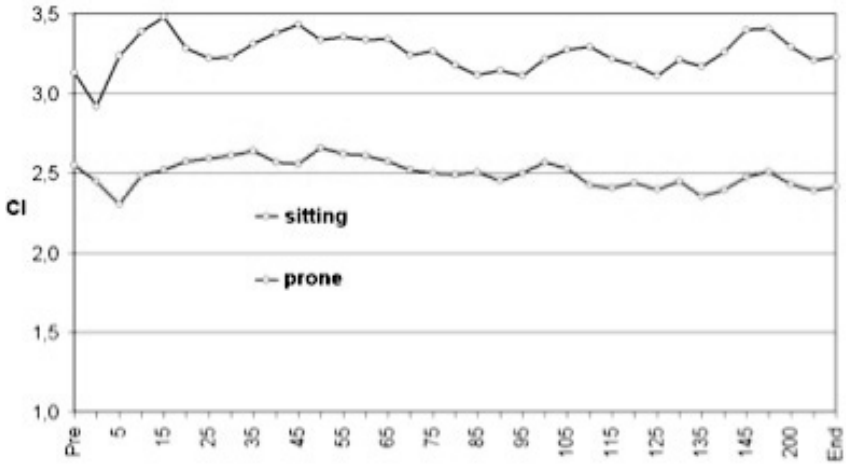
Data are presented mean ± standard deviation, ns=non significant.
HES, hydroxyethylstarch 130/0.4; RAC, Ringer's acetate

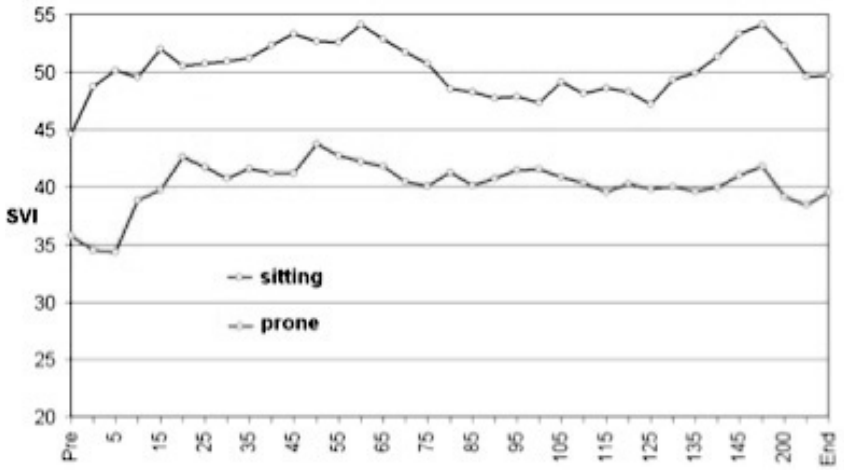
Figure 1

Mean arterial pressure (MAP), cardiac index (CI) and stroke volume index (SVI) over time

(minutes) during surgery in sitting and prone position.


MAP
90
85
80
75
70
65
60
55
50
sitting
prone
Pre
5
15
25
35
45
55
65
75
85
95
105
115
125
135
145
End


CI
3,5
3,0
2,5
2,0
1,5
1,0
sitting
prone
Pre
5
15
25
35
45
55
65
75
85
95
105
115
125
135
145
200
End


SVI
55
50
45
40
35
30
25
20
sitting
prone
Pre
5
15
25
35
45
55
65
75
85
95
105
115
125
135
145
200
End

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