

An introduction to fluid therapy

Introduction

Most hospital inpatients will need intravenous fluid therapy as a result of altered intake, extra losses and dynamic shifts within the body. This simple and basic therapy is often overlooked but can cause significant morbidity if neglected as organ perfusion, electrolyte balance and acid base equilibrium may be compromised.

Basic physiology: compartments and fluid shifts

An understanding of the distribution of body water and how it moves across compartments is key to understanding the principles of fluid therapy. About 60% of a 70 kg (42 litres) human adult is water, two-thirds is intracellular (28 litres) and one third is extracellular. The latter comprises the interstitial fluid (10.5 litres) and plasma (3.5 litres). Minor components include CSF, synovial fluid and vitreous humour.

Intracellular and extracellular water exchange takes place across the cell membrane, this is a result of osmolarity differences between two compartments. In the extracellular compartment, the interstitial and plasma components are divided by vascular endothelium and more readily move between the two compared to transcellular movements. This movement of water in the extracellular spaces is governed by differences in oncotic and hydrostatic pressures (Starling's forces). The plasma component has to be the most carefully considered as it carries blood and hence oxygen to the vital organs.

In resuscitation one aims to increase oxygen delivery (Table 1). In periods of significant blood or plasma losses, cardiac

output and hence oxygen delivery to the cells (e.g. renal, hepatic, gastrointestinal tract) is reduced. Even where there appears to be no overt blood or plasma loss, e.g. in sepsis, preoperative starvation or after bowel preparation, there still may be a relative deficit of plasma. Interstitial fluid can be thought of as a 'reservoir' for intravascular fluid as they are both in dynamic equilibrium. Interstitial fluid can quickly move into vessels if blood is lost. Fluid shifts between intracellular and extracellular spaces, however, tend to follow a longer course, but are nonetheless important.

Types of fluid

The fluids used in clinical practice are usefully classified into crystalloids, colloids and blood products. Blood products were covered in an article by Burdett and Stephens (2006).

Crystalloids

Crystalloids pass freely through a semipermeable membrane. They contain water

and electrolytes: those that are commonly used are isotonic with extracellular fluid (Table 2). Saline-based crystalloids will distribute within the extracellular space, where sodium resides. Only a third of a litre of Hartmann's solution will remain intravascular for any significant time; the rest will go into the interstitial space. Prescribing 5% glucose is effectively giving free water as the glucose is wholly metabolized and the resulting water will redistribute into all the compartments, going mainly intracellularly. Thus 5% glucose is practically useless in resuscitating patients in the acute situation for hypovolaemia.

A few other fluids have more specialized roles: 50% glucose is given for hypoglycaemia. Hypertonic saline is under investigation for use in trauma and resuscitation.

Colloids

Colloids are substances that do not dissolve into a true solution and do not pass through a semipermeable membrane. Because they are less readily filtered at the

Table 1. Terms relating to fluid management

Term	Meaning
Resuscitation	Acute treatment of relative or absolute fluid deficit
Maintenance	Delivery of ongoing fluid and electrolyte requirements
Oxygen delivery	Cardiac output* x oxygen content† of blood
Blood pressure‡	Cardiac output* x vascular resistance
Osmolarity	The concentration of osmotically active particles in solution (expressed as osmoles of solute per litre solution)
Isotonic	The same or equal osmotic pressure

* Cardiac output = heart rate x stroke volume, i.e. amount (in litres) of blood pumped by heart per minute. † Oxygen content = amount carried by haemoglobin and dissolved in plasma. ‡ Blood pressure = mean arterial pressure

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Table 2. Approximate electrolyte concentrations of common fluids

	Sodium (mmol/litre)	Chloride (mmol/litre)	Potassium (mmol/litre)	Lactate (mmol/litre)	Calcium (mmol/litre)	Glucose (g/litre)
Hartmann's solution	131	111	5	27	2	0
Saline	154	150	0	0	0	0
Colloids*	150	150	0	0	0	0
5% glucose†	0	30	0	0	0	50
Glucose saline‡	30	0	0	0	0	40

*Almost all colloids in the UK are currently formulated in saline, although some are available by special order in 5% glucose. †Commonly called dextrose. ‡Commonly called dextrose saline: Na+Cl- 0.18%, glucose 4%

kidney they tend to stay in the intravascular compartment for longer than crystalloids and also increase colloidal osmotic (or oncotic) pressure, ‘draining’ water out of the interstitial spaces into the intravascular compartment (Table 3).

Colloids are used to temporarily replace plasma components. They remain within the circulation for various time spans, depending on their molecular weights or size. The main colloids in use are Gelofusine (BBraun, Melsungen, Germany), Voluven (Fresenius Kabi, Runcorn, UK), and Elohaes (Fresenius Kabi, Runcorn, UK). In theory they are good for rapid plasma expansion but their use for resuscitation has been hotly debated (the ‘colloid vs crystalloid’ controversy) with no convincing evidence for the use of either for improved outcomes.

Basic principles of intravenous fluid therapy

The key principles are to replace losses or deficits ‘like for like’, continue maintenance and to anticipate additional ongoing losses. The average adult requires 30–40 ml/kg of water per day (2100–2800 ml for a 70 kg individual). The normal water output in a 70 kg man is 1500 ml as urine, 100 ml in faeces, 400 ml via the lungs and 500 ml through the skin as sweat. Sodium and potassium need to be replaced at 1–2 mol/kg per day.

Plasma loss

In trauma, gastrointestinal bleeding or surgical haemorrhage, fluid loss is predominantly intravascular, i.e. blood (Table 4). In these situations colloids are often initially used as they are quickly available and stay more intravascularly than crystalloids. Hartmann’s solution is often used in operating theatres for surgery because of its similarity to plasma and to replace interstitial fluid. As mentioned earlier, the interstitial reservoir of fluid can quickly enter the intravascular compartment to compensate. Patients with a low haemoglobin may require red cell transfusion (e.g. less than 8 g/dl).

Extracellular fluid

Fluid deficit in this space is commonplace in the hospitalized population. For example in gastrointestinal tract obstruction or vomiting, fluid loss is mainly isotonic, hence intravascular and interstitial fluids are lost. Intracellular water would not compensate effectively since osmolarity changes are not marked. Isotonic crystalloids are the preferred option.

Pure water loss

This is normally accompanied by some electrolytes as well. Since there is a vast reserve of intracellular water, shock does not normally present quickly. Accordingly, 5% glucose is the fluid of choice to replace

water. In severe hypernatraemia or hyperosmolar non-ketotic coma, plasma osmolarity is greatly increased with intracellular dehydration. Total body water is severely depleted and no signs of shock may be present. Most patients do not fall neatly into the three categories mentioned above. Clinical and laboratory assessment is vital to determine types and quantities of fluid to be administered.

Fluid overload

A feared complication of fluid therapy is giving too much or too fast. Elderly patients need care when starting fluid therapy as compensation mechanisms are less efficient. It is, however, far more common for patients to be underhydrated rather than overloaded because of the obligatory loss of water.

Potassium

Potassium loss from the body is continuous as there are less compensatory mechanisms to preserve it. Since most potassium is intracellular, a low serum potassium may well signal a massive total body loss. Serum potassium abnormalities cause cardiac arrhythmias and so levels need to be carefully monitored. Crystalloids do not provide enough potassium for maintenance. Adding potassium to bags of crystalloids is common practice.

Assessment: some pitfalls

Assessment is perhaps the most vital factor when initiating fluid therapy. Often a history and quick examination confirms dehydration. Be careful: because of our ability to vasoconstrict to preserve blood pressure, hypotension may not occur until over 30% of blood loss has occurred in a healthy young person. Beta blockers may mask a tachycardia response. More practically, low urine output may mean a blocked catheter and central line. Central venous pressure measurements are prone to errors. Pyrexia causes huge hidden losses. Patients who are placed on nil by mouth orders overnight for theatres or who have ‘bowel prep’ are dehydrated the next day: if a list is delayed oral or intravenous fluids should be started.

A low urine output is a regular ‘trigger’ for medical attention. At this point a fluid challenge (see below) is useful to diagnose and treat and fluid status.

Table 3. A comparison of colloids and crystalloids. Large volume saline resuscitation can cause a coagulopathy

Crystalloids	Colloids
Cheap	More expensive
Easy to manufacture and store	May interfere with clotting
Long shelf life	Small risk of anaphylaxis
No anaphylaxis/allergic reaction	Smaller volume of infusion needed

Table 4. Symptoms, signs, and investigations in hypovolaemia

History	Clinical signs	Laboratory markers
Vomiting, diarrhoea	Low urine output	Raised haematocrit
Intestinal obstruction	Increased capillary refill time	Increased serum lactate
Fluid intake	Tachycardia	Increased urea disproportionate to creatinine
Thirst	Postural hypotension (late sign)	Metabolic acidosis
	Decreased conscious level	Increased plasma osmolarity
	Low central venous pressure	

Central venous pressure monitoring

A central venous pressure is a useful tool for assessment and treatment of more complex patients: a cannula with the tip situated in the superior vena cava. Although a high pressure implies a well-filled circulation and a low one implies a dehydrated patient, changes in response to 250 ml colloid fluid challenges are more useful (Table 5).

Central lines are not the preferred way for resuscitation in acute situations. Flow rates of fluids increase with the diameter of the cannula but decrease with increasing

length. Hence, where rapid fluid administration is required (e.g. in trauma), short, peripheral cannulae with wide bores are more appropriate than small diameter, longer central lines which also take longer to insert. A central line is not mandatory for fluid challenges. Responses such as an increase in blood pressure, a slowing tachycardia and an increased urine output can be initially used as endpoints.

Conclusions

Fluid therapy should be viewed as fundamental treatment for every patient in

hospital. Careful replacement of losses has been shown to improve outcome. Knowledge of the characteristics, risks, benefits and effects of each fluid used is important. Patients may deteriorate and need intensive care as a result of poor fluid management. **BJHM**

Conflict of interest: none.

Burdett E, Stephens R (2006) Blood transfusion: a practical guide. *Br J Hosp Med* 67(4): M67-9

Table 5. Response and interpretation of central venous pressure changes after a fluid challenge of 250 ml colloid over 15 minutes

Central venous pressure response	Interpretation
Central venous pressure unchanged or rise then falls again	'Dry'
Central venous pressure rises by 4 cm H ₂ O and stays up	adequately filled
Central venous pressure rises by more than 4 cm H ₂ O	overfilled/ heart failure

KEY POINTS

- An understanding of fluid physiology and pharmacology is important to guide appropriate fluid therapy.
- Clinical assessment and re-assessment are important.
- Overlooking fluid therapy may worsen clinical outcomes.

RSM STUDENT MEMBERS' GROUP RESEARCH PRESENTATION

Use of phage display to identify novel antagonists for angiogenic receptor tyrosine kinases

The British Journal of Hospital Medicine is pleased to be publishing some abstracts from the Royal Society of Medicine's Student Members' Group Research Presentation. This is the second place poster presentation. For information about entering this year's prize, please contact young.fellows@rsm.ac.uk

Abstract

Background and purpose

The Tie-receptor tyrosine-kinase (Tie1 and Tie2) pathway is an endothelial-cell-specific proangiogenic system which has a critical role in angiogenesis. Ligands (angiopoie-

tins) have been identified for Tie2 which regulate endothelial migration, survival, permeability and suppression of vascular inflammation. This study aimed to identify small molecule inhibitors capable of blocking the binding of angiopoietins to Tie2. This could aid development of drugs against angiogenic diseases, and clarify mechanisms of angiopoietin/Tie2 signalling.

Methods

Peptides specifically binding Tie2 were identified using the PhD-7Phage-Display-Peptide-Library. It consists of random peptide 7-mers fused to a minor coat protein (pIII) of M13[bacteriophage comprising 1.28 x 10⁹ heptapeptides. The phage-displayed peptides were incubated with Tie2-Fc ('biopanning') and specifically bound phage eluted. Eluted phage was amplified and biopanning repeated. Binding clones were characterized/sequenced. Specific binding was tested on Tie2 ectodomains in

the form of ELISAs, and on HMEC/Tie2 cells. Clones showing the highest specific interaction were investigated further.

Results

After two screens and three rounds of selection 20 clones were isolated/sequenced, showing 13 different represented clones. Each selected clone was assayed by ELISA for binding to Tie2-Fc. All clones have a significant ELISA signal, demonstrating specific binding to Tie2. Four selected clones were used in cellular angiogenesis assays.

Conclusions

The four clones identified bind specifically to the Tie2 receptor. Owing to their small size, these compounds could be developed as therapeutic agents against angiogenesis. These peptides will also be useful to dissect the signal transduction mechanisms involving Tie2 in vivo. **BJHM**

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