The safety and efficacy of balanced crystalloid *vs.* normal saline in non-cardiac surgeries – A systematic review and meta-analysis

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Abstract. – OBJECTIVE: Balanced crystalloid and normal saline are routinely used in clinical anesthesia, but their safety and efficacy in non-cardiac surgeries are still unclear.

MATERIALS AND METHODS: PubMed, Embase, Web of Science, Cochrane Library, Wanfang, and CNKI, from January 1980 to March 2023, were searched. Studies comparing balanced crystalloid (BC) with normal saline (NS) during non-cardiac surgeries were included. The primary outcomes were clinical outcomes (acidosis, renal insufficiency, and mortality), and the secondary outcomes were pH value, Na+, Cl- and creatinine levels, and vasopressor requirement.

RESULTS: Forty-three RCTs were included in this meta-analysis. Low evidence revealed that the development of acidosis was lower in the BC group than in the NS group (OR: 0.05, 95% CI: 0.01-0.43, I^2=80.8%, *p*=0.00), and no between-group difference exists in renal insufficiency and mortality. At the end of surgery and on postoperative day 1 (POD 1), the pH value was higher, and the levels of Na+ and Cl- were lower in the BC group. No between-group difference exists in creatinine level and vasopressor requirement.

CONCLUSIONS: Perioperative balanced crystalloids can maintain the stability of acid-base and electrolyte balance and reduce acidosis compared with saline, but they cannot reduce postoperative renal insufficiency and mortality.

Key Words:
Balanced crystalloid, Normal saline, Non-cardiac surgery, Safety, Efficacy.

Introduction

Perioperative fluid therapy can maintain blood volume, tissue perfusion, acid-base and electrolyte balance, ultimately guaranteeing stability in the internal milieu. As the safety and efficacy of colloids have been doubted in recent years, the fluid for perioperative replacement is dominated by crystalloids in surgical patients[1,2]. Normal saline (NS) is a commonly used crystalloid in the clinic, as it has simple compositions (154 mM Na^+ and 154 mM Cl^-) and a lower price[3]. Studies[4-6] have proved that NS with large volumes can cause hyperchloremia, metabolic acidosis, gastrointestinal edema, and impair renal perfusion and function. Balanced crystalloid (BC) mimics the compositions of human plasma and reduces Na^+ and Cl^- loading; it contains metabolizable anions, such as acetic acid or lactic acid, which can maintain the neutrality of electrolytes[7]. Theoretically, it is postulated that BC is better than NS in perioperative fluid therapy to maintain the balance of acid-base and electrolytes and causes fewer adverse effects.

Till now, few meta-analyses[8-10] have been published to compare the safety between BC and NS in surgical patients, and these meta-analyses are either restricted to kidney transplantations or with a small number of included trials. Balanced hydroxyethyl starch (BC as solvent) and NS-based hydroxyethyl starch (NS as solvent) are used in the clinic, when necessary, in non-cardiac surgeries. Only one meta-analysis[11] took the solvents of colloids (BC *vs.* NS) into account when comparing the safety between buffered and non-buffered crystalloids in patients undergoing cardiac and non-cardiac surgeries, and the types of buffered crystalloids involved were much less than those used in the clinic. Many new articles comparing BC with NS have come out in non-cardiac surgeries for the past few years. As

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the sample size was small in the majority of studies, it is urgent to pool the results and elucidate the safety of perioperative administration of BC *vs.* NS, and the potentially different effects in various types of surgeries.

Thus, we conducted a systematic review and meta-analysis to compare BC with NS in non-cardiac surgeries and further conducted subgroup analysis based on the types of surgery and BC to determine which fluid is more appropriate for perioperative fluid replacement in non-cardiac surgeries.

Materials and Methods

This research was conducted in accordance with Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guidelines and registered in INPLASY (**https://inplasy.com/inplasy-2022-3-0121**) on 23 March 2022, with the registration number INPLASY202230121.

Search Strategy

We searched PubMed, Embase, Web of Science, Cochrane Library, Wanfang, and CNKI from January 1980 to March 2023 without language restrictions. All trials comparing BC with NS during non-cardiac surgery were eligible for inclusion. The search terms were: balanced crystalloid or balanced solution or plasmalyte or Hartmann's solution or Ringer's lactated or acetate buffered or sterofundin or Elomel isoton or isolyte or ringerfundin, saline or normal saline, surgery or surgical or ectomy or otomy. Various combinations of these terms were used for the trial search, and the reference lists of the included trials were checked for potentially eligible trials. Detailed search strategies were presented in **Supplementary Table I**.

Study Selection

Studies meeting the eligibility criteria were included in this meta-analysis. The inclusion criteria were: (1) studies with non-cardiac surgeries, (2) studies comparing BC with NS administered perioperatively for volume replacement, (3) studies comparing BC-based colloid with NS-based colloid, and the sole difference involving the presence or absence of a buffer in the fluids between study arms, (4) studies designed as randomized controlled trials (RCTs). The exclusion criteria were: (1) studies reporting non-surgical patients, (2) studies reporting cardiac surgeries, (3) studies comparing crystalloids with colloids, and (4) studies with hypertonic or hypotonic saline or colloid in one study arm.

Two authors (Q.-Y. Pang. and Q. Cao) independently screened the titles and abstracts to identify the appropriate studies according to the inclusion and exclusion criteria and extracted the characteristics and outcomes of each appropriate trial. Any disagreement was resolved by consultation with a third author.

Outcomes

The primary outcomes were clinical (acidosis, renal insufficiency, and mortality). The secondary outcomes were pH value, Na^+, Cl^-, and creatinine levels, as well as vasopressor requirement.

The participation, intervention, comparison, outcome, and study design were presented in **Supplementary Table II** according to PICOS criteria.

Data Extraction and Quality Assessment

Two authors (S.-F. Sun and Y. Jiang) conducted data extraction. An electronic form was used to record patients and study characteristics, including the first author, publication year, type of surgery, infusion period, allocated groups, sample size, intervention, and major outcomes. The data presented as medians or graphs was transferred to mean ± SD[12] or transformed to numbers using Plot-digitizer software.

The risk of bias was evaluated by appraising the inclusion of phrases such as "random sequence generation", "allocation concealment", " blinding of participants and personnel", "blinding of outcome assessment", "incomplete outcome data", "selective reporting" and "other bias", as recommended by the Cochrane Collaboration. Grading of Recommendations, Assessment, Development and Evaluation (GRADE) methodology was used to appraise the overall evidence-based quality of each outcome.

Statistics Analysis

The meta-analysis was conducted using Stata 16.0 software (StataCorp LP, College Station, TX, USA). The effect size for continuous data was expressed as mean difference (MD) with 95% confidential index (CI). DerSionian-Laird method for meta-analyses with random effects was used for continuous data. The effect size for dichotomous data was presented as an odds ratio (OR) with 95% CI. Between-study heterogeneity was determined by the I^2 value; the level of heterogeneity was defined as low when $I^2 \leq 50\%$ and high when $I^2 > 50\%$. For dichotomous data, when heterogeneity among studies was low, the fixed effect model was used, and the random-effect model was used when heterogeneity among studies was statistically significant or $I^2 > 50\%$. Subgroup analysis based on the types of surgery or BC was performed whenever possible to identify the source of heterogeneity and to test the consistency of the results. Publication bias was assessed using the Egger test. A *p*-value lower than 0.05 was considered statistically significant.

Trial sequential analysis (TSA) was conducted with TSA 0.9.5.5 Beta software (available at: www.ctu.dk/tsa) to estimate the required information size (RIS) using 0.05 for type 1 error, 0.20 for type 2 error and the relative risk reduction from the control group event rate from low-bias-risk trials included in the meta-analysis, according to the TSA user maual[13,14]. The TSA can be interpreted by viewing the boundaries and whether the cumulative meta-analysis has crossed them.

Results

Search Results

The literature search identified 3,600 citations. After screening titles and abstracts, 54 full-text articles were retrieved. After a detailed review, 11 articles were excluded, and 43 reports[5,6,15-54] were eventually included for the final quantitative synthesis. The search procedure is presented in Figure 1.

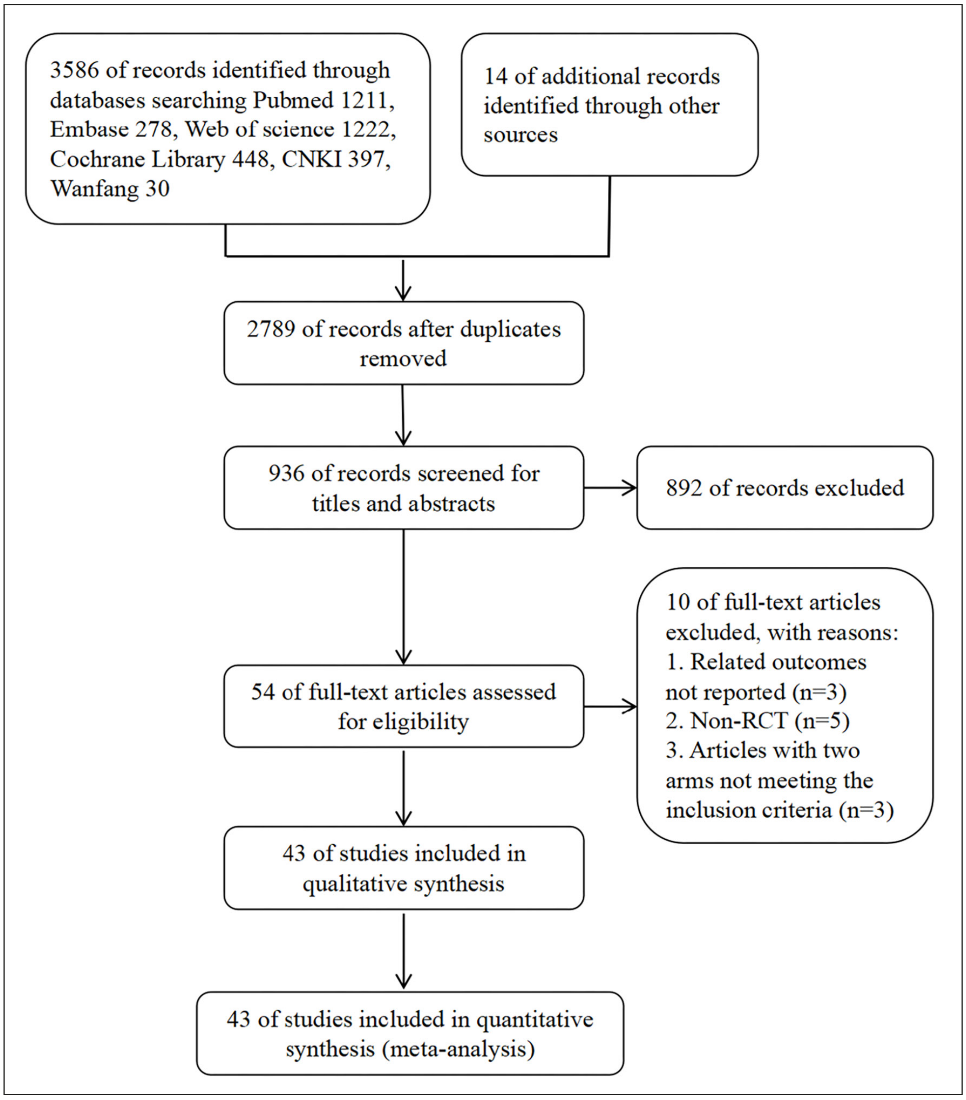

Figure 1. PRISMA flowchart.

Description of Included Studies

The characteristics of the included studies are summarized in Table I. The included studies were published from 1986 to 2021. The studied crystalloids were administered intraoperatively in 35 studies[5,6,15-38,45-47,49,51-54], preoperatively in 1 study[44], and intraoperatively with postoperatively in 7 studies[39-43,48,50]. Eighteen[5,6,15-25,38-40,45] studies reported non-renal abdominal surgery, 8 studies[28-33,37,41] reported neurosurgery, 4 studies[36,42-44] reported orthopedic and spinal surgery, 9 studies[46-54] reported renal transplantation, and 4 studies[26,27,34,35] reported other non-cardiac surgeries. The risk of bias in the included studies was presented in **Supplementary Table III**.

Results of Meta-Analysis

Supplementary Table IV shows the compositions of the studied crystalloids and colloids. Table II summarizes the meta-analysis results, publication bias, and the quality of evidence.

The results of six studies were split into two parts in the forest plots. Dong et al[24] 2015 (1), Wu et al[37] 2014 (1), Peng and Zheng[33] 2016 (1) and Li et al[45] 2006 (1) showed a comparison between lactated ringer's solution (LR) and NS. Dong et al[24] 2015 (2), Wu et al[37] 2014 (2), Peng and Zheng[33] 2016 (2) and Li et al[45] 2006 (2) showed a comparison between acetate-buffered solution (AS) and NS. Hadimioglu et al[47] 2008 (1) and Saini et al[50] 2021 (1) represented the comparison between LR and NS, Hadimioglu et al[47] 2008 (2) and Saini et al[50] 2021 (2) showed the comparison between plasmalyte and NS.

Primary Outcomes

Acidosis

Six RCTs[16,22,27,28,41,46] (n=681) compared the development of metabolic acidosis after surgery between BC and NS. Low evidence revealed that the development of acidosis was lower in the BC group than in the NS group (OR: 0.05, 95% CI: 0.01-0.43, I^2=80.8%, p=0.00, Figure 2). TSA indicated the sample size in this meta-analysis was smaller than the required sample size (n=685). Subgroup analyses suggested that acidosis was lower in the BC group in neurosurgery but not in non-renal abdominal surgery (**Supplementary Figure 1**). Acidosis was lower in the group of LR and plasmalyte (**Supplementary Figure 2**).

Renal insufficiency

Twelve RCTs[15,16,34,41,46-51,53,55] (n=1,588) reported postoperative renal insufficiency. Low evidence suggested that there was no between-group difference (OR: 0.87, 95% CI: 0.59-1.30, I^2=0%, p=0.66, Figure 2). TSA indicated the sample size as a result of renal insufficiency was smaller than the required sample size (n=16,884).

Mortality

Two RCTs[15,30] (n=186) reported postoperative mortality, and there was no between-group difference (OR: 0.67, 95% CI: 0.24-1.87, I^2=0%, p=0.76, Figure 2).

Secondary Outcomes

pH value

Twenty-four[5,15,16,19,22-24,26-28,29,31,33,36,37,39,40,42,45-47,50,51,53] RCTs (n=2,193) compared pH value at the end of surgery between BC and NS. Moderate evidence showed that the pH value in the BC group was higher (MD: 0.83, 95% CI: 0.57 – 1.10, I^2=89.0%, p=0.00) (Figure 3a). TSA indicated that the sample size in this analysis was larger than the required sample size (n=432). Subgroup analyses were conducted analyzing the types of surgeries or BC, and it showed that the pH value was higher in the BC group in neurosurgery, non-renal abdominal surgery, or renal transplantation (**Supplementary Figure 3**), and in the group of AS, LR, plasmalyte, or sterofundin/ringerfundin than in NS (**Supplementary Figure 4**). Six RCTs[19,23,30,39,40,53] (n=336) compared pH values on postoperative day 1 (POD 1). Results with moderate evidence showed that the pH value was higher in the BC group than in the NS group (MD: 1.09, 95% CI: 0.60 – 1.58, I^2=76.2%, p=0.00) (Figure 3b). TSA indicated the sample size for pH value comparison on POD 1 was larger than the required sample size (n=96). Subgroup analyses showed that the pH value was higher in the BC group in non-renal abdominal surgery (**Supplementary Figure 5**) and in the sterofundin/ringerfundin or LR group (**Supplementary Figure 6**).

Sodium level

Twenty studies[5,15,16,19,22-24,26-29,33,36,37,39,40,42,49,51,53] (n=1633) compared sodium levels between BC and NS at the end of the surgery, which was 0.55 mmol/L lower in BC group by moderate evidence (95% CI: -0.79 – -0.31; I^2=80.0%, p=0.00) (Figure 4a). TSA indicated the sample size in this -analysis was larger than the required sample size (n=976). Subgroup analyses investigating surgical types revealed that sodium levels were lower in the BC group in

Table I. Characteristics of the included studies.

First author	Publication year	Surgery	Infusion period	Allocation	Intervention	Target of fluid therapy	Major outcomes
Scheingraber et al[5]	1999	Gynecologic	Intra-op	LR (n=12) NS (n=12)	30 ml/kg/h	No detail	Acid-base, electrolytes
McFarlane and Lee[6]	1994	Hepatobiliary orpancreatic	Intra-op	Plasmalyte (n=15) NS (n=15)	15 ml/kg/h	No detail	Acid-base, electrolytes
Waters et al[15]	2001	AAA (abdominal)	Intra-op	LR (n=33) NS (n=33)	No detail	Change of PAOP/ CVP <10% baseline	Acid-base, electrolytes, renal failure, mortality
Ayebale et al[16]	2017	Cesarean section	Intra-op	LR (n=248) NS (n=252)	No detail	No detail	Renal failure, acidosis
Pfortmueller et al[17]	2018	Abdominal	Intra-op	Elomel (n=30) NS (n=30)	5 ml/kg/h	No detail	Acid-base, electrolytes, vasopressor
Zimmer et al[18]	1986	Cesarean section	Intra-op	LR (n=20) NS (n=20)	1,500 ml	No detail	Electrolytes (serum sodium)
Helmy et al[19]	2016	Urologic	Intra-op	Tetraspan (n=20) Voluven (n=20)	Ringer 10 ml/kg/h, colloid 250 ml (bolus) and 50 ml/ kg/d (maximal)	MAP>60 mmHg CVP>7 mmHg	Acid-base, electrolytes, renal function
Chen et al[20]	2008	Colorectal	Intra-op	AS (n=14) NS (n=14)	1,000 ml	No detail	Acid-base, electrolytes, renal function
Zhao et al[21]	2005	Hysterectomy	Intra-op	LR(n=20) AR (n=30) NS (n=20)	10 ml/kg/h	No detail	Acid-base, electrolyte
Brahma et al[22]	2017	Gastrointestinal	Intra-op	Plasmalyte (n=41) NS (n=41)	7 ml/kg/h	No detail	Acid-base, electrolytes, acidosis
Boldt et al[23]	2007	Abdominal	Intra-op	Ringerfundin (n=15) NS (n=15)	500 ml/h	MAP>65 mmHg CVP-PEEP>10 mmHg	Acid-base, electrolytes, renal function, vasopressors, mortality
Dong et al[24]	2015	Abdominal	Intra-op	AS (n=20) LR (n=20) NS (n=20)	1,000 ml/h	No detail	Acid-base, electrolytes, vasopressor
Deng et al[25]	2008	Liver transplantation	Intra-op	LR (n=30) NS (n=30)	8-10 ml/kg/h	No detail	Acid-base, electrolytes
Disma et al[26]	2014	Abdominal, thoracic, orthopedic	Intra-op	Sterofundin (n=114) NS (n=115)	4-2-1 rule 10 ml/kg (bolus when necessary)	No detail	Electrolytes, renal function
Wilkes et al[27]	2001	Abdominal, orthopedic, plastic	Intra-op	Hartmann's+ Hextend (n=23) NS+Hespan (n=24)	Colloid 500 ml Crystalloid 7 ml/kg/h	No detail	Acid-base, electrolytes, acidosis

Continued

Table I ***(Continued).*** Characteristics of the included studies.

First author	Publication year	Surgery	Infusion period	Allocation	Intervention	Target of fluid therapy	Major outcomes
Hafizah et al[28]	2017	Neurosurgery	Intra-op	Sterofundin (n=15) NS (n=15)	5 ml/kg/h	No detail	Acid-base, electrolytes, acidosis
Hassan et al[29]	2017	Neurosurgery	Intra-op	Sterofundin+ Venofundin (n=28) NS+Tetraspan (n=27)	Crystalloid: 4 ml/kg/h Colloid 50 ml/kg (max)	No detail	Acid-base, electrolytes
Guo et al[30]	2016	Neurosurgery	Intra-op	LR (n=60) NS (n=60)	No detail	MAP 80-110 mmHg; CVP 5-8 cm H_2O	Acid-base, electrolytes, mortality
Dey et al[31]	2018	Neurosurgery	Intra-op	Plasmalyte (n=22) NS (n=22)	2 ml/kg/h function	No detail	Acid-base, electrolytes, renal
Bhagat et al[32]	2019	Neurosurgery	Intra-op	LR vs. NS	No detail	No detail	Acid-base, electrolytes
Peng and Zheng[33]	2016	Neurosurgery	Intra-op	AS (n=30) LR (n=30) NS (n=30)	No detail	No detail	Acid-base, electrolytes, renal function, vasopressor
Xu et al[34]	2011	Non-cardiac	Intra-op	AS (n=120) NS (n=120)	10 ml/kg/h	SVV	Acid-base, electrolytes, renal failure, vasopressor
Yang et al[35]	2020	Non-cardiac	Intra-op	AS (n=125) NS (n=126)	15 ml/kg	No detail	Acid-base, electrolytes
Hou and Qiu[36]	2016	Orthopedic	Intra-op	LR (n=20) NS (n=20)	4-2-1 rule	No detail	Acid-base, electrolytes
Wu et al[37]	2014	Neurosurgery	Intra-op	AS (n=20) LR (n=20) NS (n=20)	4-2-1 rule	No detail	Acid-base, electrolytes, renal function, vasopressor
Zhang et al[38]	2019	Abdominal	Intra-op	AS (n=20) NS (n=20)	4-2-1 rule	No detail	Electrolyte
Saracoglu et al[39]	2014	Gastrectomy	Intra- and post-op	LR (n=26) NS (n=24) and 2 ml/kg/h (post-op)	15 ml/kg/h (intra-op)	No detail	Acid-base, electrolytes
Volta et al[40]	2013	Abdominal	Intra- and post-op	Sterofundin (n=20) NS (n=20)	1,500-2,000 ml	CVP 10-11 cm H_2O; MAP>60 mmHg	Acid-base, electrolytes, renal function
Lima et al[41]	2019	Neurosurgery	Intra- and post-op	Plasmalyte (n=24) NS (n=25)	4-2-1 rule	No detail	Acid-base, electrolytes, vasopressor, acidosis, renal failure
Takil et al[42]	2002	Spine surgery	Intra- and post-op	LR (n=15) NS (n=15)	20 ml/kg/h (intra-op) 2.5 ml/kg/h (post-op)	No detail	Acid-base, electrolytes

Continued

Table I *(Continued)*. Characteristics of the included studies.

First author	Publication year	Surgery	Infusion period	Allocation	Intervention	Target of fluid therapy	Major outcomes
Song et al[43]	2015	Spine surgery	Intra- and post-op	Plasmalyte (n=25) NS (n=25)	6 ml/kg/h	No detail	Acid-base, electrolytes
Veroli and Benhamou[44]	1992	Orthopedic	Pre-op	LR (n=10) NS (n=10)	15 ml/kg (LR) 13 ml/kg (NS)	No detail	Electrolytes, vasopressor, renal function, renal failure
Li et al[45]	2006	Abdominal	Intra-op	LR (n=30) AS (n=30) NS (n=30)	6-8 ml/kg/h	No detail	Acid-base
O'Malley et al[46]	2005	Renal transplantation	Intra-op	LR (n=25) NS (n=26)	No detail	No detail	Acid-base, electrolytes, renal function, renal failure
Hadimioglu et al[47]	2008	Renal transplantation	Intra-op	LR (n=30) Plasmalyte (n=30) NS (n=30)	20-30 ml/kg/h	CVP12-15 mmHg	Acid-base, electrolytes, renal function, renal failure
Potura et al[48]	2015	Renal transplantation	Intra- and post-op	Elomel (n=72) NS (n=76)	4 ml/kg/h (Intra-op) 2 ml/kg/h (Post-op)	No detail	Acid-base, electrolytes, renal function, renal failure
Weinberg et al[49]	2017	Renal transplantation	Intra-op	Plasmalyte (n=24) NS (n=25)	2,000 ml (Minimal)	MAP change within 20% of baseline	Acid-base, electrolytes, renal function, renal failure
Saini et al[50]	2021	Renal transplantation	Intra- and post-op	LR (n=60) Plasmalyte (n=60) NS (n=60)	No detail	CVP12-14 cm H_2O and PPV 13% (intra-op) CVP14-16 cm H_2O (post-op)	Acid-base, electrolytes, renal function, renal failure
Khajavi et al[51]	2009	Renal transplantation	Intra-op	LR (n=26) NS (n=26)	60 ml/kg	CVP10-15 mmHg	Acid-base, electrolytes, renal function, renal failure
Modi et al[52]	2012	Renal transplantation	Intra-op	LR (n=37) NS (n=37)	No detail	CVP 12-15 cm H_2O	Acid-base, electrolytes, renal function, renal failure
Kim et al[53]	2013	Renal transplantation	Intra-op	Plasmalyte (n=30) NS (n=30)	No detail	CVP 12-15 cm H_2O	Acid-base, electrolytes, renal function, renal failure
Pfortmueller et al[54]	2017	Renal transplantation	Intra-op	Elomel (n=72) NS (n=76)	4 ml/kg/h	MAP>60 mmHg	Electrolytes, vasopressor, renal failure

LR: lactated ringer's solution; NS: normal saline; AS: acetate-buffered solution/acetated ringer's solution; AR: acetated ringer's solution; HES: Hetastarch 130/0.42/6:1; AAA: aortic aneurism repair; PAOP: pulmonary arterial occlusion pressure; MAP: mean arterial pressure; CVP: central venous pressure; PEEP: positive end-expiratory pressure.

Table II. Summary of the outcomes with evidence quality (balanced crystalloid vs. normal saline).

Outcome	No. of reference	No. of patients	MD	OR	95% CI	I^2	*p*-value	*p*-value from egger test	Evidence quality (GRADE)
Clinical outcomes									
Acidosis	6	681	/	0.05	0.01 to 0.43	80.8%	0.00	0.01	⊕⊕⊕⊖ (low)
Renal dysfunction	12	1588	/	0.87	0.59 to 1.30	0%	0.66	0.81	⊕⊕⊕⊖ (low)
Mortality	2	186	/	0.67	0.24 to 1.87	0%	0.76	/	⊕⊕⊕ (very low)
Acid-base and electrolyte									
PH									
End of surgery	24	2193	0.83	/	0.57 to 1.10	89.0%	0.00	0.00	⊕⊕⊕⊖ (moderate)
POD 1	6	336	1.09	/	0.60 to 1.58	76.2%	0.00	0.51	⊕⊕⊕⊖ (moderate)
Na^+									
End of surgery	20	1633	-0.55	/	-0.79 to -0.31	80.0%	0.00	0.00	⊕⊕⊕⊖ (moderate)
POD 1	6	259	-0.90	/	-1.36 to -0.43	68.9%	0.00	0.41	⊕⊕⊕⊖ (moderate)
Cl^-									
End of surgery	25	2192	-1.92	/	-2.40 to -1.43	95.8%	0.00	0.01	⊕⊕⊕⊖ (moderate)
POD 1	6	309	-3.02	/	-4.55 to -1.50	96.4%	0.00	0.03	⊕⊕⊖⊖ (low)
Creatinine									
End of surgery	5	480	-0.07	/	-0.30 to 0.15	35.4%	0.52	0.08	⊕⊕⊖⊖ (low)
POD 1	6	601	-0.17	/	-0.40 to 0.07	57.2%	0.16	0.45	⊕⊕⊕⊖ (moderate)
Vasopressor requirement	7	378	/	0.79	0.47 to 1.33	1.8%	0.38	0.04	⊕⊕⊖⊖ (low)

POD: postoperative day; MD: mean difference; OR: odds ratio; CI: confidential index. GRADE: Grading of Recommendations, Assessment, Development and Evaluation.

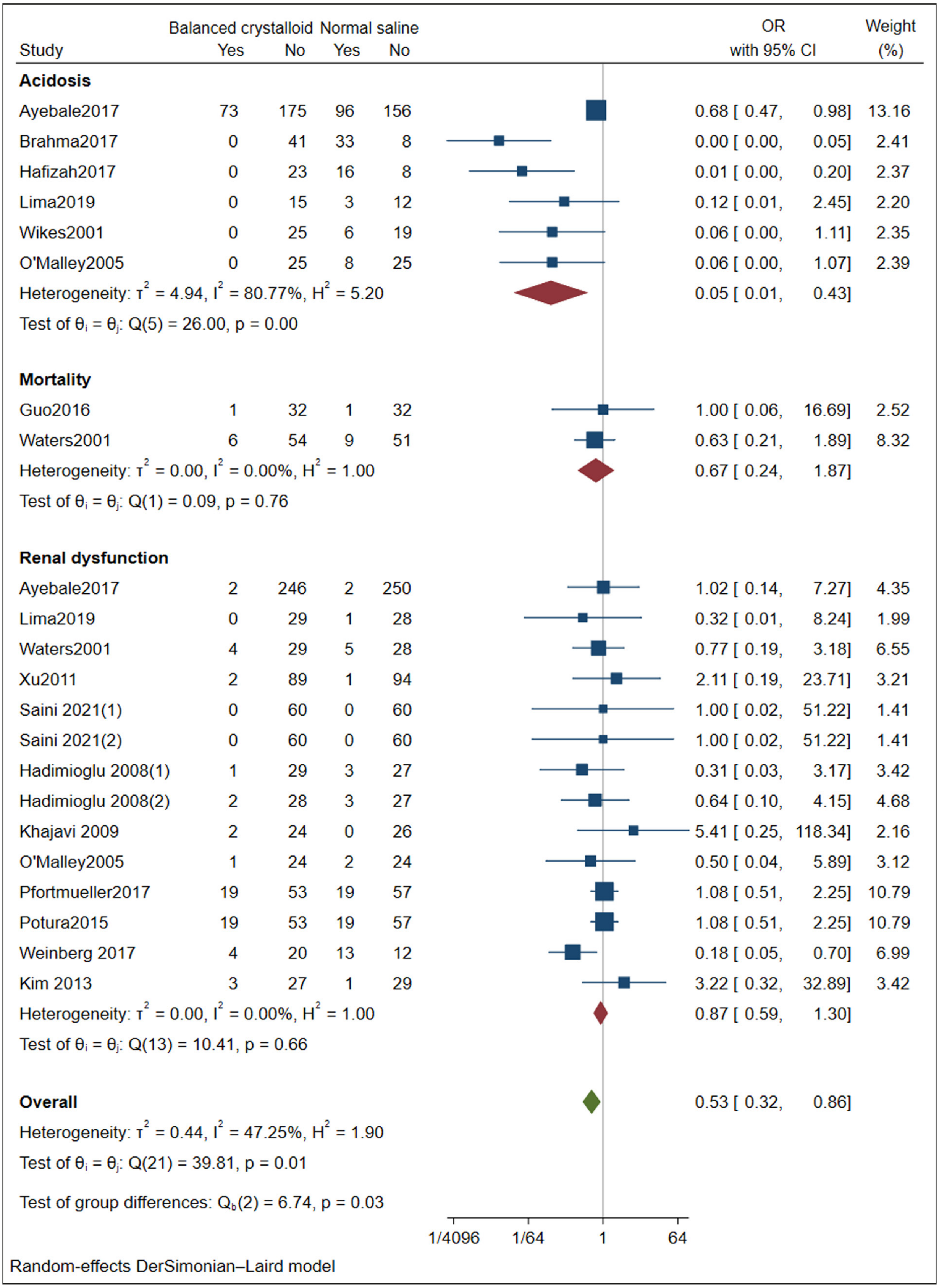

Figure 2. Forest plots of clinical outcomes.

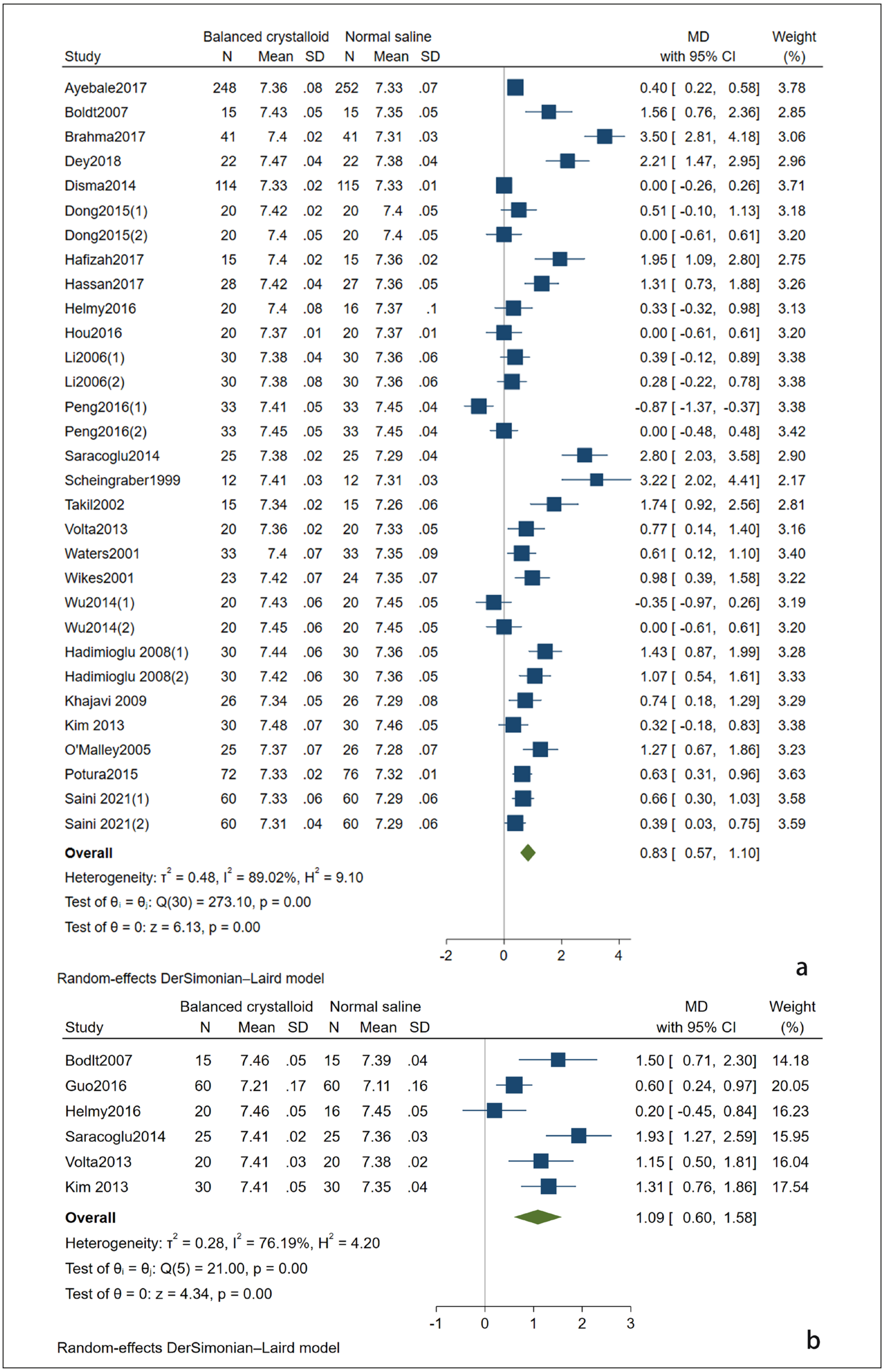

Figure 3. Forest plots of PH value. **a**, at end of surgery; (**b**) on postoperative day 1.

non-renal abdominal surgery or renal transplantation (**Supplementary Figure 7**). The analysis of balanced solution types showed that sodium level was lower in AS or LR but not in plasmalyte or sterofundin/ringerfundin group (**Supplementary Figure 8**). Six studies[19,23,39,40,49,53] (n=259) compared

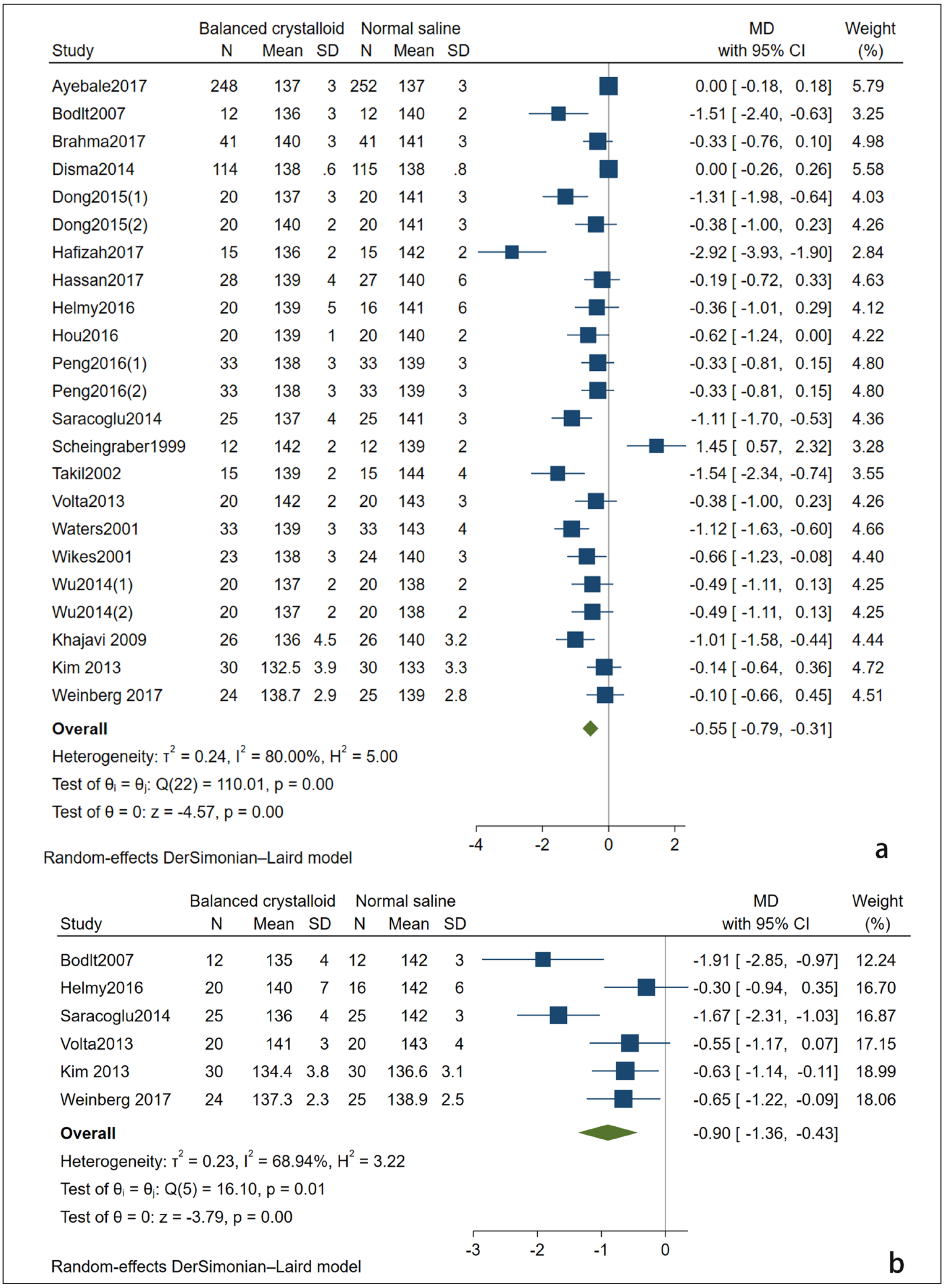

Figure 4. Forest plots of sodium level. **a**, at end of surgery; (**b**) on postoperative day 1.

sodium levels on POD 1, and moderate evidence showed that sodium level was lower in the BC group (MD: -0.90, 95% CI: -1.36 – -0.43, I^2=68.9%, *p*=0.00) (Figure 4b). TSA indicated the sample size in this analysis was larger than the required sample size (n=314). Subgroup analyses showed that sodium level was lower in the BC group in non-renal abdominal surgery but not in renal transplantation (**Supplementary Figure 9**). Moreover, it was lower in plasmalyte, but not in sterofundin/ringerfundin (**Supplementary Figure 10**).

Chloride level

Twenty-three RCTs[5,15,16,19,22-24,26-29,33,37,39,42,46-50,52-54] (n=2,192) compared chloride levels at the end of surgery. Moderate evidence revealed that chloride level was lower with an MD of -1.92 mmol/L in the BC group than in the NS group (95% CI: -2.40 – -1.43, I^2=95.8%, *p*=0.00) (Figure 5a). Subgroup analyses revealed that chloride level was lower in the BC group in neurosurgery, non-renal abdominal surgery, or renal transplantation (**Supplementary Figure 11**), and in Elomel isoton, LR, sterofundin/ringerfundin, or plasmalyte groups, but not in AS (**Supplementary Figure 12**). Six RCTs[19,23,39,47,49,53] (n=309) compared chloride levels on POD 1, but the evidence was low; it showed that chloride level was much lower in the BC group with an MD of -3.02 mmol/L (95% CI: -4.55 – -1.50, I^2=96.4%, *p*=0.00) (Figure 5b). Subgroup analyses revealed that chloride level was lower in the BC group in renal transplantation but not in non-renal abdominal surgery (**Supplementary Figure 13**) and was lower in the group of sterofundin/ringerfundin but not in AS, LR, or plasmalyte (**Supplementary Figure 14**).

Creatinine level

Five RCTs[26,33,37,43,49] (n=480) reported creatinine levels at the end of surgery, and six[47-50,52,53] (n=601) on POD 1. Low to moderate evidence suggested that there were no between-group differences at the end of surgery (MD: -0.07, 95% CI: -0.30 – 0.15, I^2=35.4%, *p*=0.52) (Figure 6a) and on POD 1 (MD: -0.17; 95% CI: -0.40 – 0.07; I^2=57.2%; *p*=0.16) (Figure 6b). TSA indicated the sample size at the creatinine level at the end of surgery was smaller than the required sample size (n=686), and the sample size at the creatinine level on POD 1 was smaller than the required sample size (n=1,699).

Vasopressor requirement

Seven RCTs[23,33-35,37,41,54] (n=378) reported the percentage of vasopressor requirement, in which 5 reported[23,33-35,37] intraoperative vasopressor requirement, including phenylephrine, norepinephrine, ephedrine, and dopamine; the other 2 reported intraoperative and postoperative (within 24 hours) vasopressors requirement including dobutamine and norepinephrine[41,54]. The result of the meta-analysis with low evidence showed that there was no between-group difference (OR: 0.79; 95% CI: 0.47 – 1.33, I^2=1.8%, *p*=0.38). TSA indicated the sample size in vasopressor requirement was smaller than the required sample size (n=4,570).

Discussion

This meta-analysis identified 43 studies that compared the safety and efficacy of BC and NS in non-cardiac surgeries; the results indicated that perioperative BC could maintain acid-base balance and electrolytes stability, cause less acidosis, but could not reduce vasopressor requirement, renal insufficiency, and mortality. It was the first subgroup analysis conducted by surgical types and balanced solution types to further clarify the differences between BC and NS in various surgeries.

Four meta-analyses[8-11] have been published to compare BC with normal saline till now. The article by Wan et al[8] included 6 studies of kidney transplantation, and NS lowered PH value and BE but increased serum chloride level compared with BC. The article by Bampoe et al[9] included 19 studies of various surgeries and compared buffered solution and non-buffered solution. The low evidence showed that non-buffered solution increased the risk of renal insufficiency and mortality, and the moderate evidence showed that non-buffered solution lowered PH value and increased serum chloride level after surgery compared with buffered crystalloid. The meta-analysis by Huang et al[10] included 9 studies with abdominal surgery, neurosurgery, and orthopedic surgery; NS lowered PH value and BE and increased serum chloride level. A recent meta-analysis[11] included 9 RCTs and 1 cohort study in kidney transplantation. NS increased serum chloride and potassium levels. The results of acid-base changes in our study are consistent with the above-mentioned results: NS reduced pH value at the end of surgery in non-cardiac surgery, which mainly resulted from hyperchloremia[4], and contributed to metabolic acidosis as a result.

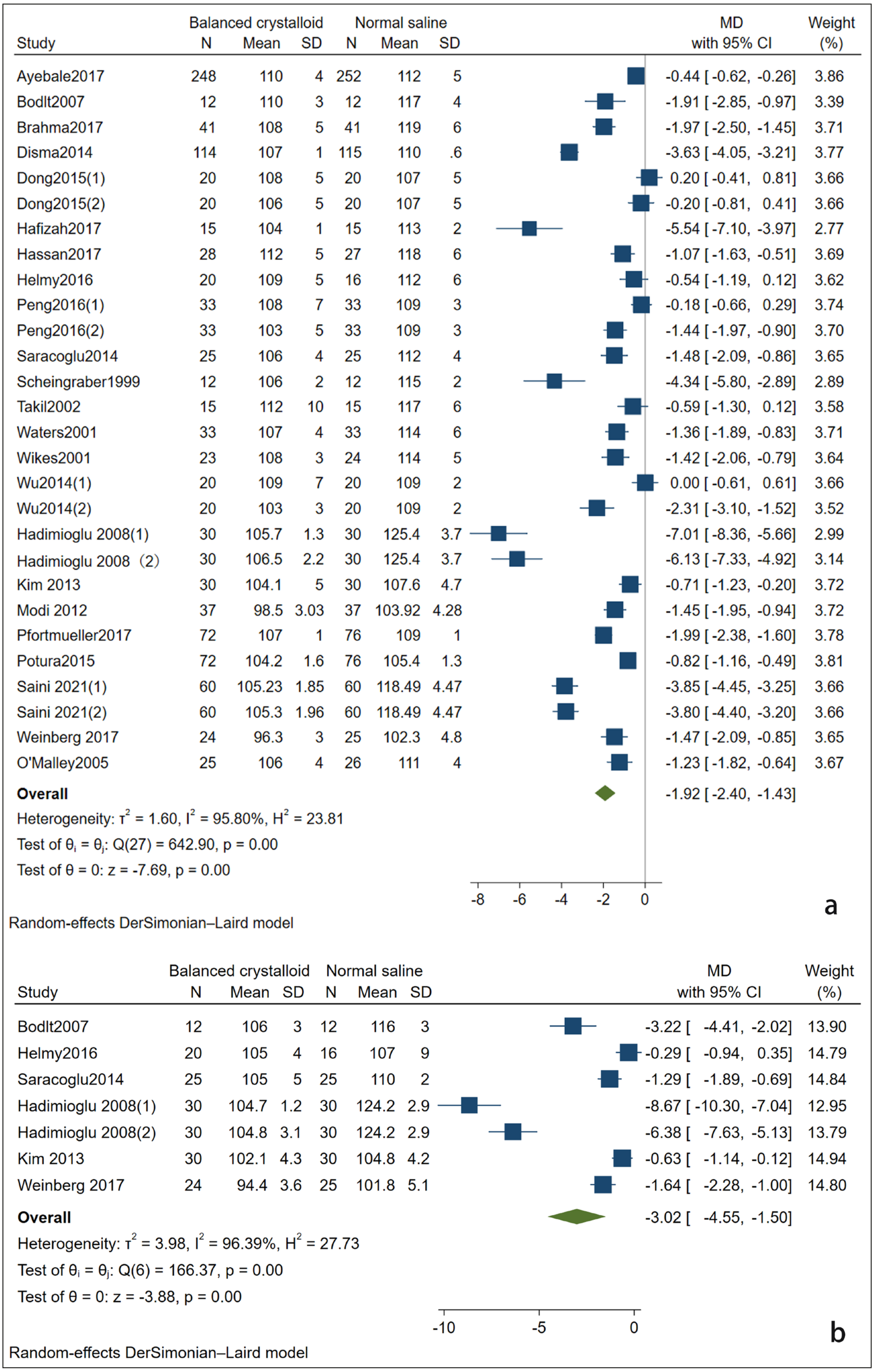

Figure 5. Forest plots of chloride level. **a**, at end of surgery; (**b**) on postoperative day 1.

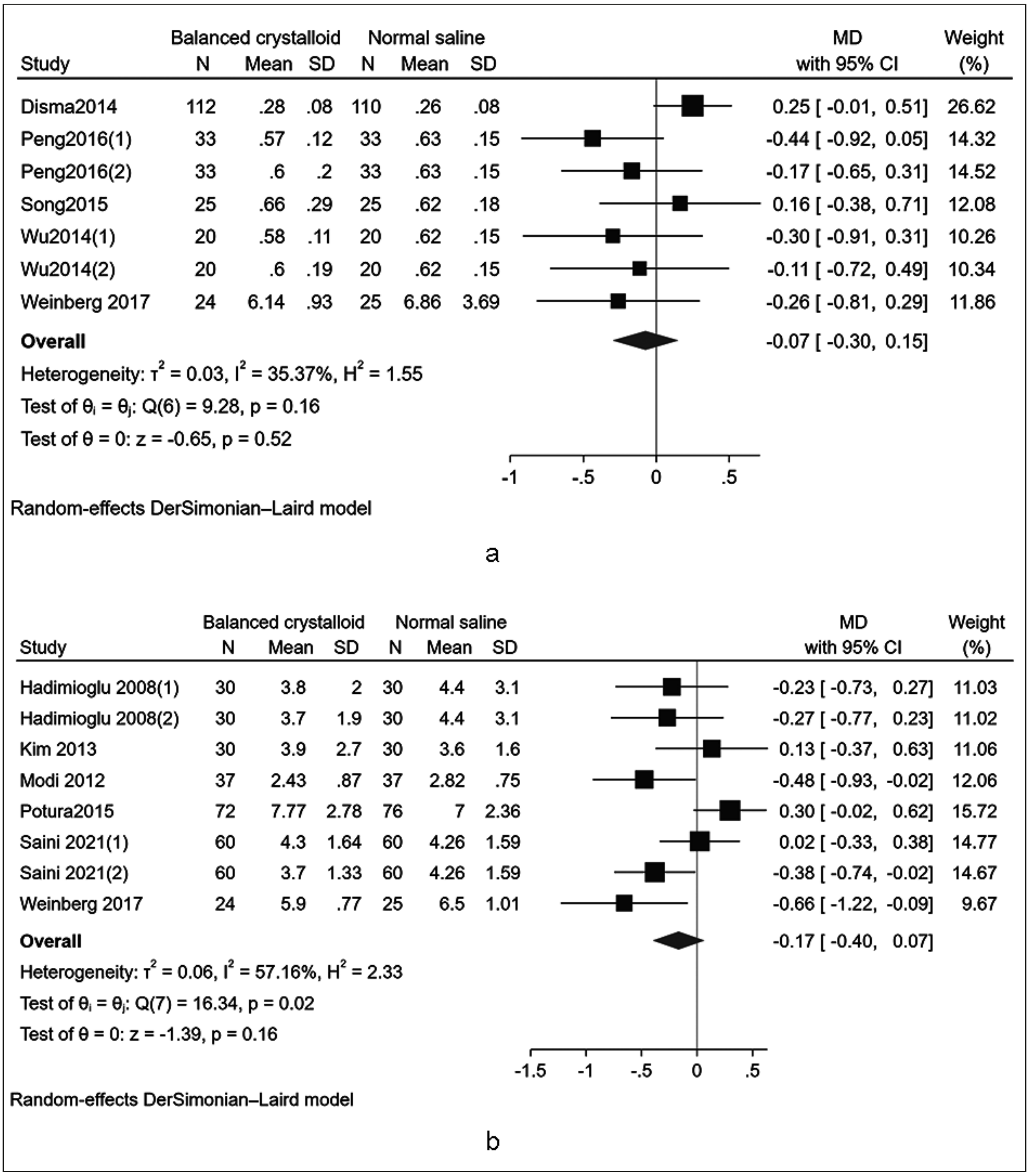

Figure 6. Forest plots of creatinine level.

Acidosis and hyperchloremia could impair renal perfusion and function theoretically[55]. NS administration induced acidosis and hyperchloremia in this meta-analysis, as creatinine is an important biomarker of renal function. The results of this meta-analysis showed that there was no difference in creatinine level between BC and NS at the end of surgery, and NS did not increase the risk of renal dysfunction and mortality. The reason might be the short duration of acidosis and hyperchloremia caused by NS administration. It has been reported[56] that hyperchloremia and acidosis caused by intraoperative administration of NS can return to normal status 24-48 hours after surgery.

Our result showed that acidosis was lower in the BC group in neurosurgery but not in non-renal abdominal surgery. However, a large cohort study[57] showed that patients administered with BC had lower morbidity compared with NS in open abdominal surgery. The application of BC in different surgical types has different results, which may be related to different fluid types or preoperative hydration and the total amount of fluid infusion. Excessive or insufficient infusion may also affect the prognosis[58]. Nearly half of the included studies in this meta-analysis did not detail how to assess the volume status and only presented an infusion rate or a fluid volume. Many methods and monitoring techniques are used to assess the volume status perioperatively to guarantee a sufficient blood volume and avoid fluid overload at the same time, such as passive leg raising test, mini-fluid challenge test, Trendelenburg manoeuver, end-expiratory occlusion tests, esophageal Doppler technique, and monitoring of CVP, stroke volume variation (SVV), pulse pressure variation (PPV), and inferior vena cava diameter[59]. It was reported[60] that implementation of fluid replacement guided by SVV *vs.* guided by CVP was associated with lesser postoperative ICU stay and reduced fluid requirements in major abdominal surgery. Pulse pressure variation-guided fluid administration decreased the total volume of crystalloids compared with CVP-guided fluid therapy during kidney transplant surgery[61]. Transesophageal Doppler-guided intraoperative fluid therapy can reduce the amount of fluid and postoperative complications[62]. So, in future studies, the assessment of volume status by optimal monitoring is necessary to guide perioperative fluid therapy when comparing the safety between BC and NS.

There are some limitations of this study: (1) the database searching was up to March 2023, and although as many as 43 studies were included in this meta-analysis, new articles might be published thereafter and not included, which might be a possible limitation, (2) the volumes or types of the studied crystalloids were not consistent in the included studies, although they are comparable between groups in each study, (3) the majority of the included studies had a small sample size, and the evidence for clinical outcomes was low, (4) non-cardiac surgeries include many surgical types and each type of surgery has a different effect on intraoperative fluid distribution in the body, bleeding, and fluid replacement. Therefore, more RCTs with large sample sizes in the specific type of surgery under the unique, balanced crystalloid therapy *vs.* saline are needed to verify these results in the near future

Conclusions

This systematic review and meta-analysis identified 43 articles to compare the safety of perioperative administration of balanced crystalloid with that of normal saline in non-cardiac surgeries. Low to moderate evidence showed that perioperative balanced crystalloid could maintain acid-base balance and electrolyte stability but did not reduce renal insufficiency and mortality. As the evidence of clinical outcomes was low, more RCTs with large sample sizes will be needed to verify these results in the future.

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Authors' Contributions

Hong-Liang Liu: conceptualization; investigation; writing - original draft; supervision; Qian-Yun Pang: project administration; formal analysis; methodology; Qian Cao: Data curation; resources; visualization; Shu-Fang Sun: formal analysis; software; Yan Jiang: data curation; validation.

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Conflict of Interest

The authors declare no conflict of interest.

Data Availability

The data are available from the corresponding author upon reasonable request.

Ethics Approval and Informed Consent

Not applicable due to the design of the study.

References

1) Verheij J, van Lingen A, Raijmakers PGHM, Rijnsburger ER, Veerman DP, Wisselink W, Girbes ARJ, Groeneveld ABJ. Effect of fluid loading with saline or colloids on pulmonary permeability, oedema and lung injury score after cardiac and major vascular surgery. Br J Anaesth 2006; 96: 21-30.

2) Jacob M, Fellahi JL, Chappell D, Kurz A. The impact of hydroxyethyl starches in cardiac surgery: a meta-analysis. Crit Care 2014; 18: 656.
3) Lobo DN. Intravenous 0.9% saline and general surgical patients: a problem, not a solution. Ann Surg 2012; 255: 830-832.
4) Chowdhury AH, Cox EF, Francis ST, Lobo DN. A randomized, controlled, double-blind crossover study on the effects of 2-L infusions of 0.9% saline and plasma-lyte® 148 on renal blood flow velocity and renal cortical tissue perfusion in healthy volunteers. Ann Surg 2012; 256: 18-24.
5) Scheingraber S, Rehm M, Sehmisch C, Finsterer U. Rapid saline infusion produces hyperchloremic acidosis in patients undergoing gynecologic surgery. Anesthesiology 1999; 90: 1265-1270.
6) McFarlane C, Lee A. A comparison of Plasmalyte 148 and 0.9% saline for intra-operative fluid replacement. Anaesthesia 1994; 49: 779-781.
7) Pfortmueller CA, Fleischmann E. Acetate-buffered crystalloid fluids: Current knowledge, a systematic review. J Crit Care 2016; 35: 96-104.
8) Wan S, Roberts MA, Mount P. Normal saline versus lower-chloride solutions for kidney transplantation. Cochrane Database Syst Rev 2016; 2016: CD010741.
9) Jahangir A, Sahra S, Niazi MRK, Siddiqui FS, Anwar MY, Jahangir A, El-Charabaty EJ. Comparison of normal saline solution with low-chloride solutions in renal transplants: a meta-analysis. Kidney Res Clin Pract 2021; 40: 484-495.
10) Huang L, Zhou X, Yu H. Balanced crystalloids vs 0.9% saline for adult patients undergoing non-renal surgery: A meta-analysis. Int J Surg 2018; 51: 1-9.
11) Bampoe S, Odor PM, Dushianthan A, Bennett-Guerrero E, Cro S, Gan TJ, Grocott MP, James MF, Mythen MG, O'Malley CM, Roche AM, Rowan K, Burdett E. Perioperative administration of buffered versus non-buffered crystalloid intravenous fluid to improve outcomes following adult surgical procedures. Cochrane Database Syst Rev 2017; 9: CD004089.
12) Hozo SP, Djulbegovic B, Hozo I. Estimating the mean and variance from the median, range, and the size of a sample. BMC Med Res Methodol 2005; 5: 13.
13) Thorlund K, Engstrom J, Wetterslev J, Brok J, Imberger G, Gluud C. User manual for trial sequential analysis (TSA). Copenhagen: Copenhagen Trial Unit, Centre for Clinical Intervention Research 2011; pp. 1-115.
14) Cassai AD, Pasin L, Boscolo A, Salvagno M, Navalesi P. Trial sequential analysis: plain and simple. Korean J Anesthesiol 2021; 74: 363-365.
15) Waters JH, Gottlieb A, Schoenwald P, Popovich MJ, Sprung J, Nelson DR. Normal saline versus lactated Ringer's solution for intraoperative fluid management in patients undergoing abdominal aortic aneurysm repair: an outcome study. Anesth Analg 2001; 93: 817-822.
16) Ayebale ET, Kwizera A, Mijumbi C, Kizito S, Roche AM. Ringer's Lactate Versus Normal Saline in Urgent Cesarean Delivery in a Resource-Limited Setting: A Pragmatic Clinical Trial. Anesth Analg 2017; 125: 533-539.
17) Pfortmueller CA, Funk GC, Reiterer C, Schrott A, Zotti O, Kabon B, Fleischmann E, Lindner G. Normal saline versus a balanced crystalloid for goal-directed perioperative fluid therapy in major abdominal surgery: a double-blind randomised controlled study. Br J Anaesth 2018; 120: 274-283.
18) Zimmer EZ, Goldstein I, Feldman E, Glik A. Maternal and newborn levels of glucose, sodium and osmolality after preloading with three intravenous solutions during elective cesarean sections. Eur J Obstet Gynecol Reprod Biol 1986; 23: 61-65.
19) Helmy A, Mukhtar A, Ahmed A, Sief NE, Hussein A. The intraoperative therapeutic equivalence of balanced vs saline-based 6% hydroxyethyl starch 130/0.4 and their influence on perioperative acid-base status and renal functions. J Clin Anesth 2016; 32: 267-273.
20) Chen MH, He LL, Yang JJ. The influence of normal saline and sodium acetate injection on acid-base, electrolyte and renal function. J Clin Anesthesiol (Chin) 2008; 24: 409-411.
21) Zhao Y, Yang B, Wang L, Zhang D, Du Y. The effect of different crystalloids on acid-base and electrolytes in patients undergoing total hysterectomy. Chin J Anesthesiol 2005; 25: 71-73.
22) Brahma SK, Mukherjee M, Chandra D, Bhattacharya D, Bhattacharya SB. The effects of balanced versus saline based colloid and crystalloid solutions on acid-base and electrolyte balance in gastrointestinal surgery. Anesth Pain Intensive Care 2017; 21: 159-165.
23) Boldt J, Schöllhorn T, Münchbach J, Pabsdorf M. A total balanced volume replacement strategy using a new balanced hydoxyethyl starch preparation (6% HES 130/0.42) in patients undergoing major abdominal surgery. Eur J Anaesthesiol 2007; 24: 267-275.
24) Dong S, Jin L, Pang L, Ma HC, Liu J. The effect of acetated ringer's solution on electrolyte, lactate and body temperature in elderly surgical patients with septic shock. Chin J Lab Diagn 2015; 19: 1131-1133.
25) Deng L, Ding Y, Liu D. Influence of transfusion of lactated Ringer's solution on arterial blood lactate concentration and acid-base balance during orthotopic liver transplantation. Chin J Mod Nurs 2008; 14: 1457-1459.
26) Disma N, Mameli L, Pistorio A, Davidson A, Barabino P, Locatelli BG, Sonzogni V, Montobbio G. A novel balanced isotonic sodium solution vs normal saline during major surgery in children up to 36 months: a multicenter RCT. Paediatr Anaesth 2014; 24: 980-986.
27) Wilkes NJ, Woolf R, Mutch M, Mallett SV, Peachey T, Stephens R, Mythen MG. The effects of balanced versus saline-based hetastarch and

crystalloid solutions on acid-base and electrolyte status and gastric mucosal perfusion in elderly surgical patients. Anesth Analg 2001; 93: 811-816.

28) Hafizah M, Liu CY, Ooi JS. Normal saline versus balanced-salt solution as intravenous fluid therapy during neurosurgery: effects on acid-base balance and electrolytes. J Neurosurg Sci 2017; 61: 263-270.

29) Hassan WMNW, Suut N, Tan PCS, Zaini RHM. Balanced versus saline-based fluid regimen for elective supratentorial craniotomy: acid-base and electrolyte changes. MEJ Anesth 2017; 24: 195-203.

30) Guo Z, Zhang X, Li Y. Influence of intraoperative use of saline and balanced salt solution on nerve function recovery in patients with brain trauma. J Reg Anat Oper Surg 2016; 25: 765-768.

31) Dey A, Adinarayanan S, Bidkar PU, Bangera RK, Balasubramaniyan V. Comparison of normal saline and balanced crystalloid (plasmalyte) in patients undergoing elective craniotomy for supratentorial brain tumors: A randomized controlled trial. Neurol India 2018; 66: 1338-1344.

32) Bhagat H, Singhal V, Dash HH, Mahajan S, Mishra N, Pandia MP. Comparative evaluation of intraoperative use of normal saline, Ringer's lactate, and combination of normal saline and Ringer's lactate in neurosurgical patients - A preliminary randomized clinical trial. Neurol India 2019; 67: 452-458.

33) Peng R, Zheng J. The application of different crystalloids in neurosurgery. World Clin Med (Chin) 2016; 10: 60-61.

34) Xu X, Wu X, Xue Z, Huang W, Deng X, Xiong L. Plasma volume expanding effect of hydroxyethyl starch 130/0.4 and electrolyte solution versus hydroxyethyl starch 130/0.4 and normal saline in patients undergoing noncardiac surgery under general anesthesia: a multicentre prospective, randomized, double-blind, controlled clinical trial. Chin J Anesthesiol 2011; 31: 1165-1169.

35) Yang X, Liu X, Wu X, Xue Z, Wang X, Deng X, Wang J. Comparison of HES 130/0.4 and acetate Ringer's solution versus HES 130/0.4 and normal saline for volume therapy in patients undergoing non-cardiac surgery with general anesthesia: a randomized, blinded, parallel-controlled, multicentre clinical trial. Chin J Anestesiol 2020; 40: 992-997.

36) Hou N, Qiu F. Effects of infusing different fluids intravenously on carbohydrate metabolism and plasma electrolytes and acid-base balance in perioperative children undergoing bone surgery. Prac J Med Pharm 2016; 33: 784-787.

37) Wu J, Wang T, Zhang Y, Ma YH, Fan L. Effects of different crystalloid solution on serum osmolality, electrolytes, lactate and blood glucose in patients indergoing intracranial tumor resection. Chin J Mod Med 2014; 24: 92-96.

38) Zhang M, Li C, Gu H. Effects of different crystalloids on electrolytes and blood glucose in infants undergoing gastrointestinal surgery. Med Information 2019; 32: 69-72.

39) Saracoglu KT, Eti Z, Ugurlu U, Orhon M, Gogus FY. The effects of peroperative fluid administration on postoperative acid-base and electrolyte balance in patients undergoing total gastrectomy. Anestezi Dergisi 2014; 22: 18-24.

40) Volta CA, Trentini A, Farabegoli L, Manfrinato MC, Alvisi V, Dallocchio F, Marangoni E, Alvisi R, Bellini T. Effects of two different strategies of fluid administration on inflammatory mediators, plasma electrolytes and acid/base disorders in patients undergoing major abdominal surgery: a randomized double blind study. J Inflamm (Lond) 2013; 10: 29.

41) Lima MF, Neville IS, Cavalheiro S, Bourguignon DC, Pelosi P, Malbouisson LMS. Balanced Crystalloids Versus Saline for Perioperative Intravenous Fluid Administration in Children Undergoing Neurosurgery: A Randomized Clinical Trial. J Neurosurg Anesthesiol 2019; 31: 30-35.

42) Takil A, Eti Z, Irmak P, Yilmaz Göğüş F. Early postoperative respiratory acidosis after large intravascular volume infusion of lactated ringer's solution during major spine surgery. Anesth Analg 2002; 95: 294-298.

43) Song JW, Shim JK, Kim NY, Jang J, Kwak YL. The effect of 0.9% saline versus plasmalyte on coagulation in patients undergoing lumbar spinal surgery; a randomized controlled trial. Int J Surg 2015; 20: 128-134.

44) Veroli P, Benhamou D. Comparison of hypertonic saline (5%), isotonic saline and Ringer's lactate solutions for fluid preloading before lumbar extradural anaesthesia. Br J Anaesth 1992; 69: 461-464.

45) Li ST, Wang ZP, Wang YT, Xu GH, Zhuang XL. Effect of lactated crystalloid solution on arterial blood lactate concentration during orthotopic liver transplantation. Chin J Anesthesiol 2006; 26: 133-135.

46) O'Malley CMN, Frumento RJ, Hardy MA, Benvenisty AI, Brentjens TE, Mercer JS, Bennett-Guerrero E. A randomized, double-blind comparison of lactated Ringer's solution and 0.9% NaCl during renal transplantation. Anesth Analg 2005; 100: 1518-1524.

47) Hadimioglu N, Saadawy I, Saglam T, Ertug Z, Dinckan A. The effect of different crystalloid solutions on acid-base balance and early kidney function after kidney transplantation. Anesth Analg 2008; 107: 264-269.

48) Potura E, Lindner G, Biesenbach P, Funk GC, Reiterer C, Kabon B, Schwarz C, Druml W, Fleischmann E. An acetate-buffered balanced crystalloid versus 0.9% saline in patients with end-stage renal disease undergoing cadaveric renal transplantation: a prospective randomized controlled trial. Anesth Analg 2015; 120: 123-129.

49) Weinberg L, Harris L, Bellomo R, Ierino FL, Story D, Eastwood G, Collins M, Churilov L, Mount PF. Effects of intraoperative and early postoperative normal saline or Plasma-Lyte 148® on hyperkalaemia in deceased donor renal transplantation: a double-blind randomized trial. Br J Anaesth 2017; 119: 606-615.

50) Saini V, Samra T, Naik B N, Ganesh V, Garg K, Sethi S, Kanwar DB, Singh S, Rawat N, Gorla D. Normal saline versus balanced crystalloids in renal transplant surgery: a double-blind randomized controlled study. Cureus 2021; 13: e18247.

51) Khajavi MR, Etezadi F, Moharari RS, Imani F, Meysamie AP, Khashayar P, Najafi A. Effects of normal saline vs. lactated ringer's during renal transplantation. Ren Fail 2008; 30: 535-539.

52) Modi MP, Vora KS, Parikh GP, Shah VR. A comparative study of impact of infusion of Ringer's Lactate solution versus normal saline on acid-base balance and serum electrolytes during live related renal transplantation. Saudi J Kidney Dis Transpl 2012; 23: 135-137.

53) Kim SY, Huh KH, Lee JR, Kim SH, Jeong SH, Choi YS. Comparison of the effects of normal saline versus plasmalyte on acid-base balance during living donor kidney transplantation using the Stewart and base excess methods. Transplant Proc 2013; 45: 2191-2196.

54) Pfortmueller C, Funk GC, Potura E, Reiterer C, Luf F, Kabon B, Druml W, Fleischmann E, Lindner G. Acetate-buffered crystalloid infusate versus infusion of 0.9% saline and hemodynamic stability in patients undergoing renal transplantation: Prospective, randomized, controlled trial. Wien Klin Wochenschr 2017; 129: 598-604.

55) Yunos NM, Bellomo R, Hegarty C, Story D, Ho L, Bailey M. Association between a chloride-liberal vs chloride-restrictive intravenous fluid administration strategy and kidney injury in critically ill adults. JAMA 2012; 308: 1566-1572.

56) Guidet B, Soni N, Rocca GD, Kozek S, Vallet B, Annane D, James M. A balanced view of balanced solutions. Crit Care 2010; 14: 325.

57) Shaw AD, Bagshaw SM, Goldstein SL, Scherer LA, Duan M, Schermer CR, Kellum JA. Major complications, mortality, and resource utilization after open abdominal surgery: 0.9% saline compared to Plasmalyte. Ann Surg 2012; 255: 821-829.

58) Makaryus R, Miller TE, Gan TJ. Current concepts of fluid management in enhanced recovery pathways. Br J Anaesth 2018; 120: 376-383.

59) Monnet X, Shi R, Teboul JL. Prediction of fluid responsiveness. What's new? Ann Intensive Care 2022; 12: 46.

60) Kumar L, Rajan S, Baalachandran R. Outcomes associated with stroke volume variation versus central venous pressure guided fluid replacements during major abdominal surgery. J Anaesthesio Clin Pharmacol 2016; 32: 182-186.

61) Kannan G, Loganathan S, Kajal K, Hazarika A, Sethi S, Sen IM, Subramanyam R, Singh S. The effect of pulse pressure variation compared with central venous pressure on intraoperative fluid management during kidney transplant surgery: a randomized controlled trial. Can J Anaesth 2022; 69: 62-71.

62) Srivastava D, Sahu S, Chandra A, Tiwari T, Kumar S, Singh PK. Effect of intraoperative transesophageal Doppler-guided fluid therapy versus central venous pressure-guided fluid therapy on renal allograft outcome in patients undergoing living donor renal transplant surgery: a comparative study. J Anesth 2015; 29: 842-849.