

Conference on ‘Malnutrition matters’

Symposium 3: Death by drowning

A meta-analysis of randomised controlled trials of intravenous fluid therapy in major elective open abdominal surgery: getting the balance right

Krishna K. Varadhan and Dileep N. Lobo*

Division of Gastrointestinal Surgery, Nottingham Digestive Diseases Centre, NIHR Biomedical Research Unit, Nottingham University Hospitals, Queen’s Medical Centre, Nottingham NG7 2UH, UK

The terminology used for describing intervention groups in randomised controlled trials (RCT) on the effect of intravenous fluid on outcome in abdominal surgery has been imprecise, and the lack of standardised definitions of the terms ‘standard’, ‘restricted’ and ‘liberal’ has led to some confusion and difficulty in interpreting the literature. The aims of this paper were to clarify these definitions and to use them to perform a meta-analysis of nine RCT on primarily crystalloid-based peri-operative intravenous fluid therapy in 801 patients undergoing elective open abdominal surgery. Patients who received more or less fluids than those who received a ‘balanced’ amount were considered to be in a state of ‘fluid imbalance’. When ‘restricted’ fluid regimens were compared with ‘standard or liberal’ fluid regimens, there was no difference in post-operative 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 $-4.36, 0.81$) d, $P = 0.18$). However, when the fluid regimens were reclassified and patients were grouped into those who were managed in a state of fluid ‘balance’ or ‘imbalance’, the former group 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 $-6.33, -0.54$) d, $P = 0.02$) than the latter. Using imprecise terminology, there was no apparent difference between the effects of fluid-restricted and standard or liberal fluid regimens on outcome in patients undergoing elective open abdominal surgery. However, patients managed in a state of fluid balance fared better than those managed in a state of fluid imbalance.

Fluid therapy: Peri-operative: Crystalloid: Saline: Overload: Restriction: Outcome: Meta-analysis

Peri-operative intravenous fluid therapy has been a much neglected area of clinical practice^(1,2) and suboptimal prescribing has often resulted in morbidity and even mortality^(3–6). The first decade of the 21st century has witnessed a surge in interest in peri-operative fluid therapy, and a number of randomised controlled trials (RCT) on the effect of different fluid regimens on outcome of elective open abdominal surgery have been published. However, the

terminology used to describe the intervention groups in these RCT has been imprecise and the lack of standardised definitions of the terms ‘standard’, ‘restricted’, ‘overload’, ‘liberal’ and ‘balance’ has led to some confusion and difficulty in interpreting the literature. Even in healthy volunteers, the effects of fluid infusions are dependent not only on the volume of fluid used, but also on the type of fluid, which may be a colloid or crystalloid, or a balanced

Abbreviations: RCT, randomised controlled trials.

*Corresponding author: Mr Dileep N. Lobo, fax +44 115 8231160, email dileep.lobo@nottingham.ac.uk

or unbalanced solution^(7–11). Colloids are retained primarily in the intravascular compartment and produce less interstitial fluid overload than crystalloids⁽⁹⁾. In addition, 0.9% saline produces a hyperchloraemic acidosis and is retained in the interstitial fluid compartment for longer than balanced crystalloids such as Ringer's lactate (or Hartmann's solution)^(10–14). Hence, pooling of the results of RCT⁽¹⁵⁾ without considering these factors further compounds the confusion and may make inferences difficult.

The goal of peri-operative fluid therapy should be to restore and maintain normal physiology, blood volume and organ function^(8,16) by using an appropriate volume of the right fluid to achieve a state of homeostasis. Both fluid overload and underhydration can detract from achieving this goal, resulting in adverse outcomes^(3,17,18).

Clarification of definitions of the terminology used to describe fluid regimens is essential in order to make a meaningful comparison of RCT. The aims of this paper were to clarify these definitions and to use them to perform a meta-analysis of RCT on primarily crystalloid-based peri-operative intravenous fluid therapy in patients undergoing elective open abdominal surgery.

Methods

Definitions

There exists a narrow range for optimal fluid therapy and provision of too much or too little fluid can result in adverse outcomes^(17–19). Maintenance requirements for water in human subjects is 25–35 ml/kg per d and that for Na and K is approximately 1 mmol/kg per d^(20–25). Hence, for the average patient without ongoing fluid deficits or losses, daily requirements for fluid range from 1.75 to 2.75 litres^(20,23,25,26). The aim of ideal peri-operative fluid therapy should be maintenance of zero fluid balance with minimal weight gain or loss^(8,18). Until recently, peri-operative maintenance fluid therapy consisted of the provision of at least 3 litres of water and 154 mmol Na. Although this is in excess of maintenance requirements, some studies have considered this to be a 'standard' fluid regimen⁽²⁷⁾. Some studies using 'restricted' fluid regimens have provided patients with appropriate maintenance requirements^(27,28), while others have used true restriction and given patients less than the desired amount^(29,30). In addition, there is often a discrepancy between the amount of fluid prescribed and that delivered. Hence, for the purpose of this meta-analysis, we used the following definitions for fluid delivered for maintenance requirements:

1. Restricted fluid therapy: <1.75 litres/d;
2. Liberal fluid therapy/fluid overload: >2.75 litres/d;
3. Fluid balance: between 1.75 and 2.75 litres/d;

For this meta-analysis, patients who received more or less fluid than those who received a balanced amount were considered to be in a state of 'fluid imbalance'. In studies where the volume of fluid delivered was not discernable, estimates of restriction, overload and balance were determined from the cumulative fluid balance and/or weight change.

Criteria for considering studies for this meta-analysis

RCT comparing the effects of peri-operative fluid therapy with primarily intravenous crystalloid in patients over 18 years of age, undergoing major elective open abdominal surgery, were included in this meta-analysis. The criteria set were that the studies should describe the peri-operative fluid regimen in both the control and intervention groups and classify the regimens as 'restricted', 'standard' or 'liberal', according to the total amount of fluids given. The studies included should also have described a minimum of two clinical outcome measures.

Non-randomised controlled studies, those that used colloids primarily and those that used flow-directed therapy were excluded. Studies that did not describe clinical outcomes were also excluded. The primary analysis was performed initially by using the terminology for fluid regimens, as stated by the authors of the included RCT, to define the control and intervention groups and subsequently, using our aforementioned definitions, for comparisons of outcome.

Outcome measures

The primary outcome measure was post-operative complications, defined as the number of patients who developed complications in the post-operative period. Secondary outcome measures were length of hospital stay and in-hospital mortality.

Search methods for identification of studies

RCT comparing the effects of 'restricted' with 'standard' or 'liberal' peri-operative fluid therapy were searched for in the Medline, Embase and Cochrane databases from 1966 until date, using the search terms, 'intravenous fluids', 'fluid therapy', 'fluid restriction', 'liberal', 'surgery', 'major surgery', 'abdom* surgery', 'gastrointestinal' and 'colorectal' in combination with the Boolean operators AND, OR and NOT. The reference lists in the studies identified were hand-searched and the 'related articles' function was also used to identify similar studies. Experts in the field were consulted for their knowledge of any ongoing studies.

Data collection and analysis

Both authors identified the studies that met the inclusion criteria, collected relevant data and analysed outcomes. The characteristics of the studies were further assessed for method of randomisation, allocation concealment, reporting of bias, protocol violations and blinding. The Jadad score⁽³¹⁾ was calculated for the methodological quality of the included RCT using the following descriptions: consecutive series of patients, allocation concealment, method of randomisation, blinding and descriptions of withdrawals or dropouts. Missing data that were required for analysis were obtained by contacting the corresponding authors of the RCT when possible.

The studies were classified according to the total amount of fluid given in the peri-operative period, as those comparing restricted v. standard and restricted or standard v. liberal fluid therapy, according to both the authors' original

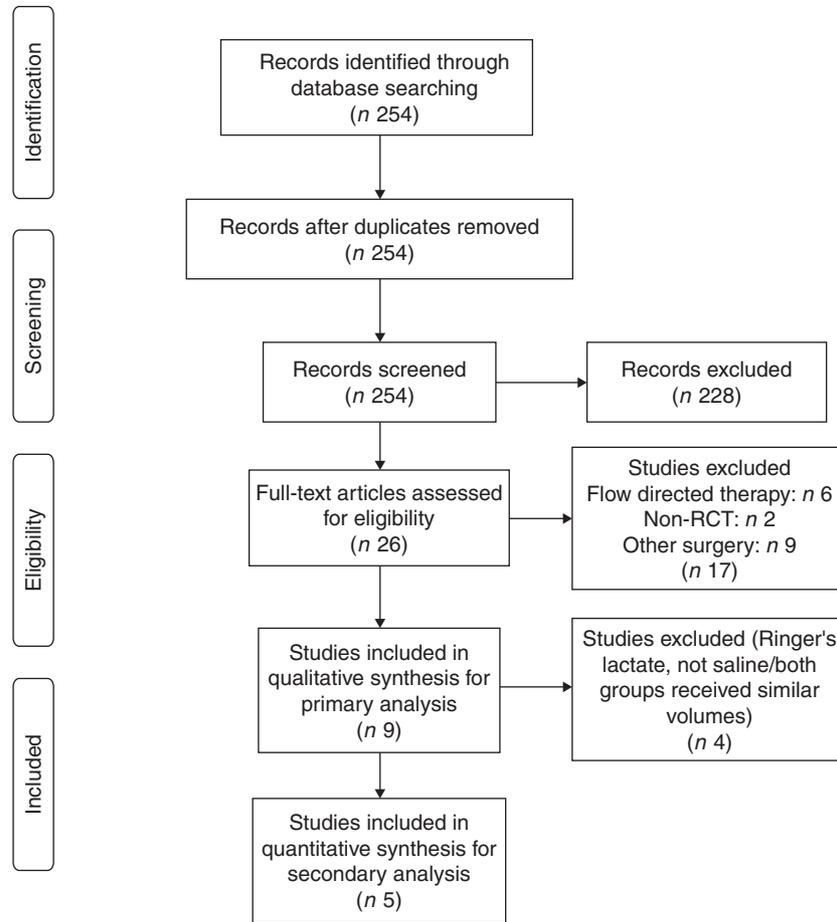


Fig. 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement summarising search for and selection of studies. RCT, randomised controlled trials.

definitions and ours. The included studies were further assessed carefully for the timing and description of interventions and the resulting outcomes for each group as described by the authors of individual studies, in an attempt to maintain uniformity for comparing different fluid regimens.

The primary analysis included all studies identified from the initial search. As 0.9% saline produces a hyperchloraemic acidosis and is retained in the interstitial fluid compartment for longer than balanced fluids such as Ringer's lactate (or Hartmann's solution)^(10–13), only those studies that used 0.9% saline primarily were included in the secondary analysis. Both the analyses were performed on an intention-to-treat basis.

Statistics

RevMan 5.0 software (The Nordic Cochrane Center, The Cochrane Collaboration, Copenhagen, Denmark) was used for the analysis of outcomes using the standard methods recommended by the Cochrane Collaboration⁽³²⁾. Pooled analyses were performed using the random-effects model with the Mantel–Haenszel method. Calculations of effect sizes for dichotomous variables are presented as risk ratio with 95% CI and for continuous outcomes as weighted

mean differences. Statistical heterogeneity was assessed by considering the I^2 statistic alongside the χ^2 P value. The threshold values of I^2 are 25%, 50% and above 50%, representing low, moderate and high heterogeneity, respectively.

Results

Characteristics of studies

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement (Fig. 1) illustrates the studies identified for inclusion in the final analysis after the initial search. All trials reported standardised peri-operative care using pre-defined criteria of fluid management.

Nine studies^(27–30,33–37) with a total of 801 patients met the inclusion criteria for the primary analysis. The characteristics of the studies are summarised in Table 1. The mean Jadad score for the nine RCT was 3.7 (range 3–5), indicating moderate methodological quality. All studies involved a consecutive series of patients using appropriate randomisation methods, including computer-generated randomisation numbers in four^(28,29,33,34), the sealed envelope method in four^(27,30,36,37) and telephone randomisation in

Table 1. Characteristics of the randomised controlled trials included in the meta-analysis

Study (timing of intervention)	Operation	Groups (study author terminology)	Number of patients	Age (years)	Fluid regimen	Complications (patients)	Length of stay (d): mean (SD)	Re-admissions
Lobo <i>et al.</i> ⁽²⁷⁾ (post-operative)	Colonic resections	Standard	10	Median (IQR) 58.9 (55–67)	At least 3 litres water and 154 mmol Na over 24 h (1 litre 0.9% saline + 2 litres 5% dextrose)	7	10.2 (3.6)	1
		Restricted	10	Median (IQR) 62.3 (52–67)	No more than 2 litres water and 75 mmol Na over 24 h (2 litres 4% dextrose/0.18% saline)	1	6.1 (1.0)	0
Brandstrup <i>et al.</i> ⁽²⁸⁾ (intraoperative and post-operative)	Colorectal resections	Standard	72	Median (range) 69 (41–88)	Intraoperative: 6% HAES in 0.9% saline preloaded before epidural analgesia. Maintenance: 500 ml of 0.9% saline independent of oral intake. 0.9% Saline for third space and external loss. Blood component therapy, if loss > 1500 ml. Post-operative: recommended departmental practice of 1000–2000 ml crystalloid	44	12.1 (10.9)	Not available
		Restricted	69	Median (range) 64 (42–90)	Intraoperative: no preloading, no replacement for third space loss. Maintenance: 500 ml of 5% glucose in water minus the oral fluid intake during fast. Blood component therapy, if loss > 1500 ml. 1000 ml of 5% glucose (with K if needed). Drain loss: Volume – Volume with 6% HAES	28	10.8 (7.5)	Not available
Kabon <i>et al.</i> ⁽³⁴⁾ (intraoperative and post-operative)	Colonic resections >2 h	Large volume	129	Mean (SD) 52 (15)	10 ml/kg Ringer's lactate bolus before induction and at 16–18 ml/kg per h intraoperatively until 1 h post-operatively. Subsequently, 2 ml/kg per h until day 1 post-operatively	19	7 (5.4)	Not available
		Small volume	124	Mean (SD) 53 (14)	8–10 ml/kg per h of Ringer's lactate intraoperatively and until 1 h post-operatively. Subsequently, 2 ml/kg per h until day 1 post-operatively	17	7.3 (4)	Not available
Nisanevich <i>et al.</i> ⁽³⁷⁾ (intraoperative)	Major intra-abdominal surgery	Liberal	75	Mean (SD) 59 (12)	Initial bolus of 10 ml/kg Ringer's lactate before skin incision + 12 ml/kg per h intraoperatively. 250 ml Boluses as needed for low urine output, low BP and high pulse rate. CVP < 15 mmHg treated by 6% HAES	23	Not available as mean (SD) 9 (7–24) Median (range)	F/U only until discharge
		Restricted	77	Mean (SD) 63 (13)	4 ml/kg per h Ringer's lactate intraoperatively. Rest same as Liberal group	13	Not available as mean (SD) 8 (6–21) Median (range)	F/U only until discharge
MacKay <i>et al.</i> ⁽³⁵⁾ (post-operative)	Colorectal resections	Standard	41	Median (IQR) 73 (67–83)	Intraoperative: 10 ml/kg per h 4% dextrose/0.18% saline and 3 × blood loss. One litre 0.9% saline and 2 litres 5% dextrose per day post-operatively	10	10.5 (12.3)	1
		Restricted	39	Median (IQR) 73 (65–78)	Intraoperative: 10 ml/kg per h 4% dextrose/0.18% saline and 3 × blood loss, total 2 litres 4% dextrose/0.18% saline at 83 ml/h post-operatively	14	9.3 (4.9)	1

A meta-analysis of randomised controlled trials of intravenous fluid therapy in major elective open abdominal surgery

Table 1 (Continued)

Study (timing of intervention)	Operation	Groups (study author terminology)	Number of patients	Age (years)	Fluid regimen	Complications (patients)	Length of stay (d): mean (SD)	Re-admissions
Holte <i>et al.</i> ⁽³⁰⁾ (intraoperative and post-operative)	Colonic resections	Liberal	16	Median (range) 76 (53–93)	Oral carbohydrate loading the evening before and 2 h before surgery. 10 ml/kg Ringer's lactate preload; 18 ml/kg per h + Voluven 7 ml/kg intraoperative. 10 ml/kg Ringer's lactate after operation on day of surgery	1	3.3 (2.3)	2
		Restricted	16	Median (range) 73 (56–87)	Oral carbohydrate loading the evening before and 2 h before surgery. No preload; 7 ml/kg per h Ringer's lactate the first hour + 5 ml/kg per h Ringer's lactate subsequent hours + Voluven 7 ml/kg intraoperatively. No i.v. fluids after operation	6	5.4 (8.2)	6
Gonzalez-Fajardo <i>et al.</i> ⁽³³⁾ (post-operative)	Elective abdominal vascular surgery	Standard	20	Mean (95% CI) 62 (57–67)	Standard intraoperative regime for both groups. 500 ml Ringer's lactate preload. 0.9% Saline for third space loss and blood loss. Hetastarch (6%) and blood if more blood loss. ICU: 3 litre 0.9% saline/d. Post-operatively: 2.5 litres/d (1.5 litres 0.9% saline and 1 litre 5% dextrose)	4	12.4 (7.9)	0
		Restricted	20	Mean (95% CI) 65 (62–69)	Standard intraoperative regime for both groups. 500 ml Ringer's lactate preload. 0.9% Saline for third space loss and blood loss. Hetastarch (6%) and blood if more blood loss. ICU: 3 litre 0.9% saline/d. Post-operatively: 1.5 litre 0.9% saline/d.	0	8.4 (1.4)	0
Vermeulen <i>et al.</i> ⁽²⁹⁾ (post-operative)	Major abdominal surgery	Standard	32	Mean (SD) 54 (15)	2.5 litres Ringer's lactate for the first 24 h after surgery. Subsequently, 1.5 litres 0.9% NaCl + 1 litre 5% dextrose	13	8.3 (4.5)	4
		Restricted	30	Mean (SD) 55 (15)	1.5 litres Ringer's lactate for the first 24 h after surgery. Subsequently, 1 litre 0.9% NaCl + 500 ml 5% dextrose	23	12.3 (12.7)	3
McArdle <i>et al.</i> ⁽³⁶⁾ (intraoperative and post-operative)	Open elective abdominal aortic aneurysm repair	Standard	11	Median (range) 75 (64–86)	10 ml/kg 0.9% saline preload; 12 ml/kg per h Hartmann's solution during surgery; 125 ml/h Hartmann's solution on day of surgery post-operatively; days 1–5: 1 litre 0.9% saline + 2 litres 5% dextrose/d	7	16 (4.8)	0
		Restricted	10	Median (range) 74 (58–80)	No preload; 4 ml/kg per h Hartmann's solution during surgery; 83 ml/h Hartmann's solution on day of surgery post-operatively; days 1–5: 0.5 litre 0.9% saline + 1.5 litres 5% dextrose/d	1	7.8 (0.64)	0

BP, blood pressure; CVP, central venous pressure; F/U, follow up; HAES, hydroxyethyl starch; ICU, intensive care unit; IQR, interquartile range.

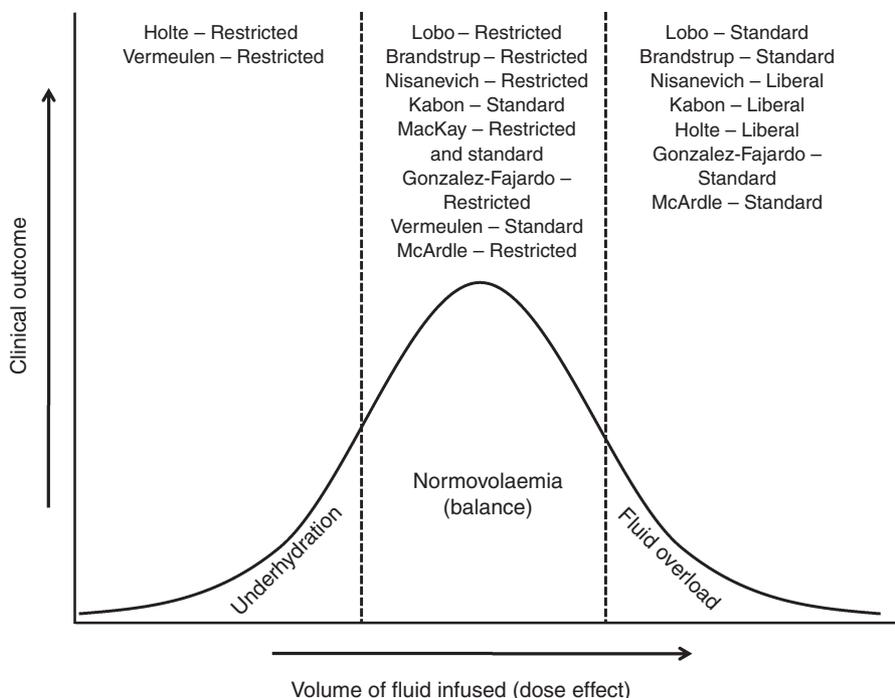


Fig. 2. Reclassification of intervention groups in the randomised controlled studies. The intervention groups, as described in the original studies, are mentioned after the authors' names.

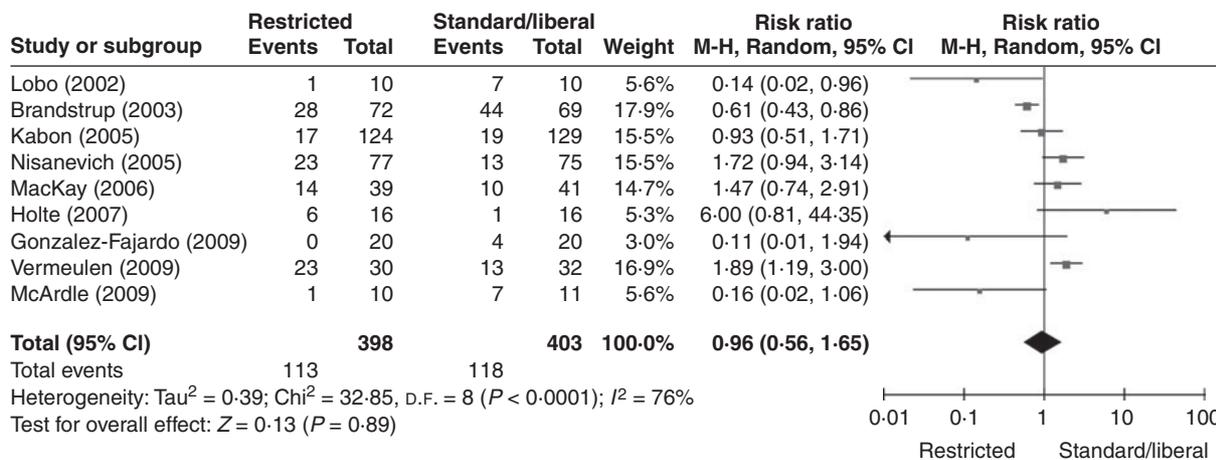


Fig. 3. Forest plot of comparison: complications using original definitions of intervention groups (restricted v. standard or liberal). Primary analysis using all nine studies. M-H, the Mantel-Haenszel test.

one⁽³⁵⁾. All studies except one⁽³⁴⁾ reported a 30-d follow-up period. Only two studies^(29,30) were performed in a double-blind manner. Two were unblinded^(27,36) and the rest^(28,33-35,37) were reported as observer-blinded.

Three studies^(30,34,37) that used Ringer's lactate primarily and another study⁽³⁵⁾ in which similar amount of fluids were given in both the 'standard' and 'restricted' groups were excluded from the secondary analysis. Thus, only five studies^(27-29,33,36) with 284 patients were subsequently included in the secondary analysis. Patients included in these studies mainly underwent colonic resections and aortic surgery was performed in two studies^(33,36).

Based on our definitions, the reclassification of intervention groups in the included RCT is shown in Fig. 2.

In one study⁽³⁵⁾, both groups received fluids within the range of normovolaemia, and in another study⁽³⁰⁾, one group received an excess of fluid and the other a deficit of fluid. In a third study⁽³³⁾, the cumulative fluid balance reported suggests that the 'restricted' group was in a state of zero fluid balance and the 'standard' group was in a state of fluid overload.

Meta-analysis

A Forest plot of complication rates (Fig. 3) using the terminology described by the authors of each of the nine studies (restricted v. standard or liberal) showed no statistically significant difference between the two groups.

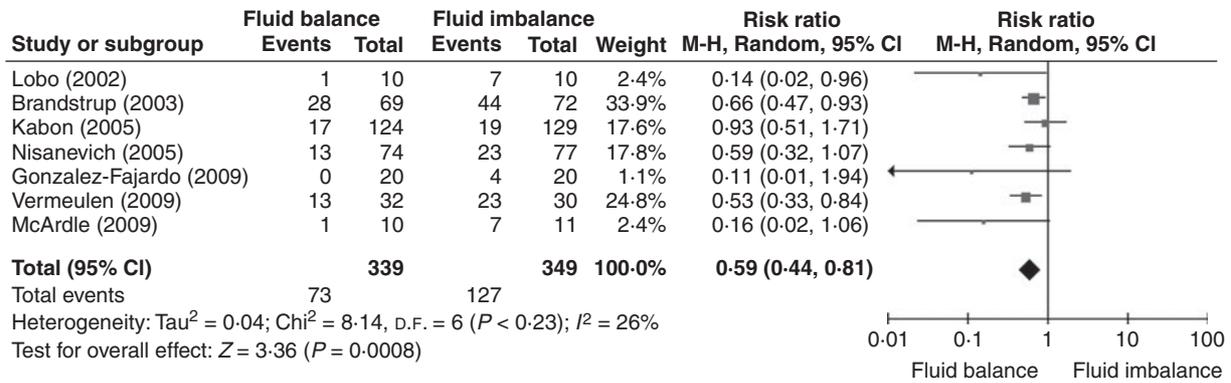


Fig. 4. Forest plot of comparison: complications using revised definitions of intervention groups (fluid balance v. fluid imbalance). Primary analysis using seven studies (studies in which both groups were in fluid balance⁽³⁵⁾ or imbalance⁽³⁰⁾ were excluded). M-H, Mantel-Haenszel test.

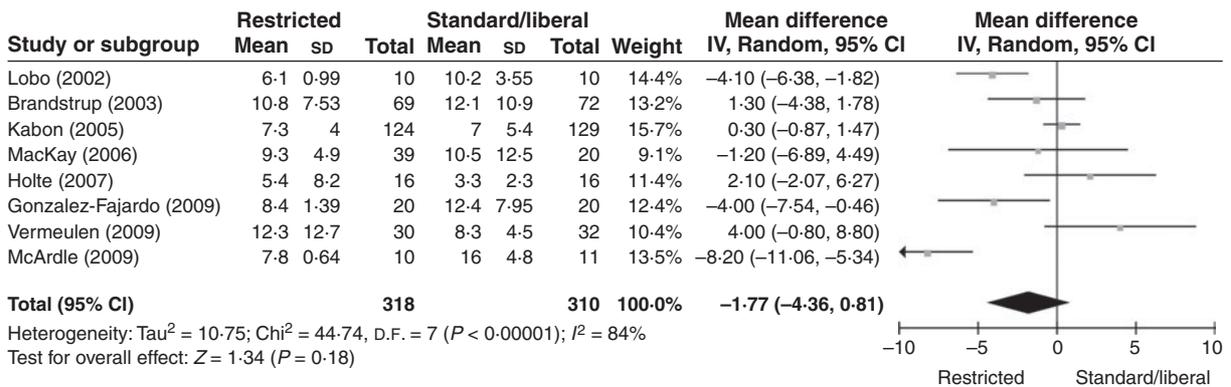


Fig. 5. Forest plot of comparison: length of hospital stay (d) using original definitions of intervention groups (restricted v. standard or liberal). Primary analysis using eight studies. Data for one study⁽³⁷⁾ were mentioned as median (range) and could not be incorporated into the Forest plot. IV, inverse variance.

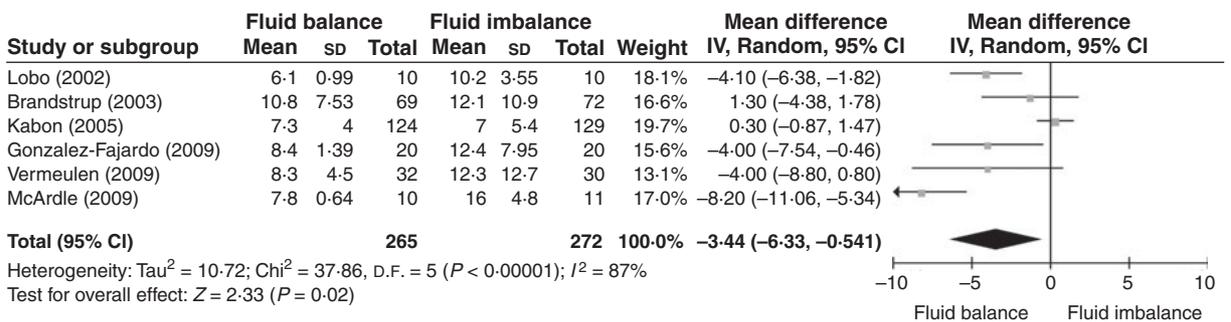


Fig. 6. Forest plot of comparison: length of hospital stay (d) using revised definitions of intervention groups (fluid balance v. fluid imbalance). Primary analysis using six studies (studies in which both groups were in fluid balance⁽³⁵⁾ or imbalance⁽³⁰⁾ were excluded). Data for one study⁽³⁷⁾ were mentioned as median (range) and could not be incorporated into the Forest plot.

However, when definitions of balance and imbalance were applied to the seven eligible studies after excluding the two studies where both intervention groups were either in balance⁽³⁵⁾ or imbalance⁽³⁰⁾, there was a 59% reduction in risk of developing complications in the group that was in a state of fluid balance when compared with the group in imbalance (Fig. 4). Using the individual authors' terminology, there was no statistically significant difference in length of hospital stay between the groups (Fig. 5), but

when the groups in fluid balance and imbalance were compared, there was a 3.4-d reduction in hospital stay in the former group (Fig. 6).

When the secondary analysis was performed on the five studies in which saline was the primary crystalloid used, there was a 49% reduction in complications (Fig. 7) and a 4.4-d reduction in length of hospital stay (Fig. 8) in the group that was in a state of fluid balance when compared with the group that was in a state of fluid imbalance.

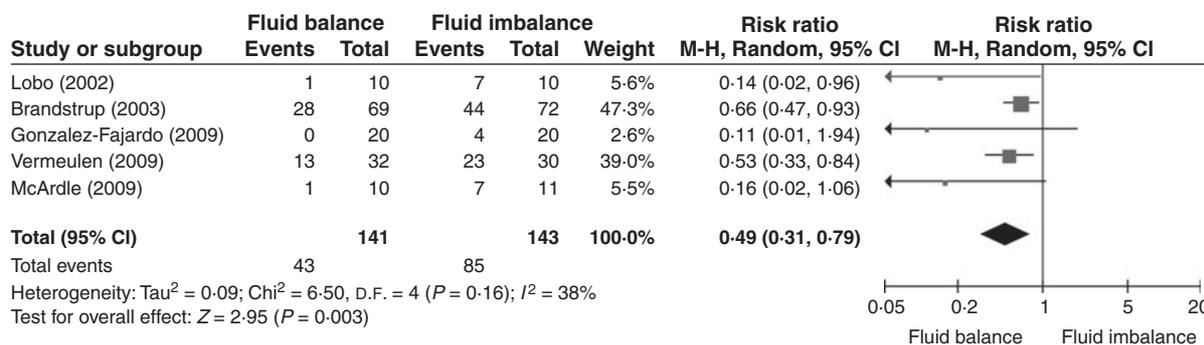


Fig. 7. Forest plot of comparison: complications using revised definitions of intervention groups (fluid balance v. fluid imbalance). Secondary analysis using five studies in which saline-based crystalloid therapy was used. (One study⁽³⁵⁾ in which both groups were in fluid balance was excluded.) M–H, Mantel–Haenszel test.

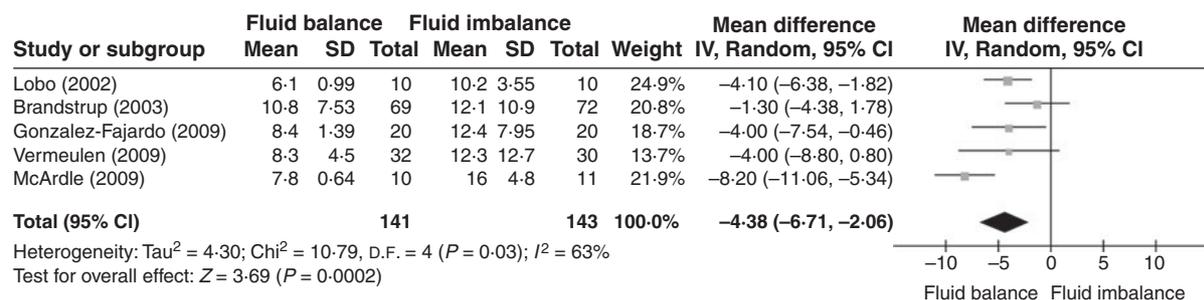


Fig. 8. Forest plot of comparison: length of hospital stay (d) using revised definitions of intervention groups (fluid balance v. fluid imbalance). Secondary analysis using five studies in which saline-based crystalloid therapy was used. (One study⁽³⁵⁾ in which both groups were in fluid balance was excluded.) IV, inverse variance.

Weight change was reported in only five^(27,28,30,35,37) of the nine studies and ranged from -1.2 to 1.3 kg in the fluid-restricted groups and from 1.6 to 3.0 kg in the standard/liberal groups. Maximum weight gain was seen in the studies in which the standard group received an excessive amount of fluid^(27,28,37). A significant dose–response relationship between the amount of intravenous fluid given and weight change as well as complications was reported in one study⁽²⁸⁾, with complications being significantly greater in those gaining >2.5 kg in weight when compared with those gaining <0.5 kg.

Patients included had an American Society of Anesthesiologists class of I–III in eight studies and of I–IV in one⁽²⁸⁾. There were a total of only six deaths and 18 readmissions in the nine studies and, therefore, a meaningful comparison for these outcomes could not be made.

Discussion

The results of this meta-analysis emphasise the importance of standardisation of definitions and a critique of methodology before making firm inferences on pooled data. On the surface, when ‘restricted’ fluid regimens were compared with ‘standard or liberal’ fluid regimens, there was no difference in either post-operative complication rates or length of hospital stay (Figs. 3 and 5). However, when the fluid regimens were reclassified and patients were grouped into those who were managed in a state of fluid ‘balance’ or ‘imbalance’, it was clear that those who were in a state

of fluid balance had 59% fewer complications (Fig. 4) and a 3.4 d shorter length of hospital stay (Fig. 6) than those who were in a state of fluid imbalance. When only primarily saline-based crystalloid therapy was considered, patients in a state of fluid balance had 49% fewer complications (Fig. 7) and a 4.4 d shorter length of hospital stay (Fig. 8) than those who were in a state of fluid imbalance. Hence, managing patients in a state of fluid balance has profound implications on clinical outcome. It also substantiates previous concepts that there is a relatively narrow range for safe fluid therapy^(8,16–19,38) and that either too little or too much fluid in the peri-operative period may be associated with increased risk of complications and prolongation of hospital stay.

There are, however, several limitations to this meta-analysis. Although we have attempted to reclassify the fluid regimens, data on fluid delivered to patients were not always available in results of the individual studies and some extrapolations were made on the basis of weight change and fluid balance. One study⁽³⁷⁾ looked at only intraoperative fluid therapy and three studies^(27,29,33,35) looked at only post-operative fluid therapy. Both intraoperative and post-operative interventions were studied in the remaining four RCT^(28,30,34,36). Fluid therapy also varied with some patients receiving colloid boluses in three of the studies^(28,29,33). Double blinding was achieved in only two studies and although five were assessor-blinded, the very nature of the intervention makes true blinding difficult. Three RCT were halted prematurely after an interim analysis as the treatment effect was much larger than

expected in one study⁽²⁷⁾, the numbers planned were deemed unlikely to show clinically important results in the second study⁽³⁴⁾ and there were increased complication rates and protocol violations in one group in the third study⁽²⁹⁾. Only six studies recruited the desired number of patients. The relatively high heterogeneity, as indicated by the I^2 values of the pooled results in the Forest plots (Figs. 3–8), suggests individual variations in the included studies that could be a reflection of methodological quality and the interventions used. In addition, studies on flow (or goal) directed fluid therapy⁽³⁹⁾ were not included as direct comparison was not possible. Nevertheless, this meta-analysis is important, as within its limitations, it emphasises the importance of maintaining peri-operative patients in a state of fluid balance and it appears that patients who gain at least 2.5–3 kg in weight, as a result of salt and water overload, in the post-operative period have a worse outcome than those maintained in a state of zero fluid balance.

Over the course of evolution, efficient mechanisms to conserve salt and water have developed as a protective response to preserve the effective circulating volume in times of injury and stress. Exposure to an excess of salt and water is a recent phenomenon and, therefore, the mechanisms to excrete this overload are inefficient and largely dependent on a slow and sustained suppression of the renin–angiotensin–aldosterone axis^(9,40). This inefficiency may be compounded by a reduction in renal blood flow and glomerular filtration rate^(13,41) caused by the hyperchloraemic acidosis produced by infusions of 0.9% saline. Healthy volunteers can take over 2 d to excrete an infusion of 2 litres of 0.9% saline over 25 min⁽⁴⁰⁾. Most of the retained fluid after acute infusions accumulates in the interstitial compartment, leading to oedema^(7,9,10). Splanchnic oedema can result in increased intra-abdominal pressure, ascites⁽⁴²⁾ and, in extreme cases, the abdominal compartment syndrome⁽⁴³⁾. Intra-abdominal hypertension may lead to reduction in mesenteric blood flow, ileus or functional obstruction of anastomoses, increased gut permeability, intestinal failure and even anastomotic dehiscence⁽⁸⁾. In addition, hyperchloraemic acidosis, as a result of saline infusions, may reduce gastric blood flow and decrease gastric intramucosal pH in elderly surgical patients⁽⁴⁴⁾. A decrease in mesenteric blood flow, along with tissue oedema, can lead to tissue hypoxia and impair anastomotic healing further^(45,46). At the tissue and cellular levels, salt and water overload can also result in membrane hyperpolarisation, disordered neurotransmitter metabolism and impairment of mitochondrial activity⁽⁴⁷⁾.

Although fluid retention in the interstitial space is less with balanced crystalloids than 0.9% saline, the amount is still appreciable after infusion of large volumes^(10,11). Hence, there may be a greater margin for error when balanced crystalloids are used instead of 0.9% saline. Nevertheless, a study in rats undergoing small-bowel resection and anastomosis has shown that an excess of even a balanced crystalloid can result in submucosal intestinal oedema, a decrease in anastomotic bursting pressure and a decrease in hydroxyproline concentration in the anastomotic region, implying impairment of collagen synthesis and wound healing⁽⁴⁸⁾.

On the other hand, true fluid restriction resulting in underhydration can be equally detrimental by resulting in decreased venous return and cardiac output, diminished tissue perfusion and oxygen delivery, increased blood viscosity, decreased saliva production with a predisposition to post-operative parotitis, and an increase in viscosity of pulmonary mucus, resulting in mucous plug formation and atelectasis⁽²⁵⁾.

Peri-operative fluid therapy should be considered in the appropriate context and although maintaining patients in a state of fluid balance is ideal, this may not always be possible or desirable. Patients such as those who have acute blood loss or sepsis have a reduction in effective circulatory volume and must be resuscitated with relatively large amounts of fluids (crystalloids, colloids or blood) in order to replace this deficit in intravascular volume and maintain tissue perfusion and oxygen delivery. Thus, fluid overload may be an inevitable consequence of the resuscitation process in these patients, without which impairment in tissue oxygen delivery could result in serious adverse events and even death. It has been shown that in the first 48 h of resuscitation with crystalloids, septic patients can gain as much as 12.5 litres in total body water (i.e. a weight gain of 12.5 kg) and that it can take up to 3 weeks to excrete this accumulation of fluid⁽⁴⁹⁾. However, even in these patients, limitation of salt and water intake in the post acute phase can aid the excretion of this accumulated fluid excess and help in recovery and convalescence⁽⁵⁰⁾. Similarly, in patients with significant ongoing losses of fluid and electrolytes, such as those with intestinal fistulae, maintenance requirements must be supplemented with like-for-like replacement, both in terms of volume and electrolytes, for what is being lost.

Conclusion

Within its limitations, this meta-analysis has underpinned the importance of considering fluid volume, electrolyte content, fluid balance and weight change when interpreting the results of studies on peri-operative fluid therapy. Terminology used in individual studies must be critically evaluated before making conclusions, as application of inappropriate terms may invalidate the results of some studies. The main aim of optimum peri-operative fluid therapy should, therefore, be to maintain patients in a state of zero fluid balance, as far as possible, by providing them with the right amount of the right fluid at the right time.

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