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+, CI- 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, l^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 CI- 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 electro-

lyte 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 price³. Studies⁴⁻⁶ 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 electrolytes7. 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-analyses⁸⁻¹⁰ 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 NSbased hydroxyethyl starch (NS as solvent) are used in the clinic, when necessary, in non-cardiac surgeries. Only one meta-analysis¹¹ 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 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 **Sup**plementary 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, 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 \pm SD¹² 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 het-

erogeneity was defined as low when $P \le 50\%$ and high when $P \ge 50\%$. 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 $P \ge 50\%$. 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-biasrisk 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.

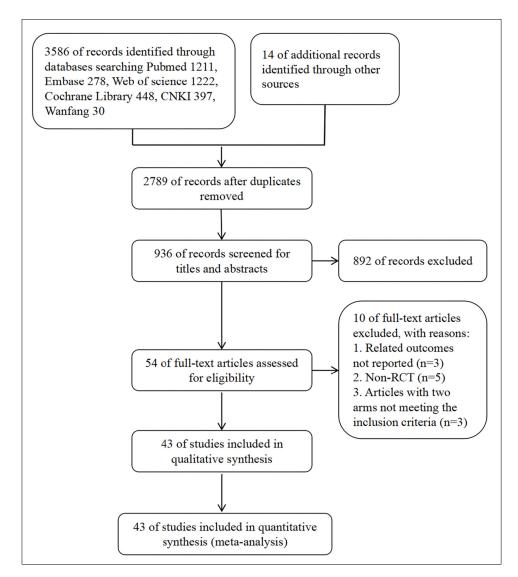


Figure 1. PRISMA flowchart.

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 study⁴⁴, 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 studies²⁶⁻⁵⁴ 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 al²⁴ 2015 (1), Wu et al³⁷ 2014 (1), Peng and Zheng³³ 2016 (1) and Li et al⁴⁵ 2006 (1) showed a comparison between lactated ringer's solution (LR) and NS. Dong et al²⁴ 2015 (2), Wu et al³⁷ 2014 (2), Peng and Zheng³³ 2016 (2) and Li et al⁴⁵ 2006 (2) showed a comparison between acetate-buffered solution (AS) and NS. Hadimioglu et al⁴⁷ 2008 (1) and Saini et al⁵⁰ 2021 (1) represented the comparison between LR and NS, Hadimioglu et al⁴⁷ 2008 (2) and Saini et al⁵⁰ 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, P=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, P=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, P=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, I²=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; l^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.	
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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		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)	AS (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) 1,000 ml/h No detail LR (n=20) NS (n=20) NS (n=20) No detail		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

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 ₂ O	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)	n=30) No detail No		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)			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 ₂ O; 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

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 ₂ O and PPV 13% (intra-op) CVP14-16 cm H ₂ O (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 ₂ O	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 ₂ O	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

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

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.

Outcome	No. of reference	No. of patients	MD	OR	95% CI	f	<i>p</i> -value	<i>p</i> -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	$\oplus \oplus \oplus \Theta$ (low)
Renal dysfunction	12	1588	/	0.87	0.59 to 1.30	0%	0.66	0.81	$\oplus \oplus \oplus \oplus \Theta$ (low)
Mortality	2	186	/	0.67	0.24 to 1.87	0%	0.76	/	$\oplus \oplus \oplus$ (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	$\oplus \oplus \oplus \oplus \ominus$ (moderate)
POD 1	6	336	1.09	/	0.60 to 1.58	76.2%	0.00	0.51	$\oplus \oplus \oplus \oplus \Theta$ (moderate)
Na ⁺									
End of surgery	20	1633	-0.55	/	-0.79 to -0.31	80.0%	0.00	0.00	$\oplus \oplus \oplus \oplus \Theta$ (moderate)
POD 1	6	259	-0.90	/	-1.36 to -0.43	68.9%	0.00	0.41	$\oplus \oplus \oplus \oplus \Theta$ (moderate)
Cl-									
End of surgery	25	2192	-1.92	/	-2.40 to -1.43	95.8%	0.00	0.01	$\oplus \oplus \oplus \oplus \Theta$ (moderate)
POD 1	6	309	-3.02	/	-4.55 to -1.50	96.4%	0.00	0.03	$\oplus \oplus \Theta \Theta$ (low)
Creatinine									
End of surgery	5	480	-0.07	/	-0.30 to 0.15	35.4%	0.52	0.08	$\oplus \oplus \Theta \Theta$ (low)
POD 1	6	601	-0.17	/	-0.40 to 0.07	57.2%	0.16	0.45	$\oplus \oplus \oplus \oplus \ominus$ (moderate)
Vasopressor requirement	7	378	/	0.79	0.47 to 1.33	1.8%	0.38	0.04	$\oplus \oplus \Theta \Theta$ (low)

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

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

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	anced cry				OR	Weigh
Study	Yes	No	Yes	No	with 95% Cl	(%)
Acidosis						
Ayebale2017	73	175	96	156	0.68 [0.47, 0.98]	13.16
Brahma2017	0	41	33	8	0.00 [0.00, 0.05]	2.41
Hafizah2017	0	23	16	8	0.01 [0.00, 0.20]	2.37
Lima2019	0	15	3	12	0.12 [0.01, 2.45]	2.20
Wikes2001	0	25	6	19	0.06 [0.00, 1.11]	2.35
O'Malley2005	0	25	8	25	0.06 [0.00, 1.07]	2.39
Heterogeneity: T ² = 4.9	$4, I^2 = 80$).77%, ⊦	l ² = 5.2	20	0.05 [0.01, 0.43]	
Test of $\theta_i = \theta_j$: Q(5) = 2	6.00, p =	0.00				
Mortality						
Guo2016	1	32	1	32	1.00 [0.06, 16.69]	2.52
Waters2001	6	54	9	51	- 0.63 [0.21, 1.89]	8.32
Heterogeneity: $\tau^2 = 0.0$	$0, I^2 = 0.$	00%, H ²	= 1.00)	0.67 [0.24, 1.87]	
Test of $\theta_i = \theta_i$: Q(1) = 0	.09, p = (0.76			· · · · ·	
Renal dysfunction						
Ayebale2017	2	246	2	250	1.02 [0.14, 7.27]	4.35
.ima2019	0	29	1	28	0.32 [0.01, 8.24]	1.99
Waters2001	4	29	5	28	0.77 [0.19, 3.18]	6.55
Ku2011	2	89	1	94	2.11 [0.19, 23.71]	3.21
Saini 2021(1)	0	60	0	60	1.00 [0.02, 51.22]	1.41
Saini 2021(2)	0	60	0	60	1.00 [0.02, 51.22]	1.41
Hadimioglu 2008(1)	1	29	3	27	0.31 [0.03, 3.17]	3.42
Hadimioglu 2008(2)	2	28	3	27	0.64 [0.10, 4.15]	4.68
Khajavi 2009	2	24	0	26	5.41 [0.25, 118.34]	2.16
D'Malley2005	1	24	2	24	0.50 [0.04, 5.89]	3.12
Pfortmueller2017	19	53	19	57	1.08 [0.51, 2.25]	10.79
Potura2015	19	53	19	57	- 1.08 [0.51, 2.25]	10.79
Weinberg 2017	4	20	13	12		6.99
Kim 2013	3	27	1	29	3.22 [0.32, 32.89]	3.42
Heterogeneity: $\tau^2 = 0.0$	$0, I^2 = 0.$	00%, H ²	= 1.00)	0.87 [0.59, 1.30]	
Test of $\theta_i = \theta_j$: Q(13) =	10.41, p	= 0.66				
Overall					0.53 [0.32, 0.86]	
Heterogeneity: $\tau^2 = 0.4$	4, $I^2 = 47$	7.25%, F	l ² = 1.9	90		
Test of $\theta_i = \theta_j$: Q(21) =	39.81, p	= 0.01				
Test of group difference	es: Q₅(2)	= 6.74,	p = 0.0	03		
					1/4096 1/64 1 64	
andom-effects DerSim	ionian-La	aird mod	lel			

The safety and efficacy of balanced crystalloid vs. normal saline in non-cardiac surgeries

Figure 2. Forest plots of clinical outcomes.

Study N Mean SD N Mean SD With 95% Cl (%) Bodlt2007 15 7.46 .05 15 7.39 .04 1.50 [0.71, 2.30] 14.18 Guo2016 60 7.21 .17 60 7.11 .16 0.60 [0.24, 0.97] 20.05 Helmy2016 20 7.46 .05 16 7.45 .05 0.20 [-0.45, 0.84] 16.23 Saracoglu2014 25 7.41 .02 25 7.36 .03 1.93 [1.27, 2.59] 15.95 Volta2013 20 7.41 .05 30 7.35 .04 1.31 [0.76, 1.86] 17.54 Overall Heterogeneity: $r^2 = 0.28$, $l^2 = 76.19\%$, $H^2 = 4.20$ 1.09 [0.60, 1.58] 1.09 [0.60, 1.58] 1.09 [0.60, 1.58] Test of $\theta_i = \theta_j$: $Q(5) = 21.00$, $p = 0.00$ Test of $\theta = 0$: $z = 4.34$, $p = 0.00$ Image: the second sec	Study	Balano N	ed cryst Mean		No N	rmal sa Mean			MD with 95% CI	Weight (%)
Bold 2007 15 7.4 0.5 15 7.3 0.6 0.7 1.5 0.7 0.2 2.7 3.8 0.4 0.00 [-0.26, 0.26] 3.7 1 0.000 [-0.26, 0.26] 3.7 1 0.000 [-0.26, 0.26] 3.7 1 0.000 [-0.26, 0.26] 3.7 1 0.000 [-0.26, 0.26] 3.7 1 0.000 [-0.26, 0.26] 3.7 1 0.000 [-0.26, 0.26] 3.7 1 0.000 [-0.26, 0.26] 3.7 1 0.000 [-0.26, 0.26] 3.7 1 0.000 [-0.26, 0.26] 3.7 1 0.000 [-0.26, 0.26] 3.7 1 0.000 [-0.26, 0.26] 3.7 1 0.000 [-0.26, 0.26] 3.7 1 0.000 [-0.26, 0.26] 3.7 1 0.000 [-0.26, 0.26] 3.7 1 0.000 [-0.26, 0.26] 3.7 1 0.000 [-0.26, 0.26] 3.7 1 0.000 [-0.26, 0.26] 3.7 1 0.000 [-0.26, 0.26] 3.7 1 0.000 [-0.26, 0.26] 3.7 1 0.000 [-0.26, 0.26] 3.7 1 0.000 [-0.26, 0.26] 3.7 1 0.000 [-0.26, 0.26] 3.7 1 0.000 [-0.26, 0.26] 3.7 1 0.000 [-0.26, 0.26] 3.7 1 0.000 [-0.26, 0.26] 3.7 1 0.000 [-0.26, 0.26] 3.7 1 0.000 [-0.26, 0.26] 3.7 1 0.000 [-0.26, 0.26] 3.7 1 0.000 [-0.26, 0.26] 3.7 1 0.000 [-0.26, 0.26] 3.7 1 0.000 [-0.26, 0.26] 3.7 1 0.000 [-0.26, 0.26] 3.7 1 0.000 [-0.26, 0.26] 3.7 1 0.000 [-0.26, 0.26] 3.7 1 0.000 [-0.26, 0.26] 3.7 1 0.000 [-0.26, 0.26] 3.7 1 0.000 [-0.26, 0.26] 3.7 1 0.000 [-0.26, 0.26] 3.7 1 0.000 [-0.26, 0.26] 3.7 1 0.000 [-0.26, 0.26] 3.7 1 0.000 [-0.26, 0.26] 3.7 1 0.000 [-0.26, 0.26] 3.7 1 0.000 [-0.26, 0.26] 3.7 1 0.000 [-0.26, 0.26] 3.7 1 0.000 [-0.26, 0.26] 3.7 1 0.000 [-0.26, 0.26] 3.7 1 0.000 [-0.26, 0.26] 3.7 1 0.000 [-0.26, 0.26] 3.7 1 0.000 [-0.26, 0.26] 3.7 1 0.000 [-0.26, 0.26] 3.7 1 0.000 [-0.26, 0.26] 3.7 1 0.000 [-0.26, 0.26] 3.7 1 0.000 [-0.26, 0.26] 3.7 1 0.000 [-0.26, 0.26] 3.7 1 0.000 [-0.26, 0.26] 3.7 1 0.000 [-0.26, 0.26] 3.7 1 0.000 [-0.26, 0.26] 3.7 1 0.000 [-0.26, 0.26] 3.7 1 0.000 [-0.26, 0.26] 3.7 1 0.000 [-0.26, 0.26] 3.7 1 0.000 [-0.26, 0.26] 3.7 1 0.000 [-0.26, 0.26] 3.7 1 0.000 [-0.26, 0.26] 3.7 1 0.000 [-0.26, 0.26] 3.7 1 0.000 [-0.26, 0.26] 3.7 1 0.000 [-0.26, 0.26] 3.7 1 0.000 [-0.26, 0.26] 3.7 1 0.000 [-0.26, 0.26] 3.7 1 0.000 [-0.26, 0.26] 3.7 1 0.000 [-0.26, 0.26] 3.7 1 0.000 [-0.26, 0.26] 3.7 1 0.000 [-0.26, 0.26] 3.7 1 0.000 [-0.26, 0.26] 3.7 1 0.000 [-0.26, 0.26] 3.0000 [-0.26, 0.26] 3.0000 [-0.26, 0.26]	Avebale2017	248	7.36	.08	252	7.33	.07		0.40 [0.22, 0.5	
Brahma2017 41 7.4 0.2 41 7.31 0.3 Deg2016 22 7.47 0.4 22 7.38 0.4 Dong2015(1) 20 7.4 0.5 2.21 1.47, 2.86 2.96 Dong2015(2) 20 7.4 0.5 0.00 0.00 0.00 0.00 0.00 0.00 0.00 0.00 0.00 0.00 0.00 0.00 0.00 0.00 0.00 0.00 0.00 0.00 0.00 0.00 0.00 0.00 0.00 0.00 0.00 0.00 0.00 0.00 0.00 0.00 0.00 0.00 0.00 0.00 0.00 0.00 0.00 0.00 0.00 0.00 0.00 0.00 0.00 0.00 0.00 0.00 0.00 0.00 0.00 0.00 0.00 0.00 0.00 0.00 0.00 0.00 0.00 0.00 0.00 0.00 0.00 0.00 0.00 0.00 0.00 0.00 0.00 0.00 0.00 0.00 0.00 0.00 0.00									•	-
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Dong2015(1) 20 7.42 02 20 7.4 0.5 Dong2015(2) 20 7.4 0.5 20 7.4 0.5 Haltzah2017 15 7.4 0.2 15 7.36 0.5 Helmy2016 20 7.4 0.8 16 7.37 0 Helmy2016 20 7.37 01 20 7.37 01 Hou2016 20 7.37 01 20 7.37 0 Li2006(1) 33 7.45 0.6 30 7.36 0.6 Helmy2016 20 7.37 0.7 20 7.37 0.0 Helmy2016 20 7.37 0.0 20 7.37 0.0 Helmy2016 20 7.38 0.8 30 7.36 0.6 Helmy2016 20 7.38 0.8 30 7.36 0.6 Helmy2016 20 7.37 0.0 20 7.37 0.0 Helmy2016 20 7.38 0.8 30 7.36 0.6 Helmy2016 20 7.38 0.2 25 7.29 0.4 Helmy2014 25 7.38 0.2 25 7.29 0.4 Helmy2014 25 7.38 0.2 25 7.29 0.4 Helmy2014 25 7.38 0.2 20 7.33 0.5 Helmy2014 20 7.45 0.6 20 7.45 0.5 Helmy2016 33 7.44 0.7 33 7.35 0.9 Helmi2010 33 7.4 0.7 33 7.35 0.9 Helmi2010 208(1) 30 7.44 0.6 30 7.36 0.5 Helmi202001 23 7.42 0.7 30 7.36 0.5 Helmi202001 23 7.42 0.7 30 7.36 0.5 Helmi202001 33 7.4 0.7 33 7.35 0.9 Helmi202001 33 7.4 0.7 33 7.35 0.9 Helmi202001 33 7.4 0.7 30 7.36 0.5 Helmi202001 33 7.4 0.7 30 7.36 0.5 Helmi202005 25 7.37 0.7 26 7.28 0.7 Helmi202005 25 7.37 0.7 26 7.28 0.7 Helmi202016 0 7.21 1.7 60 7.11 1.6 Helmi202016 20 7.44 0.5 15 7.39 0.4 Helerogeneity: $r^2 = 0.48$ 1.52 7.60 0.3 His [0.60 [0.24, 0.97] 20.5 Helmi202016 20 7.44 0.5 15 7.39 0.4 Helerogeneity: $r^2 = 0.28$ 1.57 1.90 0.4 Helerogeneity: $r^2 = 0.28$ 1.57 1.90 0.73 1.90 0.73 1.91 0.71 1.93 1.27 2.59 1.95 0.73 0.92 0.95 0.93 0.92 0.95 0.93 0.92 0.95 0.93 0.92 0.95 0.93 0.92 0.95 0.93 0.92 0.95 0.93 0.92 0.95 0.93 0.92 0.95 0.93 0.92 0.95 0.93 0.92 0.95 0.93 0.92 0.95 0.9	Dey2018	22	7.47	.04	22	7.38	.04			-
Deng2015(2) 20 7.4 05 20 7.4 0.5 Halizab2017 16 7.4 0.2 15 7.8 0.2 Halizab2017 16 7.4 0.2 15 7.8 0.2 Halizab2017 28 7.42 0.4 27 7.8 0.5 Halizab2017 28 7.42 0.4 27 7.8 0.5 Halizab2017 28 7.42 0.4 27 7.8 0.5 Halizab2016 20 7.37 0.1 20 7.37 0.1 Hou2016 20 7.37 0.1 20 7.37 0.1 Hou2016 20 7.37 0.1 20 7.37 0.1 Hou2016 20 7.37 0.1 20 7.37 0.6 Halizab201 30 7.48 0.8 0.3 7.45 0.6 Halizab201 33 7.45 0.5 33 7.45 0.4 Halizab202 15 7.34 0.2 15 7.26 0.6 Halizab202 15 7.34 0.2 15 7.26 0.6 Halizab202 15 7.34 0.2 15 7.26 0.6 Halizab202 15 7.34 0.2 15 7.26 0.6 Halizab201 23 7.42 0.7 24 7.35 0.7 Wu2014(1) 20 7.43 0.6 20 7.45 0.5 Halimioglu 2008(2) 30 7.44 0.7 33 7.46 0.5 Halimioglu 2008(2) 30 7.42 0.6 30 7.36 0.5 Halimioglu 2008(2) 30 7.42 0.6 30 7.36 0.5 Halimioglu 2008(2) 30 7.44 0.7 30 7.36 0.5 Halimioglu 2008(2) 30 7.44 0.7 30 7.36 0.5 Halimioglu 2008(2) 30 7.44 0.7 30 7.46 0.5 Halimioglu 2008(2) 30 7.42 0.6 30 7.36 0.6 Halimioglu 2008(2) 30 7.42 0.6 30 7.36 0.6 Halimioglu 2008(2) 30 7.44 0.7 30 7.46 0.5 Halimioglu 2008(2) 30 7.44 0.7 30 7.46 0.5 Halimioglu 2008(2) 30 7.44 0.7 30 7.46 0.5 Halimioglu 2008(2) 30 7.42 0.6 30 7.36 0.6 Halimioglu 2008(2) 30 7.42 0.6 30 7.36 0.6 Halimioglu 2008(1) 30 7.41 0.5 30 7.35 0.4 Halimioglu 2008(1) 30 7.41 0.5 30 7.35 0.4 Halimioglu 2008(1) 4.7 (1.16 1.4 (1.10 1.4 (1.10 1.4 (1.10 1.4 (1.10 1.4 (1.10 1.4 (1.10 1.4 (1.10 1.4 (1.10 1.4 (1.10 1.4 (1.10 1.4 (1.10 1.4 (1.10 1.4 (1.10 1.4 (1.10 1.4 (1.1	Disma2014	114	7.33	.02	115	7.33	.01		0.00 [-0.26, 0.2	6] 3.71
Halizah2017 15 7.4 02 16 7.36 02 Hassan2017 28 7.4 04 27 7.36 0.6 Helmy2016 20 7.4 0.8 16 7.37 0.1 Li2006(1) 30 7.38 0.4 30 7.36 0.6 Helmy2016 20 7.37 0.1 Li2006(2) 30 7.38 0.4 30 7.36 0.6 Helmy2016 21 7.41 0.5 33 7.45 0.4 Peng2016(1) 33 7.45 0.5 33 7.45 0.4 Peng2016(2) 33 7.44 0.7 33 7.35 0.9 Wukes2001 23 7.44 0.7 33 7.36 0.5 Hadimiogl 2008(1) 30 7.44 0.6 30 7.36 0.5 Hadimiogl 2008(2) 30 7.42 0.6 20 7.45 0.5 Polura2015 72 7.33 0.2 76 7.28 0.7 Polura2015 72 7.35 0.9 Polura2016 00 7.21 1.7 60 7.11 1.6 Polura2016 00 7.21 1.7 60 7.11 1.6 Polura2017 15 7.46 0.5 15 7.39 0.4 Polura2018 20 7.41 0.3 20 7.38 0.2 Polura2013 30 7.41 0.5 30 7.35 0.4 Polura2013 00 7.41 0.2 55 7.36 0.3 Polura2013 00 7.41 0.5 30 7.35 0.4 Polura2013 00 7.41 0.5 30 7.35 0.4 Polura2013 00 7.41 0.5 30 7.35 0.4 Polura2013 00 7.41 0.5 30 7.35 0.4	Dong2015(1)	20	7.42	.02	20	7.4	.05		0.51 [-0.10, 1.1	3] 3.18
Hassan2017 28 7.42 0.4 27 7.36 0.5 1.31 0.31 0.32 0.32 0.32 0.32 0.32 0.32 0.32 0.32 0.32 0.32 0.32 0.32 0.32 0.32 0.32 0.32 0.32 0.32 0.32 0.32 0.32 0.32 0.32 0.32 0.32 0.32 0.32 0.32 0.32 0.32 0.32 0.32 0.32 0.32 0.32 0.32 0.32 0.32 0.32 0.32 0.32 0.32 0.32 0.32 0.32 0.32 0.32 0.32 0.32 0.32 0.32 0.32 0.33 0.33 0.32 0.33 0.32 0.32 0.32 0.32 0.32 0.32 0.33 0.33 0.32 0.33 0.32 0.33 0.33 0.33 0.33 0.32 0.33 0.33 0.32 0.33 0.33 0.32 0.33 0.32 0.33 0.33 0.32 0.33 0.32 0.33 0.32 0.33 0.32 <th0.33< th=""> 0.33 <th0.33< th=""></th0.33<></th0.33<>	Dong2015(2)	20	7.4	.05	20	7.4	.05		0.00 [-0.61, 0.6	1] 3.20
Helmy2016 20 7.4 0.8 16 7.37 .1 0.0 [-0.61] 0.20 [-0.61] 0.20 [-0.61] 0.20 [-0.61] 0.20 [-0.61] 0.20 [-0.61] 0.20 [-0.61] 0.20 [-0.61] 0.20 [-0.61] 0.20 [-0.61] 0.20 [-0.61] 0.20 [-0.61] 0.20 [-0.61] 0.20 [-0.61] 0.20 [-0.61] 0.20 [-0.61] 0.20 [-0.61] 0.20 [-0.61] 0.20 [-0.61] 0.20 [-0.61] 0.20 [-0.61] 0.20 [-0.61] 0.20 [-0.61] 0.20 [-0.61] 0.20 [-0.61] 0.20 [-0.61] 0.20 [-0.61] 0.20 [-0.61] 0.20 [-0.61] 0.20 [-0.61] 0.20 [-0.61] 0.20 [-0.61] 0.20 [-0.61] 0.20 [-0.61] 0.20 [-0.61] 0.20 [-0.61] 0.20 [-0.61] 0.20 [-0.61] 0.20 [-0.61] 0.20 [-0.61] 0.20 [-0.61] 0.20 [-0.61] 0.20 [-0.61] 0.20 [-0.61] 0.20 [-0.61] 0.20 [-0.61] 0.20 [-0.61] 0.20 [-0.61] 0.20 [-0.61] 0.20 [-0.61] 0.20 [-0.61] 0.20 [-0.61] 0.20 [-0.61] 0.20 [-0.61] 0.20 [-0.61] 0.20 [-0.61] 0.20 [-0.61] 0.20 [-0.61] 0.20 [-0.61] 0.20 [-0.61] 0.20 [-0.61] 0.20 [-0.61] 0.20 [-0.61] 0.20 [-0.61] 0.20 [-0.61] 0.20 [-0.61] 0.20 [-0.61] 0.20 [-0.61] 0.20 [-0.61] 0.20 [-0.61] 0.20 [-0.61] 0.20 [-0.61] 0.20 [-0.61] 0.20 [-0.61] 0.20 [-0.61] 0.20 [-0.61] 0.20 [-0.61] 0.20 [-0.61] 0.20 [-0.61] 0.20 [-0.61] 0.20 [-0.61] 0.20 [-0.61] 0.20 [-0.61] 0.20 [-0.61] 0.20 [-0.61] 0.20 [-0.61] 0.20 [-0.61] 0.20 [-0.61] 0.20 [-0.61] 0.20 [-0.61] 0.20 [-0.61] 0.20 [-0.61] 0.20 [-0.61] 0.20 [-0.61] 0.20 [-0.61] 0.20 [-0.61] 0.20 [-0.61] 0.20 [-0.61] 0.20 [-0.61] 0.20 [-0.61] 0.20 [-0.61] 0.20 [-0.61] 0.20 [-0.61] 0.20 [-0.61] 0.20 [-0.61] 0.20 [-0.61] 0.20 [-0.61] 0.20 [-0.61] 0.20 [-0.61] 0.20 [-0.61] 0.20 [-0.61] 0.20 [-0.61] 0.20 [-0.61] 0.20 [-0.61] 0.20 [-0.61] 0.20 [-0.61] 0.20 [-0.61] 0.20 [-0.61] 0.20 [-0.61] 0.20 [-0.61] 0.20 [-0.61] 0.20 [-0.61] 0.20 [-0.61] 0.20 [-0.61] 0.20 [-0.61] 0.20 [-0.61] 0.20 [-0.61] 0.20 [-0.61] 0.20 [-0.61] 0.20 [-0.61] 0.20 [-0.61] 0.20 [-0.61] 0.20 [-0.61] 0.20 [-0.61] 0.20 [-0.61] 0.20 [-0.61] 0.20 [-0.61] 0.20 [-0.61] 0.20 [-0.61] 0.20 [-0.61] 0.20 [-0.61] 0.20 [-0.61] 0.20 [-0.61] 0.20 [-0.61] 0.20 [-0.61] 0.20 [-0.61] 0.20 [-0.61] 0.20 [-0.61] 0.20 [-0.61] 0.20 [-0.61] 0.20 [-0.61] 0.20 [-0.61] 0.20 [-0.61] 0.20 [-0.61] 0.20 [-0.61]	Hafizah2017	15	7.4	.02	15	7.36	.02		1.95 [1.09, 2.8	0] 2.75
Hou2016 20 7.37 .01 20 7.37 .01 Li2006(1) 30 7.38 .04 30 7.36 .06 Peng2016(1) 33 7.45 .05 33 7.45 .04 Peng2016(2) 33 7.45 .05 33 7.45 .04 Saracoglu2014 25 7.38 .02 25 7.29 .04 Scheingraber1999 12 7.41 .03 12 7.31 .03 Taki2002 15 7.34 .02 15 7.26 .06 0.32 [-0.22, 0.44] 2.17 Analyzo 12 7.36 .02 20 7.33 .05 $0.71 [0.14, 1.40] 3.16 Wu2014(1) 20 7.45 .06 20 7.45 .05 Mu2014(2) 20 7.45 .06 20 7.45 .05 Hadimioglu 2008(1) 30 7.44 .06 30 7.36 .05 Hadimioglu 2008(2) 30 7.48 .07 30 7.46 .05 Hadimioglu 2008(2) 30 7.48 .07 30 7.46 .05 0.33 [0.57, 1.10]Wu2014(2) 20 7.45 .06 20 7.45 .050.33 [0.57, 1.10]Wu2014(2) 20 7.45 .06 20 7.46 .050.33 [0.57, 1.10]-2 0 2 4-2 0 2 4-2 0 2 4-2 0 2 4-2 0 2 4-2 0 2 4-2 0 2 4-2 0 2 4-2 0 2 4-2 0 2 4-2 0 2 4-2 0 2 4-2 0 2 4-2 0 2 4-2 0 2 4-2 0 2 4-2 0 2 4-2 0 2 4-2 0 2 4-2 0 2 4-2 0 2 4-2 0 2 4-2 0 2 4-2 0 2 4-2 0 2 4-2 0 2 4-2 0 2 4-2 0 2 4-2 0 2 4-2 0 2 4-2 0 2 4-2 0 2 4-2 0 2 4-2 0 2 4-2 0 2 4-2 0 2 4-2 0 2 4-2 0 2 4-2 0 2 4-2 0 2 4-2 0 2 4-2 0 2 4-2 0 2 4-2 0 2 4-2 0 2 4-2 0 2 4-2 0 2 4-2 0 2 4-2 0 2 4-2 0 2 4-2 0 2 4-2 0 2 4-2 0 2 4-2 0 2 4-2 0 2 4-2 0 2 4-2 0 2 4-2 0 2 4-2$	Hassan2017	28	7.42	.04	27	7.36	.05		1.31 [0.73, 1.8	8] 3.26
Li2006(1) 30 7.38 0.4 30 7.36 0.6 Li2006(2) 30 7.38 0.8 30 7.36 0.6 Peng2016(1) 33 7.41 0.5 33 7.45 0.4 Peng2016(2) 33 7.45 0.5 33 7.45 0.4 Peng2016(2) 33 7.45 0.5 33 7.45 0.4 Peng2016(2) 33 7.45 0.5 33 7.45 0.4 Saracoglu2014 25 7.34 0.2 15 7.29 0.4 Withes2001 23 7.42 0.7 33 7.35 0.9 Withes2001 23 7.42 0.7 24 7.35 0.7 With 92% Cl 0.33 1.20 Polyale 2008(2) 30 7.42 0.6 30 7.35 0.5 Hadimioglu 2008(2) 30 7.42 0.6 30 7.45 0.5 Hadimioglu 2008(2) 30 7.42 0.6 30 7.45 0.5 Polyale 2013 30 7.42 0.6 30 7.45 0.5 Polyale 2014 0.5 26 7.29 0.8 King 2013 30 7.42 0.6 30 7.45 0.5 Polyale 2015 7.2 7.33 0.2 76 7.42 0.6 Polyale 2015 7.2 7.33 0.2 76 7.42 0.6 Salari 202(1) 60 7.31 0.4 60 7.29 0.6 Salari 202(1) 60 7.21 1.0 40 7.29 0.6 Salari 202(1) 60 7.21 1.7 60 7.11 1.6 Heterogeneity: $r^2 = 0.48$, $r^2 = 8.02\%$, $H^2 = 9.10$ Test of $\theta = 0$; $z = 6.13$, $p = 0.00$ Parameter substantiane salare MD with 95% Cl (%) BodIt2007 15 7.46 0.5 15 7.39 0.4 Gua2016 60 7.21 1.7 60 7.11 1.6 Heterogeneity: $r^2 = 0.48$, $r^2 = 76.19\%$, $H^2 = 4.20$ Test of $\theta = 0$; $z = 6.13$, $p = 0.00$ Test of $\theta = 0$; $z = 6.13$, $p = 0.00$ Test of $\theta = 0$; $z = 6.34$, $h^2 = 76.19\%$, $H^2 = 4.20$ Test of $\theta = 0$; $z = 4.34$, $p = 0.00$ Test of $\theta = 0$; $z = 4.34$, $p = 0.00$	Helmy2016	20	7.4	.08	16	7.37	.1		0.33 [-0.32, 0.9	8] 3.13
Li2006(2) 30 7.38 .08 30 7.36 .06 Peng2016(1) 33 7.41 .05 33 7.45 .04 Peng2016(2) 33 7.45 .05 33 7.45 .04 Peng2016(2) 33 7.45 .05 33 7.45 .04 Saracoglu2014 25 7.38 .02 25 7.29 .04 Saracoglu2014 25 7.34 .02 15 7.26 .06 Volta2013 20 7.36 .02 20 7.33 .05 Wikes2001 23 7.4 .07 33 7.35 .09 Wikes2001 23 7.42 .07 24 7.35 .07 Wikes2001 23 7.42 .07 24 7.35 .09 Wikes2001 23 7.42 .07 24 7.35 .09 Wikes2001 23 7.44 .06 30 7.36 .05 Hadimioglu 2008(1) 30 7.44 .06 30 7.36 .05 Hadimioglu 2008(2) 30 7.42 .06 30 7.36 .05 Hadimioglu 2008(2) 30 7.44 .05 26 7.29 .08 ONale 20 7.31 .04 .05 .05 Hadimioglu 2008(2) 30 7.48 .07 30 7.46 .05 Potura2015 72 7.33 .02 76 7.32 .01 Saini 2021(1) 60 7.33 .06 60 7.29 .06 Saini 2021(2) 60 7.31 .04 60 7.29 .06 Oxerall Heterogeneity: $r^2 = 0.48$, $r^2 = 89.02\%$, $r^2 = 9.10$ Test of $\theta = 0$: $z = 6.13$, $p = 0.00$ z = 2 - 2 - 2 - 4 z = 0 - 2 - 4 - 5 - 28 z = 0 - 2 - 4 - 4 - 28 z = 0 - 2 - 4 - 4 -	Hou2016	20	7.37	.01	20	7.37	.01		0.00 [-0.61, 0.6	1] 3.20
Peng2016(1) 33 7.41 .05 33 7.45 .04 Peng2016(2) 33 7.45 .05 33 7.45 .04 Peng2016(2) 33 7.45 .05 33 7.45 .04 Peng2016(2) 33 7.45 .05 33 7.45 .04 Scheingraber 1999 12 7.41 .03 12 7.31 .03 Scheingraber 1999 12 7.41 .03 12 7.31 .03 Paikl2002 15 7.34 .02 15 7.26 .06 Waters2001 23 7.42 .07 24 7.35 .09 Wu2014(1) 20 7.45 .06 20 7.45 .05 Hadimioglu 2008(1) 30 7.44 .06 30 7.36 .05 Hadimioglu 2008(2) 30 7.42 .06 30 7.36 .05 Potura2015 72 7.33 .02 76 7.29 .06 Saini 2021(1) 60 7.33 .06 60 7.29 .06 Saini 2021(1) 60 7.33 .02 66 7.29 .06 Saini 2021(1) 60 7.33 .02 76 7.32 .01 Balanced crystalloid Mean SD N Mean SD Potura2015 72 7.31 .04 60 7.29 .06 Saini 2021(1) 60 7.31 .04 60 7.29 .06 Saini 2021(2) 60 7.21 .17 60 7.11 .16 Heterogeneity: $r^2 = 0.48$, $l^2 = 80.02\%$, $H^2 = 9.10$ Test of $\theta = 0$: $z = 6.13$, $p = 0.00$ Heterogeneity: $r^2 = 0.48$, $l^2 = 80.02\%$, $H^2 = 9.10$ Test of $\theta = 0$: $z = 6.13$, $p = 0.00$ Heterogeneity: $r^2 = 0.48$, $l^2 = 80.02\%$, $H^2 = 9.10$ Test of $\theta = 0$: $z = 6.13$, $p = 0.00$ Heterogeneity: $r^2 = 0.48$, $l^2 = 80.02\%$, $H^2 = 9.10$ Test of $\theta = 0$: $z = 6.13$, $p = 0.00$ Heterogeneity: $r^2 = 0.48$, $l^2 = 76.19\%$, $H^2 = 4.20$ Test of $\theta = 0$: $z = 6.13$, $p = 0.00$ Test of $\theta = 0$: $z = 4.34$, $p = 0.00$ Heterogeneity: $r^2 = 0.28$, $l^2 = 76.19\%$, $H^2 = 4.20$ Test of $\theta = 0$: $z = 4.34$, $p = 0.00$ Heterogeneity: $r^2 = 0.28$, $l^2 = 76.19\%$, $H^2 = 4.20$ Test of $\theta = 0$: $z = 4.34$, $p = 0.00$	Li2006(1)	30	7.38	.04	30	7.36	.06		0.39 [-0.12, 0.8	9] 3.38
Peng2016(2) 33 7.45 0.5 33 7.45 0.4 Saracoglu2014 25 7.38 0.2 25 7.29 0.4 Saracoglu2014 25 7.38 0.2 25 7.29 0.4 Saracoglu2014 25 7.38 0.2 25 7.29 0.4 Takil2002 15 7.34 0.2 15 7.26 0.6 0.00 [-0.48, 0.48] 3.42 2.80 [2.03, 3.58] 2.90 3.22 [2.02, 4.41] 2.17 Takil202 15 7.36 0.2 07.33 0.5 Withse2001 23 7.42 0.7 24 7.35 0.7 Wu2014(1) 20 7.45 0.6 20 7.45 0.5 Hadimioglu 2008(2) 30 7.42 0.6 30 7.36 0.5 Hadimioglu 2008(2) 30 7.48 0.7 30 7.46 0.5 O'Maley2005 25 7.37 0.7 26 7.28 0.7 Potura2015 72 7.33 0.2 76 7.32 0.1 Saini 2021(1) 60 7.31 0.4 60 7.29 0.6 Saini 2021(2) 60 7.31 0.4 60 7.29 0.6 O'Maley2015 72 7.33 0.02 76 7.32 0.1 Saini 2021(2) 60 7.31 0.4 60 7.29 0.6 O'Maley2015 72 7.33 0.02 76 7.32 0.1 Saini 2021(2) 60 7.31 0.4 60 7.29 0.6 O'Maley2015 72 7.31 0.0 = 0.00 Test of $\theta = 0$: $z = 6.13$, $p = 0.00$ z = 0 2 2 4 z = 0 2 4 z = 0 2 2 4 z = 0 2 4 z = 0 2 2 4 z = 0 2 4	Li2006(2)	30	7.38	.08	30	7.36	.06	-	0.28 [-0.22, 0.7	8] 3.38
Saracoglu 2014 25 7.38 02 25 7.29 0.4 Scheingraber 1999 12 7.41 0.3 12 7.31 0.3 Takil2002 15 7.34 0.2 15 7.26 0.6 Volta2013 20 7.36 0.2 20 7.33 0.5 Waters 2001 23 7.42 07 24 7.35 0.9 Waters 2001 23 7.42 07 24 7.35 0.9 Waters 2001 23 7.42 07 24 7.35 0.9 Wu2014(1) 20 7.43 0.6 20 7.45 0.5 Hadimic glu 2008(1) 30 7.44 0.6 30 7.36 0.5 Hadimic glu 2008(2) 30 7.42 0.6 30 7.36 0.5 Hadimic glu 2008(2) 30 7.44 0.6 30 7.36 0.5 Hadimic glu 2008(2) 30 7.45 0.7 26 7.29 0.8 King 2013 30 7.45 0.7 26 7.29 0.8 Saini 2021(1) 60 7.33 0.6 60 7.29 0.6 Saini 2021(2) 60 7.31 0.4 60 7.29 0.6 Saini 2021(2) 60 7.31 0.7 1 1.16 Heterogeneity: $r^2 = 0.48$, $r^2 = 80.02\%$, $H^2 = 9.10$ Test of $\theta = 0$: $z = 6.13$, $p = 0.00$ z = 0.2 $z = 7.41$ 0.2 25 7.36 0.3 Saini 2021(2) 60 7.41 0.3 20 7.38 0.2 With 95% CI (%) Saini 2021 4 25 7.41 0.2 25 7.36 0.3 Saini 2021 2 0.745 0.5 16 7.45 0.5 Saini 202 7.45 0.5 16 7.45 0.5 Saini 202 7.46 0.5 16 7.45 0.5 Saini 207 7.46 0.5 16 7.45 0.5 Sain	Peng2016(1)	33	7.41	.05	33	7.45	.04		-0.87 [-1.37, -0.3	7] 3.38
Scheingraber1999 12 7.41 .03 12 7.31 .03 Takil2002 15 7.34 .02 15 7.26 .06 Volta2013 20 7.36 .02 20 7.33 .05 Waters2001 23 7.42 .07 24 7.35 .09 Wikes2001 23 7.42 .07 24 7.35 .09 Wikes2001 23 7.42 .07 24 7.35 .09 Wikes2001 23 7.42 .07 24 7.35 .05 Wukes2001 20 7.45 .06 20 7.45 .05 Wukes2001 20 7.45 .06 20 7.45 .05 Hadimioglu 2008(1) 30 7.44 .06 30 7.36 .05 Hadimioglu 2008(2) 30 7.42 .06 30 7.36 .05 Hadimioglu 2008(2) 30 7.42 .06 30 7.36 .05 Hadimioglu 2008(2) 30 7.42 .07 26 7.28 .07 Potura2015 72 7.33 .02 76 7.32 .01 Saini 2021(1) 60 7.33 .06 60 7.29 .06 Saini 2021(2) 60 7.31 .04 60 7.29 .06 Saini 2021(2) 60 7.46 .05 15 7.39 .04 MD with 95% Cl (%) Compatible with 95% Cl (%) Point 2 2 0.25 7.36 .03 Volta2013 20 7.41 .03 20 7.38 .02 Heterogeneity: $r^2 = 0.28$, $l^2 = 76.19\%$, $l^2 = 4.20$ Test of $\theta = 0$: $z = 4.34$, $p = 0.00$ Test of $\theta = 0$: $z = 4.34$, $p = 0.00$	Peng2016(2)	33	7.45	.05	33	7.45	.04		0.00 [-0.48, 0.4	8] 3.42
Takil2002 15 7.34 .02 15 7.26 .06 Volta2013 20 7.36 .02 20 7.33 .05 Waters2001 33 7.4 .07 33 7.35 .09 Wike2001 23 7.42 .07 24 7.35 .07 Wu2014(1) 20 7.43 .06 20 7.45 .05 Hadimiogli 2008(2) 30 7.45 .06 20 7.45 .05 Hadimiogli 2008(2) 30 7.42 .06 30 7.36 .05 Hadimiogli 2008(2) 30 7.43 .07 26 7.29 .08 Saini 2021(1) 60 7.33 .06 60 7.29 .06 Saini 2021(1) 60 7.33 .06 60 7.29 .06 Saini 2021(2) 60 7.31 .04 60 7.29 .06 Coverall Heterogeneity: $r^2 = 0.48$, $l^2 = 89.02\%$, $H^2 = 9.10$ Test of $\theta = 0$: $z = 6.13$, $p = 0.00$ -2 -2 -2 -2 -2 -2 -2 -2 -2 -2	Saracoglu2014	25	7.38	.02	25	7.29	.04		- 2.80 [2.03, 3.5	8] 2.90
Volta2013 20 7.36 .02 20 7.33 .05 Waters2001 33 7.4 .07 33 7.35 .09 Wikes2001 23 7.42 .07 24 7.35 .07 Wu2014(1) 20 7.43 .06 20 7.45 .05 Hadimioglu 2008(2) 30 7.44 .06 30 7.36 .05 Hadimioglu 2008(2) 30 7.42 .06 30 7.36 .05 Hadimioglu 2008(2) 30 7.44 .06 30 7.36 .05 Hadimioglu 2008(2) 30 7.48 .07 30 7.46 .05 Overall Heterogeneity: $r^2 = 0.48$, $l^2 = 89.02\%$, $H^2 = 9.10$ Test of $\theta = 0$: $z = 6.13$, $p = 0.00$ z = 0.13, $p = 0.00z = 0.13$, $p = 0.00z = 0 z = 6.13$, $p = 0.00z = 0.22 = 0 2 4z = 0 2 4z = 0 2 2 4z = 0 2 4z$	Scheingraber1999	12	7.41	.03	12	7.31	.03		3.22 [2.02, 4.4	1] 2.17
Waters2001 33 7.4 .07 33 7.35 .09 .061 0.12 1.10 3.40 Wikes2001 23 7.42 .07 24 7.35 .07 .061 0.12 1.10 3.40 Wu2014(1) 20 7.43 .06 20 7.45 .05 .05 .05 .035 .001 .061 0.22 3.19 Wu2014(2) 20 7.44 .06 30 7.36 .05 .05 .07 .07 0.41 1.43 0.87 1.99 .28 Hadimioglu 2008(2) 30 7.44 .06 30 7.36 .05 .07 1.43 0.83 1.43 0.83 .33 Othalley2005 25 7.37 .07 26 7.28 .07 .026 .032 .032 .031 .046 0.53 .032 .031 .043 .033 .036 .032 .031 .031 .035 Saini 2021(1) 60 7.33 .02 7.6 .32 .01 .033 .05	Takil2002	15	7.34	.02	15	7.26	.06		1.74 [0.92, 2.5	6] 2.81
Wikes2001 23 7.42 .07 24 7.35 .07 .08 [0.39, 1.88] 3.22 Wu2014(1) 20 7.43 .06 20 7.45 .05 .07 .0.35 [-0.97, 0.26] 3.19 Wu2014(2) 20 7.45 .06 20 7.45 .05 .05 .00 [-0.61, 0.61] 3.20 Hadimioglu 2008(1) 30 7.44 .06 30 7.36 .05 .143 [0.87, 1.99] 3.28 Hadimoglu 2008(2) 30 7.42 .06 30 7.36 .05 .143 [0.87, 1.99] 3.28 Hadimoglu 2008(2) 30 7.42 .06 30 7.36 .05 .143 [0.87, 1.99] 3.28 Hadimoglu 2008(2) 30 7.44 .07 30 7.46 .05 .07 .0.7 [0.54, 1.61] 3.33 O'Maley2005 25 7.37 .07 26 7.28 .07 .0.26 [3.31, 0.96] 3.63 Saini 2021(1) 60 7.33 .06 60 7.29 .06 .0.66 [0.30, 1.03] 3.58 Saini 2021(2) 60 7.31 .04 60 7.29 .06 .0.83 [0.57, 1.10] .0.63 [0.31, 0.96] 3.63 Saini 2021(2) 60 7.31 .04 60 7.29 .06 .0.83 [0.57, 1.10] .0.83 [0.57, 1.10] .0.83 [0.57, 1.10] .0.83 [0.57, 1.10] .0.83 [0.57, 1.10] .0.83 [0.57, 1.10] .0.83 [0.57, 1.10] .0.83 [0.57, 1.10] .0.83 [0.57, 1.10] .0.83 [0.57, 1.10] .0.83 [0.57, 1.10] .0.83 [0.57, 1.10] .0.83 [0.57, 1.10] .0.83 [0.57, 1.10] .0.83 [0.57, 1.10] .0.83 [0.57, 1.10] .0.83 [0.57, 1.10] .0.83 [0.57, 1.10] .0.83 [0.57, 1.10] .0.83 [0.57, 1.10] .0.83 [0.57, 1.10] .0.83 [0.57, 1.10] .0.83 [0.57, 1.10] .0.83 [0.57, 1.10] .0.83 [0.57, 1.10] .0.83 [0.57, 1.10] .0.83 [0.57, 1.10] .0.83 [0.57, 1.10] .0.83 [0.57, 1.10] .0.83 [0.57, 1.10] .0.83 [0.57, 1.10] .0.83 [0.57, 1.10] .0.83 [0.57, 1.10] .0.83 [0.57, 1.10] .0.83 [0.57, 1.10] .0.83 [0.57, 1.10] .0.83 [0.57, 1.10] .0.83 [0.57, 1.10] .0.83 [0.57, 1.10] .0.83 [0.57, 1.10] .0.83 [0.57, 1.10] .0.83 [0.57, 1.10] .0.83 [0.57, 1.10] .0.83 [0.57, 1.10] .0.83 [0.57, 1.10] .0.83 [0.57, 1.10] .0.83 [0.57, 1.10] .0.83 [0.57, 1.10] .0.83 [0.57, 1.10] .0.83 [0.57, 1.10] .0.83 [0.57, 1.10] .0.83 [0.57, 1.10] .0.83 [0.57, 1.10] .0.83 [0.57, 1.10] .0.83 [0.57, 1.10] .0.83 [0.57, 1.10] .0.83 [0.57, 1.10] .0.83 [0.57, 1.10] .0.83 [0.57, 1.10] .0.83 [0.57, 1.10] .0.83 [0.57, 1.10] .0.83 [0.57, 1.10] .0.83 [0.57, 1.10] .0.83 [0.57, 1.10] .0.83 [0.57, 1.10] .0.83 [0.57, 1.10] .0.83 [0.57, 1.10]	Volta2013	20	7.36	.02	20	7.33	.05		0.77 [0.14, 1.4	0] 3.16
Wu2014(1) 20 7.43 .06 20 7.45 .05 -0.36 -0.36 -0.36 -0.36 -0.36 -0.36 -0.36 -0.36 -0.36 -0.36 -0.36 -0.36 -0.36 -0.36 -0.36 -0.36 -0.36 -0.36 -0.36 -0.36 -0.36 -0.36 -0.36 -0.36 -0.36 -0.36 -0.36 -0.36 -0.36 -0.36 -0.36 -0.36 -0.36 -0.36 -0.36 -0.36 -0.36 -0.36 -0.36 -0.36 -0.36 -0.36 -0.36 -0.36 -0.36 -0.36 -0.36 -0.36 -0.36 -0.36 -0.36 -0.36 -0.36 -0.36 -0.36 -0.36 -0.36 -0.36 -0.36 -0.36 -0.36 -0.36 -0.36 -0.36 -0.36 -0.36 -0.36 -0.36 -0.36 -0.36 -0.36 -0.36 -0.36 -0.36 -0.36 -0.36 -0.36 -0.36 -0.36 -0.36 -0.36 -0.36	Waters2001	33	7.4	.07	33	7.35	.09		0.61 [0.12, 1.1	0] 3.40
Wu2014(2) 20 7.45 .06 20 7.45 .05 Hadimioglu 2008(1) 30 7.44 .06 30 7.36 .05 Hadimioglu 2008(2) 30 7.42 .06 30 7.36 .05 Khajavi 2009 26 7.34 .05 26 7.29 .08 Kim 2013 30 7.46 .07 30 7.46 .05 Potura2015 72 7.33 .02 76 7.32 .01 Saini 2021(1) 60 7.33 .06 60 7.29 .06 Saini 2021(2) 60 7.31 .04 60 7.29 .06 Overall Heterogeneity: $r^2 = 0.48$, $l^2 = 89.02\%$, $H^2 = 9.10$ Test of $\theta = 0$: $z = 6.13$, $p = 0.00$ -2 0 2 4 0.83 [0.57, 1.10] Heterogeneity: $r^2 = 0.48$, $l^2 = 89.02\%$, $H^2 = 9.10$ Test of $\theta = 0$: $z = 6.13$, $p = 0.00$ -2 0 2 4 -4 0.60 [0.24, 0.97] 20.05 Balanced crystalloid Normal saline M Mean SD	Wikes2001	23	7.42	.07	24	7.35	.07		0.98 [0.39, 1.5	8] 3.22
Hadimioglu 2008(1) 30 7.44 .06 30 7.36 .05 Hadimioglu 2008(2) 30 7.42 .06 30 7.36 .05 Khajavi 2009 26 7.34 .05 26 7.29 .08 Kim 2013 30 7.48 .07 30 7.46 .05 O'Malley2005 25 7.37 .07 26 7.28 .07 Potura2015 72 7.33 .02 76 7.32 .01 Saini 2021(1) 60 7.33 .06 60 7.29 .06 Saini 2021(2) 60 7.31 .04 60 7.29 .06 Saini 2021(2) 60 7.31 .04 60 7.29 .06 Overall Heterogeneity: $r^2 = 0.48$, $l^2 = 89.02\%$, $H^2 = 9.10$ Test of $\theta = 0$: $z = 6.13$, $p = 0.00$ Test of $\theta = 0$: $z = 6.13$, $p = 0.00$ Balanced crystalloid Normal saline Study N Mean SD N Mean SD Volta2017 15 7.46 .05 15 7.39 .04 Helmy2016 20 7.41 .03 20 7.38 .02 Kim 2013 30 7.41 .05 30 7.35 .04 MD Weight With 95% Cl (%) Saracoglu2014 25 7.41 .02 25 7.36 .03 Volta2013 20 7.41 .05 30 7.35 .04 MD Weight Heterogeneity: $r^2 = 0.28$, $l^2 = 76.19\%$, $H^2 = 4.20$ Test of $\theta = 0$: $z = 4.34$, $p = 0.00$	Wu2014(1)	20	7.43	.06	20	7.45	.05		-0.35 [-0.97, 0.2	6] 3.19
Hadimiogiu 2008(2) 30 7.42 .06 30 7.36 .05 Khajavi 2009 26 7.34 .05 26 7.29 .08 Kim 2013 30 7.48 .07 30 7.46 .05 O'Malley2005 25 7.37 .07 26 7.28 .07 Potura2015 72 7.33 .02 76 7.32 .01 Saini 2021(1) 60 7.33 .06 60 7.29 .06 Saini 2021(2) 60 7.31 .04 60 7.29 .06 Overall Heterogeneity: $r^2 = 0.48$, $r^2 = 89.02\%$, $H^2 = 9.10$ Test of $\theta = 0$: $z = 6.13$, $p = 0.00$ z = 6.13, $p = 0.00z = 6.13$, $p = 0.00z = 0$, $z = 6.13$, $p = 0.00z = 0$, $z = 6.13$, $p = 0.00z = 0$, $z = 6.13$, $p = 0.00z = 0$, $z = 6.13$, $p = 0.00z = 0$, $z = 6.13$, $p = 0.00z = 0$, $z = 6.13$, $p = 0.00z = 0$, $z = 4.34$, $p = 0.00z = 0$, $z = 4.34$, $p = 0.00z = 0$, $z = 4.34$, $p = 0.00$	Wu2014(2)	20	7.45	.06	20	7.45	.05	-#-	0.00 [-0.61, 0.6	1] 3.20
Khajavi 2009 26 7.34 .05 26 7.29 .08 Kim 2013 30 7.48 .07 30 7.46 .05 0.32 -0.18 0.83 3.38 O'Malley2005 25 7.37 .07 26 7.28 .07 -0.63 0.32 -0.18 0.83 3.38 O'Malley2005 25 7.37 .07 26 7.28 .07 -0.63 0.66 0.33 0.66 0.33 0.66 0.39 0.63 0.30 0.63 0.39 0.30 0.75 3.59 Overall Heterogeneity: $r^2 = 0.48$, $l^2 = 89.02\%$, $H^2 = 9.10$ Test of $\theta = 0$: $z = 6.13$, $p = 0.00$ -2^2 0 2 4 0.83 0.57 1.03 3.58 Study N Mean SD N Mean SD MD Weight Study N Mean SD N Mean SD 0.20 $(-44$ $(-9)^2$ $(-6)^2$ $(-6)^2$ $(-6)^2$ $(-6)^2$ $(-6)^2$ $(-6)^2$	Hadimioglu 2008(1)	30	7.44		30	7.36	.05		1.43 [0.87, 1.9	9] 3.28
Kin 2013 30 7.48 .07 30 7.46 .05 O'Malley2005 25 7.37 .07 26 7.28 .07 Potura2015 72 7.33 .02 76 7.32 .01 .063 [0.32 [-0.48, 0.83] 3.38 Saini 2021(1) 60 7.33 .06 60 7.29 .06 .0.66 [0.30, 1.03] 3.58 Saini 2021(2) 60 7.31 .04 60 7.29 .06 .0.33 [0.67, 1.09 [0.63 [0.39 [0.03, 0.75] 3.59 Overall Iterrogeneity: $r^2 = 0.48$, $l^2 = 89.02\%$, $H^2 = 9.10$ Iterrogeneity: $r^2 = 0.48$, $l^2 = 89.02\%$, $H^2 = 9.10$ Iterrogeneity: $r^2 = 0.48$, $l^2 = 89.02\%$, $H^2 = 9.10$ Iterrogeneity: $r^2 = 0.48$, $l^2 = 89.02\%$, $H^2 = 9.10$ Iterrogeneity: $r^2 = 0.48$, $l^2 = 89.02\%$, $H^2 = 9.10$ Iterrogeneity: $r^2 = 0.48$, $l^2 = 89.02\%$, $H^2 = 9.10$ Iterrogeneity: $r^2 = 0.48$, $l^2 = 89.02\%$, $H^2 = 9.10$ Iterrogeneity: $r^2 = 0.48$, $l^2 = 76.13\%$, $H^2 = 7.57$ Iterrogeneity: $r^2 = 0.48$, $l^2 = 76.13\%$, $H^2 = 7.61$ Iterrogeneity: $r^2 = 0.28$, $l^2 = 76.19\%$, $H^2 = 4.20$ Iterrogeneity: $r^2 = 0.28$, $l^2 = 76.19\%$, $H^2 = 4.20$ Iterrogeneity: $r^2 $	Hadimioglu 2008(2)	30			30				1.07 [0.54, 1.6	1] 3.33
O'Malley2005 25 7.37 .07 26 7.28 .07 Potura2015 72 7.33 .02 76 7.32 .01 .063 0.61 0.63 0.31 0.96 3.63 Saini 2021(2) 60 7.31 .04 60 7.29 .06 0.66 0.39 0.03 0.75 3.59 Overall Heterogeneity: $r^2 = 0.48$, $l^2 = 89.02\%$, $H^2 = 9.10$ Test of $\theta = 0$: $z = 6.13$, $p = 0.00$ MD Weight with 95% Cl % atandom-effects DerSimonian-Laird model Balanced crystalloid Normal saline MD Weight with 95% Cl (%) Bodit2007 15 7.46 .05 15 7.39 .04 - 1.50 [0.71 , 2.30] 14.18 Guo2016 60 7.21 .17 60 7.11 .16 - - 0.20 [-0.45, 0.84] 16.23 Saracoglu2014 25 7.41 .02 25 7.36 .03 1.35 [0.50, 1.81] 16.04 Kim 2013 30 7.41 .03 20 7.38									•	-
Potura2015 72 7.33 .02 76 7.32 .01 Saini 2021(1) 60 7.33 .06 60 7.29 .06 Saini 2021(2) 60 7.31 .04 60 7.29 .06 Overall Heterogeneity: $r^2 = 0.48$, $l^2 = 89.02\%$, $H^2 = 9.10$ Test of $\theta = 0$: $z = 6.13$, $p = 0.00$ Test of $\theta = 0$: $z = 6.13$, $p = 0.00$ Balanced crystalloid Study N Mean SD N Mean SD Heterogeneity: $r^2 = 0.48$, $l^2 = 89.02\%$, $H^2 = 9.10$ Test of $\theta = 0$: $z = 6.13$, $p = 0.00$ Test of $\theta = 0$: $z = 6.13$, $p = 0.00$ Test of $\theta = 0$: $z = 6.13$, $p = 0.00$ Test of $\theta = 0$: $z = 6.13$, $p = 0.00$ Test of $\theta = 0$: $z = 6.13$, $p = 0.00$ Test of $\theta = 0$: $z = 6.13$, $p = 0.00$ Test of $\theta = 0$: $z = 4.34$, $p = 0.00$ Test of $\theta = 0$: $z = 4.34$, $p = 0.00$									•	-
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Saini 2021(2) 60 7.31 .04 60 7.29 .06 Overall Heterogeneity: $r^2 = 0.48$, $l^2 = 89.02\%$, $H^2 = 9.10$ Test of $\theta = 0$: $z = 6.13$, $p = 0.00$ Test of $\theta = 0$: $z = 6.13$, $p = 0.00$ Test of $\theta = 0$: $z = 6.13$, $p = 0.00$ Test of $\theta = 0$: $z = 6.13$, $p = 0.00$ Test of $\theta = 0$: $z = 6.13$, $p = 0.00$ Test of $\theta = 0$: $z = 6.13$, $p = 0.00$ Test of $\theta = 0$: $z = 6.13$, $p = 0.00$ Test of $\theta = 0$: $z = 6.13$, $p = 0.00$ Test of $\theta = 0$: $z = 6.13$, $p = 0.00$ Test of $\theta = 0$: $z = 6.13$, $p = 0.00$ Test of $\theta = 0$: $z = 6.13$, $p = 0.00$ Test of $\theta = 0$: $z = 6.13$, $p = 0.00$ Test of $\theta = 0$: $z = 6.13$, $p = 0.00$ Test of $\theta = 0$: $z = 6.13$, $p = 0.00$ Test of $\theta = 0$: $z = 4.34$, $p = 0.00$ Test of $\theta = 0$: $z = 4.34$, $p = 0.00$									•	-
Overall Belanced crystalloid Normal saline MD Weight andom-effects DerSimonian–Laird model Study N Mean SD MD Weight Study N Mean SD MD Weight Study N Mean SD MD Weight Study N Mean SD Bodit2007 15 7.46 .05 1.50 [0.71, 2.30] 14.18 Guo2016 60 7.21 .17 60 .20 2 0 2 4 a Bodit2007 15 7.46 .05 1.31 [0.05 Staracoglu2014 <th< td=""><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td>-</td><td>•</td><td>-</td></th<>								-	•	-
Heterogeneity: $r^2 = 0.48$, $l^2 = 89.02\%$, $H^2 = 9.10$ Test of $\theta_1 = \theta_1$: Q(30) = 273.10, p = 0.00 Test of $\theta = 0$: z = 6.13, p = 0.00 Ealanced crystalloid Normal saline Study N Mean SD N Mean SD Bodlt2007 15 7.46 .05 15 7.39 .04 Guo2016 60 7.21 .17 60 7.11 .16 Helmy2016 20 7.46 .05 16 7.45 .05 Helmy2016 20 7.46 .05 16 7.45 .05 Saracoglu2014 25 7.41 .02 25 7.36 .03 Volta2013 20 7.41 .03 20 7.38 .02 Kim 2013 30 7.41 .05 30 7.35 .04 Overall Heterogeneity: $r^2 = 0.28$, $l^2 = 76.19\%$, $H^2 = 4.20$ Test of $\theta_1 = \theta_1$: Q(5) = 21.00, p = 0.00 Test of $\theta = 0$: z = 4.34, p = 0.00	Saini 2021(2)	60	7.31	.04	60	7.29	.06		0.39 [0.03, 0.7	5] 3.59
Study N Mean SD N Mean SD N Mean SD with 95% Cl (%) Bodlt2007 15 7.46 .05 15 7.39 .04 1.50 [0.71, 2.30] 14.18 Guo2016 60 7.21 .17 60 7.11 .16 - 0.60 [0.24, 0.97] 20.05 Helmy2016 20 7.46 .05 16 7.45 .05 0.20 [-0.45, 0.84] 16.23 Saracoglu2014 25 7.41 .02 25 7.36 .03 1.93 [1.27, 2.59] 15.95 Volta2013 20 7.41 .05 30 7.35 .04 - 1.31 [0.76, 1.86] 17.54 Overall Heterogeneity: $\tau^2 = 0.28$, $I^2 = 76.19\%$, $H^2 = 4.20$ - - - - 1.09 [0.60, 1.58] Test of $\theta_1 = \theta_1$; $Q(5) = 21.00$, $p = 0.00$ - - - - - - - - - - - - - -	Test of $\theta_i = \theta_i$: Q(30) Test of $\theta = 0$: z = 6.1	= 273.1 3, p = 0.	0, p = 0. 00	00	= 9 .10		-2	0 2		
Bodlt2007 15 7.46 .05 15 7.39 .04 Guo2016 60 7.21 .17 60 7.11 .16 Helmy2016 20 7.46 .05 16 7.45 .05 Saracoglu2014 25 7.41 .02 25 7.36 .03 Volta2013 20 7.41 .03 20 7.38 .02 Kim 2013 30 7.41 .05 30 7.35 .04 Overall Heterogeneity: $r^2 = 0.28$, $l^2 = 76.19\%$, $H^2 = 4.20$ Test of $\theta_1 = \theta_1$: Q(5) = 21.00, p = 0.00 Test of $\theta = 0$: z = 4.34, p = 0.00					Norm	al salin	е		MD	Weight
Guo2016 60 7.21 $.17$ 60 7.11 $.16$ Helmy2016 20 7.46 $.05$ 16 7.45 $.05$ Saracoglu2014 25 7.41 $.02$ 25 7.36 $.03$ Volta2013 20 7.41 $.03$ 20 7.38 $.02$ Kim 2013 30 7.41 $.05$ 30 7.35 $.04$ Overall Heterogeneity: $r^2 = 0.28$, $l^2 = 76.19\%$, $H^2 = 4.20$ Test of $\theta_1 = \theta_1$; $Q(5) = 21.00$, $p = 0.00$ Test of $\theta = 0$; $z = 4.34$, $p = 0.00$	Study	N N	/lean S	D	NN	/lean	SD		with 95% CI	(%)
Helmy2016 20 7.46 .05 16 7.45 .05 Saracoglu2014 25 7.41 .02 25 7.36 .03 Volta2013 20 7.41 .03 20 7.38 .02 Kim 2013 30 7.41 .05 30 7.35 .04 Overall Heterogeneity: $r^2 = 0.28$, $l^2 = 76.19\%$, $H^2 = 4.20$ Test of $\theta_i = \theta_i$: Q(5) = 21.00, p = 0.00 Test of $\theta = 0$: z = 4.34, p = 0.00	Bodlt2007	15	7.46 .0	5 1	5	7.39 .	04		1.50 [0.71, 2.30)] 14.18
Saracoglu2014 25 7.41 .02 25 7.36 .03 Volta2013 20 7.41 .03 20 7.38 .02 Kim 2013 30 7.41 .05 30 7.35 .04 Overall Heterogeneity: $\tau^2 = 0.28$, $I^2 = 76.19\%$, $H^2 = 4.20$ Test of $\theta_i = \theta_i$: Q(5) = 21.00, p = 0.00 Test of $\theta = 0$: z = 4.34, p = 0.00	Guo2016								-	-
Volta2013 20 7.41 .03 20 7.38 .02 Kim 2013 30 7.41 .05 30 7.35 .04 Overall 1.31 0.76 1.86 17.54 Heterogeneity: $\tau^2 = 0.28$, $I^2 = 76.19\%$, $H^2 = 4.20$ 1.09 0.60 , 1.58 Test of $\theta_i = \theta_i$: Q(5) = 21.00, p = 0.00 Test of $\theta = 0$: $z = 4.34$, $p = 0.00$	Helmy2016	20	7.46 .0	5 ´	6	7.45 .	05		0.20 [-0.45, 0.84] 16.23
Kim 2013 30 7.41 .05 30 7.35 .04 1.31 [0.76 , 1.86] 17.54 Overall 1.09 [0.60 , 1.58] 1.09 [0.60 , 1.58] Heterogeneity: $\tau^2 = 0.28$, $l^2 = 76.19\%$, $H^2 = 4.20$ 1 1 0.9 [0.60 , 1.58] Test of $\theta_i = \theta_i$: Q(5) = 21.00, p = 0.00 1 1 0.01 0.76 , 1.86 0.76 , 1.86 0.76 , 1.86 0.76 , 1.86 0.76 , 1.86 0.76 , 1.86 0.76 , 1.86 0.76 , 1.86 0.76 , 1.86 0.76 , 1.86 0.76 , 1.86 0.76 , 1.86 0.60 , 1.58 0.60 , 1.58 0.60 , 1.58 0.60 , 1.58 0.60 , 1.58 0.60 , 1.58 0.76 , 0.60 0.76 , 0.60 0.76 , 0.60 0.76 , 0.60 0.76 , 0.60 0.76 , 0.60 0.76 , 0.60 0.76 , 0.60 0.76 , 0.60 0.76 , 0.60 0.76 , 0.60 0.76 , 0.60 0.76 , 0.60 0.76 , 0.60 0.76 , 0.60 0.76 , 0.60 0.76 , 0.60 0.76 , 0.60 0.76 , 0.60 0.76 , 0.60 0.76 , 0.60 0.76 , 0.60 0.76 , 0.60 0.76 , 0.60 0.76 , 0.60 0.76 , 0.60 0.76 , 0.60 0.76 , 0.60	Saracoglu2014	25	7.41 .0	2 2	25	7.36 .	03		— 1.93 [1.27, 2.59] 15.95
Overall Heterogeneity: $\tau^2 = 0.28$, $I^2 = 76.19\%$, $H^2 = 4.20$ Test of $\theta_i = \theta_j$: Q(5) = 21.00, p = 0.00 Test of $\theta = 0$: z = 4.34, p = 0.00	Volta2013	20	7.41 .0	3 2	20	7.38 .	02		1.15 [0.50, 1.81] 16.04
Heterogeneity: $\tau^2 = 0.28$, $l^2 = 76.19\%$, $H^2 = 4.20$ Test of $\theta_l = \theta_l$: Q(5) = 21.00, p = 0.00 Test of $\theta = 0$: z = 4.34, p = 0.00	Kim 2013	30	7.41 .0	5 3	30	7.35 .	04		1.31 [0.76, 1.86	6] 17.54
Test of $\theta_i = \theta_j$: Q(5) = 21.00, p = 0.00 Test of $\theta = 0$: z = 4.34, p = 0.00	Overall								1.09 [0.60, 1.58	5]
Test of $\theta_i = \theta_j$: Q(5) = 21.00, p = 0.00 Test of $\theta = 0$: z = 4.34, p = 0.00	Heterogeneity: $\tau^2 =$	0.28, I ²	= 76.19	%, H	² = 4.	20				
Test of θ = 0: z = 4.34, p = 0.00										
-1 () 1 2 3							-1	0 1 2	3	

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

Study	Balano N	ced cryst Mean		l No N	rmal sa Mean				MD with 95% CI	Weight (%)
Ayebale2017	248	137	3	252	137	3			0.00 [-0.18, 0.18]	5.79
Bodlt2007	12	136	3	12	140	2	∎ ⊤		-1.51 [-2.40, -0.63]	3.25
Brahma2017	41	140	3	41	141	3			-0.33 [-0.76, 0.10]	4.98
Disma2014	114	138	.6	115	138	.8			0.00 [-0.26, 0.26]	5.58
Dong2015(1)	20	137	3	20	141	3			-1.31 [-1.98, -0.64]	4.03
Dong2015(2)	20	140	2	20	141	3			-0.38 [-1.00, 0.23]	4.26
Hafizah2017	15	136	2	15	142	2			-2.92 [-3.93, -1.90]	2.84
Hassan2017	28	139	4	27	140	6			-0.19 [-0.72, 0.33]	4.63
Helmy2016	20	139	5	16	141	6			-0.36 [-1.01, 0.29]	4.12
Hou2016	20	139	1	20	140	2			-0.62 [-1.24, 0.00]	4.22
Peng2016(1)	33	138	3	33	139	3			-0.33 [-0.81, 0.15]	4.80
Peng2016(2)	33	138	3	33	139	3			-0.33 [-0.81, 0.15]	4.80
Saracoglu2014	25	137	4	25	141	3			-1.11 [-1.70, -0.53]	4.36
Scheingraber1999	12	142	2	12	139	2			- 1.45 [0.57, 2.32]	3.28
Takil2002	15	139	2	15	144	4			-1.54 [-2.34, -0.74]	3.55
Volta2013	20	142	2	20	143	3			-0.38 [-1.00, 0.23]	4.26
Waters2001	33	139	3	33	143	4			-1.12 [-1.63, -0.60]	4.66
Wikes2001	23	138	3	24	140	3			-0.66 [-1.23, -0.08]	4.40
Wu2014(1)	20	137	2	20	138	2			-0.49 [-1.11, 0.13]	4.25
Wu2014(2)	20	137	2	20	138	2			-0.49 [-1.11, 0.13]	4.25
Khajavi 2009	26	136	4.5	26	140	3.2			-1.01 [-1.58, -0.44]	4.44
Kim 20 1 3	30	132.5	3.9	30	133	3.3	-#-		-0.14 [-0.64, 0.36]	4.72
Weinberg 2017	24	138.7	2.9	25	139	2.8			-0.10 [-0.66, 0.45]	4.51
Overall	2			2			•		-0.55 [-0.79, -0.31]	
Heterogeneity: $\tau^2 =$				2 = 5.0	00					
Test of $\theta_i = \theta_j$: Q(22)			0.00							
Test of $\theta = 0$: $z = -4$.57, p =	0.00							-	
andom-effects Der	Simonia	n-Laird	mode	el		-	-2 0	2		а
I	Balance	ed crysta	Illoid	Nor	mal sal	ine			MD	Weigh
Study	Ν	Mean	SD	Ν	Mean	SD			with 95% CI	(%)
Bodlt2007	12	135	4	12	142	3			-1.91 [-2.85, -0.97]	12.24
Helmy2016	20	140	7	16	142	6	_		0.30 [-0.94, 0.35]	16.70
Saracoglu2014	25	136	4	25	142	3			-1.67 [-2.31, -1.03]	16.87
Volta2013	20	141	3	20	143	4			-0.55 [-1.17, 0.07]	17.15
Kim 2013	30	134.4		30	136.6				-0.63 [-1.14, -0.11]	18.99
Weinberg 2017	24	137.3		25	138.9				-0.65 [-1.22, -0.09]	18.06
Overall									-0.90 [-1.36, -0.43]	
Heterogeneity: τ^2 =	= 0.23	1 ² = 68 0.	4% F	H ² = 3	22				5.55 [- 1.55, -0.45]	
Test of $\theta_i = \theta_i$: Q(5				0						
Test of $\theta = 0$; $z = -$	-									
						-:	-2 -1	0	-	
								0		b

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, P=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, P=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, P=35.4%, p=0.52) (Figure 6a) and on POD 1 (MD: -0.17; 95% CI: -0.40 – 0.07; P=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).

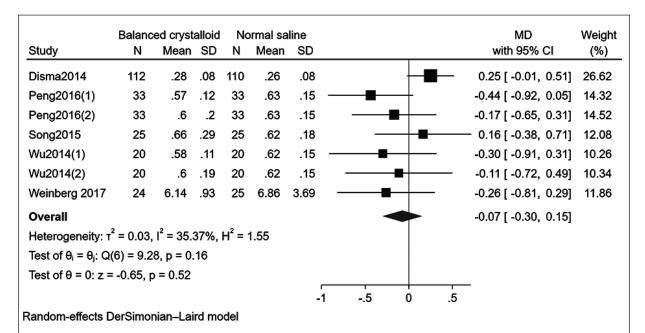
Discussion

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-analyses⁸⁻¹¹ have been published to compare BC with normal saline till now. The article by Wan et al⁸ 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 al⁹ 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 al¹⁰ included 9 studies with abdominal surgery, neurosurgery, and orthopedic surgery; NS lowered PH value and BE and increased serum chloride level. A recent meta-analysis¹¹ 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 hyperchloremia⁴, and contributed to metabolic acidosis as a result.

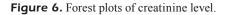
	Bala	nced cryst	alloid	No	ormal sa	line		MD	Weight
Study	Ν	Mean	SD	Ν	Mean	SD		with 95% CI	(%)
Ayebale2017	248	110	4	252	112	5		-0.44 [-0.62, -0.26]	3.86
Bodlt2007	12	110	3	12	117	4		-1.91 [-2.85, -0.97]	3.39
Brahma2017	41	108	5	41	119	6		-1.97 [-2.50, -1.45]	3.71
Disma2014	114	107	1	115	110	.6		-3.63 [-4.05, -3.21]	3.77
Dong2015(1)	20	108	5	20	107	5		📕 0.20 [-0.41, 0.81]	3.66
Dong2015(2)	20	106	5	20	107	5		-0.20 [-0.81, 0.41]	3.66
Hafizah2017	15	104	1	15	113	2		-5.54 [-7.10, -3.97]	2.77
Hassan2017	28	112	5	27	118	6	-	-1.07 [-1.63, -0.51]	3.69
Helmy2016	20	109	5	16	112	6	-	-0.54 [-1.19, 0.12]	3.62
Peng2016(1)	33	108	7	33	109	3	1	-0.18 [-0.66, 0.29]	3.74
Peng2016(2)	33	103	5	33	109	3		-1.44 [-1.97, -0.90]	3.70
Saracoglu2014	25	106	4	25	112	4		-1.48 [-2.09, -0.86]	3.65
Scheingraber1999	12	106	2	12	115	2		-4.34 [-5.80, -2.89]	2.89
Takil2002	15	112	10	15	117	6	-	-0.59 [-1.30, 0.12]	3.58
Waters2001	33	107	4	33	114	6	-	-1.36 [-1.89, -0.83]	
Wikes2001	23	108	3	24	114	5		-1.42 [-2.06, -0.79]	
Wu2014(1)	20	109	7	20	109	2		0.00 [-0.61, 0.61]	
Wu2014(2)	20	103	3	20	109	2		-2.31 [-3.10, -1.52]	
Hadimioglu 2008(1)	30	105.7	1.3	30	125.4	3.7		-7.01 [-8.36, -5.66]	
Hadimioglu 2008 (2)	30	106.5	2.2	30	125.4	3.7		-6.13 [-7.33, -4.92]	
Kim 2013	30	104.1	5	30	107.6	4.7		-0.71 [-1.23, -0.20]	
Modi 2012	37	98.5		37	103.92			-1.45 [-1.95, -0.94]	
Pfortmueller2017	72	107	1	76	109	1		-1.99 [-2.38, -1.60]	3.78
Potura2015	72	104.2	1.6	76	105.4	1.3	_	-0.82 [-1.16, -0.49]	3.81
Saini 2021(1)	60	105.23		60	118.49		-	-3.85 [-4.45, -3.25]	3.66
Saini 2021(2)	60	105.3		60	118.49		· · · ·	-3.80 [-4.40, -3.20]	
Weinberg 2017	24	96.3	3	25	102.3	4.8		-1.47 [-2.09, -0.85]	
O'Malley2005	25	106	4	26	111	4	-	-1.23 [-1.82, -0.64]	3.67
Overall	2						•	-1.92 [-2.40, -1.43]	
Heterogeneity: $\tau^2 = 1.6$			= 23.	81					
Test of $\theta_i = \theta_j$: Q(27) =									
Test of $\theta = 0$: $z = -7.69$,	p = 0.0	0						<u> </u>	
							-8 -6 -4 -2	0	а
andom-effects DerSim	onian–L	aird mode.							
	Balance	ed crystall	oid I	Norma	al saline			MD	Weigh
Study	N	Mean S			lean Sl	C		with 95% Cl	(%)
Bodlt2007	12	106	3 1	2	116 3	3		-3.22 [-4.41, -2.02]	13.90
Helmy2016	20	105				9		-0.29 [-0.94, 0.35]	14.79
Saracoglu2014	25	105	5 2			2		-1.29 [-1.89, -0.69]	14.84
Hadimioglu 2008(1)	30	104.7 1			24.2 2.9			-8.67 [-10.30, -7.04]	12.95
Hadimioglu 2008(2)	30	104.8 3			24.2 2.9			-6.38 [-7.63, -5.13]	13.79
Kim 2013	30 30	104.8 3			04.8 4.2			-0.63 [-1.14, -0.12]	14.94
Weinberg 2017	30 24	94.4 3)4.0 4.2)1.8 5.1		_	-0.63 [-1.14, -0.12] -1.64 [-2.28, -1.00]	14.94
•	24	34.4 3	.u Z	JI	1.0 0.	•			14.00
Overall			.2					-3.02 [-4.55, -1.50]	
Heterogeneity: $\tau^2 = 3.9$			- 1⁻ = 2	7.73					
Test of $\theta_i = \theta_j$: Q(6) =									
Test of $\theta = 0$: $z = -3.88$	8, p = 0	.00						-	
						-10	-5 0		b
andom-effects DerSir	nonian-	-Laird mo	del						

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



а

	Balan	ced crys	talloid	Normal saline							MD		Weight
Study	Ν	Mean	SD	Ν	Mean	SD					with 95% C		(%)
Hadimioglu 2008(1)	30	3.8	2	30	4.4	3.1			∎┼─		-0.23 [-0.73,	0.27]	11.03
Hadimioglu 2008(2)	30	3.7	1.9	30	4.4	3.1			⊢		-0.27 [-0.77,	0.23]	11.02
Kim 2013	30	3.9	2.7	30	3.6	1.6		_	╶┤═╸		0.13 [-0.37,	0.63]	11.06
Modi 2012	37	2.43	.87	37	2.82	.75			_		-0.48 [-0.93, -	0.02]	12.06
Potura2015	72	7.77	2.78	76	7	2.36				—	0.30 [-0.02,	0.62]	15.72
Saini 2021(1)	60	4.3	1.64	60	4.26	1.59		_	-	_	0.02 [-0.33,	0.38]	14.77
Saini 2021(2)	60	3.7	1.33	60	4.26	1.59			_		-0.38 [-0.74, -	0.02]	14.67
Weinberg 2017	24	5.9	.77	25	6.5	1.01			-		-0.66 [-1.22, -	0.09]	9.67
Overall											-0.17 [-0.40,	0.07]	
Heterogeneity: $\tau^2 = 0$.	.06, I ² =	57.16%	, H ² = :	2.33									
Test of $\theta_i = \theta_j$: Q(7) =	16.34,	o = 0.02											
Test of θ = 0: z = -1.3	9, p = 0	.16											
						-1.5	-1	5	0	.5			
Random-effects DerSi	monian-	-Laird m	odel				-		-				
						b							



Acidosis and hyperchloremia could impair renal perfusion and function theoretically⁵⁵. 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 reported⁵⁶ 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 study⁵⁷ 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 prognosis⁵⁸. 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 diameter⁵⁹. It was reported⁶⁰ 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 surgery⁶¹. Transesophageal Doppler-guided intraoperative fluid therapy can reduce the amount of fluid and postoperative complications⁶². 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.

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