Systematic Review and Meta-Analysis

Intraoperative goal-directed fluid therapy in adult patients undergoing craniotomies under general anaesthesia: A systematic review and meta-analysis with trial sequential analysis

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ABSTRACT

Background and Aims: Goal-directed fluid therapy (GDFT) has conflicting evidence regarding outcomes in neurosurgical patients. This meta-analysis aimed to compare the effect of GDFT and conventional fluid therapy on various perioperative outcomes in patients undergoing neurosurgical procedures. Methods: A comprehensive literature search was conducted using PubMed, EMBASE, Scopus, ProQuest, Web of Science, EBSCOhost, Cochrane and preprint servers. The search was conducted up until 16 October 2023, following PROSPERO registration. The search strategy included terms related to GDFT, neurosurgery and perioperative outcomes. Only randomised controlled trials involving adult humans and comparing GDFT with standard/liberal/traditional/restricted fluid therapy were included. The studies were evaluated for risk of bias (RoB), and pooled estimates of the outcomes were measured in terms of risk ratio (RR) and mean difference (MD). Results: No statistically significant difference was observed in neurological outcomes between GDFT and conventional fluid therapy [RR with 95% confidence interval (CI) was 1.10 (0.69, 1.75), two studies, 90 patients, low certainty of evidence using GRADEpro]. GDFT reduced postoperative complications [RR = 0.67 (0.54, 0.82), six studies, 392 participants] and intensive care unit (ICU) and hospital stay [MD (95% CI) were -1.65 (-3.02, -0.28) and -0.94 (-1.47, -0.42), respectively] with high certainty of evidence. The pulmonary complications were significantly lower in the GDFT group [RR (95% CI) = 0.55 (0.38, 0.79), seven studies, 442 patients, high certainty of evidence]. Other outcomes, including total intraoperative fluids administered and blood loss, were comparable in GDFT and conventional therapy groups [MD (95% CI) were -303.87 (-912.56, 304.82) and -14.79 (-49.05, 19.46), respectively]. Conclusion: The perioperative GDFT did not influence the neurological outcome. The postoperative complications and hospital and ICU stay were significantly reduced in the GDFT group.

Keywords: Craniotomy, fluid therapy, goal-directed, meta-analysis, neurosurgery, neurological outcomes

INTRODUCTION

Fluid therapy during intraoperative period is vital since significant haemodynamic variations may occur during surgery due to blood loss and fluid shifts.^[1] Hypovolemia decreases the perfusion of end organs, such as the This is an open access journal, and articles are distributed under the terms of the Creative Commons Attribution-NonCommercial-ShareAlike 4.0 License, which allows others to remix, tweak, and build upon the work non-commercially, as long as appropriate credit is given and the new creations are licensed under the identical terms.

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brain, heart and kidneys, while hypervolemia may lead to congestion and compromise their functioning.^[2] In neurosurgical patients, hypovolemia results in cerebral ischaemia, while hypervolemia may cause cerebral oedema.^[3,4] Conventionally, intraoperative fluid therapy was managed based on clinical parameters, haemodynamic monitoring including central venous pressure (CVP), and formulas such as Holliday and Segar.^[5,6] The role of conventional therapies is being challenged as they fail to detect dynamic circulatory changes.^[1] Thus, goal-directed fluid therapy (GDFT) may be required to optimise fluid administration. GDFT refers to the titration of fluids and inotropes according to the predefined haemodynamic goals to maintain adequate organ and tissue perfusion.^[7]

In neurosurgical cases, fluid and electrolyte imbalances are commonly seen, and maintaining a tight fluid balance is crucial.^[8,9] The literature regarding perioperative GDFT in the neurosurgical population is sparse. A few randomised controlled trials (RCTs) in neurosurgical patients report variable results for neurological outcomes. All existing studies are single-centre studies and they assessed different outcome parameters.

A pooled estimate of the effects of GDFT can help neurosurgeons and anaesthesiologists understand the phenomenon better and assist in clinical decision-making during intraoperative fluid therapy. Hence, this systematic review and meta-analysis (SRMA) of RCTs was planned to compare intraoperative GDFT and conventional fluid therapy in neurosurgical patients undergoing craniotomy for intracranial pathology, with the primary objective of determining the proportion of patients having good neurological outcomes. The secondary outcomes included total fluids administered, blood loss, postoperative complications and intensive care unit (ICU) and hospital length of stay.

METHODS

The research question of this meta-analysis was 'What is the effect (good or worse) of intraoperative GDFT in adult patients undergoing craniotomies under general anaesthesia on neurological outcomes?' The study was registered with the International Prospective Register of Systematic Reviews (PROSPERO, CRD42023388850)). The Preferred Reporting Standard of Systematic Reviews and Meta-analysis (PRISMA)^[10] guidelines were followed.

Study design and literature search

independent (KJ Two reviewers and NM) systematically searched the databases, including PubMed, EMBASE, Scopus, ProQuest, Web of Science, EBSCOhost, and Cochrane, on 15 March 2023 for the relevant articles. A top-up search was conducted on 16 October 2023, in which two new studies were found eligible and added. Preprint servers like arXiv, BioRN, ChiRN, ChiRxiv, medRxiv, bioRxiv and SSRN were also searched for relevant articles. The following keywords were used: (neurosurgery, supratentorial, posterior craniotomy, fossa. infratentorial. intracranial aneurysm, traumatic brain injury, head injury); and (goal-directed fluid therapy, goal-oriented fluid therapy, goal-target fluid therapy, restrictive fluid therapy); and [neurological outcome, Glasgow outcome score (GOS), mortality, postoperative complications, cerebral oedema, vasospasm, modified Rankin scale (mRS), kidney injury, hospital duration, total fluid] in both Medical Subject Headings (MeSH) and free terms (title/ abstract). The syntaxes used for searching were framed by following the participants, intervention, control and outcome statement [Supplemental Table S1]. The search strategies used in all the included databases are enumerated in Supplemental Table S2. The database output was imported to Mendeley Desktop V1.19.5 software for macOS (Elsevier, Amsterdam, The Netherlands), where duplicate articles were removed.

Inclusion and exclusion criteria

All RCTs conducted in adult humans undergoing craniotomy for intracranial pathologies comparing GDFT and liberal/traditional/standard fluid management were included. GDFT is defined using an objective physiological parameter to guide fluid therapy intraoperatively with or without inotropes and with or without colloids. The accepted parameters as primary goals are stroke volume variation (SVV), pulse pressure variation (PPV), left ventricular outflow tract velocity-time integral (VTI), cardiac index, stroke volume, cardiac output, pleth variability index (PVI), global end-diastolic volume, and oxygen delivery index. There is no restriction on the type of modality used to achieve GDFT.

The exclusion criteria included animal experiments, retrospective studies, incomplete data for review and quantitative analysis (abstracts only, protocols only, review articles and case reports/series, where elective neurosurgical patients cannot be isolated from conditions like ventriculoperitoneal shunts, or minor procedures such as burr holes or studies where outcomes are not reported).

Outcome measures

The primary outcome was to assess the effect of intraoperative GDFT on neurological outcomes as measured by $GOS^{[11]}$ or $mRS^{[12]}$ at discharge.

Measures of effect: Neurological outcomes in terms of GOS on a scale of 1–5: lower scores (1-3) were considered as poor and higher scores (4-5) as functionally good, and mRS of 0–3 was a good outcome and 4–6 was a poor outcome. The effect estimate was taken as a risk ratio (RR) with 95% confidence interval (CI). For analysis, we have included the proportion of patients with good neurological outcomes suggested by mRS and GOS.

Secondary outcomes included the following:

- 1. Postoperative complications [Supplemental Box S1]:
 - a. Medical renal failure, pulmonary complications, cardiac complications, electrolyte abnormalities requiring interventions
 - b. Surgical cerebral oedema, intracranial haematoma, re-exploration surgery, vasospasm, use of radiological interventions
- 2. Total intraoperative fluid requirements
- 3. Intraoperative blood loss
- 4. Duration of hospital (total days in hospital)/ ICU stay (defined as from the day of surgery to discharge from ICU).
- 5. Mortality.

Postoperative complications and mortality within the same hospital admission or till the patient is discharged or death happens were measured as a ratio with 95% CI. Duration of hospital/ICU stay, blood loss and total fluid infused were measured as mean differences (MDs).

Data on study characteristics like authors, year, place, intervention/control and outcomes, and demographic characteristics were extracted. Other disease and patient characteristics were extracted.

Study evaluation and selection

Screening of title abstracts

Two independent reviewers (KJ and NM) reviewed the articles' title abstracts derived from the systematic search for suitability for a full-text review. Any discrepancies regarding the article's suitability were resolved by a third independent reviewer (APG).

Full-text screening and extraction of data

Studies found suitable for full-text review were evaluated independently by two reviewers (KJ and NM) based on the eligibility criteria, and data extraction was done subsequently. Any discrepancies regarding the article's eligibility for data extraction were settled by the third reviewer (APG). A data extraction table was formulated in a Microsoft Excel sheet to facilitate the analysis.

Risk-of-bias (quality) assessment

The studies were evaluated for risk of bias (RoB) by independent assessors (KJ, MAS and NM) using the RoB2 tool from the Cochrane Collaboration (London, UK).^[13] We analysed the bias in the following domains: 'randomisation, deviations from intended intervention, missing outcome data, outcome measurement and selection of reported result'. In case of disagreements, the discrepancies were settled by discussion among all the reviewers (KJ, NM, AGP, MAS and BKP). Each domain's RoB was categorised as either low, with some concerns, or high. RoB is represented (Robvis in R software, Version 4.3.1 for Mac; RStudio, Boston, MA, USA) at each study's outcome level and is presented alongside the study estimates in the respective forest plots.

Data analysis

The pooled estimates of the outcomes, along with a 95% CI, were measured in terms of RR and MD, depending on the outcomes. The median and interquartile range parameters were converted to mean and standard deviation for analysis using an online converter.^[14] The heterogeneity of studies was assessed using the I^2 test. If P > 0.05 for the Q test or $I^2 < 50\%$, the fixed effects model (the Mantel Haenszel method)^[15] was used to estimate RR. If I² > 50%, a random effects model was planned. The prediction interval (PI) was calculated based on the Tau² statistics.^[16] Assessment of publication bias was planned by using the funnel plot and Egger's test if more than ten studies were found eligible for meta-analysis and the doi plot if more than five studies were found eligible. A trim-and-fill method was also planned if publication bias was identified. A sensitivity analysis was planned after removing the studies of high RoB and using a leave-one-out meta-analysis. A post hoc trial sequential analysis was done for the seven critical outcomes, and it was finally used to assess evidence certainty. A P value of <0.05 was deemed to be significant. All analyses were undertaken using R Studio software following the standard code.^[17]

Certainty in the evidence

The study evaluated and summarised the pooled estimate's certainty for each outcome with the Grading of Recommendations, Assessment, Development and Evaluations (GRADE) methodology^[18] using the GRADEpro software.

RESULTS

Study selection

The sequential process of study selection and review, as per the PRISMA flow chart for reporting systematic reviews, is depicted in Figure 1. A total of 125 articles were identified after a comprehensive search of the Cochrane (n = 39), EBSCOhost (n = 23), EMBASE (n = 21), ProQuest (n = 6), PubMed (n = 5), Scopus (n = 17) and Web of Science (n = 14). After removing the duplicates using Mendeley, 78 articles were screened for title and abstract. After reviewing the title abstract, 16 articles were screened for full-text reading. Of these, seven articles did not meet the inclusion criteria. The bibliography screening and grey literature search provided one more article. Finally, ten studies were included for SRMA.^[19-28]

Study characteristics

The individual study demographics are presented in Table 1. A total of 608 patients were included for analysis, with 309 and 299 patients in the experimental (E) and control (C) groups, respectively, and with sample sizes ranging from 10 to 72 in the control group and 16 to 73 patients in the experimental group. Five studies were conducted in patients with intracranial tumours, one in intracranial aneurysms and four in all craniotomies (brain abscess, aneurysms, tumours). The patients' mean age in the experimental group varied from 41 to 61 years, while 39 to 58.4 years in the control group.

Outcomes of pooled studies

a. Primary outcomes:

Neurological outcomes: Only two RCTs reported neurological outcomes measured by GOS and mRS at discharge.^[19,21] The proportion of patients with favourable outcomes was extracted from the studies. The pooled estimate did not show a significant difference in favourable neurological outcomes between the GDFT and control groups [RR (95% CI) = 1.10 (0.69–1.75), I² = 74%] [Figure 2a].

b. Secondary outcomes:

Postoperative complications: Six of the included RCTs reported the incidence of overall postoperative complications.^[19,22,24-26,28] The pooled estimate revealed that GDFT patients had a significantly lower risk of

PRISMA flow diagram template for Systematic Reviews, 2020



Figure 1: Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) flow chart

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Count China China Brno, Czech Republ India Egypt China China	Table 1: Characteristics of included studies (<i>n</i> =10)	Country Study Population GDFT technique Number of Male/female Age Mean (SD) Outcomes reported design		China RCT Meningioma LiDCO rapid 42 42 13/29 13/29 53 (12) 54 (9) Composite complication resection system, SVV <13%, A memodynamics and fluids, postoperative complications, encephaledema, GI function recovery, ICU and hospital stay and mortality	Brno, RCT Elective Starling SV monitor, 17 17 5/12 2/15 58.4 (9.5) 56.9 (16.8) BRS at the end of surgery and brain oedema requiring therapy, total crystalloids, colloids, transfusions and blood czech neurosurgical CI <2.5, SVV <15% Czech patients correction and the end of surgery and branches (MAP <65 Torr), vasoactive drug intervention, urine output till 24 h postoperatively, blood transfused, postoperative complications, duration of ICU and hospital stay and 28-day mortality	India RCT Intracranial TEE measured 25 25 8/17 9/16 53.8 (11.9) 50.9 (7.7) Haemodynamic parameters, intraoperative blood loss, aneurysms LVOT-VTI <15 cm, clipping variation <12% of mechanical ventilation, length of stay in ICU and hospital, mRS at discharge and GOS-E at 6 months	India RCT Large Flotrac Vigileo, 20 20 11/9 14/6 39 (11) 44 (12.6) Duration of hospital stay and ICU stay, neurological outcomes, incidence of tight brain, intraoperative blood tumours xumours <12% <	USA RCT Elective Flotrac Vigileo, 10 16 7/3 8/8 56 55 Intraoperative fluid administered, blood loss, craniotomy CI >2.5 and SVV CI >2.5 and SVV craniotomy cranication staticate craniotomy cranicated craniotomy cranicated complications	Korea RCT Elective Flotrac Vigileo 24 24 7/17 9/15 51.3 (13) 48.6 (14) Intraoperative fluid administered, phenylephrine and craniotomy monitor, SVV <13% ephedrine, haemodynamic parameters, acid-base parameters, blood loss	Egypt RCT Supratentorial (GE solar 8000M/I 30 31 12/18 16/15 39 (13) 41 (12) Brain relaxation scores, haemodynamic parameters, tumours monitor), PPV <13%	China RCT Brain tumours, Flotrac Vigileo, Cl 72 73 32/40 30/43 62 (13) 61 (13) Amount of crystalloids and colloids, postoperative abscess, <2.5 and SVV <15 complications, duration of ICU stay and hospital stay, and unsurvise and solve abscess, <2.5 and SVV <15 complexity abscess, <2.5 and SVV <15 complexit	India RCT Supra- and Philips Intellivue 29 28 12/17 11/17 43.4 (10.3) 39.9 (13.9) Intraoperative haemodynamic parameters, intraoperative infratentorial MP50 monitor, PPV tumours <13%	China RCT Supratentorial Flotrac Vigileo, SVV 30 33 14/16 15/18 50 (9) 50 (9) Amount of intraoperative and postoperative fluids, tumours <12%	length of ICU and hospital stay, postoperative complications. biochemical parameters
	ry Study Po design RCT Me ree	RCT Me	RCT Me ree		RCT Ele ne lic pa	RCT Int an clij	RCT La su tur	RCT	RCT Ele	RCT Su tur	RCT Br ab an	RCT Su inf tur	RCT Su tur	e, C=control, Cl=(DT-VTl=left ventri V=stroke volume
		Author, year		Feng <i>et al</i> . ^[24] 2023	Hrdy <i>et al.</i> ^[25] (2023)	Bloria <i>et al</i> . ^{[21,} (2022)	Mishra <i>et al.</i> '' (2022)	Mitrev <i>et al.</i> ^{izt} (2019)	Kim <i>et al.</i> ^[27] (2019)	Hassanin <i>et al</i> . ^[23] (2019	Luo <i>et al.</i> ^[22] (2017)	Sundaram <i>et al.</i> ^[20] (2016	Wu <i>et al.</i> ^[28] (2016)	BRS=brain rela: dilution cardiac

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Figure 2: Forest plots of outcomes represented as proportions: (a) neurological outcomes, (b) postoperative complications, (c) pulmonary complications, and (d) renal complications. CI = confidence interval, FEM = fixed effects model; GDFT = goal-directed fluid therapy, REM = random effects model, RoB = risk of bias, Std = standard care

postoperative complications than the control group [RR (95% CI) = 0.67 (0.54, 0.82), 95% PI = 0.39, 1.41,

 $I^2 = 37\%$] [Figure 2b]. Pulmonary complications were reported in seven studies.^[19,21,22,24-26,28] The pooled estimate showed a significant reduction in pulmonary complications with the use of GDFT compared to the control group [RR (95% CI) = 0.55 (0.38, 0.79), 95% PI = 0.35, 1.10, I² = 0%] [Figure 2c]. Renal complications were reported in three studies.^[21,22,24] However, no significant difference was seen in the incidence of postoperative kidney injury with the use of GDFT compared to the control group [RR (95% CI) = 0.63 (0.32, 1.25), 95% PI = 0.01, 50.87, I² = 0%] [Figure 2d].

Total amounts of fluids: Six RCTs reported the total amount of intravenous fluids used perioperatively.^[19,21,23,24,26,28] The pooled MD did not show a significant difference in the volume of fluids used between the GDFT and control groups intraoperatively [MD (95% CI) = -303.87 (-912.56, 304.82), 95% PI = -2397.76, 1790.02, I² = 94%] [Figure 3a]. The pooled estimate for average total fluids remained consistent with the exclusion of any study except Bloria *et al.*^[21] Excluding this study led to statistical significance.

Amount of intraoperative blood loss: Mean blood loss was reported by eight RCTs included in this meta-analysis.^[19–24,27,28] The pooled MD did not show a significant difference in intraoperative blood loss between the GDFT and control groups [MD (95% CI) = -14.79 (-49.05, 19.46), 95% PI = -66.82, 38.38, I² = 33%] [Figure 3b].

Duration of ICU and hospital stay: A total of six RCTs reported the duration of ICU stay,^[19,21-23,25,28] and eight studies reported the duration of hospital stay.^[19,21-26,28] Patients in the GDFT group had significantly shorter ICU stays than the patients in the control group [MD (95% CI) = -1.6 (-3.02, -0.28)]. The PI ranged from -5.63 to 2.33 [Figure 3c]. Moderate heterogeneity was found between the studies for the duration of ICU stay (I² = 77%, P = 0.01). The pooled estimate for average ICU stay remained fairly consistent, excluding any study except Luo *et al.*^[22] Excluding this study led to statistical insignificance. The pooled MD showed a significant difference in the overall duration of hospital stay favouring GDFT [MD (95% CI) = -0.97 (-1.5, -0.4), 95% PI - 3.17, 0.64, I² = 41%] [Figure 3d].

RoB assessment

RoB assessed by the independent reviewers (NM, KJ, MAS) is shown in Figure 4. Three of the studies have some concerns due to bias arising from allocation concealment^[19,24] and measurement of outcomes,^[20] and two studies had an overall high RoB arising due

to some concerns in allocation concealment and deviations from assigned interventions.^[27,28] All other studies had a generally low RoB, with none displaying a high RoB either overall or in any of the domains.

Sensitivity analysis

Sensitivity analysis was conducted for the outcome where the studies with high RoB were included in the pooled estimate. The neurological outcome was not affected by considering only the studies with low RoB [RR (95% CI) = 1.43 (0.96, 2.13)] [Figure 5]. The sensitivity analysis for overall and pulmonary complications also showed a similar effect, omitting studies with high RoB [Figure 5, Figure 1S]. The direction of the total fluid pooled estimate was similar for both high- and low-RoB studies, but omitting Bloria et al.[21] caused a significant change in the pooled estimate [Figure 6, Figure 2S]. This may be due to the use of different fluid management algorithms. The pooled estimate for the duration of hospital stay showed similar results when considering only low-risk bias studies groups [MD (95% CI) = -0.70 (-1.33, -0.07)] compared to the earlier overall estimate groups [MD (95% CI) = -0.94 (-1.47, -0.42) [Figure 6]. Omitting any study does not change the direction of the effect [Figure 2S].

Trial sequential analysis

A trial sequential analysis was done *post hoc* and showed that the required sample size was met for blood loss, hospital stay, and ICU stay. However, a much greater sample size is needed for pulmonary and renal complications [Table S3]. The software could not compute this for neurological outcomes and overall complications due to small number of studies.

GRADE profile

There was high certainty of evidence for overall complications, pulmonary complications and hospital and ICU stay. The other outcomes showed a low to very low certainty of evidence [Table 2].

DISCUSSION

The present comprehensive meta-analysis revealed no significant effect of GDFT on neurological outcomes. However, postoperative complications were significantly lower, and the hospital and ICU stay duration was significantly less in the GDFT group. Other outcome parameters were comparable among the groups.

There are a few studies where GDFT was used in the ICU or the postoperative period. Anetsberger *et al.*^[29]

				GDFT			Std care		Mean		F	ROB					-
	Study	Total	Mean	SD	Total	Mean	SD	Total fluids	Difference	95% C	Weight	D1 [D2 D3	D4	D5 (Overa	-
	Bloria et al., (2022) Feng et al., (2023) Hassanin et al., (2019) Mishra et al., (2022) Mitrev et al., (2019) Wu et al., (2017)	25 42 31 20 16 33	2504.00 2435.00 3155.00 4600.00 2766.00 1478.00	534.00 534.00 452.00 1300.00 1134.00 312.00	25 42 30 20 10 30	3733.00 2150.00 2790.00 5700.00 4238.00 1183.00	676.00 592.00 443.00 1600.00 2915.00 294.00		-1229.00 285.00 365.00 -1100.00 -1472.00 295.00	[-1566.69; -891.31 [43.89; 526.11 [140.40; 589.60 [-2003.50; -196.50 [-3362.22; 418.22 [145.33; 444.67	19.2% 19.8% S 19.9% 14.1% S 6.9% S 20.2%	Low La come La come La come La come So Low La	ow Lov ow Lov ow Lov ow Lov ome Lov ow Lov	v Low v Low v Low v Low v Low v Low v Low	Low Low Low Low Low	Low Some Some High Low	
	Pooled estimate [REM] Prediction interval	167			157				-303.87	[-912.56; 304.82] [-2397.76; 1790.02]	100.0%						
а	Heterogeneity: / ² = 94% [8 Mantel–Haenszel method ROB: Risk Of Bias; D1–5	9%; 97 i; Maxir : Doma	%], τ ² = 4 mum–like ins 1–5;	72311.197 elihood es Some: So	/5 [1783 timato me cor	348.0248; r and Q–p ncerns	- Lo 4355875.! rofile for	-3000 - 1000 0 1000 3000 wer with GDFT Higher with GDI 895], $\chi_5^2 = 82.53 (p < 0.01)$ tau^2 and its CI	FT								_
	Study	Total	Mean	GDFT SD	Total	Ste Mean	d care SD	Blood loss [Mean Difference	95% CI W	RO reight D1	B I D2	D3	D4	D5 (Overa	
	Bloria et al., (2022) Feng et al., (2023) Hassanin et al., (2019) Kim et al., (2019) Luo er al., (2017) Mishra et al., (2022) Sundaram et al., (2016) Wu et al., (2017) Pooled estimate [FEM]	25 42 31 24 73 20 28 33 276	478.00 632.00 887.00 614.00 287.00 903.00 974.00 435.00	82.00 518.00 377.00 474.00 179.00 643.00 1003.00 92.00	25 42 30 24 72 20 29 30 272	534.00 1 567.00 3 897.00 4 825.00 5 305.00 2 665.00 7 600.00 3 420.00 1	22.00 390.00 430.00 591.00 273.00 740.00 311.00 135.00		-56.00 65.00 -10.00 -211.00 -18.00 238.00 374.00 15.00 -14.79	[-113.62; 1.62] : [-131.10; 261.10] [-213.20; 193.20] [-514.10; 92.10] [-93.25; 57.25] : [-191.64; 667.64] [-14.37; 762.37] [-42.61; 72.61] : [-49.05; 19.46]	34.6% Low 3.4% Som 3.1% Lov 1.4% Som 21.4% Low 0.7% Som 0.9% Low 34.6% Low	w Low ne Low w Low ne Som w Low ne Low w Low w Low	Low Low Low Low Low Low Low Low	Low Low Low Low Low Some Low	Low Low Low Low Low Low Low	Low Some Low High Low Some Some Low	
b	Prediction interval Heterogeneity: / ² = 33% [0 Mantel-Haenszel methoc ROB: Risk Of Bias; D1–5	0%; 70% d; Maxi i: Doma	%], τ ² = 1; mum–lik ains 1–5;	21.3598 [0 elihood e Some: S	0.0000; stimate ome co	1213.598 or and Q- oncerns	Lowe 2], $\chi_7^2 = 10$ profile fo	-600 -200 0 200 400 600 er with GDFT Higher with GDF .43 (p = 0.17) r tau^2 and its Cl	т	[–66.82;́ 38.38]							
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	Bloria et al., (2022) Hassanin et al., (2019 Hrdy et al., (2023) Luo er al., (2017) Mishra et al., (2022) Wu et al., (2017)	9)	25 5. 31 2. 17 7. 73 3. 20 1. 33 15.	.60 2.2 .10 1.2 .00 10.0 .00 3.0 .50 2.3 .10 8.1	0 2 0 3 0 1 0 7 0 2 0 3	5 6.50 0 2.10 7 8.00 2 6.70 0 3.70 0 18.00	3.70 1.30 10.00 6.00 6.00 5.50		- - -	0.90 [-2.59; 0.7 0.00 [-0.63; 0.6 1.00 [-7.72; 5.7 3.70 [-5.25; -2.1 2.20 [-5.02; 0.6 2.90 [-6.29; 0.4	9] 21.0% 3] 29.1% 2] 3.6% 5] 22.2% 2] 13.4% 9] 10.6%	Low Low Low Low Some Low	Low L Low L Low L Low L Low L Low L	-ow L -ow L -ow L -ow L -ow L -ow L	.ow L .ow L .ow L .ow L .ow L	ow ow ow ow ow S ow	Low Low Low Low Some Low
	Pooled estimate [RE Prediction interval	EM]	199		19	4			-	1.65 [–3.02; –0.28 [–5.63; 2.33	3] 100.0% 3]						
С	Heterogeneity: / ² = 77% Mantel-Haenszel meti ROB: Risk Of Bias; D1	% [49% hod; M 1–5: De	; 90%], ∕ laximun omains	τ ² = 1.56) n–likeliho 1–5; Sor	71 [0.2 ood es ne: So	414; 10.5 stimator : me conc	Lον 5286], χ ₅ and Q–p cerns	were with GDFT Higher with ($p < 0.01$) = 21.97 ($p < 0.01$) rofile for tau^2 and its Cl	GDFT								
	Study	То	tal Mea	GDFT an SD) Tota	Sto I Mean	d care SD	Hospital stay	Me Differer	ean nce 95% Cl	Weight	ROB D1	D2	D3	D4 I	D5 O	verall
	Bloria et al., (2022) Feng et al., (2023) Hassanin et al., (2019) Hrdy et al., (2023) Luo et al., (2017) Mishra et al., (2017) Mitrev et al., (2019) Wu et al., (2017) Pooled estimate [FEI Prediction interval)) M] 2	25 12.9 42 14.0 31 5.2 17 14.0 73 15.0 20 5.0 16 11.0 33 10.4	90 2.70 00 1.50 20 1.30 00 6.50 00 12.00 00 3.00 00 14.00 40 3.90) 25) 42) 30) 17) 72) 20) 10) 30 240	5 13.90 2 14.60) 5.70 7 15.00 2 17.70) 8.00) 7.00) 12.20	4.80 3.80 1.50 8.50 13.60 1.60 3.00 5.10		-1 -0 -0 -1 -2 -3 -3 -1 -1 -0	.00 [-3.16; 1.16] .60 [-1.84; 0.64] .50 [-1.21; 0.21] .00 [-6.09; 4.09] .70 [-6.88; 1.48] .00 [-4.49; -1.51] .00 [-3.11; 11.11] .80 [-4.06; 0.46] 0.94 [-1.47; -0.42] [-3.11; 0.73]	10.9% 21.7% 31.9% 2.5% 3.6% 17.8% 1.3% 10.2%	Low Some Low Low Low Some Some Low	Low Low Low Low Low Some Low	Low I Low I Low I Low I Low I Low I Low I	Low L Low L Low L Low L Low L Low L Low L	OW OW OW OW OW OW OW	Low Some Low Low Low Some High Low
d	Heterogeneity: / ² = 43% Mantel–Haenszel meth ROB: Risk Of Bias; D1	6 [0%;] nod; M -5: D o	75%], τ ² aximum omains	= 0.4359 I-likeliho 1-5; Som	[0.000 ood es ne: So	00; 10.55 timator a me conc	88], χ ₇ ² = Ind Q–pi erns	rofile for tau ² and its Cl	ישר ו								

Figure 3: Forest plots of outcomes reported as mean differences: (a) total amount of the fluid; (b) total amount of intraoperative blood loss; (c) duration of ICU stay; (d) duration of hospital stay. CI = confidence interval, FEM = fixed effects model, GDFT = goal-directed fluid therapy, REM = random effects model, RoB = risk of bias, SD = standard deviation, Std = standard



Figure 4: Risk of bias summary for individual study: (a) using traffic signal light plot designed via Robvis tool; (b) using weighted plot designed via RoB tool. All studies were given equal weight for qualitative assessment

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Figure 5: Sensitivity analysis of the proportion data: (a) neurological outcomes, (b) overall complications, (c) pulmonary complications and (d) renal complications. CI = confidence interval, FEM = fixed effects model, GDFT = goal-directed fluid therapy, REM = random effects model, RR = risk ratio, Std = standard care

Study T	otai		30	Total	Mean	50	Total fluids	MD	9	5%-CI	Weight
Some Feng et al., (2023) Mishra et al., (2022) Pooled estimate [REM] Heterogeneity: J ² = 88% [54%	42 24 20 44 62 6; 97%]	435.00 600.00 1	534.00 300.00	42 2 20 5 62 $\chi_1^2 = 8$	2150.00 5700.00	592.00 1600.00		285.00 -1100.00 [- -258.03 [-	[43.89; 5 2003.50; -1 -1173.06; 6	26.11] [96.50] [56.99]	19.8% 14.1% 33.9%
Low Bloria et al. (2022)	25.2	504.00	534.00	25.5	733.00	676.00		-1229.00 [-	1566 69 8	91 311	19.2%
Hassanin et al., (2019) Wu et al., (2017) Pooled estimate [REM] Heterogeneity: J ² = 97% [94%	31 3 33 14 89	155.00 478.00	452.00 312.00	30 2 30 1 85 $\chi^2_2 = 7$	2790.00 183.00	443.00 294.00		365.00 295.00 -176.70	[140.40; 5 [145.33; 4 _997.95; 6	89.60] 44.67] 44.55]	19.9% 20.2% 59.3%
High				1 42				Teacher and			
Mitrev et al., (2019)	16 2	766.00 1	134.00	10 4	238.00	2915.00		-1472.00	-3362.22; 4	18.22]	6.9%
Prediction Interval Heterogeneity: I ² = 94% [89% Test for subgroup differences	6; 97%] ; 2 ² = 1	$\tau^2 = 472$.56, df = 2	311.1975 2 (p = 0.4	6)	8.0248; 4	– Loi 355875.5	-1000 0 1000 300 wer with GDFT Higher with GE $\chi_{5}^{2} = 82.53 (p < 0.01)$	0 DFT	2397.76; 17	90.02]	
Subgroup analysis based o	on over	all risk o	bias I R	andom	Effects	14					
Study	Total	Mean	SD	Total	Mean	SD	Blood loss	MD	95	5%-CI	Weigh
Some Feng et al., (2023) Mishra et al., (2022) Sundaram et al., (2016) Pooled estimate [FEM]	42 20 28 90	632.00 903.00 974.00	518.00 643.00 1003.00	42 20 29 91	567.00 665.00 600.00	390.00 740.00 311.00		- 238.00 - 374.00 143.47	[-131.10; 2 [-191.64; 6 [-14.37; 7 [-18.64; 3	61.10] 67.64] 62.37] 05.57]	3.1° 0.6° 0.8° 4.5°
Heterogeneity: I ² = 7% [0%	; 90%],	, τ ² = 0,)	2 = 2.15	(p = 0.3	34)						
Low Bloria et al., (2022) Hassanin et al. (2010)	25	478.00	82.00	25	534.00	122.00	_	-56.00	[-113.62;	1.62]	35.3
Luo er al., (2017) Wu et al., (2017)	73	287.00	179.00	72	305.00	273.00	+	-18.00	[-93.25;	57.25] 72.611	20.7
Pooled estimate [FEM] Heterogeneity: I ² = 0% [0%	162 ; 85%],	$\tau^2 = 73.$	1833, χ ₃ ²	157 = 2.93	(p = 0.40))	ſ	-19.63	[-54.91;	15.65]	94.3
High Kim et al., (2019)	24	614.00	474.00	24	825.00	591.00		-211.00	[-514.10:	92.10]	1.3
Pooled estimate [FEM]	276			272	-		1	-14.79	[-49.05;	19.46]	100.04
Prediction interval							· · · · * · · · ·		[-66.82; 3	38.38]	
Heterogeneity: I ² = 33% (0 ⁴ Test for subgroup difference Subgroup analysis based	%; 70% s: $\chi_2^2 =$ on ove	6], τ ² = 12 = 5.34, df erall risk	1.3598 [= 2 (p = of bias	0.0000; 0.07) I Fixed	1213.59 Effects St	Lo 82], χ ² ₇ = d care	-800 -200 0 200 400 80 wer with GDFT Higher with (10.43 (p = 0.17)	GDFT	1 12		
Heterogeneity: /² = 33% (0' Test for subgroup difference Subgroup analysis based Study	%; 70% es: χ ₂ ² = on ove	6], τ ² = 12 = 5.34, df erall risk al Mear	(1.3598 [= 2 (p = of bias GDFT SD	0.0000; 0.07) I Fixed	Effects St Mean	Lo 82], χ ² ₇ = d care SD	-000 -200 0 200 0	gdft Md	95	%–CI	Weig
Heterogeneity: l^2 = 33% (0 ⁷ Test for subgroup difference Subgroup analysis based Study Some Mishra et al., (2022) Low	%; 70% ss: χ ² ₂ = on ove Tota	b), t ² = 12 = 5.34, df = al Mear 0 1.5(GDFT GDFT 2.30 GDFT 3.30 3.30 3.30 3.30 3.30 3.30 3.30 3.3	0.0000; 0.07) I Fixed Tota	Effects St Mean 3.70	Lo 82], χ ² ₇ = d care SD 6.00	-000 -200 0 2004000 rewrith OBFT Higher with (10.43 (p = 0.17) ICU stay	GDFT MD -2.20	9 95 [-5.02;	% -CI 0.62]	Weig
Heterogeneity: P^2 = 33% (07 Test for subgroup difference Subgroup analysis based Study Some Mishra et al., (2022) Low Bloria et al., (2022) Hassanin et al., (2019)	%; 70% ss: χ^2_2 = on ove Tota 20 21 3	b), $t^2 = 12$ = 5.34, df erall risk al Mear 0 1.5(5 5.6(1 2.1((1.3598 [= 2 (p = of bias GDFT 3 SD 3 2.30 3 2.20 3 1.20	0.0000; 0.07) I Fixed Tota 20 25 30	Effects St I Mean 3.70 5 6.50 2.10	Lo 82], χ ² ₇ = d care SD 6.00 3.70 1.30	-000 - 200 0	GDFT 2.20 0.90 0.00	95 [-5.02; [-2.59; [-0.63;	% -CI 0.62] 0.79] 0.63]	Weig 13.4 21.0 29.1
Heterogeneity: P^2 = 33% (07 Test for subgroup difference Subgroup analysis based Study Some Mishra et al., (2022) Low Bloria et al., (2022) Hassanin et al., (2019) Hrdy et al., (2023) Luo er al., (2017)	%; 70% ss: χ_2^2 = on ove Tota 20 21 3 1 7;	6], t ² = 12 5.34, df erall risk al Mear 0 1.50 5 5.60 1 2.10 7 7.00 3 3.00	GDFT GDFT 3 SD 3 2.30 3 2.20 3 1.20 3 3.00 3 3.00	0.0000; 0.07) I Fixed Tota 20 25 30 17 72	Effects St Mean 3.70 5 6.50 9 2.10 7 8.00 2 6.70	Lo 82], χ ² ₇ = d care SD 6.00 3.70 1.30 10.00 6.00	-000 -200 0 2040 00 400 00 wer with GDFT Higher with (10.43 (p = 0.17) ICU stay	GDFT -2.20 -0.90 -0.00 -1.00 -3.70	9 95 9 [-5.02; 9 [-0.63; 9 [-7.72; 9 [-5.25:	%- CI 0.62] 0.63] 5.72] -2.15]	Weig 13.4 21.0 29.1 3.6 22.2
Heterogeneity: P = 33% (07 Test for subgroup difference Subgroup analysis based Study Some Mishra et al., (2022) Low Bioria et al., (2022) Hassanin et al., (2023) Luo er al., (2017) Wu et al., (2017) Pooled estimate (FREM	%; 70% ss: χ^2_2 = on ove Tota 20 21 3 3 1 7 7 3 3	 b) t² = 12 5.34, df erall risk al Mear 0 1.50 5 5.60 1 2.10 7 7.00 3 3.00 3 15.10 9 	GDFT GDFT CONT CONT CONT CONT CONT CONT CONT CONT CONT CONT CONT CONT CONT CONT CONT CONT CONT CONT CONT CONT CONT CONT CONT CONT CONT CONT CONT CONT CONT CONT CONT CONT CONT CONT CONT CONT CONT CONT CONT CONT CONT CONT CONT CONT CONT CONT CONT CONT CONT CONT CONT CONT CONT CONT CONT CONT CONT CONT CONT CONT CONT CONT CONT CONT CONT CONT CONT CONT CONT CONT CONT CONT CONT CONT CONT CONT CONT CONT CONT CONT CONT CONT CONT CONT CONT CONT CONT CONT CONT CONT CONT CONT CONT CONT CONT CONT CONT CONT CONT CONT CONT CONT CONT CONT CONT CONT CONT CONT CONT CONT CONT CONT CONT CONT CONT CONT CONT CONT CONT CONT CONT CONT CONT CONT CONT CONT CONT CONT CONT CONT CONT CONT CONT CONT CONT CONT CONT CONT CONT CONT CONT CONT CONT CONT CONT CONT CONT CONT CONT CONT CONT CONT CONT CONT CONT CONT CONT CONT CONT CONT CONT CONT CONT CONT CONT CONT CONT CONT CONT CONT CONT CONT CONT CONT CONT CONT CONT CONT CONT CONT CONT CONT CONT CONT CONT CONT CONT CONT CONT CONT CONT CONT CONT CONT CONT CONT CONT CONT CONT CONT CONT CONT CONT CONT CONT CONT CONT CONT CONT CONT CONT CONT CONT CONT CONT CONT CONT CONT CONT CONT CONT CONT CONT CONT CONT CONT CONT CONT CONT CONT CONT CONT CONT CONT CONT CONT CONT CONT CONT CONT CONT CONT CONT CONT CONT CONT CONT CONT CONT CONT CONT CONT CONT CONT	0.0000 0.07) I Fixed 20 25 30 17 20 17 20 17 20 17 20 17 20 17 20 17 20 17 20 17 17 20 17 17 17 17 17 17 17 17 17 17	Effects St Mean 3.70 3.70 3.70 3.70 3.70 3.70 4.00 2.6.50 3.00 2.10 8.00 2.10 18.00	Lo 82], $\chi_7^2 =$ d care SD 6.00 3.70 1.30 10.00 6.00 5.50		-2.20 -0.90 -0.00 1.00 -1.58	9 95 [-5.02; [-0.63; [-7.72; [-5.25; - [-6.29; [-3.12] -	%-CI 0.62] 0.63] 5.72] -2.15] 0.49] -0.05]	Weig 13.4 21.0 29.1 3.6 22.2 10.6 86.6
Heterogeneity: P = 33% (07 Test for subgroup difference Subgroup analysis based Study Some Low Boria et al., (2022) Low Boria et al., (2022) Hassanin et al., (2012) Hassanin et al., (2012) Hassanin et al., (2017) Pooled estimate [REM] Heterogeneity: F = 81% [2	%; 70% ss: $\chi_2^2 = 0$ on over Tota 24 22 3 1 7 7 3 3 1 77 3 55%; 9	b), $\tau^2 = 12$ = 5.34, df erall risk al Mean 0 1.50 5 5.60 1 2.10 7 7.00 3 3.00 3 15.10 9 12%], τ^2	GDFT GDFT 3 SD 3 2.30 3 2.20 3 1.20 3 3.00 3 3.00 3 8.10 3 1.789	0.0000; 0.07) 1 Fixed 2 (25) 30(174 30(174 2, $\chi^2_4 =$	Effects St Mean 3.70 5.6.50 0.2.10 7.8.00 2.00 7.8.00 2.0.01 7.8.00 2.0.01 7.8.00 2.0.01 7.8.00 2.0.01 7.8.00 2.0.01 7.8.00 2.0.01 7.8.00 2.0.01 7.8.00 2.0.01 7.8.00 2.0.01 7.8.000 7.8.000 7.8.000 7.8.000 7.8.000 7.8.000 7.8.000 7.8.000 7.8.000 7.8.000 7.8.000 7.8.0000 7.8.0000 7.8.0000 7.8.0000 7.8.0000 7.8.00000 7.8.00000 7.8.0000000 7.8.00000000000000000000000000000000000	Lo 82], χ ² ₇ = d care SD 6.00 3.70 1.30 10.00 6.00 5.50 0 < 0.01		-2.20 -0.90 0.00 -1.00 -1.00 -1.58	9 95 9 [-5.02; 9 [-0.63; 9 [-7.72; 9 [-5.25; - 9 [-6.29; 9 [-3.12; -	% -CI 0.62] 0.63] 5.72] -2.15] 0.49] -0.05]	Weig 13.4 21.0 29.1 3.6 22.2 10.6 86.6
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Heterogeneity: r^2 = 33% (07 Test for subgroup difference Subgroup analysis based Mishra et al., (2022) Low Bloria et al., (2022) Hassanin et al., (2022) Hassanin et al., (2023) Luo et al., (2017) Wu et al., (2017) Pooled estimate [REM] Prediction interval Heterogeneity: r^2 = 87% [2 Test for subgroup differenc Subgroup analysis based	%; 70% so; χ_2^2 = o on over Tota 2(2; 3 3 2; 7; 7; 3; 3; 17; 55%; 9] 19; 49%; 9 2;95%; 21 d on o	-j), τ ² = 12 5.5.4, df orall risk al Mear 0 1.5(5 5.6(1 2.1(7 7.0(3 3.0(9 9 99 9 90%), τ ² = 0.14, veverall r r	(1.3598 [c) = 2 (p = of blass GDFT SD) 2.30) 2.20) 1.20) 1.20) 3.00) 3.00) 8.10 = 1.769; = 1.567 cf = 1 (j isk of b	0.0000 0.07) I Fixed 20 22 30 17 72 30 17 72 30 17 72 30 17 72 19 4 10.24 4 p = 0.7 iias I R	Effects St 1 Mean 3.70 5.6.50 2.10 7.8.00 8.00 18.00 14; 10.5 10 andom	Lo e2), $\chi_7^2 =$ d care SD 6.00 1.30 10.00 5.50 2.50 0 < 0.01 Lo 2286], χ_6^2	-0.0 2.00 0 2.00 4.00 00 wer with GDFT Higher with -6 -4 -2 0 2 4 wer with GDFT Higher wi = 21.97 (p < 0.01)	-2.20 -0.90 -0.00 -1.00 -1.00 -1.58 -1.65	9 95 9 [-5.02; 1 [-0.63; 9 [-7.72; 1 [-5.25; - 9 [-3.12; - 1 [-5.63; 9 [-3.02; - 1 [-5.63;	%-CI 0.62] 0.63] 5.72] -2.15] 0.49] -0.05] 0.28] 2.33]	Weig 13.4 29.1 3.6 22.2 10.6 86.6 100.0
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Heterogeneily: $l^2 = 33\%$ [07 Subgroup analysis based Study Some Mishra et al., (2022) Low Bioria et al., (2022) Hassanin et al., (2022) Hassanin et al., (2022) Hassanin et al., (2022) Hassanin et al., (2022) Pooled estimate [REM] Prediction interval Heterogeneity: $l^2 = 77\%$ [4 Test for subgroup different Subgroup analysis based tudy tudy tudy tudy Dorded estimate [REM] Prediction interval Heterogeneity: $l^2 = 37\%$ [5 Subgroup analysis based Subgroup analysis bas	(%; 70%) (%) 70% (%) 70% (b), $t^2 = 12$ 5.34, df dear erall risk al Mear 0 1.5(5 5.6(1 2.1(1) 5 5.6(1 2.1(1) 3 3.0(0) 3 3.0(0)	(1.3598 [= 2 (p = of bias GDFT SD) 2.300) 2.200) 1.200) 1.200) 3.000) 3.000 = 1.789 (d = 1 (isk of b 1.50 3.00 0.9466 2.700 1.30	0.0000; 0.007) 1 Fixed 2 C 2 2 2 2 3 3 1 $(0.24)^2$ 1 $(0.24)^2$ 1 $(0.24)^2$ 1 $(0.24)^2$ 1 $(0.24)^2$ 1 $(0.24)^2$ 2 $(2.5)^2$ 1 $(0.24)^2$ 1 $(0.24)^2$ 2 $(2.5)^2$ 1 $(0.24)^2$ 2 $(2.5)^2$ 1 $(0.24)^2$ 2 $(2.5)^2$ 1 $(0.24)^2$ 2 $(2.5)^2$ 1 $(0.24)^2$ 2 $(2.5)^2$ 1 $(0.24)^2$ 2 $(2.5)^2$ 2 $(2.5)^2$	1213.59 Effects St I Mean) 3.70 5 6.50 18.00 20.81 () 20.81 () 20.81 () 4 20.81 () 4 20	Lo e2), $\chi_7^2 = \frac{1}{2}$ 6.00 3.70 1.30 6.00 5.50 2.86], $\chi_5^2 = \frac{1}{2}$ Effects 2.86 2.86 2.86 2.86 2.86 2.86 2.86 2.86		MD -2.20 -0.90 -0.00 -0.00 -1.00 -1.00 -1.60 -1.60 -0.60 -3.00 -1.56 -1.00 -0.50	9 95 9 [-5.02; 9 [-2.59; 9 [-7.72; 9 [-5.25; - 9 [-5.25; - 1 [-6.29; - [-5.63; 1 [-3.02; - [-5.63; 9 95 9 95 9 [-1.84; 9 [-4.49; - 1 [-2.53; - 1 [-2.53] - 1 [-2.53] - 1 [-2.53] - 1 [-2.53] - 1 [-2.53] - 1 [-3.02; - 1 [-3.02; - 1 [-3.02] - 1 [%-Cl 0.62] 0.79] 0.63] 2.215] 0.49] 0.05] 0.28] 2.33] 0.28] 2.33] 0.64] -1.51] -0.63] 1.16] 0.21]	Weig 13.4 21.0 29.1 3.6 86.6 100.0 Weig 18.0 12.4 30.4
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Figure 6: Sensitivity analysis of the data with mean difference: (a) total fluids; (b) blood loss; (c) ICU stay and (d) hospital stay. CI = confidence interval, FEM = fixed effects model, GDFT = goal-directed fluid therapy, ICU = intensive care unit, MD = mean difference, REM = random effects model, SD = Standard deviation, Std = standard care



Patient or population: Adult patients undergoing craniotomies Intervention: Goal-directed fluid therapy (GDFT)

Comparison: Standard therapy

Outcomes	No. of participants	Certainty of	Relative effect	Anticipated absolute effects				
	(studies) Follow-up	the evidence (GRADE)	(95% CI)	Risk with standard therapy	Risk difference with GDFT			
Neurological outcomes	90 (2 RCTs)	⊕⊖⊖⊖ Very low ^{a,b}	RR 1.10 (0.69-1.75)	711 per 1,000	71 more per 1,000 (220 fewer to 533 more)			
Overall complications	392 (6 RCTs)	⊕⊕⊕⊕ High	RR 0.67 (0.54-0.82)	487 per 1,000	161 fewer per 1,000 (224 fewer to 88 fewer)			
Pulmonary complications	442 (7 RCTs)	⊕⊕⊕⊕ High	RR 0.55 (0.38-0.79)	245 per 1,000	110 fewer per 1,000 (152 fewer to 52 fewer)			
Renal complications	279 (3 RCTs)	⊕⊕⊖⊖ Low ^c	RR 0.63 (0.32-1.35)	115 per 1,000	43 fewer per 1,000 (78 fewer to 40 more)			
Total fluids	324 (6 RCTs)	⊕⊖⊖⊖ Very low ^{a,c}	-	The mean total fluids ranged from 1183 to 5700 ml	MD 303.87 ml lower (912.56 lower to 304.82 higher)			
Hospital stay	503 (8 RCTs)	⊕⊕⊕⊕ High	-	The mean hospital stay ranged from 5.7 to 17.70 days	MD 0.94 days higher (1.47 lower to 0.42 lower)			
ICU stay	393 (6 RCTs)	⊕⊕⊕⊕ High	-	The mean ICU stay ranged from 2.1 to 18 days	MD 1.65 days lower (3.02 lower to 0.28 lower)			

*The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI). CI: confidence interval; MD: Mean difference; RR: Risk ratio. GRADE Working Group grades of evidence, ICU: Intensive care unit; RCT: Randomised controlled trial. High certainty: we are very confident that the true effect lies close to that of the estimate of the effect. Moderate certainty: we are moderately confidence in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different. Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect. Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect. Point estimates are present on both the sides of line of no effect, hence we have downgraded evidence certainty by one levels. "The point estimate suggests harm, and the CI includes the possibility of important benefit, hence we have downgraded the evidence certainty by two levels."

compared GDFT with standard therapy throughout the hospital stay in patients with aneurysmal subarachnoid haemorrhage (SAH) and observed that the GDFT group had a significantly lesser incidence of delayed cerebral ischaemia and better neurological outcome (GOS 5) at 3 months following discharge. Mutoh *et al.*^[30] observed similar results when comparing GDFT with conventional treatment in post-clipping or post-coiling poor-grade patients. Hence, it is suggested that GDFT should be continued till the patient needs systemic fluid administration in future studies. This may enable us to appreciate its effect on neurological outcomes better.

The pooled data has shown that the number of postoperative complications was significantly lower in the GDFT group. Similar observations were made in various high-risk non-neurosurgical patients as well.^[31-33] A meta-analysis conducted in major gastrointestinal and non-cardiac surgeries showed a reduction in the major postoperative complications in the GDFT group.^[34] In contrast, a multicentric retrospective analysis of a before–after study conducted in neurosurgical patients showed that GDFT did not reduce the major postoperative complications in elective neurosurgical patients.^[35] In the present meta-analysis, there was a lot

of heterogeneity in reporting other medical and surgical complications. Only pulmonary and renal complications could be analysed separately. Intraoperative GDFT may reduce postoperative complications due to better systolic blood pressure maintenance and optimum volume without over- or underhydration. The overall certainty of evidence about this outcome was high.

The pooled data showed that the total amount of intraoperative fluid was similar in both groups. The studies included in this meta-analysis have used different algorithms and various tools to guide fluid therapy, including SVV (>12%^[19,27] and >15%),^[22] PPV (>13%)^[20,23] and VTI (>12%),^[21] and various protocols of type of fluids. A study by Dev et al.^[36] compared SVV with PVI and found that the amount of crystalloids was significantly different in these techniques of GDFT. Wu et al.^[37] Compared with a low SVV of 10% to a high SVV of 18%, it was found that lower SVV was superior in terms of shorter ICU stay, postoperative neurological events, serum lactate, and Barthel index at discharge. Hence, high heterogeneity was observed for this outcome, and it is suggested that larger multicentric trials with uniform targets and algorithms be included to reach a firm conclusion on this outcome.

Intraoperative blood loss was comparable among the groups. Even though a previous study in major hepatectomy showed that blood loss was significantly lesser in the GDFT group (SVV guided) compared to the control group (CVP guided),^[38] most of the studies in neurosurgical patients failed to show the direct benefit of GDFT in reducing blood loss. A lesser amount of blood loss was observed during hepatectomy due to the favourable effect of GDFT on haemodynamic parameters. In neurosurgical procedures, intraoperative blood loss primarily depends upon vascularity, size and location of the lesions, technical difficulties and surgical expertise.^[39] GDFT may not directly influence the blood loss as it does in hepatectomy.

The duration of ICU and hospital days was significantly less in the GDFT group. The reduction in postoperative complications may explain the lesser duration of ICU and hospital stay in the GDFT group. A previous meta-analysis conducted in major abdominal surgeries showed that hospital length of stay was significantly lesser in the GDFT group. Similarly, Benes *et al.*^[32] reported significantly fewer days of ICU stay in surgical patients in a heterogeneous population. This may, in turn, improve patient-reported outcomes such as the cost of care. This outcome has a high certainty of evidence.

Strength and limitations

This is the first comprehensive SRMA conducted to examine the effect of GDFT on multiple outcomes in neurosurgical patients. The major limitation was the smaller number of high-quality studies to assess the role of GDFT in neurosurgical patients. The composition of fluids governing the osmolarity and solute content also affects the outcome. In the current meta-analysis, the studies have used different types of fluids, including balanced crystalloids, normal saline and colloids. Hence, there is a heterogeneity in the type of fluid infused, the fluid protocol followed, the technique of GDFT and the outcome studied. The certainty of evidence was of low grade for the primary outcome parameter. Furthermore, large multicentric RCTs with uniform techniques and tools to measure the targets of GDFT and outcomes are required to understand the effect of GDFT among neurosurgical patients.

CONCLUSIONS

The pooled data of this meta-analysis showed that the neurological outcome was not affected by the intraoperative GDFT. Still, it was associated with reduced postoperative complications and ICU and hospital stays, reducing the overall cost.

Authors' contribution

Authors KJ and APG contributed equally as the first authors. All the authors have participated sufficiently in the work to merit authorship and publicly defend the manuscript contents.

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Conflicts of interest

There are no conflicts of interest.

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REFERENCES

- Shin CH, Long DR, McLean D, Grabitz SD, Ladha K, Timm FP, et al. Effects of intraoperative fluid management on postoperative outcomes: A hospital registry study. Ann Surg 2018;267:1084-92.
- Michard F, Giglio MT, Brienza N. Perioperative goal-directed therapy with uncalibrated pulse contour methods: Impact on fluid management and postoperative outcome. Br J Anaesth 2017;119:22-30.
- Buletko AB, Thacker T, Cho SM, Mathew J, Thompson NR, Organek N, *et al.* Cerebral ischemia and deterioration with lower blood pressure target in intracerebral haemorrhage. Neurology 2018;91:e1058-66.
- 4. Shimoda M, Oda S, Tsugane R, Sato O. Intracranial complications of hypervolemic therapy in patients with a delayed ischemic deficit attributed to vasospasm. J Neurosurg 1993;78:423-9.
- Mtaweh H, Trakas EV, Su E, Carcillo JA, Aneja RK. Advances in monitoring and management of shock. Pediatr Clin North Am 2013;60:641-54.
- 6. Holliday MA, Segar WE. The maintenance needs for water in parenteral fluid therapy. Pediatrics 1957;19:823-32.
- 7. Cove ME, Pinsky MR. Perioperative hemodynamic monitoring. Best Pract Res Clin Anaesthesiol 2012;26:453-62.
- 8. Chui J, Craen R, Dy-Valdez C, Alamri R, Boulton M, Pandey S, *et al.* Early goal-directed therapy during endovascular coiling procedures following aneurysmal subarachnoid hemorrhage:

A pilot prospective randomized controlled study. J Neurosurg Anesthesiol 2022;34:35-43.

- Raabe A, Beck J, Keller M, Vatter H, Zimmermann M, Seifert V. Relative importance of hypertension compared with hypervolemia for increasing cerebral oxygenation in patients with cerebral vasospasm after subarachnoid hemorrhage. J Neurosurg 2005;103:974-81.
- Page MJ, Moher D, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. PRISMA 2020 explanation and elaboration: Updated guidance and exemplars for reporting systematic reviews. BMJ 2021;29:n160. doi: 10.1136/bmj.n160.
- 11. Jennett B. Assessment of outcome after severe brain damage: A practical scale. Lancet 1975;305:480-4.
- 12. Wilson JTL, Hareendran A, Grant M, Baird T, Schulz UGR, Muir KW, *et al.* Improving the Assessment of Outcomes in Stroke. Stroke 2002;33:2243-6.
- 13. Minozzi S, Cinquini M, Gianola S, Gonzalez-Lorenzo M, Banzi R. The revised Cochrane risk of bias tool for randomized trials (RoB 2) showed low interrater reliability and challenges in its application. J Clin Epidemiol 2020;126:37-44.
- 14. Luo D, Wan X, Liu J, Tong T. Optimally estimating the sample mean from the sample size, median, mid-range, and/or mid-quartile range. Stat Methods Med Res 2018;27:1785-805.
- Mantel N, Haenszel W. Statistical aspects of the analysis of data from retrospective studies of disease. J Natl Cancer Inst 1959;22:719-48.
- Gandhi AP, Shamim MA, Padhi BK. Steps in undertaking meta-analysis and addressing heterogeneity in meta-analysis. Evidence 2023;1:78–92.
- Shamim MA, Gandhi AP, Dwivedi P, Padhi BK. How to perform meta-analysis in R: A simple yet comprehensive guide. Evidence 2023;1:93–113.
- Guyatt GH, Oxman AD, Vist GE, Kunz R, Falck-Ytter Y, Alonso-Coello P, *et al.* GRADE: An emerging consensus on rating quality of evidence and strength of recommendations. BMJ 2008;336:924-6.
- Mishra N, Rath GP, Bithal PK, Chaturvedi A, Chandra PS, Borkar SA. Effect of goal-directed intraoperative fluid therapy on duration of hospital stay and postoperative complications in patients undergoing excision of large supratentorial tumors. Neurol India 2022;70:108-14.
- 20. Sundaram SC, Salins SR, Kumar AN, Korula G. Intra-operative fluid management in adult neurosurgical patients undergoing intracranial tumour surgery: Randomised control trial comparing pulse pressure variance (PPV) and central venous pressure (CVP). J Clin Diagn Res 2016;10:UC01-5.
- 21. Bloria SD, Panda NB, Jangra K, Bhagat H, Mandal B, Kataria K, et al. Goal-directed fluid therapy versus conventional fluid therapy during craniotomy and clipping of cerebral aneurysm: A prospective randomized controlled trial. J Neurosurg Anesthesiol 2022;34:407-14.
- Luo J, Xue J, Liu J, Liu B, Liu L, Chen G. Goal-directed fluid restriction during brain surgery: A prospective randomized controlled trial. Ann Intensive Care 2017;7:16. doi: 10.1186/ s13613-017-0239-8.
- Hasanin A, Zanata T, Osman S, Abdelwahab Y, Samer R, Mahmoud M, et al. Pulse pressure variation-guided fluid therapy during supratentorial brain tumour excision: A randomized controlled trial. Open Access Maced J Med Sci 2019;7:2474-9.
- 24. Feng S, Xiao W, Zhang Y, Ma Y, Yang S, He T, *et al.* Effect of goal-directed fluid therapy based on both stroke volume variation and delta stroke volume on the incidence of composite postoperative complications among individuals undergoing meningioma resection. Chin Med J (Engl) 2023;136:1990-2.
- 25. Hrdy O, Duba M, Dolezelova A, Roskova I, Hlavaty M, Traj R, et al. Effects of goal-directed fluid management guided by a non-invasive device on the incidence of postoperative

complications in neurosurgery: A pilot and feasibility randomized controlled trial. Perioper Med (Lond) 2023;12:32. doi: 10.1186/s13741-023-00321-3.

- 26. Mitrev LV, Sehdev JS, Turtz AR, Trivedi KC, Misbin MM, Torjman MC, *et al.* Goal-directed fluid therapy in craniotomy surgery: A prospective, randomized controlled trial. Acta Anaesth Belg 2019;70:31-8.
- 27. Kim N, Lee JH, Kim DH, Choi KW, Kim E, Choi SH. Effects of goal-directed fluid management with 0.9% normal saline on metabolic acidosis in patients undergoing brain surgery: A prospective and randomized-controlled study. Int J Clin Exp Med 2019;12:3994-4002.
- 28. Wu J, Ma Y, Wang T, Xu G, Fan L, Zhang Y. Goal-directed fluid management based on the auto-calibrated arterial pressure-derived stroke volume variation in patients undergoing supratentorial neoplasms surgery. Int J Clin Exp Med 2017;10:3106-14.
- 29. Anetsberger A, Gempt J, Blobner M, Ringel F, Bogdanski R, Heim M, *et al.* Impact of goal-directed therapy on delayed ischemia after aneurysmal subarachnoid hemorrhage: Randomized controlled trial. Stroke 2020;51:2287-96.
- Mutoh T, Kazumata K, Terasaka S, Taki Y, Suzuki A, Ishikawa T. Early intensive versus minimally invasive approach to postoperative hemodynamic management after subarachnoid hemorrhage. Stroke 2014;45:1280-4.
- Lopes MR, Oliveira MA, Pereira VOS, Lemos IP, Auler JO Jr, Michard F. Goal-directed fluid management based on pulse pressure variation monitoring during high-risk surgery: A pilot randomized controlled trial. Crit Care 2007;11:R100. doi: 10.1186/cc6117.
- 32. Benes J, Chytra I, Altmann P, Hluchy M, Kasal E, Svitak R, *et al.* Intraoperative fluid optimization using stroke volume variation in high-risk surgical patients: Results of prospective randomized study. Crit Care 2010;14:R118. doi: 10.1186/cc9070.
- 33. Mayer J, Boldt J, Mengistu AM, Röhm KD, Suttner S. Goal-directed intraoperative therapy based on autocalibrated arterial pressure waveform analysis reduces hospital stay in high-risk surgical patients: A randomized, controlled trial. Crit Care 2010;14:R18. doi: 10.1186/cc8875.
- 34. Som A, Maitra S, Bhattacharjee S, Baidya DK. Goal directed fluid therapy decreases postoperative morbidity but not mortality in major non-cardiac surgery: A meta-analysis and trial sequential analysis of randomized controlled trials. J Anesth 2017;31:66-81.
- 35. Le Guen M, Le Gall-Salaun A, Josserand J, Gaudin de Vilaine A, Viquesnel S, Muller D, et al. Goal-directed fluid therapy and major postoperative complications in elective craniotomy. A retrospective analysis of a before-after multicentric study. BMC Anesthesiol 2023;23:11. doi: 10.1186/ s12871-022-01962-5.
- Dey A, Bidkar PU, Swaminathan S, M MK, Joy JJ, Balasubramanian M, *et al.* Comparison of two techniques of goal directed fluid therapy in elective neurosurgical patients-A randomized controlled study. Br J Neurosurg 2023;3:1-9. doi: 10.1080/02688697.2023.2173722.
- 37. Wu CY, Lin YS, Tseng HM, Cheng HL, Lee TS, Lin PL, *et al.* Comparison of two stroke volume variation-based goal-directed fluid therapies for supratentorial brain tumour resection: A randomized controlled trial. Br J Anaesth 2017;119:934-42.
- Mei X, Liu J, Wang Y, Wei L, Tan S. Application of stroke volume variation-guided liquid therapy in laparoscopic precision hepatectomy. Zhong Nan Da Xue Xue Bao Yi Xue Ban 2019;44:1163-8.
- 39. Rajagopalan V, Chouhan RS, Pandia MP, Lamsal R, Rath GP. Effect of intraoperative blood loss on perioperative complications and neurological outcome in adult patients undergoing elective brain tumor surgery. J Neurosci Rural Pract 2019;10:631. doi: 10.1055/s-0039-3399487.

LIST OF SUPPLEMENTAL DIGITAL CONTENT

Supplemental digital content 1

Box 1: Definitions for secondary outcomes

- 1. Renal failure: Increased creatinine >1.5 times from baseline, decreased urine out put <0.5 ml/kg, acute kidney injury
- 2. Pulmonary complication: Pneumonitis, pleural effusion, pulmonary thromboembolism, consolidation
- 3. Cardiac complication: hypotension and arrhythmias requiring intervention
- 4. Electrolyte abnormalities requiring treatment
- 5. Re-exploration: Redo surgery during same hospital admission

	Supplemental Table S1: PICO statement o	f the study
	Inclusion	Exclusion
Participants	Patients undergoing craniotomies for neurosurgical conditions	Emergency room resuscitation
	All genders	Emergency surgical procedure
	Adults	
Intervention	Goal-directed fluid therapy	
Outcome	 Postoperative complications 	
	Mortality	
Study designs	Randomised controlled trials	Retrospective, case reports and opinion reports
	Geography- global level	
	Date of Search- published till 16 October 2023	
	English language	
	Human studies	
	Published and unpublished data	

PICO=Participants, intervention, control and outcome

Su	ppleme	ental Table S2: The search strategies and results of various databases included (as of 16.10.202	:3)
Database	No.	Search query	Results
		Cochrane	
	#1	(((((Neurosurgery: ti, ab)) OR (Craniotomy: ti, ab)) OR (Supratentorial: ti, ab)) OR (Posterior fossa: ti, ab) OR (Infratentorial: ti, ab) OR (Intracranial aneurysm: ti, ab) OR (Traumatic brain injury: ti, ab) OR (Head Injury: ti, ab))	11,387
	#2	(((((goal directed fluid therapy: ti, ab)) OR (goal oriented fluid therapy: ti, ab)) OR (goal target fluid therapy: ti, ab)) OR (restrictive fluid therapy: ti, ab))	890
	#3	(((((((((((((((((((((((((((((((())) (() (()))) (())))))	174,556
	#4	#1 AND #2 AND #3 AND (English)	39
		EBSCOhost-academic search complete	
	#1	TX neurosurgery OR TX craniotomy OR TX supratentorial OR TX posterior fossa OR TX Infratentorial OR TX Intracranial aneurysm OR TX traumatic brain injury OR TX head Injury	138,431
	#2	TX goal-directed fluid therapy OR TX goal-oriented fluid therapy OR TX goal-target fluid therapy OR TX restrictive fluid therapy	281
	#3	TX neurological outcome OR TX Glasgow outcome score OR TX mortality OR TX postoperative complications OR TX cerebral edema OR TX vasospasm OR TX modified Rankin scale OR TX Kidney injury OR TX Hospital duration OR TX Total fluid	672,597
	#4	1 AND #2 AND #3 AND (English[Filter])	23
		EMBASE	
	#1	(neurosurgery: ti, ab OR craniotomy: ti, ab OR supratentorial: ti, ab OR (posterior AND fossa: ti, ab) OR infratentorial: ti, ab OR (intracranial AND aneurysm: ti, ab) OR (traumatic AND ('brain'/exp OR brain) AND injury: ti, ab) OR (('head'/exp OR head) AND injury: ti, ab)) AND [english]/lim	224,839
	#2	(((((goal directed fluid therapy: ti, ab)) OR (goal oriented fluid therapy: ti, ab)) OR (goal target fluid therapy: ti, ab)) OR (restrictive fluid therapy: ti, ab)) AND [english]/lim	2105
	#3	(((((((((neurological outcome: ti, ab)) OR (glasgow outcome score: ti, ab)) OR (mortality: ti, ab)) OR (postoperative complications: ti, ab)) OR (cerebral edema: ti, ab)) OR (vasospasm: ti, ab)) OR (modified rankin scale: ti, ab)) (Kidney injury: ti, ab)) OR (Hospital duration: ti, ab)) OR (Total fluid: ti, ab)) AND [english]/lim	550,892
	#4	#1 AND #2 AND #3 AND	21
		ProQuest	
	#1	((TI, AB (neurosurgery)) OR (TI, AB (craniotomy))) OR (TI, AB (supratentorial)) OR (TI, AB (posterior fossa)) OR (TI, AB (infratentorial)) OR (TI, AB (intracranial aneurysm)) OR (TI, AB (traumatic brain injury)) OR (TI, AB (head Injury))	22,986
	#2	(((TI, AB (goal directed fluid therapy)) OR (TI, AB (goal oriented fluid therapy))) OR (TI, AB (goal target fluid therapy))) OR (TI, AB (restrictive fluid therapy))	280
	#3	((((TI, AB (neurological outcome)) OR (TI, AB (Glasgow outcome score))) OR (TI, AB (Mortality))) OR ((((TI, AB (postoperative complications)) OR (TI, AB (cerebral edema))) OR (TI, AB (vasospasm))) OR (TI, AB (Modified Rankin scale))) OR (TI, AB (kidney injury))) OR ((TI, AB (Hospital duration))) OR (TI, AB (total fluid))	275,195
	#4	1 AND 2 AND 3 AND (English[Filter])	6
		PubMed	
	#1	((((((Neurosurgery[Title/Abstract]) OR (Craniotomy[Title/Abstract])) OR (Supratentorial[Title/Abstract])) OR (Posterior fossa[Title/Abstract])) OR (Infratentorial[Title/Abstract])) OR (Intracranial aneurysm[Title/ Abstract])) OR ('Traumatic brain injury'[Title/Abstract])) OR ('Head Injury'[Title/Abstract])	13,421
	#2	(((goal-directed fluid therapy[Title/Abstract]) OR (goal-oriented fluid therapy[Title/Abstract])) OR (goal-target fluid therapy[Title/Abstract])) OR (Restrictive fluid therapy[Title/Abstract])	436
	#3	((((((((neurological outcome[Title/Abstract]) OR (Glasgow outcome scales[Title/Abstract])) OR (Modified Rankin scale[Title/Abstract])) OR (Mortality[Title/Abstract])) OR (postoperative complications[Title/ Abstract])) OR (Kidney injury[Title/Abstract])) OR (cerebral edema[Title/Abstract])) OR (vasospasm[Title/ Abstract])) OR (Hospital duration[Title/Abstract])) OR (Total fluid[Title/Abstract])	1,125,206
	#4	#1 AND #2 AND #3 AND (English[Filter])	5
		Scopus	
	#1	(TITLE-ABS (neurosurgery)) OR (TITLE-ABS (craniotomy)) OR (TITLE-ABS (supratentorial)) OR (TITLE-ABS (posteriorAND fossa)) OR (TITLE-ABS (infratentorial)) OR (TITLE-ABS (intracranial AND aneurysm)) OR (TITLE-ABS (traumatic AND brain AND injury)) OR (TITLE-ABS (head AND injury))	204,602
	#2	((TITLE-ABS(goal-directed fluid therapy))OR(TITLE-ABS(goal-oriented fluid therapy)))OR(TITLE-ABS(goal target fluid therapy))OR(TITLE-ABS(restrictive fluid therapy))	1402

		Supplemental Table S2: Contd	
Database	No.	Search query	Results
		Scopus	
	#3	(TITLE-ABS (neurological outcome)) OR (TITLE-ABS (Glasgow outcome score)) OR (TITLE-ABS (Mortality)) OR (TITLE-ABS (kidney injury)) OR (TITLE-ABS (hospital duration)) OR (TITLE-ABS (postoperative complications)) OR (TITLE-ABS (cerebral oedema)) OR (TITLE-ABS (vasospasm)) OR (TITLE-ABS (Modified Rankin scale)) OR (TITLE-ABS (Total fluid))	1,766,902
	#4	#1 AND #2 AND #3 AND (English[Filter])	17
		Web of Science	
	#1	(TI=neurosurgery OR AB=neurosurgery) OR (TI=craniotomy OR AB=craniotomy) OR (TI=supratentorial OR AB=supratentorial) OR (TI=posterior fossa OR AB=posterior fossa) OR (TI=infratentorial OR AB=infratentorial) OR (TI=intracranial aneurysm OR AB=intracranial aneurysm) OR (TI=traumatic brain injury OR AB=traumatic brain injury) OR (TI=head Injury OR AB=head Injury)	142,856
	#2	(TI=goal-directed fluid therapy OR AB=goal-directed fluid therapy) OR (TI=goal-oriented fluid therapy OR AB=goal-oriented fluid therapy) OR (TI=goal target fluid therapy OR AB=goal target fluid therapy) OR (TI=restrictive fluid therapy OR AB=restrictive fluid therapy)	1062
	#3	(TI=neurological outcome OR AB=neurological outcome) OR (TI=Glasgow outcome score OR AB=Glasgow outcome score) OR (TI=Mortality OR AB=Mortality) OR (TI=kidney injury OR AB=kidney injury) OR (TI=hospital duration OR AB=hospital duration) OR (TI=postoperative complications OR AB=postoperative complications) OR (TI=cerebral edema OR AB=cerebral edema) OR (TI=vasospasm OR AB=vasospasm) OR (TI=Modified Rankin scale OR AB=Modified Rankin scale) OR (TI=total fluid OR AB=total fluid)	1,242,843
	#4	#1 AND #2 AND #3 AND (English[Filter])	14

Study	Overall complications	RR	95%-CI	P-value	Tau2	Tau	12
Omitting Mishra et al., (2022)		0.68	[0.56; 0.84]	< 0.01	0.0267	0.1634	43%
Omitting Feng et al., (2023)		0.59	[0.43; 0.81]	< 0.01	0.1405	0.3749	48%
Omitting Mitrev et al. (2019)		0.61	[0.46, 0.79] [0.56, 0.84]	< 0.01	0.0538	0.2320	37%
Omitting Wu et al., (2017)		0.70	[0.57; 0.86]	< 0.01	0.0169	0.1301	33%
Omitting Luo er al., (2017)		0.71	[0.58; 0.87]	< 0.01	0.0082	0.0907	33%
Sensitivity analysis [FEM]							
[Leave-one-out meta-analysis		0.67	[0.54; 0.82]	< 0.01	0.0348	0.1866	37%
2	0.5 1 2						
L	ower with GDFT Higher with GI	DFT					
Study	Pulmonary complications	R	R 95%-	CI P-val	ue Ta	u2 1	lau 12
Omitting Mishra et al., (2022)	i	0.5	6 [0.39: 0.8	0] < 0.	01 0.01	66 0.12	290 0%
Omitting Bloria et al., (2022)	— — ——————————————————————————————————	0.5	5 [0.37; 0.8	1] < 0.	01 0.03	64 0.19	909 0%
Omitting Feng et al., (2023)	— # —	0.5	5 [0.38; 0.8	0] < 0.	01 0.03	14 0.17	773 0%
Omitting Hrdy et al., (2023)		0.4	7 [0.29; 0.7	7] < 0.	.01	0	0 0%
Omitting Mitrev et al., (2019)		0.5	6 [0.39; 0.8	1 < 0	01 0.01	43 0.11	195 0%
Omitting Vu et al., (2017)		0.6	1 [0.41; 0.9	2] U	01 0 01	0 62 0 12	
		0.5	0 [0.39, 0.0	0] < 0.	01 0.01	02 0.12	213 0%
Sensitivity analysis [FEM]		0.5	5 [0.38; 0.7	9] < 0.	01 0.01	75 0.13	323 0%
[Leave-one-out meta-analysis			-	-			
b .	0.5 1 2						
L	ower with GDFT Higher with C	3DFT					
Study	Renal complication	S	RR 9	5% - CI I	-value	Tau2	Tau I2
Omitting Bloria et al., (2022)			0.53 [0.15	; 1.90]	0.33	0	0 0%
Omitting Feng et al., (2023)			0.66 [0.33	3; 1.33]	0.25	0	0 0%
Omitting Luo er al., (2017)			0.65 [0.30); 1.41]	0.28	0	0 0%
Sensitivity analysis [FEM]			0 62 10 20	. 1 051	0.10	0	0.09/
[Leave-one-out meta-analys	sis]		0.03 [0.32	; 1.25]	0.19	U	0 0%
	0.2 0.5 1 2	5					
	Lower with GDFT Higher w	ith GD	FT				
C	•						

Figure 1S: Leave-one-out analysis of the proportion data: (a) overall complications; (b) pulmonary complications; (c) renal complications. CI = confidence interval, FEM = fixed effects model, GDFT = goal-directed fluid therapy, RR = risk ratio



Figure 2S: Leave-one-out analysis of the mean difference: (a) total fluids; (b) blood loss; (c) ICU stay; (d) hospital stay. CI = confidence interval, FEM = fixed effects model, GDFT = goal-directed fluid therapy, ICU = intensive care unit, MD = mean difference, REM = random effects model

Table S3: Trial sequential analysis
This is a retrospective meta-analysis sample size calculation. The sample size calculation assumes a two-sided test, equal group sizes, a type-I error of 0.01428571 and a type-II error of 0.2
The type-1 error is based on <i>P</i> value adjustment for the seven critical outcomes used for assessing evidence quality. ^[1] TSA could not be
computed for neurological outcomes and overall complications
Blood loss
Minimal clinically important mean difference: 100 ml
Fixed effects required information size:
The number of participants required for a fixed-effect meta-analysis has reached a certain point
Random effects required information size:
Adjusted by inconsistency (D^2): The number of required participants for a random effects meta-analysis is reached
Adjusted by inconsistency (I^2): The number of required participants for a random effects meta-analysis is reached
Hospital stay
Minimal clinically important mean difference: 3 days
Fixed effects required information size:
The number of participants required for a fixed-effect meta-analysis has reached a certain point
Random effects required information size:
Adjusted by inconsistency (D^2): The number of required participants for a random effects meta-analysis is reached
Adjusted by inconsistency (I^2): The number of required participants for a random effects meta-analysis is reached
ICU stay
Minimal clinically important mean difference: 2 days
Fixed effects required information size:
The number of participants required for a fixed-effect meta-analysis has reached a certain point
Random effects required information size:
Adjusted by inconsistency (D^2): The number of required participants for a random effects meta-analysis is reached
Adjusted by inconsistency (I ²): The number of required participants for a random effects meta-analysis is reached
Pulmonary complications
Minimal clinically important risk reduction: 5%
Fixed effects required information size: 51,957 participants in total are additionally required
Renal complications
Minimal clinically important risk reduction: 5%
Fixed effects required information size: 130,078 participants in total are additionally required
Neurological outcomes and overall complications
Could not be computed
1. Jakobsen JC, Wetterslev J, Winkel P, Lange T, Gluud C. Thresholds for statistical and clinical significance in systematic reviews with meta-analytic methods. BMC Med Res Methodol. 2014;14.

TSA=Trial sequential analysis