



The Australian approach to peri-operative fluid balance

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Purpose of review

The role of fluid balance as an important contributor to patient morbidity and mortality in the peri-operative period is only now being understood. Numerous studies in disparate populations undergoing different surgeries suggest that.

Recent findings

There is wide disparity in fluid administration regimen between speciality, country, and clinician. Recent meta-analyses of published studies have shown that restrictive fluid administration strategies may improve patient-centred outcomes when compared to liberal regimens. Current evidence suggests a significant role for fluid accumulation in the development of peri-operative complications. Fluid balance is best achieved using goal-directed techniques. The evidence base is, at present, sub-optimal, with a paucity of level 1 evidence for clinical decision-making.

Summary

In the absence of level 1 evidence it is difficult to make firm recommendations about practice, though observational and single-centre data suggest a significant survival advantage may be conferred by the peri-operative administration of fluids to monitored physiological targets only. The Australian approach to peri-operative fluid management is to create level 1 evidence. To this end, the development of a large multicentre randomized controlled trial of peri-operative fluid administration is underway.

Keywords

acidosis, fluids, hyperchloraemia, hypotension, oedema, outcome, postoperative, resuscitation, shock, surgery

INTRODUCTION

Intravenous fluids have been part of the medical armamentarium for over a century, first being used to treat cholera in the early 1800s [1]. Surgery and anaesthesia present a variety of haemodynamic challenges and fluid therapy has been a part of standard peri-operative practice for more than 50 years [2]. In currently published guidelines, maintenance fluid therapy (MFT) is recommended in the peri-operative setting to correct any pre-existing deficit due to fasting and gastrointestinal losses, supply basal needs, and replace blood loss, and maintain fluid and electrolyte homeostasis [3,4^{***}].

There is a widely held belief that the first-line intervention for hypotension occurring as a consequence of the induction of anaesthesia and the inflammation induced by surgical intervention should be bolus fluid therapy (BFT) [3,4^{***}]. Often several such boluses may be given. Only in the face of persistent hypotension are bolus vasoconstrictor medications such as metaraminol used. Continuous infusions of vasopressors, such as noradrenaline,

may follow [3,4^{***},5]. This approach typically results in a positive fluid balance often by several litres over a 48–72-h period. Whether this approach represents an ideal practice in postoperative patients, however, remains controversial.

THE PHYSIOLOGICAL AND PSYCHOLOGICAL RATIONALE FOR FLUID THERAPY

There are many reasons why BFT is an attractive choice for the correction of peri-operative

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KEY POINTS

- There is no level 1 evidence to guide clinicians in their choice of fluid therapy in the peri-operative period.
- Current practice is based on tradition, physiological experiments and animal studies.
- Many clinical and animal studies provide contradictory evidence concerning the amount and timing of fluid therapy.
- The Australian anaesthesiology and intensive care community are preparing for a large multicentre trial to test whether patients having major surgery are best treated with a restrictive or liberal approach to peri-operative fluid therapy.

hypotension. First, it appears to make physiological sense. Patients can become dehydrated pre-operatively, or be hypovolaemic from trauma [6] or other pathophysiological processes with fluid redistributing to the hypothetical 'third space' [7]. The induction of anaesthesia results in systemic vasodilatation [8] and surgical insults can lead to blood loss [3,4²²].

This true and relative loss of intravascular volume is understood to result in hypotension through a reduction in preload. In the presence of additional evidence of physiological distress such as oligoanuria, tachycardia or hyperlactataemia it is assumed that vital organ blood flow (described as 'perfusion') and/or cardiac output are impaired [9]. The need for BFT resuscitation becomes self-evident; it becomes the 'best' means to increase venous return, to optimize preload, improve arterial blood pressure, and restore cardiac output and organ blood flow.

A study in 56 patients undergoing colorectal surgery showed a significant increase in peripheral tissue oxygen partial pressure in patients given 16–18 ml/kg/h of fluid compared to those given 8 ml/kg/h [10]. Tissue oxygen delivery was improved by targeted fluid therapy. Better oxygen delivery has been associated with an improvement in outcome [11]. Occult hypovolaemia and intra-operative gut hypoperfusion may also occur in around 60% of major surgery patients, and this is associated with increased morbidity and mortality [12].

Some studies demonstrate that a liberal fluid replacement strategy may also improve exercise capacity and shorten hospital stay [13,14]. In the critical care setting, some small trials exist which suggest fluid supplementation and cardiovascular support can reduce organ dysfunction, postoperative morbidity and death [11]. In patients undergoing minor surgery, mostly in the ambulatory

setting, liberal fluid administration may improve early recovery measures and symptoms such as dizziness, nausea and thirst [15–17].

IS FLUID ADMINISTRATION REALLY PHYSIOLOGICALLY LOGICAL?

The widely held paradigm, over a century old, that peri-operative fluid administration is physiologically logical has had its opponents. Evans led the charge in 1911 [18] with Coller *et al.* [19] and Le Quesne and Lewis [20] following in the 1940s and 1950s. New voices are joining the dispute, and there is emerging evidence that, in a number of surgical and peri-operative settings, positive fluid balance and excessive sodium load is associated with worse patient-centred outcomes [21²²,22]. In general surgery [23²⁴], complex vascular surgery [24], surgery requiring cardiopulmonary bypass [25] and in intensive care patients, there is a convincing and independent association between fluid accumulation and duration of ventilation, duration of ICU stay, ICU and in-hospital mortality, as well as in the development of complications such as acute respiratory distress syndrome and acute kidney injury (AKI) [26²⁷,27,28²⁹,29,30], possibly as a consequence of at least three different pathological processes: the accumulation of fluid (with organ oedema), the retention of sodium, and hyperchloraemia (Fig. 1).

The natural renal response to stress or injury is salt and water retention and oliguria, mediated by the renin-angiotensin-aldosterone system (RAAS), catecholamine and vasopressin release [31]. RAAS activation can cause hypokalaemia, further reducing sodium excretion [32]. Inflammation results in sustained capillary leak of albumin with osmotic drag of fluid, leading to interstitial oedema [33]. Tissue oedema can cause acute kidney injury directly, by increasing intra-capsular pressure, reducing renal vein blood flow and glomerular filtration [34], or indirectly, as in the abdominal compartment syndrome [35]. The movement of fluid into the interstitium further reduces intravascular volume, creating a positive feedback system of RAAS activation [31]. In catabolic patients, who require or who have undergone extensive surgery, nitrogen excretion competes with sodium and chloride excretion, worsening the retention of salt and water [36]. States of cellular hypoxia result in failure of the energy-dependent Na/K/ATPase causing intracellular fluid and sodium accumulation, disordered intracellular signalling, and worsening cellular, tissue and organ dysfunction [37].

Most fluids have a supra-physiological concentration of chloride [38³⁹], and administration

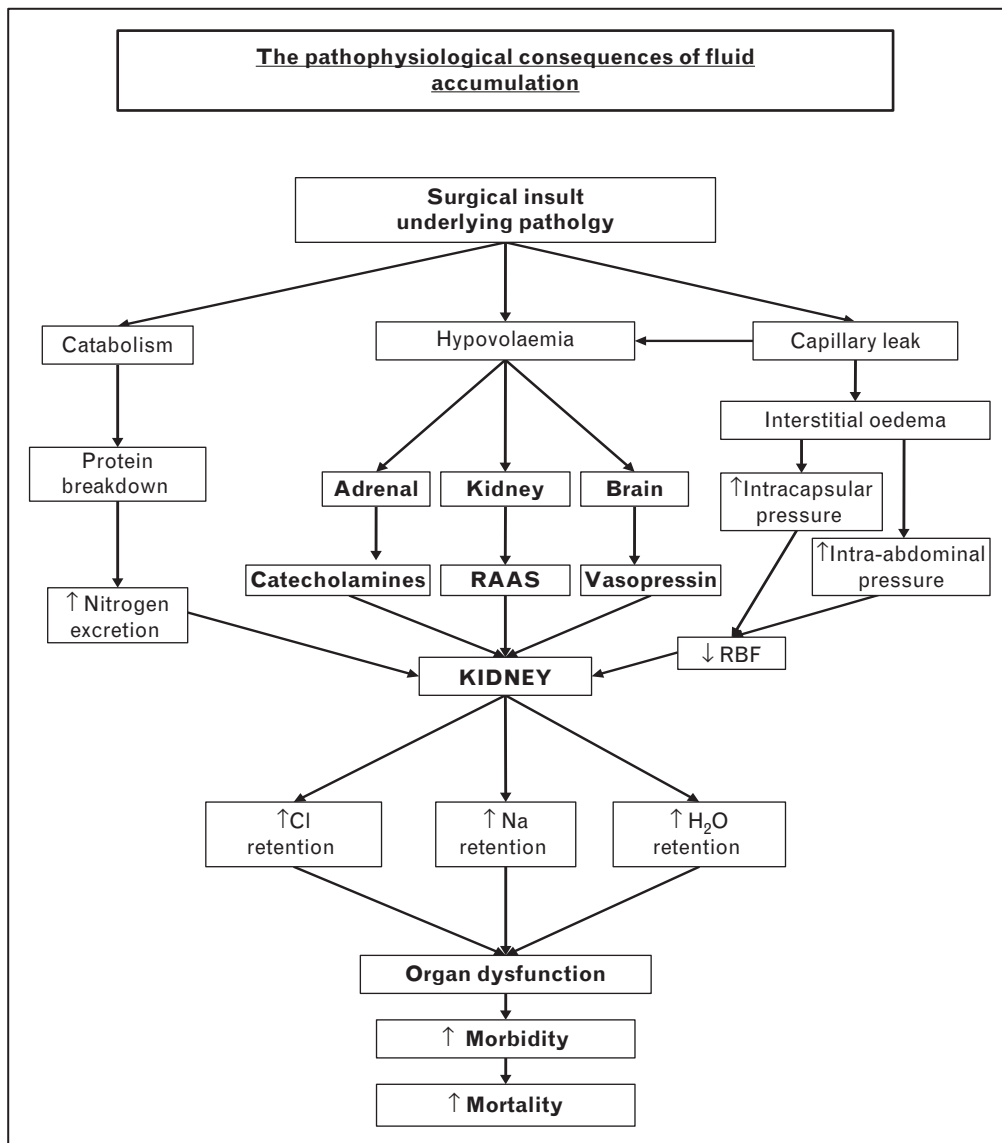


FIGURE 1. The pathological consequences of fluid accumulation. A graphical representation of the potential consequences of liberal fluid administration during the peri-operative period. RAAS, renin-aldosterone-angiotensin system; RBF, renal blood flow.

has been shown to result in the development of hyperchloraemic acidosis [39]. This is explained by Stewart’s physicochemical approach to acid–base balance [40]. Hyperchloraemia is associated with higher circulating concentrations of proinflammatory cytokines in septic animal models [41]. It has also been associated with renal vasoconstriction in experimental situations [42] and after administration to volunteers [43]. This results in a reduction of salt and water clearance, and disorders of haemostasis through haemodilution [44]. All of these observations raise serious concerns that fluid bolus treatment and a positive fluid balance might well be more injurious to the patient than a more conservative approach to fluid therapy (Fig. 2).

THE MAP IS NOT THE TERRITORY AND THERE IS NO MAP

In most countries, BFT and MFT are still accepted as standard practice. Yet, even expert guidelines and consensus statements on peri-operative fluid management admit that high-grade evidence regarding the optimal regimen in terms of timing, type of fluid, and risk stratification is currently lacking [3,4^{***}]. These guidelines warn against excess fluid administration with the potential for tissue and pulmonary oedema, but also state that BFT should be the first-line therapy for hypotension. Patients, as a result, tend to be resuscitated far beyond their probable requirements, with an average gain of 3–7 kg in weight in the postoperative period [45].

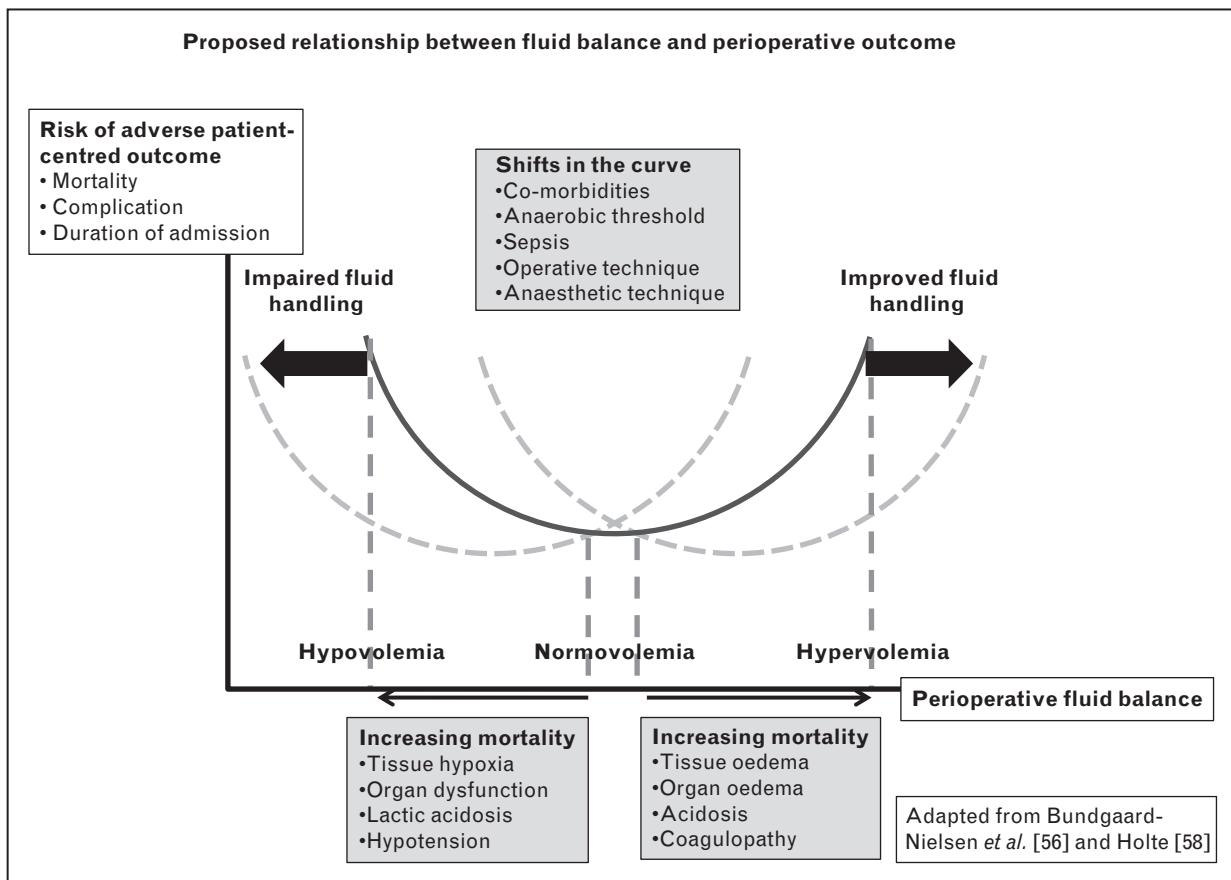


FIGURE 2. The proposed relationship between fluid balance and peri-operative outcome. This graph demonstrates the proposed influence of fluid balance on patient-centred outcomes. A right shift of the fluid balance–risk curve indicates optimal surgical technique, optimal anaesthetic technique, preoperative optimization, and so on. A left shift of the curve indicates a reduced fluid handling capacity through comorbidity, poor operative technique or the presence of sepsis or the systemic inflammatory response syndrome.

Practice across the world is inconsistent. A recent survey of Spanish colorectal surgeons demonstrated that 57.7% of those surveyed prescribe 3000 ml or more of maintenance i.v. fluids on the first postoperative day, and 6.2% less than 2000 ml [46]. Less than 50% of junior doctors in UK hospitals were aware of daily sodium requirements, though they were responsible for peri-operative fluid prescribing in 89% of instances, and more than 25% prescribed more than 2000 ml of 0.9% saline daily [47]. Only 22% of UK hospitals have written peri-operative fluid guidelines [48]. A single-centre survey of Canadian surgeons, anaesthetists and intensivists identified a significant difference between both the quantities of fluid administered, and the resuscitation end-points targeted, by the different specialties [49].

It is clear that many questions regarding the risks and benefits of fluid therapy remain unanswered. Assuming that basal metabolic requirements still need to be met in the intra-operative period

[3,4²²], then an optimal regimen for fluid administration needs to be identified. If the rationale for intra-operative BFT is correct, then beneficial physiological changes should be demonstrable using the many commercially available forms of haemodynamic monitoring, and should translate into improved patient-centred outcomes [50]. The increasing interest in the study of liberal versus restricted fluid regimens and the introduction of goal-directed therapy has begun to identify how peri-operative fluid balance can be optimized to maximize the beneficial and minimize the harmful effects of BFT and MFT.

CONSERVATIVE LIBERALS AND RADICAL RESTRICTION

Traditional peri-operative i.v. fluid regimens are based around the administration of fluid at a fixed infusion rate, determined by estimation of peri-operative fluid loss. Clinicians are notoriously poor

at such estimation [51]. In abdominal surgery this approach can lead to patients receiving 3.5–7 litres of fluid on the day of surgery and more than 3 litres/day for the following 3–4 days [45]. There have been multiple single-centre studies investigating the effects of liberal versus restrictive peri-operative fluid strategies, with some individual studies suggesting that fluid restriction may improve gastric emptying time, reduce the risk of ileus and reduce the duration of in-patient stay [52], and even mortality [53]. Others have found either no evidence of benefit [54] or harm [55]. A systematic review [56] and two meta-analyses [21¹¹,57] have recently been published.

The systematic review served to highlight the wild heterogeneity of these small trials. There is no doubt that definitions of what constitutes liberal or restrictive i.v. fluid therapy confuse interpretation of most studies. The range of 'liberal' i.v. fluid replacement varied from 2750 to 5388 ml compared with 998 to 2740 ml in the 'restrictive' regimen. The period for fluid therapy and outcome end-points were inconsistently defined. Only two studies reported peri-operative care principles and discharge criteria [56].

The first meta-analysis examined randomized trials investigating the manner of fluid administration and goal-directed fluid therapy by oesophageal Doppler in patients undergoing colorectal surgery. They identified nine randomized trials and found that both a restrictive fluid strategy [odds ratio (OR) 0.41, 95% confidence interval (CI) 0.22–0.77, $P=0.005$] and goal-directed therapy (OR 0.43, 95% CI 0.26–0.71, $P=0.001$) significantly reduced overall morbidity [57]. Varadhan and Lobo [21¹¹] identified six randomized trials with 452 patients and found that a restrictive fluid strategy did not reduce complication rates (risk ratio 0.96, 95% CI 0.56, 1.65, $P=0.89$) or length of hospital stay [weighted mean difference (WMD) -1.77 , 95% CI -4.36 , 0.81 , $P=0.18$] and there was no significant difference in readmission and mortality rates. However, when corrected for fluid balance, not merely administration, those patients managed with a less positive fluid balance had significantly fewer complications (risk ratio 0.59, 95% CI 0.44, 0.81 , $P=0.0008$) and a shorter length of stay (WMD -3.44 , 95% CI -6.33 , -0.54 , $P=0.02$) [21¹¹].

The conclusions that can be drawn from the examination of these meta-analyses are limited. The trials included are small, and single-centre. The number of patients examined in each meta-analysis is small. The populations studied are heterogeneous in terms of sex and age, comorbidity, preoperative hydration, extent of surgery, and anaesthetic technique. Each of these factors is likely

to influence fluid needs, and therefore outcome, particularly if outcome is linked to fluid balance, rather than a fixed volume administration [21¹¹]. Clinical equipoise remains – is fluid restriction beneficial? Is liberal administration harmful? Large multicentre retrospective observational studies looking at fluid balance and administration, as well as large, methodologically sound, randomized, multicentre controlled trials prospectively comparing liberal and restrictive fluid administration strategies are desperately needed to adequately appraise the role of peri-operative MFT.

AIMING FOR A GOAL

If fluid balance is important, and fluid overload is harmful, then clinicians need to be able to identify when patients are adequately filled. Conventional intra-operative monitoring of the circulation and tissue perfusion includes heart rate, blood pressure, urine output and central venous pressure with occasional measurement of arterial blood gases and haematocrit. Unfortunately, these variables are not reliable predictors of intravascular fluid status and thus do not offer a sufficiently accurate and rational guide to peri-operative fluid therapy [58¹¹]. As monitoring becomes more invasive, through the use of central vein catheterization, pulmonary artery catheterization, oesophageal Doppler, and other minimally invasive devices, pressure-derived variables can be estimated. These include the traditional measures of central venous and estimated left atrial pressure, as well as more recent additions such as intrathoracic blood volume, extra-vascular lung water, and stroke volume variation.

The use of haemodynamic variables to resuscitate patients to predefined end-points was first described in the 1970s [59] and demonstrated a survival benefit in high-risk surgical patients [60]. Goal-directed therapy (GDT) is based on the assumption that fluid resuscitation to maximize flow-related parameters as a surrogate for oxygen delivery may improve outcome [58¹¹]. These approaches tend to utilize not only BFT, but also vasoactive medications including vasoconstrictors and inotropic agents [58¹¹]. Whether they are beneficial, however, has not been adequately tested.

Central venous pressure is unreliable as a measure of intravascular status intra-operatively and in the critically ill [61¹¹]. Central venous catheterization carries the risk of thrombosis and site infection [62], but also allows central venous oxygen saturation (ScvO₂) monitoring. This is being used increasingly as a surrogate for mixed venous oxygen saturation measurement, despite only being

an estimate of torso, upper limb and cerebral oxygen extraction [63].

Pulmonary artery catheters are used both in the operating theatre and the intensive care settings. A degree of equipoise remains regarding their use as there is a degree of morbidity associated with their

insertion [64]. In clinical trials of GDT in elective surgical patients the pulmonary artery catheter has largely been disappointing [65]. Capillary wedge pressures, primarily due to nonlinear variations in vascular compliance, are also relatively poor measures of intravascular status [66].

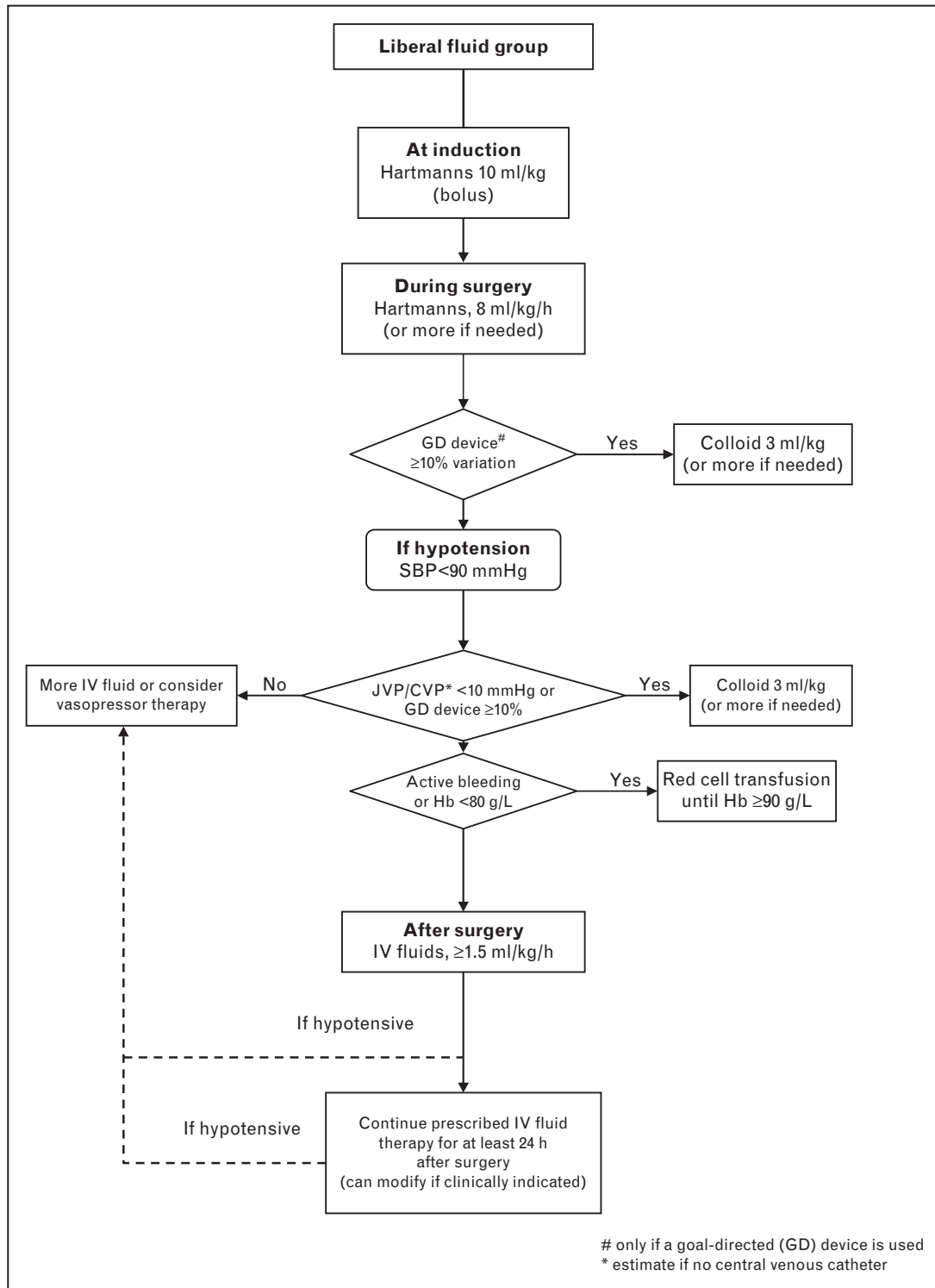


FIGURE 3. Proposed fluid management protocol for the RELIEF study's liberal fluid management arm. Central venous pressure (CVP) is either directly measured via central venous line or jugular venous pressure (JVP) is estimated by examination of neck veins.

GDT targeted using minimally invasive monitors such as oesophageal Doppler is becoming popular for intra-operative and ICU use [67]. Two recent meta-analyses confirm the findings of individual trials that their use may be associated with improved patient-centred outcomes in major abdominal surgery [68,69], despite 1000–2000 ml more fluid being administered on average intra-operatively [68].

The first of these analysed four trials and 393 patients demonstrating a significant decrease

in postoperative complications (POR 0.32, 95% CI 0.19–0.52, $P < 0.0001$) and duration of in-patient stay (WMD 1.68 days, 95% CI 2.39–0.98, $P < 0.0001$), despite some heterogeneity being observed in the quantities of intra-operative fluid being administered [68]. Similar results in the same population were reported by Abbas and Hill [69] who included an additional trial for a total of 420 patients. GDT reduced ICU admissions (POR 0.2, 95% CI 0.07–0.57, $P = 0.002$), and hastened the return of normal gastrointestinal function (POR 1.66, 95% CI 1.47–1.85,

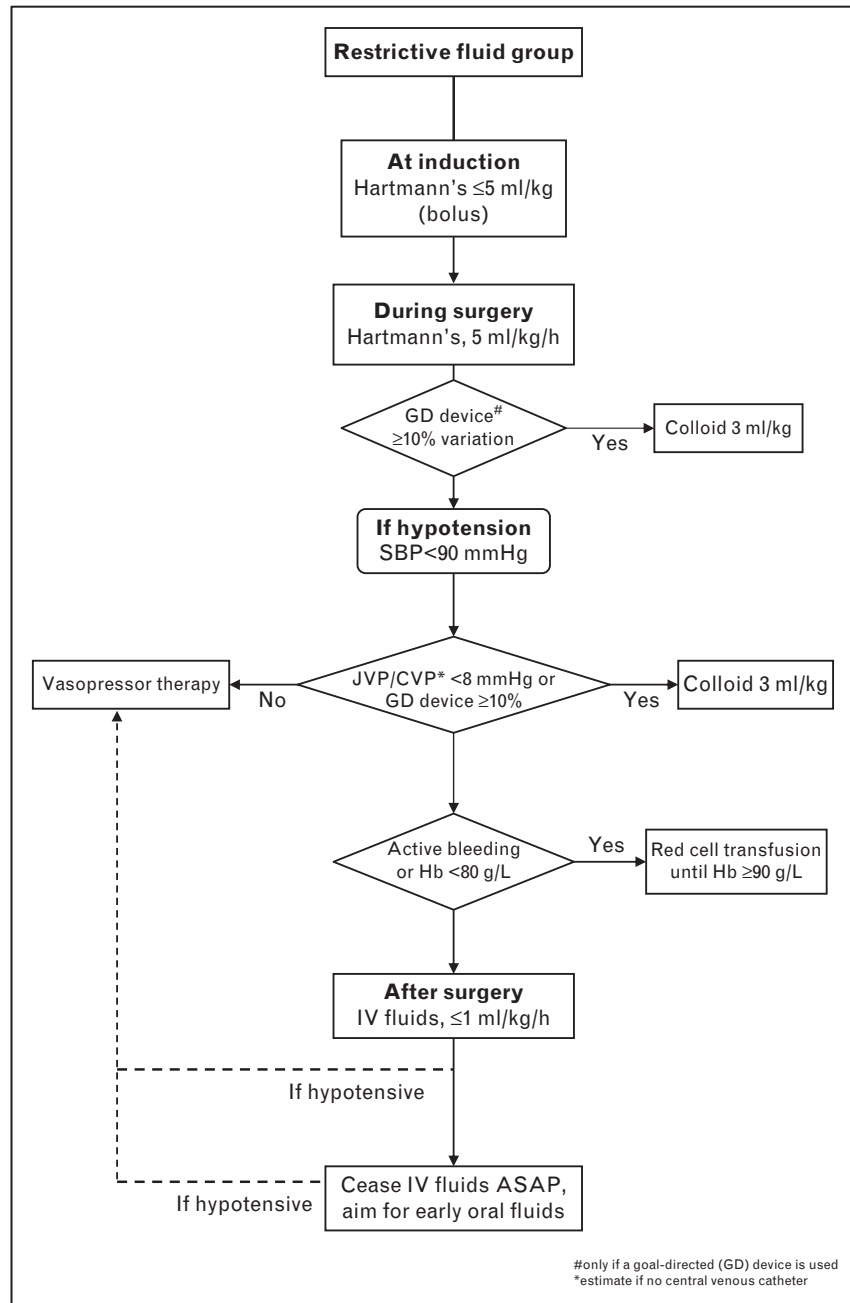


FIGURE 4. Proposed fluid management protocol for the RELIEF study’s conservative fluid management arm. Central venous pressure (CVP) is either directly measured via central venous line or jugular venous pressure (JVP) is estimated by examination of neck veins.

$P < 0.0001$) in the intervention group. It would appear that GDT may offer a survival advantage and reduce morbidity, at least in high-risk surgical patients. The meta-analyses need to be interpreted with caution, however, due to the small population and limited number of events and the potential for bias in studies in which the intervention is delivered by protagonists in single centres and with the inability to achieve blinding.

THE AUSTRALIAN APPROACH

The wide current variation in practice between countries, units, specialities and individuals suggests that clinical equipoise exists regarding the use of liberal versus conservative fluid therapy in the peri-operative period. It is also clear that the evidence base for peri-operative fluid management is lacking, but there is good evidence that fluid balance may affect outcome. The Australian anaesthesiology and intensive care community has agreed that this is now an area of priority in clinical research. Surveys indicate that, in Australia, as in other jurisdictions, there is significant practice variation with regard to fluid administration as well as equipoise for a randomized controlled trial of liberal versus conservative peri-operative fluid management. Accordingly, a pilot feasibility study is being undertaken to prepare for a large multicentre randomized controlled trial. Such a pilot investigation is studying the ability of clinicians to recruit and randomize patients to two different approaches to peri-operative fluid therapy. It also aims to define the incidence of several relevant outcomes so that appropriate power calculations can be performed and to assess whether clinicians can adhere to the principles of the study protocol (Figs 3 and 4) across the different phases of treatment from the operating room, to the recovery room, to the ICU, to the step-down unit to the ward. Achievement of these goals and completion of the pilot study are expected by the end of 2011. If successful, this approach will likely open the door for a large multicentre study called RELIEF (REstrictive versus LIBeral Fluid Therapy in Major Abdominal Surgery), which should begin in 2013 and achieve completion in 2016.

CONCLUSION

The entire field of fluid therapy in the peri-operative period is bereft of level 1 evidence to guide clinicians in their choice of treatment. The Australian anaesthesiology and intensive care community feel that this is an area of priority because of the likely importance of such therapy and its impact on

patient outcomes. In response, a process of preparation is underway for the design and completion of a large multicentre trial. Thus the Australian approach to peri-operative fluid balance is to pursue the creation of level 1 evidence to help rationalize a field in which a lack of such evidence leads to extreme practice variability and endless and fruitless discussions at the bedside.

Acknowledgements

None.

Conflicts of interest

There are no conflicts of interest.

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- of special interest
- of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (p. 120).

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