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Crit Care Nurse 2013;33:18-24 doi: 10.4037/ccn2013395
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Permissive Hypotension in Bleeding Trauma Patients: Helpful or Not and When?

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Severity of hemorrhage and rate of bleeding are fundamental factors in the outcomes of trauma. Intravenous administration of fluid is the basic treatment to maintain blood pressure until bleeding is controlled. The main guideline, used almost worldwide, Advanced Trauma Life Support, established by the American College of Surgeons in 1976, calls for aggressive administration of intravenous fluids, primarily crystalloid solutions. Several other guidelines, such as Prehospital Trauma Life Support, Trauma Evaluation and Management, and Advanced Trauma Operative Management, are applied according to a patient's current condition. However, the ideal strategy remains unclear. With permissive hypotension, also known as hypotensive resuscitation, fluid administration is less aggressive. The available models of permissive hypotension are based on hypotheses in hypovolemic physiology and restricted clinical trials in animals. Before these models can be used in patients, randomized, controlled clinical trials are necessary. (*Critical Care Nurse*. 2013;33[6]:18-25)

Trauma remains the leading cause of mortality among persons 1 to 44 years old in the United States¹ and accounts for almost 9% of total mortality worldwide.² In 2008 a total of 663 000 injury-related deaths occurred in Europe (6.9% of total deaths).² Uncontrolled bleeding and exsanguination are the leading cause of preventable death after trauma³ and require early detection of potential bleeding sources and prompt action to minimize blood loss, restore tissue perfusion, and achieve a stable hemodynamic status.

CNE Continuing Nursing Education

This article has been designated for CNE credit. A closed-book, multiple-choice examination follows this article, which tests your knowledge of the following objectives:

1. State the purpose of permissive hypotension
2. Identify factors that affect fluid resuscitation
3. Discuss the physiologic response of permissive hypotension

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Table 1 Phases before the definitive surgical control of hemorrhage

Phase	Where/Current trends	Principles
First: before the arrival of trained medical assistance	At the scene of injury	Bleeding control with compression when possible
Second: management by prehospital personnel	At the scene of injury and in transit to the hospital (depending on location) PHTLS guidelines suggest the scoop and run policy (no resuscitation or hypotensive resuscitation) ¹⁰ Advanced Care Practice performed by medical staff (central venous catheterization, intubation, etc)	Duration of the evacuation chain Maintenance of adequate mentation and/or a palpable radial pulse (systolic blood pressure of 80 mm Hg)
Third: management before transfer to the operating room	In the emergency department ATLS algorithm mandates the rapid infusion of up to 2 L of isotonic fluid or blood in an adult ¹¹	For patients who are estimated to have lost $\geq 30\%$ of the normal circulating volume Restoration of lost intravascular volume followed by packed red blood cells and plasma as needed to maintain a normal systolic blood pressure, adequate tissue perfusion, and vital organ function

Abbreviations: ATLS, Advanced Trauma Life Support; PHTLS, Prehospital Trauma Life Support.

Managing hemorrhage from the first minute after an injury is crucial in preventing death. Despite the development of trauma resuscitation strategies and the implementation of algorithm guidelines such as Advanced Trauma Life Support⁴ and Prehospital Trauma Life Support,⁵ health care professionals still struggle against the physiological consequences of trauma.

Hemorrhage Due to Trauma

Acute blood loss leads to multiple organ dysfunction syndrome through extended tissue hypoperfusion and lactic acidosis due to diminished oxygenation.⁶ Therefore, arrest of bleeding and restoration of circulating blood volume with sufficient oxygen transport are 2 of the main goals in management strategies.

Hemorrhage is considered responsible for approximately 50% of trauma deaths within the first few hours,

and 34% of the deaths occur in the hospital.⁷ Surgical control of hemorrhage remains the best method of resuscitation in hemorrhaging, hypotensive trauma patients.⁸ Application of a finger, pack, clamp, tourniquet, or ligature can easily be achieved if the hemorrhage is external and therefore compressible. Such action, which can be taken in a nonhospital environment, drastically limits blood loss and consequently improves survival rate.⁹ In patients with noncompressible hemorrhage (eg, injury of the subclavian artery, rupture of the spleen), laparotomy, thoracotomy, and groin or neck exploration are the methods of choice for surgical control of hemorrhage. These procedures are almost exclusively performed in an operating room.

The period before definitive surgical control of hemorrhage can be divided into 3 phases on the basis of the time first aid was provided^{10,11} (Table 1). In Australia, 66%

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Table 2 Studies of permissive hypotension in animals

Authors, year	Immediate normotension resuscitation (mean arterial pressure >80 mm Hg)		Permissive hypotension resuscitation (mean arterial pressure <80 mm Hg)		P	Sample size
	No. of animals	No. (%) that died	No. of animals	No. (%) that died		
Bickell et al, ¹⁵ 1991	8	5 (62)	8	0 (0)	<.05	16 (swine)
Capone et al, ¹⁶ 1995	10	10 (100)	10	4 (40)	>.05	20 (rats)
Rafie et al, ¹⁷ 2004	7	0 (0)	6	2 (33)	.11	13 (sheep)
Li et al, ¹⁸ 2011	10	8 (80)	50	28 (56)	<.05	80 (rats)
Schmidt et al, ¹⁹ 2012	6	6 (100)	6	6 (100)	.20	24 (rats)

of trauma patients died during the first phase of first aid (74% of the deaths were due to penetrating injuries).⁷ Involvement of trained medical personnel during the second phase and implementation of Prehospital Trauma Life Support guidelines require an immediate transport from the scene of injury, often without resuscitation, especially in massive casualties. This approach is known as scoop and run and refers to immediate retrieval and transport of a trauma victim to a hospital because of extreme severe injury and insufficient time for medical stabilization.¹²

A patient's response to the rapid infusion of isotonic fluid or blood, as dictated by the Advanced Trauma Life Support guidelines, is a strong indicator of his or her hemodynamic equilibrium. However, this standard approach may contribute to continuous bleeding and consequently to increased mortality. Increasing the hydrostatic pressure on blood clots with aggressive

Uncontrolled bleeding and exsanguination are the leading cause of preventable death after trauma.

administration of intravenous fluid adversely affects the

endogenous coagulopathy that has already occurred through excessive fibrinolysis and anticoagulation, particularly in patients with penetrating trauma.¹³ Moreover, in patients whose hemorrhage cannot be controlled, infusion of large volumes of fluid results in increased blood loss.¹⁴ The dilemma that emerges concerns an alternative approach to treatment of hypotensive trauma patients with internal (abdominal and thoracic) hemorrhage: can permissive hypotension be helpful, and, if so, when?

Experimental Assessment of Permissive Hypotension in Animals

In the early 1990s, experimental models of permissive hypotension were developed and evaluated in rats and swine (Table 2). Some results^{15,20} suggested that aggressive fluid administration might increase bleeding and decrease survival rates in cases of uncontrollable hemorrhage (hemostasis not possible through compression), whereas other findings²⁰ indicated that moderate, permissive hypotension might prolong survival. Bickell et al¹⁵ developed a model to study resuscitation in uncontrolled hemorrhage. A 5-mm aortotomy was inflicted in 16 anesthetized pigs, and the animals were separated into 2 groups. In the treatment group, resuscitation was started 6 minutes after aortotomy with aggressive infusion of crystalloid fluid containing only electrolytes (4 mL/kg per minute physiological saline). In the control group, none of the animals were infused with fluid. The results were impressive. After a 30-minute sample time, 5 animals in the treatment group had died, and all 8 animals in the control group had survived. The volumes of blood lost were much greater ($P < .05$) in the treatment group (mean, 1340 mL; SD, 230 mL) than in the control group (mean, 783 mL; SD, 85 mL). In the treatment group, increases in mean arterial pressure (MAP) and blood flow velocity due to volume replacement disrupted the hydrostatic forces that contributed to the formation of platelet thrombi formed in the 6 minutes before resuscitation efforts began.

More recent studies^{18,19} in animals focused on permissive hypotension in uncontrolled bleeding. Attempts were made to determine the effects of early or delayed hypotensive blood resuscitation.¹⁸ The results suggested

Table 3 Studies of permissive hypotension in humans

Authors, year	Immediate normotension resuscitation (mean arterial pressure = 100 mm Hg)		Permissive hypotension resuscitation (mean arterial pressure <80 mm Hg)		P	Sample size	Method	Conclusions
	No. of patients	No. (%) who died	No. of patients	No. (%) who died				
Bickell et al, ²³ 1994	309	116 (37.5)	289	86 (29.8)	.04	598	Prospective trial	Mortality rate difference statistically significant
Dunham et al, ²⁴ 1991	16	5 (31)	20	5 (25)	.36	36	Randomized control study	Mortality rate difference not statistically significant
Dutton et al, ²⁵ 2002	55	4 (7.3)	55	4 (7.3)	.31	110	Randomized control study	Mortality unaffected by permissive hypertension

that attempts to restore normotension (a MAP of 90 mm Hg) by rapid volume expansion resulted in significant increase in hemorrhage volume and mortality, and the goal of normotension was often unachievable.¹⁹

Moderately underresuscitated animals (MAPs 40-80 mm Hg) tended to experience less intraperitoneal hemorrhage than did animals with higher MAPs.¹⁹ These findings suggest that MAP alone does not lead to a poor outcome. The peak of maximum pulse pressures occurred much later in the underresuscitated animals than in the other animals, giving the temporary platelet plug of the vascular injury time to promote hemostasis by transforming into a fibrinous, rigid hemostatic plug.¹⁸ Aggressive fluid resuscitation may reverse vasoconstriction by replacing volume, displace early formed thrombus by increasing blood flow, and therefore magnify the establishment of coagulopathy due to hypovolemic shock.²⁰ A systematic meta-analysis of preclinical data (52 animal trials)²¹ indicated an increased adjusted relative risk of death, from 0.69 to 1.80, when aggressive resuscitation was used in animals with less severe hemorrhage (ie, tail resection). In other trials,^{16,17} attempts to increase MAP to 80 mm Hg with fluid resuscitation in animals with established hypovolemic shock were associated with decreased oxygen supply to the tissues, metabolic acidosis, and a poor outcome.

All the experimental models just described had common features: the studies were done in a large premedicated and anesthetized mammal that was invasively monitored and surgically manipulated. Before implementation of the experimental protocol, hemodynamic

stabilization and splenectomy were performed to minimize the effects of splanchnic sequestration and auto-transfusion. The combination of these conditions and excessive resuscitation does not fully coincide with everyday medical practice, and the findings cannot easily be extrapolated to humans. Therefore, the results cannot be interpreted appropriately because of significant bias.²² However, the encouraging results of the trials in animals prompted prospective, controlled studies of patients with hemorrhagic shock due to trauma.

Studies of Permissive Hypotension in Humans

Several studies of permissive hypotension in humans have been reported (Table 3). Bickell et al²³ compared the effects of immediate (before surgical intervention) and delayed (after entering the hospital) fluid resuscitation with isotonic crystalloid in 598 hypotensive patients (systolic blood pressure <90 mm Hg) with penetrating torso injuries from gunshot or stab wounds. Mortality was lower ($P = .04$) in the 289 patients who received delayed resuscitation (38.9%; 86 fatalities) than in the 309 patients who received immediate resuscitation (37.5%; 116 fatalities). In addition, 23% of patients in the delayed resuscitation group had one or more serious complications, including adult respiratory syndrome, acute renal failure, wound infection, and pneumonia, compared with 30% of patients in the immediate resuscitation group ($P = .08$). However, this trial was not formally randomized because randomization was not considered logistically feasible.

Dunham et al²⁴ reported mortality and coagulation time for a total of 36 hypotensive trauma patients (systolic blood pressure <90 mm Hg). Mortality was 31% (5 of 16 patients) in the group who received a larger volume of fluids (total amount 5069 mL) administered conventionally and 25% (5 of 20 patients) in the group who received a smaller volume of fluids (total amount 3001 mL). The difference between the 2 groups was not significant ($P = .36$).

Dutton et al²⁵ compared 2 fluid resuscitation protocols in 110 patients with blunt and penetrating trauma. The goal was to maintain a systolic blood pressure of 70 mm Hg (low) or one greater than 100 mm Hg (conventional). The mortality rate (7.3%) was the same for both groups of patients. However, comparison of Injury Severity Scores²⁶ indicated that patients in the low group (scores, 16-24) were more severely injured ($P = .02$) than were patients in the conventional group (scores, 9-15). Thus, permissive hypotensive resuscitation may benefit restoration of blood circulation and cause a modest increase in blood pressure (reducing the risk of additional blood loss due to continued bleeding or rebleeding) with minimal fluid requirements.

The Triad of Death and Damage Control Surgery

Currently, damage control surgery is a major area of interest in trauma management.²⁷ Principles of damage control apply not only to the abdomen but also to many other regions of the body.²⁸

Damage control surgery is defined as a series of operations performed to definitively repair injuries of the abdomen or other parts of the torso in accordance with a patient's ability to tolerate the physiological consequences of injury and repair.²⁹ The main tenet of damage control surgery is that patients die from the so-called

triad of death.

In patients whose hemorrhage can not be controlled, infusion of large volumes of fluid results in increased blood loss.

The triad consists of 3 main conditions—hypothermia,

acidosis, and coagulopathy—that occur in a vicious cycle that often cannot be interrupted.³⁰ Diminished blood volume and cardiac output lead to immediate vasoconstriction and tachycardia as a compensatory mechanism.³¹ Further blood loss results in hypothermia and peripheral tissue hypoperfusion due to prolonged

vasoconstriction. Hypothermia gradually derails the hemostatic system by increasing the tendency for fibrinolysis.³² This increase marks the limit of a patient's ability to cope with the physiological consequences of injury. The already established acidosis, coagulopathy, and hypothermia may be aggravated by resuscitation with crystalloid fluids. The volume of crystalloid administered most likely has an adverse effect on the activation of hemostatic factors at the blood vessel endothelium, leading to clotting disturbances and then exsanguination.^{33,34}

Therefore, recent trends include the use of blood products in the emergency department, a practice already supported by the Advanced Trauma Life Support algorithm: warm whole blood, packed red blood cells and thawed fresh frozen plasma in a ratio of 1:1,^{35,36} platelets, thrombocytopenesis cryoprecipitate, and recombinant activated factor VII.³⁷ The definitive role of factor VII, however, still needs to be determined. Only a few prospective randomized trials with recombinant factor VII have been done, and the results showed no significant differences in mortality rates between patients given the factor and patients given a placebo.³⁸

Establishment of the triad of death leads to irreversible physiological conditions. Damage control surgery should be implemented to disrupt this cycle as soon as possible to contain hemorrhaging, the basic cause of fatality. Stopping the triad of death provides a chance to restore the patient's response to blood loss. Use of damage control surgery has led to improved survival and decreases in hemorrhage until the physiological derangement is limited and the patient can undergo an operation for definitive repair.³⁰

Discussion

The primary goal in management of hemorrhagic hypovolemia is control of blood loss. Hypotension due to acute and severe blood loss represents a state of shock and can lead to organ failure and death. Supporters of early aggressive resuscitation in acute bleeding thought that the need to improve perfusion of vital organs was more important than any risk of aggravating hemorrhage.³⁹ Patients in severe hemorrhagic shock benefit from the use of intravenous crystalloids and colloids along with blood products.⁴⁰ Blood products are not widely available before arrival in the emergency department and should, when possible, be the initial fluid of resuscitation in the hospital environment, especially if a patient's estimated

blood loss is 30% or more of normal circulating volume (stage 2 hypovolemia).⁴¹

Clearly, however, fluid resuscitation that results in a MAP greater than 80 to 90 mm Hg before surgical hemostasis is associated with increased bleeding.²⁶ Several pathophysiological factors are responsible. Increased intravascular volume affects active bleeding by hindering clotting. Administration of intravenous fluids can also lead to hemodilution, because the fluids do not contain clotting factors or erythrocytes, and to hypothermia, if unwarmed, because of the increased infusion rate (>4 mL/kg per minute).³²

Current evidence⁴² suggests that moderate hypotension for less than 30 minutes can be tolerated by trauma patients without progression to end-organ failure. These patients respond better to a possible delay in surgical management of the hemorrhage in a definitive care facility than do patients with greater hypotension. Hypotensive resuscitation seems, also, to reduce bleeding via administration of lower volumes of fluid but does not markedly affect the metabolic acidosis that occurs due to hypoxic tissue conditions. Therefore, hypotensive resuscitation is a reasonable approach for trauma patients who have lost up to 30% of total blood volume (stage 2 hypovolemia).¹¹ Use of permissive hypotension avoids the adverse effects of early aggressive resuscitation mentioned in the Advanced Trauma Life Support guidelines yet maintains a level of tissue perfusion that, although lower than normal, seems to be adequate.

However, as promising as permissive hypotension can be, it can be fatal in some patients.⁴³ Of note, permissive hypotension is contraindicated in patients with traumatic brain injuries, because adequate perfusion pressure is crucial to ensure tissue oxygenation of the central nervous system,⁴⁴ and in patients who are near circulatory collapse (ie, stages 3 and 4 of hypovolemic shock). Preexisting conditions such as hypertension, angina pectoris, coronary disease, and carotid stenosis may also lead to severe cardiovascular dysfunction when trauma patients are hypotensive. These conditions are common mainly in the elderly (>65 years old), but also occur in other age groups because of occult disease.

Undoubtedly, the best way to manage life-threatening hemorrhage is surgical control in the operating room.⁸ Any resuscitation strategy is only a temporary measure, a tool in the management of patients with hypovolemia. Therefore, whatever strategy is followed, it should not

lead to additional delay in the transfer of a patient to the operating room if indicated. Attempts to place a catheter and administer intravenous fluids may delay the delivery of definitive hospital care.⁴⁴ Sampalis et al⁴⁵ reported that mortality was significantly higher ($P < .001$) after on-site (at the trauma scene) resuscitation (23%) than after in-hospital resuscitation (6%). Because of the immediacy needed in evacuation of patients,¹⁰ the scoop and run approach and the strategy suggested by the Prehospital Trauma Life Support guidelines are considered the most credible approach to on-site trauma.

Conclusion

A major challenge in research on hypovolemic resuscitation is the development of an appropriate strategy via an algorithm that considers all available physiological parameters. The Advanced Trauma Life Support algorithm for rapid administration of intravenous crystalloid and/or blood in bleeding patients¹¹ provides an established and effective strategy when combined with an appropriate monitoring of a patient's physiological responses to changes in

blood volume. Clearly, intravenous

Permissive hypotensive resuscitation may benefit restoration of blood circulation and cause a modest increase in blood pressure with minimal fluid requirements.

crystalloid must be tailored to each patient's particular physiological needs.¹⁹ Therefore, the emergency department physician is obligated to adjust treatment strategy by observing the patient's response as indicated by vital signs (systolic blood pressure, heart rate, oxygen saturation).

Life-threatening hemorrhage, however, can also be managed by maintaining a state of permissive hypotension (systolic blood pressure <80 mm Hg) while the patient is transferred from the accident site to the operating room. Evidence indicates that the hypotensive state may be more beneficial to patients, by limiting coagulopathy and hypothermia. The data supporting this strategy, however, are mainly extrapolated from trials in laboratory animals. The urgency in trauma management, the variability of conditions and environments, and the differences in the experience and mobilization of medical personnel increase the difficulty of defining solid end points in favor of permissive hypotension.

Prospective clinical trials are needed. These trials must provide conclusive information that will challenge the

medical community to consider readjusting the well-established status quo in hypovolemic resuscitation. CCN

Financial Disclosures
None reported.

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To learn more about caring for trauma patients, read "Demographic Differences in Systemic Inflammatory Response Syndrome Score After Trauma" by NeSmith et al in the *American Journal of Critical Care*, January 2012;21:35-41. Available at www.ajconline.org.

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CNE Test Test ID C136: Permissive Hypotension in Bleeding Trauma Patients: Helpful or Not and When?

Learning objectives: 1. State the purpose of permissive hypotension 2. Identify factors that affect fluid resuscitation 3. Discuss the physiologic response of permissive hypotension

1. Which of the following statements about massive fluid resuscitation in the trauma patient is true?

- a. Increases circulating volume thereby increasing perfusion pressure
- b. Hinders hemostasis leading to increased bleeding
- c. Does nothing to improve patient outcomes
- d. Allows stabilization of the patient until surgical interventions are required

2. The goal to decrease mortality in trauma patients includes which of the following?

- a. Minimize blood loss and restore tissue perfusion
- b. Improve hemostasis with massive fluid administration
- c. Immediate surgical repair
- d. Administration of clotting factors

3. Further investigation of the efficacy of permissive hypotension is needed because of which of the following?

- a. Advanced Trauma Life Support algorithm has proven success in patient outcomes.
- b. Rapid volume resuscitation with crystalloids and/or blood products affects patient physiology differently.
- c. There is no conclusive data to support permissive hypotension in humans.
- d. The most effective management of bleeding is surgical intervention.

4. The scoop and run method in trauma may contribute to increase blood loss because of which of the following?

- a. Stabilization of the bleeding is not possible without surgical intervention.
- b. Coagulopathy has developed due to massive loss of clotting factors.
- c. Prehospital Trauma Life Support guidelines mandate immediate transport of severe trauma victims.
- d. Rapid infusions of isotonic solutions only increase blood loss.

5. According to some studies, mortality was lower in subjects with permissive hypotension (systolic pressure <90 mm Hg) because of which of the following?

- a. Rapid crystalloid administration has an adverse effect on hemostatic factors.
- b. Permissive hypotension leads to hypothermia and acidosis.
- c. Insufficient research completed on humans to result in any conclusive findings.
- d. Minimum fluid resuscitation is enough to maintain perfusion.

6. Principles involved with damage control surgery include which of the following?

- a. Control of hemorrhagic hypovolemia
- b. Prevent the triad of death
- c. Stabilize the body's own fibrinolytic system
- d. All of the above

7. Which of the following is associated with rapid fluid resuscitation in hypovolemic shock?

- a. Decreased oxygenation and perfusion to tissues leading to acidosis
- b. Improved mean arterial (MAP) pressure providing stabilization of the patient until surgical intervention
- c. Increased coagulopathy
- d. A and C

8. Fluid resuscitation that results in which of the following MAPs is associated with increased bleeding?

- a. Less than 60 mm Hg
- b. Greater than 100 mm Hg
- c. 90 mm Hg
- d. 70 mm Hg

9. Which of the following is a major component of hemorrhagic hypovolemia that leads to a high mortality?

- a. Patient's inability to cope with physiologic consequences of traumatic injury
- b. Hemodilution due to massive fluid resuscitation
- c. Development of coagulopathy with massive blood loss
- d. Fluid replacement with crystalloids

10. In stage 2 hypovolemia, blood products are the initial treatment of choice because of which of the following?

- a. There is a circulating volume loss of greater than 30%.
- b. Massive blood loss leads to coagulopathy with loss of clotting factors.
- c. Fluid resuscitation with crystalloids alone leads to hemodilution.
- d. End organ failure is a major consequence of hemorrhagic hypovolemia.

11. Issues that hinder support of permissive hypotension include which of the following?

- a. Inability to stabilize a severe trauma victim at the scene
- b. Insufficient evidence in human subjects
- c. Experience levels of health care providers
- d. All of the above

12. Permissive hypotension is most appropriate for patients in which of the following stages?

- a. Stage 1 hypovolemic shock
- b. Stage 2 hypovolemic shock
- c. Stage 3 hypovolemic shock
- d. Stage 4 hypovolemic shock

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