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Editorial

Blood pressure in trauma resuscitation: 'pop the clot' vs. 'drain the brain'?

Introduction

In this issue of *Anaesthesia*, Nevin and Brohi [1] eloquently discuss the role of permissive hypotension in the management of the actively bleeding trauma patient. Since the advent of major trauma centres in the UK, there has been widespread adoption of permissive hypotension as part of 'damage control resuscitation' in the immediate management of haemorrhage secondary to trauma. As the authors themselves note, this is a contentious area with many uncertainties and, as a neuro-anaesthetist, I feel that it is important to consider the potential risks and limited

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benefits of permissive hypotension when applied to all trauma patients, but especially in the context of traumatic brain injury (TBI).

Analysis of the Trauma Audit and Research Network (TARN) database has shown that over 25% of trauma patients have a significant brain injury (defined as an Abbreviated Injury Score ≥ 3) [2], and brain injury remains the commonest cause of death after trauma. In a review of 69,499 trauma patients with an injury severity score (ISS) > 9, the overall mortality rate was 19%, of which 68% had suffered brain injury, but interestingly only 9% had received massive transfusion [3]. The challenge for clinicians involved in the management of the shocked trauma patient is to balance the need for cerebral perfusion against the fear that any increase in systemic blood pressure may worsen uncontrolled haemorrhage. The Major Trauma Guidelines produced by the National Institute for Health and Care Excellence (NICE) appear to be similarly conflicted [4]. For trauma patients with haemorrhagic shock and TBI, the authors recommend restrictive volume resuscitation if haemorrhagic shock is the dominant condition, and a 'less restrictive volume resuscitation approach' if TBI is the dominant condition. No details are provided as to how this differentiation can be made in the early stages of trauma management, or as to what consists a less restrictive volume strategy. Analysis of TARN data shows that physiological parameters are of limited diagnostic value in assessing major haemorrhage or TBI in severely injured trauma patients [5]. These difficulties are compounded by the fact that 45% of UK patients with TBI are intoxicated with alcohol, making the early pre-imaging, exclusion of significant brain injury challenging [6].

Other consensus guidelines have also supported the use of permissive hypotension. The pan-European, multidisciplinary Task Force for Advanced Bleeding Care in Trauma updated their guidelines for the management of major bleeding after trauma, and suggested a target systolic blood pressure (SBP) of 80–90 mmHg until haemorrhage control [7]. This was, however, a grade 1C recommendation (strong recommendation, based on low-quality or very low-quality evidence) and was limited to patients without TBI; in patients with a Glasgow Coma Scale (GCS) ≤ 8, the target was revised to a mean arterial pressure ≥ 80 mmHg (also graded 1C).

Given the paucity of high-quality evidence supporting the use of permissive hypotension in trauma, there are several assumptions which I feel should be considered before instituting its use into routine clinical management.

Permissive hypotension reduces mortality following trauma

The Cochrane group recently undertook a meta-analysis examining the timing and volume of fluid administration in haemorrhage, which included six trials involving 2128 patients [8]. The authors concluded that there was 'no evidence for or against the use of early or larger volume intravenous fluid administration in uncontrolled haemorrhage'. Only three of the included studies were relevant to permissive hypotension in the management of traumatic haemorrhage, and two further relevant studies have been published subsequently (summarised in Table 1). The majority of studies had TBI as an exclusion criterion and only the study by Bickell et al. [9] was able to demonstrate a reduction in mortality with the use of permissive hypotension. This study, however, has a number of significant weaknesses [10], most notably immortal time bias; when this is corrected for, there is no difference in survival rates for patients managed with permissive hypotension compared with liberal fluid administration [11].

It is often argued that the physiological rationale for permissive hypotension has been established in animal models of haemorrhage. However, systematic reviews of animal studies have noted a large degree of heterogeneity between studies and inadequate allotment concealment [12, 13]. This is primarily due to the model used in animal studies of uncontrolled haemorrhage. With severe bleeding (induced by aortic injury or > 50% of rat tail removal), fluid resuscitation decreases animal mortality. However, with injury to non-aortic vasculature or < 50% rat tail removal, fluid resuscitation increases death rates [12]. Given the limitations of the models used, this would imply that, if permissive hypotension does indeed have any beneficial effects, these are likely to be dependent on exactly what type of injury is received, namely a very specific type of penetrating trauma. So while it

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Table 1 Summary of the randomised controlled trails investigating permissive hypotension after trauma.

	Bickell et al. [9]	Turner et al. [42]	Dutton et al. [27]	Schreiber et al. [28]	Carrick et al. [29]
n	598	1309	110	191	168
Years	1989–1992	1996–1997	1996–1999	2012–2013	2007–2013
Age; years	31 (mean)	80% aged ≤ 64	31 (mean)	42 (mean)	31 (median)
Sex; male	89%	64%	80%	76%	90%
Penetrating trauma	100%	1.8%	51%	34%	100%
Inclusion criteria	Gunshot/stab wounds with SBP < 90 mmHg	Significant trauma injury as determined by admission destination, length of stay and death	Evidence of haemorrhage after trauma and SBP < 90 mmHg at least once in the first 60 min	Traumatic injury with an out-of-hospital SBP ≤ 90 mmHg	Age ≤ 45; penetrating trauma with SBP ≤ 90 mmHg requiring laparotomy/ thoracotomy
Exclusion criteria	Revised Trauma Score 0; fatal gunshot wound to head; minor injuries not requiring surgery	Burns; hangings; pregnancy; drowning; isolated traumatic injury	Central nervous system injury; age > 55; coronary artery disease; diabetes mellitus	Severe head injury; GCS ≤ 8; burns; hangings; pregnancy; drowning; 250 ml fluid administered before randomisation; ground level falls	Known or suspected head injury; pregnancy.
Brain injury included	Unclear	Yes; 24.4% some degree of head injury	No	No	No
Intervention arm	Delayed resuscitation: minimal i.v. fluid until arrival in theatre (mean 375 ml)	Delayed resuscitation: i.v. fluids withheld for the first hour of pre-hospital care	Target SBP 70 mmHg	Controlled resuscitation: maintain SBP 70 mmHg/ radial pulse with 250 ml fluid bolus as necessary	Intra-operative minimal MAP 50 mmHg
Control arm	Immediate resuscitation: if SBP < 100 mmHg then given i.v. crystalloid (mean 2478 ml)	Immediate resuscitation: i.v. fluids administered following primary patient assessment	Target SBP > 100 mmHg with fluids/PRC	Standard resuscitation: 2000 ml fluid bolus and further fluids to maintain SBP 110 mmHg	Intra-operative minimal MAP 65 mmHg
Primary outcome	Survival to hospital discharge. 70% in delayed resuscitation group vs. 64% in immediate resuscitation group (p = 0.04)	Composite of mortality and morbidity. Mortality 9.8%% in delayed resuscitation group vs. 10.4% in immediate resuscitation group (Adjusted OR [95%CI] 0.93 [0.58–1.49])	Mortality. 93% survival in both groups.	Feasibility study. Primary safety end-point 24 h mortality. Mortality at 24 h was 5.2% vs. 14.7% in controlled and standard groups, respectively (adjusted OR [95%CI] 0.39 [0.12–1.25])	30-day mortality

(continued)

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Table 1 (*continued*)

	Bickell et al. [9]	Turner et al. [42]	Dutton et al. [27]	Schreiber et al. [28]	Carrick et al. [29]
Coagulation measured	Coagulopathy (not defined) similar incidence in both groups. Admission PT/APTT higher in immediate resuscitation group	Coagulopathy (not defined) similar incidence in both groups	No	Yes; PT, APTT and platelet counts similar in both groups	Coagulopathy (not defined) similar incidence in both groups
Coagulation factors used	FFP (≈ 300 ml) given with PRC (≈ 1800 ml)	No	Not stated	Yes. In the first 2 h total blood products (including PRC) 400 ml vs. 1050 ml in controlled and standard groups, respectively.	Yes. Similar between groups: median 1125–1500 ml PRC, with PRC: FFP ratios of 2.2–2.3.
Weaknesses	Randomisation by day of week; immortality bias; single-centre study	Poor compliance with protocol. Only 30.9% of patients in the immediate resuscitation groups received i.v. fluids. Randomisation by treating paramedic rather than patient	Target not achieved in hypotensive group (mean SBP 100).	Not powered for mortality outcomes. Only 35% of patients had ISS > 15	Early termination or study due to because of clinical equipoise and futility (168 of planned 271 patients recruited). Little difference between groups in terms of MAP (intra-operative MAP was 66 mmHg in the intervention group and 69 mmHg in the control group)

FFP, fresh frozen plasma; i.v., intravenous; ISS, injury severity score; MAP, mean arterial pressure; OR, odds ratio; PRC, packed red blood cells; SBP, systolic blood pressure; PT, prothrombin time; APTT, activated partial thromboplastin time.

may be possible to extrapolate this to a single penetrating entry (such as a knife wound), given that the vast majority of the UK trauma is multi-system and blunt in nature (penetrating trauma accounting for < 3% of cases [14]), it is difficult to suggest that this should be applied to every bleeding trauma patient in the UK.

Normalisation of blood pressure will worsen uncontrolled haemorrhage following trauma

Although first described during the First World War [15], the use of permissive hypotension as a strategy to minimise active bleeding became established in the 1990s as part of the management of ruptured abdominal aortic aneurysms. The proposed theory was that normalisation of blood pressure in the bleeding, shocked patient, may result in clot dislodgement, often described as the 'pop the clot' phenomenon. However, it is interesting to reflect on how this theory was developed. It was first described in an editorial by a US vascular surgeon, who reflected on his management of 87 cases of ruptured abdominal aortic aneurysms over a 33-year career [16]. His belief was that the use of permissive hypotension (SBP 50–70 mmHg) was a contributing factor for his improved outcomes in comparison with other centres. It is unlikely that this type of analysis (retrospective, single-centre, no adjustment for case-mix or confounding factors) would result in alterations in clinical practice in the 21st century. Indeed, a recent Cochrane review was unable

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to identify a single randomised controlled trial comparing hypotensive and normotensive fluid resuscitation in the management of ruptured abdominal aortic aneurysms [17]. Permissive hypotension is widely employed by military medical teams [18] and the dramatic improvements in survival of combat-injured soldiers over the past 15 years [19] has been used to support its implementation into civilian practice. However, it is vital that the differences between civilian and combat injuries are recognised, as these may limit the extrapolation of the care paradigms. Compared with civilian trauma patients, soldiers have a higher incidence of penetrating trauma, are of younger age (mean 25 years) with no significant medical comorbidities, and have a lower incidence of head/brain injury (8–10%) [19, 20]. In addition, the pre-hospital care provided by medical emergency retrieval teams (MERT) is also dramatically different from that seen in the civilian environment.

Permissive hypotension is appropriate for UK trauma patients admitted to a major trauma centre

The other difficulty in comparing fluid management strategies in the bleeding trauma patient is that many are now several years old, and the historical 'standard' trauma haemorrhage techniques are not reflective of contemporary treatment protocols. Advanced Trauma Life Support (ATLS) recommendations have been criticised for failing to keep pace with developments in management techniques [21], and the proponents of permissive hypotension often suggest that the only alternative strategy is the liberal administration of large volumes of intravenous crystalloid. This is clearly not the solution, as several observational studies have demonstrated increased mortality with aggressive fluid administration [22]. This is, in part, likely to be due to an increased incidence of complications, especially dilutional coagulopathy, hypothermia and acute lung injury. This type of management was typical in the control groups of the studies investigating permissive hypotension, with often more than 2000 ml of crystalloid administered (Table 1). However, this is does not reflect current practice with packed red cells given in combination with fresh frozen plasma, platelet concentrate and fibrinogen [23, 24]. The use of a major trauma transfusion pack will typically result in the administration of around 2000 ml fluid (4 units packed red cells, 4 units fresh frozen plasma, 1 unit of platelets, 1 adult dose of cryoprecipitate), which may well produce an increase in blood pressure; thus, it may be that permissive hypotension is beneficial, not because of avoidance of blood pressure normalisation, but rather that it avoids the liberal use of crystalloid solutions. In addition, none of the studies described in Table 1 reported the use of tranexamic acid, which is now considered standard practice [25, 26].

A further complication of liberal intravenous fluid use in older studies was the associated delay in definitive haemorrhage control in the operating theatre, due to extended attempts at fluid resuscitation. In the study by Bickell et al., management in the emergency department until the transfer to the operating theatre was prolonged by current standards, with a mean time of 45–50 min, with large standard deviations [9]. In the study by Dutton et al., haemorrhage control was achieved after 2.5–3 h [27] and in the Screiber et al. paper, over 75% of patients had a combined on-scene and transfer time in excess of 30 min [28]. Only in the more contemporary study by Carrick et al. [29], was the time of treatment in line with current best practice (mean time from arrival to hospital to starting surgery 20 min), and no mortality benefit was demonstrated with the use of permissive hypotension.

Short periods of low cerebral perfusion pressure are well tolerated by trauma patients

The outcome following TBI remains poor, with over 60% of patients having an unfavourable outcome, namely death or severe disability, at 6 months [6]. Numerous randomised controlled trials have been unable to identify a 'magic bullet' intervention to improve outcomes [30], leaving the focus on primary prevention and the avoidance of secondary brain injury. Hypotension is well recognised as a risk factor for poor outcomes, with an admission SBP < 110 mmHg being associated with a 92–98% increase in the risk of death [31]. It is important to note that this does not tell the whole story, as death is not necessarily the worst possible outcome with TBI, with poor neurological recovery often judged as

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being even less desirable. In light of this, it is of note that a small, retrospective study suggested that duration of hypotension (SBP < 120 mmHg) within the first 48 h of admission with severe TBI was predictive of neurological outcome at 1 year [32].

The situation is complicated further by the changing demographics of trauma patients. The most common trauma patient in the England and Wales is now an older female who has suffered a fall from less than 2 m [33]. Mortality rates following trauma in patients aged over 70 years are 200–300% higher than those under 60 years of age, although it is unclear what proportion of these are directly attributable to the initial traumatic injury [33]. The efficacy and safety of permissive hypotension in older patients with medical comorbidities (especially hypertension, ischaemic heart and cerebrovascular disease) has not been investigated, as this population has largely been excluded from the relevant research studies (Table 1); as such, perhaps a different treatment paradigm is needed, as trauma in the older patient may represent a distinct disease process compared with younger patients [34, 35]. Thus, rather than applying guidelines broadly to all trauma patients, it may be better to focus future efforts on how to best individualise treatment goals and strategies.

If permissive hypotension isn't the answer, then what is?

Given the paucity of available evidence, hypotension in the trauma patient cannot be considered a treatment strategy or physiological target; there appears to be little evidence of a mortality benefit with its use and it potentially places the injured brain at risk. Traumatic brain injury is far more common than penetrating trauma in the UK population, and I would suggest that treatment strategies should take this into account, especially as exclusion of TBI is very challenging in the early stages of trauma management. Haemorrhagic shock is quite rightly a major focus of immediate management, but there is little benefit in surviving that insult if irreparable cerebral damage occurs. A post-hoc analysis of the PROPPR study demonstrated an almost three-fold increase in mortality in patients with TBI compared to those with haemorrhagic shock (50% vs. 17.5%, respectively) [36]. Interestingly, the mortality rate in patients with TBI and haemorrhagic shock was similar to those with TBI alone (51.6% vs. 50%), suggesting that the brain injury may be the primary determinant of survival.

My concern is that permissive hypotension is viewed by some clinicians as a management strategy, rather than a sign of critical illness. I would prefer hypotension to instead be viewed as a trigger for aggressive management and should be 'permitted' for as short a time as possible. However, this does not mean a return to the use of liberal crystalloid solutions and delay in achieving definitive haemorrhage control. The remaining components of 'haemostatic resuscitation' [25] should be aggressively pursued: normalisation of coagulation with relevant clotting factors; avoidance/treatment of hypothermia, hypocalcaemia, and acidaemia; and rapid movement to definitive haemorrhage control in the operating theatre or interventional radiology suite. This can occur in tandem with the maintenance of an adequate, individualised cerebral perfusion pressure, taking into account factors such as age, medical comorbidities and type and severity of associated injuries. The challenge for future research studies is to determine how this can be achieved. Low-volume resuscitation with hypertonic solutions would appear to be a potential solution, but has not been shown improve mortality when administered in the pre-hospital setting to non-brain injured trauma patients [37]. The use of vasopressors would be an alternative strategy, as is commonplace in the intensive care management of patients with TBI. Animal studies using vasopressin after induced haemorrhagic shock have shown promise [38], but human studies are lacking and the optimal agent, dose and timing of vasopressor therapy are unknown [38] and concerns remain regarding the potential for iatrogenic harm induced by excessive vasoconstriction in a hypovolaemic patient. A retrospective analysis of critically ill trauma patients suggested that the use of vasoconstrictor therapy (which included dopamine, adrenaline, phenylephrine, noradrenaline or vasopressin) within the first 24 h of admission was independently associated with increased mortality in hypovolaemic patients [39]. However, this excluded patients with TBI and the

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diagnosis of hypovolaemia was made on an arbitrary central venous pressure of ≤ 8 mmHg, despite the poor correlation between this and systemic blood volume [40].

Within the context of UK trauma management, if significant TBI cannot be reliably excluded, attempts should be made to achieve adequate cerebral perfusion pressure using judicious, small volume boluses of fluid (either crystalloid or packed red cells) and/or vasopressor therapy, in conjunction with the other elements of haemostatic resuscitation (coagulation factors and tranexamic acid), while rapidly transporting the patient for computed tomographic (CT) imaging and definitive haemorrhage control in theatre or radiology. This would be in line with recent recommendations of a bundle of care for resuscitation of the shocked patient with TBI [41]. The risk of the 'pop the clot' phenomenon appears to be overstated and it may be that the use of permissive hypotension in all shocked trauma patients, with the potential for a 'drain the brain' effect, could be doing more harm than good.

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