Review Article

Intraoperative goal-directed fluid therapy in neurosurgical patients: A systematic review

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ABSTRACT

Background: Perioperative fluid management is critical in neurosurgery as over perfusion can lead to brain edema whereas under perfusion may lead to brain hypoperfusion or ischemia. We aimed to determine the effectiveness of intraoperative goal-directed fluid therapy (GDFT) in patients undergoing intracranial surgeries.

Methods: We searched MEDLINE, Cochrane, and PubMed databases and forward-backward citations for studies published between database inception and February 22, 2024. Randomized controlled trials where intraoperative GDFT was performed in neurosurgery and compared to the conventional regime were included in the study. GDFT was compared with the conventional regime as per primary outcomes – total intraoperative fluid requirement, serum lactate, hemodynamics, brain relaxation, urine output, serum biochemistry, and secondary outcomes – intensive care unit and hospital length of stay. The quality of evidence was assessed with the Cochrane risk of bias tool. This study is registered on PROSPERO (CRD42024518816).

Results: Of 75 records identified, eight were eligible, the majority of which had a low to moderate risk of overall bias. In four studies, more fluid was given in the control group. No difference in postoperative lactate values was noted in 50% of studies. In the remaining 50%, lactate was more in the control group. Three out of four studies did not find any significant difference in the incidence of intraoperative hypotension, and four out of six studies did not find a significant difference in vasopressor requirement. The majority of studies did not show significant differences in urine output, brain relaxation, and length of stay between both groups. None found any difference in acid base status or electrolyte levels.

Conclusion: GDFT, when compared to the conventional regime in neurosurgery, showed that the total volume of fluids administered was lesser in the GDFT group with no increase in serum lactate. There was no difference in the hemodynamics, urine output, brain relaxation, urine output, length of stay, and biochemical parameters.

Keywords: Fluid management, Goal-directed fluid therapy, Neuroanesthesia, Neurosurgery

INTRODUCTION

Optimal fluid administration during the intraoperative period is a vital component in the management of surgical patients. Hypovolemia, on the one hand, can lead to inadequate organ perfusion. Whereas, hypervolemia can cause interstitial edema, decreased tissue healing, local inflammation, increased wound infection, and wound dehiscence.[14] A change in fluid

management strategy introduced alone on the day of surgery itself is shown to reduce perioperative complications by 50%.[14] A wide variety of intraoperative fluid administration practices are being followed, but the three major strategies of fluid management can be divided into "restricted," "liberal," and "goal-directed."[1] Goal-directed fluid therapy (GDFT) can be defined as the technique aimed at achieving maximum tissue oxygen delivery by titrating fluids, vasopressors, or inotropes to a predefined physiological target hemodynamic value.[25] There are emerging evidences that show the advantages of GDFT in terms of decreased complication rate, morbidity, and mortality, especially in major surgery.[5,6,21] In spite of the favorable evidence, GDFT is still not widely implemented in routine clinical practice.[25] In most neurosurgical procedures, fluid management can be affected by various factors, such as major fluid shifts, the use of osmotic diuretics, and prolonged surgical duration. A low fluid input can lead to decreased cerebral perfusion and excessive fluid can result in cerebral edema.[10] Studies have been done to assess the effect of GDFT in the neurosurgical patient population, targeting various parameters such as pulse pressure variation (PPV), stroke volume variation (SVV), and cardiac index (CI) with variable results.[10,12,16] Hence, this systematic review was conducted with the objective of determining the effectiveness of intraoperative GDFT in patients undergoing intracranial surgeries.

MATERIALS AND METHODS

The current systematic review was conducted as per the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement.[20] The review was registered in the International Prospective Register of Systematic Reviews (PROSPERO; CRD42024518816).

Objective

The objective of this study was to determine the effectiveness of intraoperative GDFT in patients undergoing intracranial surgeries with regard to the following outcome variables:

Primary outcomes

1. Total intraoperative fluid requirement
2. Serum lactate levels
3. Intraoperative hemodynamics – Total number of hypotensive episodes, total vasopressor requirement
4. Brain relaxation
5. Urine output
6. Serum biochemistry – pH, serum electrolytes

Secondary outcomes

1. Intensive care unit (ICU) and hospital length of stay.

Study selection criteria

Patient groups

Adult patients (over 18 years) undergoing elective or emergency craniotomy surgery were included in the study. The studies were not limited in terms of the type or location of the intracranial pathology.

Intervention and comparison

The patient participants had to be randomly assigned to either receive GDFT or conventional fluid management intraoperatively. We defined intraoperative GDFT as any fluid administration guided by continuously measured hemodynamic variables targeted to maximize tissue perfusion and oxygen delivery. These hemodynamic variables included cardiac output, stroke volume, SVV, PPV, or other factors, as measured by any device. Studies in which the control group also received any other form of GDFT were excluded from the study. Conventional fluid management was considered in the form of protocol-driven standard care, for example, maintaining mean arterial pressure > 65 mmHg or central venous pressure (CVP) >8 mmHg or care at the discretion of the attending physicians.

Types of studies

Randomized controlled trials (RCTs) where intraoperative GDFT was performed in adult patients scheduled for intracranial surgery. Non-randomized trials, cohort studies, retrospective studies, animal model trials, studies with incomplete text, and studies in languages other than English were excluded from the study.

Search strategies and data collection

The literature search was conducted on PubMed, MEDLINE, and Science Direct. Keywords for database search included the terms "goal-directed fluid neurosurgery." The last search was done on February 22, 2024. Independent reviewers screened the articles for titles and abstracts. Studies were "included" if the selection criteria were met. In case of doubt, if any, they were resolved by the other author. Full-text articles were retrieved. The final inclusion of any study was based on full-text reading. Two review authors independently extracted data from the included studies, and a third review author rechecked the data. The reference lists were scanned, and any relevant citations were identified and included for analysis. A spreadsheet-based data extraction form was used to collect study information. We extracted the following study characteristics:

1. General information: Year of study
2. Methods: Study design, randomization method, and blinding method

3. Participants: Total number (*n*), age range, types of surgery, comorbidities, inclusion criteria, and exclusion criteria
4. Interventions: Intervention, comparison, medications, or interventions excluded
5. Outcomes: Primary and secondary outcomes specified and collected
6. Notes: Funding for study and conflicts of interest of study authors.

As only qualitative analysis of available data was planned, alternative data synthesis methods and meta-analyses were not considered.

Risk of bias assessment

The risk of bias and the certainty assessment were done by risk of bias-2 by two review authors.[26] Disagreements were resolved by discussion or by consultation with another review author. We assessed the risks of bias according to the following domains:
1. Random sequence generation
2. Allocation concealment
3. Blinding of participants and personnel
4. Blinding of outcome assessment
5. Incomplete outcome data
6. Selective outcome reporting
7. Other potential bias

Studies were considered to be at low risk of bias if they adequately met the first five criteria with no evidence of significant selective reporting bias or any other major sources of bias.

RESULTS

Literature search and study selection

PubMED, Science Direct and Cochrane search initially retrieved 75 citations with 7 RCTs meeting the inclusion criteria [PRISMA Flowchart, Figure 1].[8,10,12,16,18,24,27] From the list of references, one study was deemed suitable and was added to the final pool of studies for review.[29] Hence, the final number of studies included was *n* = 8. (572 patients).

The studies included in this review were heterogeneous and varied in design [Table 1]. As the studies were heterogeneous, statistical pooling and meta-analysis were not possible. Narrative synthesis by making a qualitative summary of available data was performed on 8 RCTs.

Baseline characteristics of included RCTs

The salient baseline characteristics of included RCTs are shown in Table 1a. The patient population in all the studies included adults except Sae-Phua *et al.*, who conducted a study in elderly patients aged >60 years.[24] The majority of the patients in all the trials belonged to the American Society of Anesthesiologists, physical status I–II. In seven studies, only elective surgeries were included from the study. The nature of surgery, whether elective or emergency, was not mentioned by Sundaram *et al.*[27] Only supratentorial lesions were included in four studies.[8,10,18,29] Two studies included both supra- and infratentorial lesions.[24,27] The data regarding the intracranial location of the lesion were not mentioned by Luo and Hrdy *et al.*[12,16] Only intracranial tumors were included by five authors.[8,10,18,27,29] Two studies incorporated both tumors and aneurysms in their studies.[16,24] The type of intracranial pathology was not specified by Hrdy *et al.*[12]

As per the risk of bias assessment tool, the overall score was two for three studies,[12,24,27] three for three studies,[8,10,18] four for one study,[16] and six for one study[29] [Table 1b]. Blinding of participant and personnel was mentioned only by Gopal *et al.*[8]

Three (37.5%) studies considered PPV as the therapeutic goal for GDFT.[8,10,27] The remaining 5 (62.5%) studies used SVV to guide GDFT.[12,16,18,24,29] The therapeutic values were obtained using an invasive arterial line in all the studies except by Hrdy *et al.*, who utilized a non-invasive hemodynamic system.[12] In all eight studies, a fluid bolus was given as the first line of intervention in the GDFT group, with crystalloid bolus given in 4 (50%) studies[8,10,24,27] and colloid bolus in 4 (50%) studies.[12,16,18,29] The specific hemodynamic monitoring technique used was the GE solar 8000M/I monitor by Hasanin *et al.*[10] Four authors used the Flotrac Vigileo monitor[16,18,24,29] A non-invasive (Starling SV hemodynamic monitor, Cheetah Medical Inc., 600SE Maritime Ave Suite 220, Vancouver, WA, USA) was utilized in only 1 study by Hrdy *et al.*[10] Sundaram *et al.* used the Philips Intellivue MP50 monitor.[27] The hemodynamic monitoring technique was not mentioned by Gopal *et al.*[8] The hemodynamic target for GDFT was variable, with three studies considering PPV of <13%,[8,10,27] two studies considering CI >2.5 L/min/m^2, SVV <15%,[12,16] and three studies targeting CI >2.5 L/min/m^2, SVV<12%.[18,24,29]

Primary outcomes

Total intraoperative fluid requirement

The total intraoperative fluid requirement was significantly higher in the control group in 3 (37.5%) studies [Table 2].[8,16,24] However, in 2 (25%) studies, more fluid was received by the intervention (GDFT) group.[10,29] Mishra *et al.* found that the total crystalloids infused were higher in the control group, but the amount of total fluid and total colloid were comparable.[18] Hrdy *et al.* observed that the GDFT group received significantly less crystalloid but more colloid than the control group.[12] Sundaram *et al.* found that the GDFT

Identification of studies via databases and registers
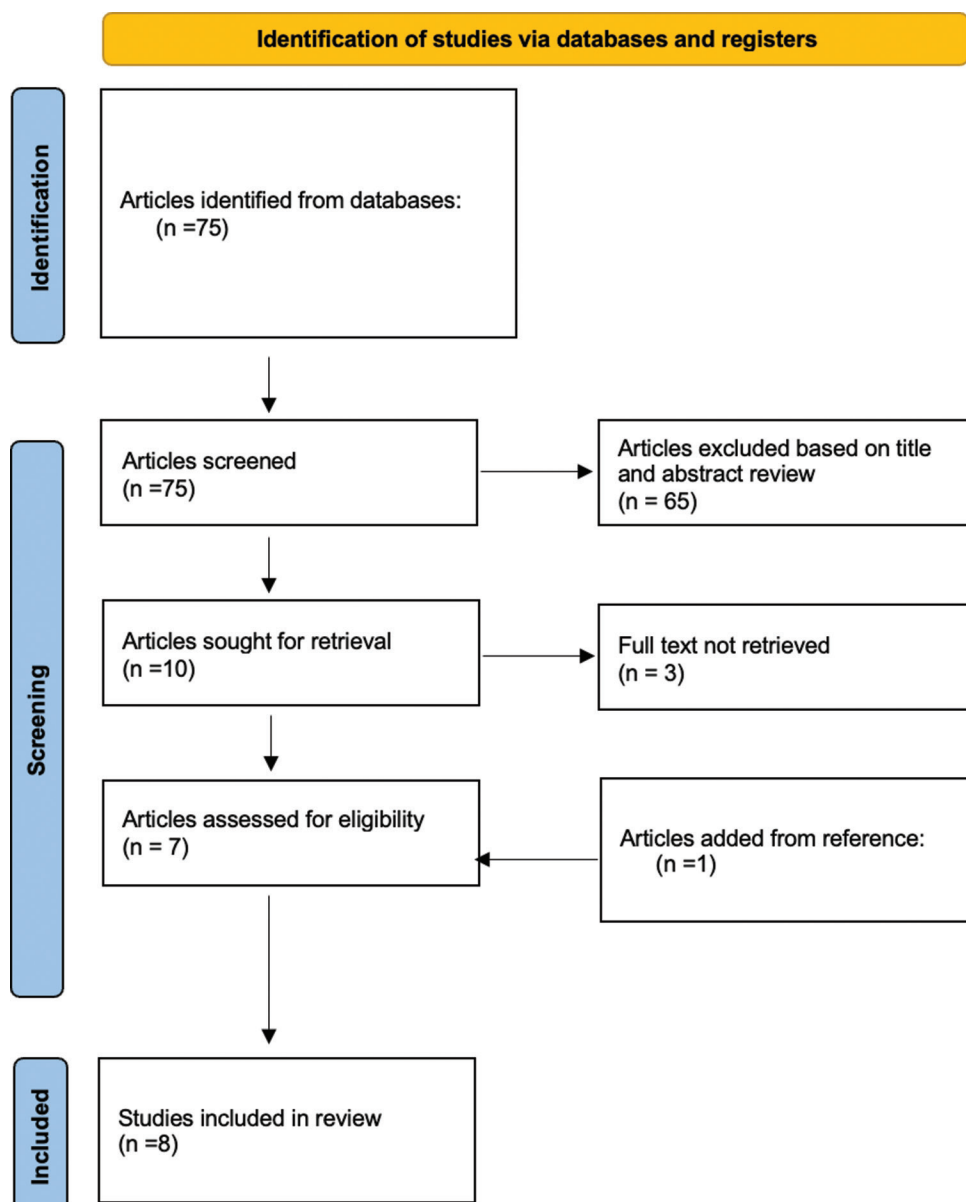
Figure 1: PRISMA flow chart depicting the study selection process. PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

group received more crystalloids but similar colloids as compared to the control group.[27]

Serum lactate levels

Serum lactate levels at the end of surgery were significantly higher in the control group than in the GDFT group in 4 (50%) studies [Table 2].[10,16,18,29] Gopal *et al*. and Sundaram *et al*. observed the baseline, postoperative, and rise in serum lactate levels. Both studies found no significant difference in lactate levels at all-time points.[8,27] Similarly, 2 (25%) studies also found no statistical difference in the postoperative lactate levels between both groups.[12,24]

Intraoperative hemodynamics

Four authors mentioned the incidence of intraoperative hypotension [Table 3].[8,12,18,24] Gopal *et al*. found that the incidence of intraoperative hypotension was more in the group receiving CVP-guided fluids.[8] Whereas, the rest three studies did not find any significant difference in the incidence of hypotension between both the groups.[12,18,24] The vasopressor requirement was noted in six studies.[8,10,12,16,24,29] Of which 4 (50%) studies noticed no significant difference in the vasopressor requirement between both groups.[8,10,12,29] Luo *et al*. found that the number of patients requiring metaraminol and

Table 1a: PICO characteristics of included trials.

Study	Year	Patients	Intervention	Comparator	Outcome	Study design
Gopal *et al.*[8]	2023	ASA I–II, aged 18–60 years, undergoing elective supratentorial tumor surgery; supine position	PPV guided fluid therapy (*n*=36)	CVP-guided fluid therapy (*n*=36)	Primary outcome • Intraoperative fluid requirement • Secondary outcome • Intraoperative hypotension • S. lactate • BRS • Conjunctival and periorbital edema • PONV	RCT
Hasanin *et al.*[10]	2019	Adult patients >18 years for supratentorial mass excision, ASA I–II	PPV-guided fluid therapy (*n*=31)	Standard fluid management (*n*=30)	Primary outcome • Brain relaxation scale • Other outcomes • Demographics • Intraoperative fluid requirements • Patient positioning • Arterial-jugular O_2 saturation difference • Arterial-Jugular lactate difference • Urine output • Vital signs (heart rate and MAP) • ABGs • Intraoperative ephedrine consumption • Postoperative electrolytes (Na, K, Mg, and Ca); serum lactate; 24-h urine output; hemoglobin • Length of hospital stay	RCT

Luo *et al.*[16]	2017	Elective craniotomy for brain tumor resection, brain abscess, or intracranial aneurysm, age >18, ASA score III or IV, and expected duration of surgery >2 h	GDFR group – CI, SVV-guided fluid therapy (*n*=730	Control group – fluid therapy at the discretion of the attending anesthesiologist and intensivist (*n*=72)	Primary outcome-ICU LOS
					Secondary outcome
					• Lactates at the end of surgery
					  • Postoperative complications at day 30; morbidity and mortality at day 30
					  • hospital LOS, and costs
						RCT

Mishra *et al.*[18]	2022	ASA status I–II, 18–65 years, with large supratentorial tumors (tumor size≥4 cm in at least one dimension) undergoing elective craniotomy and excision	GDFT group- SVV, CI guided fluid therapy (*n*=20)	Control group – fluid therapy based on routine hemodynamic monitoring: MAP, CVP, and urinary output (*n*=20)	Primary objective- duration of hospital stay Secondary objectives- • The volume of fluid used • Perioperative complications • Requirement of inotropes	RCT
Hrdy *et al.*[12]	2023	Age≥18 years, expected duration of surgery≥2 h, and ASA categories 1–3 scheduled for elective neurosurgery	GDHT group- non-invasive hemodynamic monitoring (PPV) guided (*n*=17)	Control group-standard therapy (*n*=17)	• Hospital and ICU LOS • 28-day mortality • Incidence of adverse events • Brain tissue relaxation • Amounts of infused crystalloids, colloids, transfusions, blood loss during	RCT

(Contd...)

Table 1a: *(Continued).*

Study	Year	Patients	Intervention	Comparator	Outcome	Study design
Sae-Phua *et al.*[24]	2023	Age≥60 years, ASA status 2–3, and scheduled for elective craniotomy with a surgical duration >2 h	GDT group – SVV guided (*n*=50)	Conventional group – fluid therapy at the discretion of the attending anesthesiologist (*n*=50)	• Number of patients with hypotensive episodes (MA*P*<65 torr) and vasoactive drug intervention • Urine output • Serum hemoglobin and lactate levels • 24 h after surgery • Postoperative complications • ICU and hospital LOS • Total fluid intake • Urine output, blood loss • Ephedrine consumption • BRS • Lactate levels • Postoperative fluid balance, complications, and mortality rate	RCT
Sundaram *et al.*[27]	2016	Age group 20–80; ASA grade 1 and 2, planned for excision of supra and infratentorial tumors	PPV guided (*n*=28)	CVP guided (*n*=29)	• Fall in BP from the baseline and severity of hypotension • Lactate levels • Acid base status	RCT
Wu *et al.*[29]	2017	ASA status I or II undergoing supratentorial neoplasms (meningioma, glioma, or metastatic tumor) surgery	APCO group-SVV, CI guided (*n*=33)	Control group-CVP, MAP guided (*n*=30)	• Intraoperative measurements • Infused total fluid volumes • Urine output • Blood loss • Plasma lactate, pH, glucose, and BE • Creatinine, urea • Usage of vasoactive agents • Postoperative data • Incidents of complications • Length of postoperative hospitalization and ICU stay • Hemodynamic parameters, intravenous fluids, and blood product amounts administered in the first 24 h	RCT

BE Base excess, ICU: Intensive care unit, ASA: American Society of Anesthesiologists, RCT: Randomized controlled trials, CVP: Central venous pressure, MAP: Mean arterial pressure, PPV: Pulse pressure variation, SVV: Stroke volume variation, CI: Cardiac index, LOS: Length of stay, BRS: Brain relaxation score, LOS: Length of stay, GDT: Goal-directed therapy, Na: Sodium, K: Potassium, Mg: Magnesium, Ca: Calcium, O_2: Oxygen. PICO: population intervention comparator outcome, GDFR: goal directed fluid restriction, GDHT: goal directed hemodynamic therapy, PONV: post operative nausea vomiting, APCO: arterial pressure continuous output)

Table 1b: Risk of bias assessments for randomized control trials using RoB-2.

Study	Sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective outcome reporting	Other sources of bias (funding, COI)	Overall score
Gopal *et al.*[8]	0	0	0	2	0	0	1	3
Hasanin *et al.*[10]	0	0	1	2	0	0	0	3
Luo *et al.*[16]	0	0	2	2	0	0	0	4
Mishra *et al.*[18]	0	2	1	0	0	0	0	3
Hrdy *et al.*[12]	0	0	1	1	0	0	0	2
Sae-Phua *et al.*[24]	0	0	1	0	0	1	0	2
Sundaram *et al.*[27]	0	0	1	1	0	0	0	2
Wu *et al.*[29]	2	1	2	1	0	0	0	6

RoB-2=The Cochrane risk-of-bias tool for randomized trials version 2: 0-Low risk of bias; 1-Uncertain risk of bias; 2-High risk of bias. RoB-2: Risk of Bias-2, COI: conflicts of interest

Table 2: Primary outcomes.

Outcome	Study	Intervention group	Control group	Conclusion	Significance
Total intraoperative fluid requirement	Gopal *et al.*[8]	PPV group 3540±740 mL	CVP group 4340±1010 mL	The CVP group had higher intraoperative fluid-infused	Statistically significant (*P*<0.01)
	Hasanin *et al.*[10]	PPV group 3155±452 mL	Control group 2790±443 mL	The GDT group had higher total fluid consumption	Statistically significant (*P*=0.002)
	Luo *et al.*[16]	GDFR group Colloid: 1.9±1.1 mL/kg/h Crystalloid 3±0 mL/kg/h	Control group Colloid: 3.9±1.6 mL/kg/h	The GDFR group received less colloid and crystalloid	Statistically significant for both (*P*<0.001)
	Mishra *et al.*[18]	GDFT group Total fluids 4.6±1.3 L Crystalloids 3.7±0.9 L Colloids 0.89±0.4L	Control group Total fluids 5.7±1.6 L Crystalloids 5±1.44 L Colloids 0.65±0.25 L	The control group received higher total intraoperative fluids	Not statistically significant for total fluids (*P*=0.024) and colloids (*P*=0.03) infused; statistically significant for the total crystalloids (*P*=0.002)
	Hrdy *et al.*[12]	GDFT group Crystalloids 1288±591.22 mL Colloids 471±522.03 mL	Control group Crystalloids 1935±648.98 mL Colloids 88±196.48 mL	The GFT group received lesser crystalloids but more colloid	Differences between crystalloid and colloid administration both are statistically significant (*P*=0.001 and *P*=0.015)
	Sae-Phua *et al.*[24]	GDT group Crystalloid 1311.5±823 mL	Control group Crystalloid 2080±1420 mL	The GDT group received lesser fluids	Statistically significant (*P*<0.001)
	Sundaram *et al* [27]	PPV group Crystalloids 2250 mL (1500, 3000) Colloid 500 mL (250,1000)	Control group Crystalloids 1500 mL (1200, 2000) Colloid 500 mL (500, 500)	The PPV group received more crystalloids, but the amount of colloid infused was similar.	The difference between crystalloids was statistically significant (*P*=0.002), but for colloids not significant.
	Wu *et al.*[29]	APCO Group 1478±312 mL	Control group 1183±294mL	Total fluid volume in the APCO group was significantly higher	Statistically significant (*P*<0.001)
Serum lactate levels	Gopal | *et al.*[8]	Baseline- 11.97±5.22 mg/dL At the end of surgery- 16.74±7.66 mg/dL Rise- 42.92±6.79%	Baseline- 11.61±4.90 mg/dL At the end of surgery- 17.69±8.90 mg/dL Rise- 63.0±9.97%	No significant difference was found in serum lactate levels at any point	No statistically significant difference at baseline, at the end of surgery, and at the percentage rise. (*P*=0.77, *P*=0.61 and *P*=0.09 respectively)
	Hasanin *et al.*[10]	At the end of surgery- 2.5±1.1 mmol/L	At the end of surgery- 0.9±1	The GDT group had lower serum lactate postoperatively	Statistically significant (*P*=0.03)
	Luo *et al.*[16]	At the end of surgery- 1.79±0.85 mmol/L	At the end of surgery- 2.23±1.36 mmol/L	At the end of the surgical procedure, lactates were lower in the GDFR group.	Statistically significant (*P*=0.003)

(Contd...)

Table 2: *(Continued).*

Outcome	Study	Intervention group	Control group	Conclusion	Significance
	Mishra *et al.*[18]	Baseline- 0.67±0.24 mmol/L At the end of surgery- 4.1±1.1 mmol/L	Baseline- 0.81±0.33 mmol/L At the end of surgery- 5.1±1.2 mmol/L	Lactate levels at the end of surgery were lower in the GDFT group	Statistically significant (*P*=0.018)
	Hrdy *et al.*[12]	At the end of surgery- 1.5±0.92 mmol/L	At the end of surgery- 2.1±0.92 mmol/L	Postoperative lactate levels were similar	Not statistically significant (*P*=0.407)
	Sae-Phua *et al.*[24]	Baseline- 1.6±0.79 mmol/L At the end of surgery- 2.46±1.37 mmol/L	Baseline- 1.59±0.74 mmol/L At the end of surgery- 2.31±1.33 mmol/L	No significant differences in lactate levels	Not statistically significant for both baseline and postoperative lactates (*P*=0.990 and 0.597, respectively)
	Sundaram *et al.*[27]	Baseline- 2.40±1.65 mmol/L At the end of surgery- 3.83±1.84 mmol/L Rise-range of−0.6 to 5.1 mmol/L with a median of 1.7	Baseline- 1.95±0.67 mmol/L At the end of surgery- 5.49±10.17 mmol/L Rise-range of−0.3 to 4.9 mmol/L with a median of 1.4	The intra-operative change in lactate in both groups was similar	Not statistically significant (*P*=0.992)
	Wu *et al.*[29]	Baseline- 1.26±0.48 mmol/L At the end of surgery- 0.91±0.25 mmol/L	Baseline- 1.33±0.63 mmol/L At the end of surgery- 1.31±0.46 mmol/L	Lactate concentration by the end of the operation in the GDFT group was much lower.	Statistically significant (*P*<0.001)
Intraoperative hemodynamics	Gopal *et al.*[8]	Incidence of intraoperative hypotension- 0 (0) % Vasopressor/inotrope requirement- 0 (0) %	Incidence of intraoperative hypotension- 4 (11.1) % Vasopressor requirement- 1 (2.8) %	incidence of intraoperative hypotension was higher in the CVP group; the requirement for vasopressors among groups was similar	The difference in intraoperative hypotension was statistically significant (*P*=0.04) but not for vasopressor requirement (*P*=0.31)
	Hasanin *et al.*[10]	Vasopressor/inotrope requirement- 0 (0.1)	Vasopressor/inotrope requirement- 0 (0.1)	No significant differences between both groups in vasopressor bolus required	Not statistically significant (*P*=0.093)
	Luo *et al.*[16]	Number of patients requiring: metaraminol- 39, ephedrine- 40, dopamine- 5, dobutamine- 1, norepinephrine- 3	Number of patients requiring: metaraminol- 18, ephedrine- 21, dopamine- 3, dobutamine- 0, norepinephrine- 3	The number of patients requiring metaraminol and ephedrine was more in the GDFT group.	Statistically significant for metaraminol (*P*<0.001) and ephedrine (*P*<0.001) but not for other agents
	Mishra *et al.*[18]	Incidence of intraoperative hypotension- 2 patients	Incidence of intraoperative hypotension- 1 patient	No difference in the incidence of hypotension	Not statistically significant (*P*=0.61)
	Hrdy *et al.*[12]	Incidence of intraoperative hypotension- 7±41.2	Incidence of intraoperative hypotension- 6±35.3 Vasopressor/inotrope	No difference in the incidence of hypotension and	Not statistically significant for hypotension (*P*=0.628) and vasoactive drugs (*P*=0.724)

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Table 2: *(Continued).*

Outcome	Study	Intervention group	Control group	Conclusion	Significance
	Sae-Phua *et al.*[24]	Vasopressor/inotrope requirement- 7±41.2 Incidence of intraoperative hypotension- 1 (0, 3) Vasopressor/inotrope requirement- Ephedrine 18 (36%) Norepinephrine 15 (30%)	requirement- 4±23.5 Incidence of intraoperative hypotension- 2 (0, 5) Vasopressor/inotrope requirement- Ephedrine 28 (56%) Norepinephrine 12 (24%)	vasopressor requirement The GDT group received significantly less ephedrine	Statistically significant for ephedrine consumption (*P*=0.045) but not for hypotensive episodes (*P*=0.144) or norepinephrine requirement (*P*=0.499)
	Sundaram *et al.*[27]	Lowest systolic BP (mm Hg) 80.40- (11.19) Lowest diastolic BP (mm Hg)- 45 (7.14)	Lowest systolic BP (mm Hg)- 79.14 (8.10) Lowest diastolic BP (mm Hg)- 46.76 (9.33	The fall in BP (>20% from baseline) and heart rate between the groups were comparable.	Not statistically significant for both lowest systolic (*P*=0.63) and diastolic pressure (*P*=0.43)
	Wu *et al.*[29]	Vasopressor/inotrope requirement- 0 [0, 1]	Vasopressor/inotrope requirement- 1 [1, 2]	Vasopressor/ inotrope requirement similar	Not statistically significant (*P*=0.502)
Brain relaxation	Gopal *et al.*[8]	BRS (1:2:3:4)- 3:32:0:1	BRS (1:2:3:4)- 2:32:2:0	BRS was comparable among groups	Not statistically significant (*P*=0.36)
	Hasanin *et al.*[10]	BRS (1: 2: 3)- 1.54: 1.8: 1.58	BRS (1: 2: 3)- 1.8: 1.9: 1.7	No difference in BRS	Not statistically significant (*P*=0.15, 0.66, and 0.34 for BRS 1, 2, and 3, respectively)
	Luo *et al.*[16]	-	-	-	-
	Mishra *et al.*[18]	BRS (1:2:3:4)- 9:7:3:1	BRS (1:2:3:4)- 3:5:3:9	The occurrence of tight brain was higher in the control group	Statistically significant (*P*=0.005)
	Hrdy *et al.*[12]	Patients with brain edema requiring intervention- 0	Patients with brain edema requiring intervention- 0	No incidence of brain edema	Not significant`
	Sae-Phua *et al.*[24]	BRS (1:2:3:4)- 37:10:3:0	BRS (1:2:3:4)- 29:12:7:2	BRS found comparable	Not statistically different (*P*=0.191)
	Sundaram *et al.*[27]	-	-	-	-
	Wu *et al.*[29]	Degree of brain edema- 3 [2, 4]	Degree of brain edema- 3 [2, 4]	No difference in the degree of brain edema	Not statistically different (*P*=0.960)
Urine output	Gopal *et al.*[8]	1,008.13±477.59 mL	1,283.75±783.51 mL	The CVP group had greater urine output	Statistically significant (*P*=0.04)
	Hasanin *et al.*[10]	2019 (449) mL	1410 (382) mL	Higher urine output in the GDT group	Statistically significant (*P*<0.001)
	Luo *et al.*[16]	Diuresis (mL/kg/h) at the end of surgery 4.12±1.39	Diuresis (mL/kg/h) at the end of surgery 4.12±1.39	No difference in both groups	Not significant

(Contd...)

Table 2: *(Continued).*

Outcome	Study	Intervention group	Control group	Conclusion	Significance
	Mishra *et al.*[18]	1780 mL	1920 mL	No difference in both groups	Not statistically significant (*P*=0.67)
	Hrdy *et al.*[12]	2041±605.50 mL	2191±775.45 mL	No difference in both groups	Not statistically significant (*P*=0.603)
	Sae-Phua *et al.*[24]	700 (460, 1005) mL	877.5 (620, 1200) mL	No difference in both groups	Not statistically significant (*P*=0.069)
	Sundaram *et al.*[27]	-	-	-	-
	Wu *et al.*[29]	774±351 mL	804±394 mL	No difference in both groups	Not statistically significant (*P*=0.752)
Serum biochemistry	Gopal *et al.*[8]	-	-	-	-
	Hasanin *et al.*[10]	pH 7.39 (0.06)	pH 7.38 (0.09)	No difference in postoperative pH	Not statistically significant (*P*=0.56)
	Luo *et al.*[16]	Sodium (mmol/L) 137.3±4.5	Sodium (mmol/L) 137.5±5.1	No difference in sodium levels at the end of surgery	Not statistically significant (*P*=0.84)
	Mishra *et al.*[18]	0 electrolyte abnormalities	0 electrolyte abnormalities	No episode of electrolyte imbalances	
	Hrdy *et al.*[12]	-	-	-	-
	Sae-Phua *et al.*[24]	pH 7.43±0.06 HCO3 22.14±1.73 BE −2.46±1.9	pH 7.41±0.04 HCO3 21.58±1.92 BE −3.26±2.33	No difference in pH, bicarbonate levels, and BE	Not statistically significant for pH (*P*=0.058), bicarbonate levels (*P*=0.226) and BE (*P*=0.061)
	Sundaram *et al.*[27]	pH 7.36 (.05) HCO$_3$ 22.12 (3.09) BE −2.89 (3.41) Sodium (mmol/L) 138.18 (3.56) Potassium (mmol/L) 3.85 (0.38) Calcium (mmol/L) 1.023 (0.09) Chloride (mmol/L) 113.31 (2.89)	pH 7.38 (.05) HCO$_3$ 22.73 (2.52) BE −1.63 (3.82) Sodium (mmol/L) 137.45 (3.73) Potassium (mmol/L) 3.84 (0.45) Calcium (mmol/L) 1.01 (0.14) Chloride (mmol/L) 111.93 (2.98)	Acid base status in both groups was comparable postoperatively	Not statistically significant for pH (*P*=0.23), bicarbonate (*P*=0.42), BE (*P*=0.20), sodium (*P*=0.45), potassium (*P*=0.94), calcium (*P*=0.80), and chloride (*P*=0.20) levels
	Wu *et al.*[29]	pH 7.38±0.04 BE (mmol/L) -0.22±1.76	pH 7.38±0.03 BE (mmol/L) -0.51±1.61	No difference between both groups	

CVP: Central venous pressure, BE: Base excess, GDFR: Goal-directed fluid restriction, GDFT: Goal directed fluid therapy, BRS: Brain relaxation score, BP: Blood pressure, PPV: Pulse pressure variation, GDT: Goal-directed therapy, GFT: goal directed fluid therapy, APCO: arterial pressure continuous output, HCO3: bicarbonate ion

ephedrine was significantly higher in the GDFT group.[16] However, Sae-Phua *et al.* observed that the GDFT group received significantly less ephedrine than the control group.[24] Sundaram *et al.* studied the fall in BP (>20% from baseline) and heart rate between the groups and found them to be comparable among both groups.[27]

Brain relaxation

Six out of eight studies studied brain relaxation in both groups [Table 2].[8,10,12,18,24,29] In only one out of the six studies, it was found that the occurrence of tight brain was higher in the control group, with the brain relaxation score (BRS) being significantly higher in the control population.[18] The

Table 3: Secondary outcomes.

Outcome	Study	Intervention group	Control group	Conclusion	Significance
LOS	Gopal *et al.*[8]	-	-	-	-
	Hasanin *et al.*[10]	ICU stay- 2.1 (1.2) days Hospital stay- 5.2 (1.3) days	ICU stay- 2.1 (1.3) days Hospital stay- 5.7 (1.5)	Postoperative ICU and hospital stay were comparable between both groups	Not statistically significant for both ICU stay (*P*=0.93) Hospital stay (*P*=0,13)
	Luo *et al.*[16]	ICU stay 3 (1–5) days Hospital stay 15 (7–23) day ICU costs 1776±459 $	ICU stay 6 (3–11) Hospital stay 17 (9–27) ICU cost 3080±700 $	ICU LOS was significantly shorter in the GDFR group Median hospital LOS was decreased by 2 days in the GDFR group ICU cost lesser in the GDFR group	Statistically significant for ICU stay (*P*=0.001), ICU cost (*P*=0.037) and not statistically significant for hospital stay (*P*=0.069)
	Mishra *et al.*[18]	ICU stay 1.5±2.3 days Hospital stay 5.0±3 days	ICU stay 3.7±6.0 days Hospital stay 8.0±1.6 days	The duration of ICU and hospital stay was slightly lower in the GDFT group	Not statistically significant for ICU (*P*=0.06) and hospital stay (*P*=0.16) both
	Hrdy *et al.*[12]	ICU stays 7±9.9 days Hospital stay 14±6.5	ICU stays 8±9.6 days Hospital stay 15±8.5	The ICU LOS and hospital LOS were similar between groups	Not statistically significant for ICU (*P*=0.569) and hospital stay (*P*=0.976) both
	Sae-Phua *et al.*[24]	ICU stay 14 (12, 16.75) h Hospital stay 7 (6, 10)	ICU stay 15 (13, 18) h Hospital stay 8 (6, 11)	Postoperative ICU and hospital stay were comparable between both groups	Not statistically significant for ICU (*P*=0.116) and hospital stay (*P*=0.582) both
	Sundaram *et al.*[27]	-	-	-	-
	Wu *et al.* [29]	ICU stay 15.1±8.1 h Hospital stay 10.4±3.9 d	ICU stay 18.0±5.5 h Hospital stay 12.2±5.1 d	No significant differences in postoperatively hospitalized days and ICU stay between the two groups.	Not statistically significant for ICU (*P*=0.126) and hospital stay (*P*=0.100)

ICU: Intensive care unit, GDFR: Goal-directed fluid restriction, GDFT: Goal directed fluid therapy, LOS: Length of stay

BRS was comparable between both groups in three studies.[8,10,24] Hrdy *et al.* noted the patients with brain edema requiring intervention and found no incidence of brain edema in any group.[12] Similarly, the degree of brain edema was comparable in both groups in the study by Wu *et al.*[29]

Urine output

Seven out of eight studies noted the urine output of patients [Table 2].[8,10,12,16,18,24,29] The urine output was similar between both groups in five studies.[12,16,18,24,29] In only one study, it was found that the urine output was significantly higher in the control group.[8] Whereas Hasanin *et al.* found that the urine output was more in the GDFT group.[10]

Serum biochemistry

Six out of eight studies examined the serum biochemical parameters, that is, pH and electrolytes [Table 2].[10,16,18,24,27,29]

None of the studies found any difference in the acid-base status or electrolyte levels between the groups.

Secondary outcomes

ICU and hospital length of stay

Six out of eight studies examined the ICU and hospital length of stay of patients [Table 3].[10,12,16,18,24,29] Only one study found that the ICU length of stay and the ICU costs were more in the control group.[16] The rest of the studies found no significant difference in the ICU and hospital length of stay between both groups.[10,12,18,24,29]

DISCUSSION

This systematic review included eight RCTs comparing GDFT with conventional regimes for intraoperative fluid administration in neurosurgery with a total of 572 patients.

It was found that in the majority of studies that compared the total intraoperative fluid administration, more fluid was given in the control group. The postoperative serum lactate values were similar between both groups in 50% of the studies. Whereas in the remaining half studies, it was found to be more in the control group. Regarding hemodynamics, the majority of studies did not find any significant difference in the incidence of intraoperative hypotension and vasopressor requirement in both groups. Similarly, in a greater number of studies, there was no significant difference in the urine output, brain relaxation, and length of stay between both groups. None of the studies found any difference in the acid-base status or electrolyte levels between the groups.

The main aim of perioperative fluid management is to maintain an optimum cardiac output and tissue perfusion. GDFT utilizes certain hemodynamic targets such as PPV, SVV, and CI to identify the fluid responsiveness of patients. This helps in preventing fluid overload in patients and the deleterious effects such as pneumonia, respiratory failure, pulmonary edema, and delayed wound healing.[11] GDFT has been shown to be beneficial in studies.[13,15] In a meta-analysis of 6325 patients, Giglio *et al.*[7] analyzed the effect of GDFT on postoperative complications in different surgeries. They concluded that GDFT was beneficial in abdominal surgery, orthopedic surgery, and neurosurgery in terms of a decrease in postoperative complications.

Perioperative fluid management is critical in neurosurgery as over perfusion can lead to brain edema, whereas under perfusion may lead to brain hypoperfusion or ischemia. Other concerning points specific to neurosurgery are the use of osmotic diuretics, the significance of the type of fluid used, the probability of long duration surgeries, major fluid shifts, difficult assessment of blood loss under the drapes, intraoperative diabetes insipidus, and distinct type of surgeries such as vascular surgeries which require unique fluid management. Thus, it becomes essential to use a proper parameter to guide fluid management in neurosurgery. To date, only one meta-analysis has been done, which individually evaluated the effect of GDFT on neurosurgical patients.[7]

As per the results, it is seen that the majority of the authors found that the intraoperative fluid administration was higher in the group following the conventional fluid management strategy.[8,16,18,24] As per Gopal *et al.*, more fluid administration in the control group was attributed to the conventional method of calculating cumulative losses accounting for vasodilation during anesthetic induction, estimated blood loss, and urine output every hour.[8] In addition, 100 mL fluid boluses were given whenever CVP was <8 mmHg. Whereas in the GDFT group, conventional calculation of fluid administration was not used and only PPV-guided fluid bolus was given along with the maintenance fluid. In spite of receiving lesser total fluid by the GDFT group, in all the

above four studies, the lactate levels were not higher than in the control group which suggests that GDFT can maintain adequate organ perfusion with less fluid intake. Luo *et al.* also observed that the GDFT group did not develop any hypovolemia related complications such as acute kidney injury or myocardial injury.[16] Improved fluid balance could be beneficial in patients who are prone to fluid overload, such as patients with severely impaired cardiac or kidney function. In an RCT studying perioperative GDFT using noninvasive pleth variability index monitoring in gynecologic oncology surgery, it was observed that the amount of intraoperatively administered crystalloid solution was significantly lower in patients who received GDFT.[30] The authors also found a stable serum lactate concentration, reduced postoperative complications, and ICU admissions. However, the OPTIMISE trial, which evaluated the effectiveness of cardiac output-guided hemodynamic therapy in major gastrointestinal surgery, found no difference in the intravenous fluid volume infused in both the intervention and conventional groups.[21]

It was observed that the serum lactate levels were either similar or higher in the control group. It is noteworthy that in none of the studies the serum lactate was higher in the patients receiving GDFT. This point indicates that GDFT might be able to maintain adequate end organ perfusion. A retrospective cohort study demonstrated that elevated intraoperative serum lactate in craniotomy patients is associated with new neurological deficits and longer length of stay.[3] The authors suggested that in some cases, serum lactate may be an early marker of regional cerebral hypoperfusion. Perioperative lactate values from microdialysis catheters have shown the relation of lactate with neurological outcomes.[2] Whether the results from microdialysis studies can be extrapolated to serum lactate values which should be studied more.

In our review, we only included studies comparing GDFT versus conventional fluid management in neurosurgery. However, few other studies in the literature have compared two different methods of GDFT in neurosurgery. PPV or SVV constitute the dynamic variables for predicting fluid responsiveness with no fixed single cut off value. Both these parameters have a "gray zone" of two cutoffs within which the validity is inconclusive.[4] Wu *et al.* investigated GDFT protocols based on two SVV cut offs in the grey zone in supratentorial tumor resection.[28] The authors compared two cutoff values for SVV, that is, 10% and 18%. They found that the low SVV group (10%) received a higher volume of colloid, had a higher urine output, higher average cardiac index, shorter ICU stay, fewer postoperative neurological events, attenuated changes in the neuronal biomarker levels, lower intraoperative serum lactate, and a higher Barthel index at discharge. Overall, the authors concluded that fluid boluses targeting a lower SVV are more beneficial than a restrictive protocol.

Another RCT by Nayak *et al.* compared PPV with pleth variability index (PVI) in patients undergoing supratentorial lesion surgeries.[19] It was seen that Both PVI- and PPV-guided GDFT showed no significant difference in the postoperative lactate values, mean total fluid administered, mean blood loss, length of ICU stay, and emetic and hypotension episodes. Authors concluded that PVI is comparable to PPV to guide GDFT regarding tissue perfusion and postoperative complications. However, it was mentioned that both the parameters had low sensitivity and specificity as far as GDFT was concerned.

PPV and SVV both serve as a reliable dynamic parameter to assess fluid responsiveness provided that the physiological limitations are avoided.[17] Many of these limitations, such as atrial fibrillation, spontaneous breathing activity, and low tidal volume, are usually excluded in patients intraoperatively under general anesthesia. Unlike SVV, PPV monitoring has the practical advantage of the non-requirement of any extra cardiac output monitoring device. SVV and PPV have been shown to have comparable performance in predicting fluid responsiveness in patients undergoing major surgeries. PPV monitoring is cost-effective since the SVV transducer is more expensive. Furthermore, we are almost regularly putting an arterial line for invasive BP monitoring in neurosurgery. Hence, targeting PPV as a guide to monitor fluid administration intraoperatively can be proposed as a feasible option in neuroanesthesia.

Hrdy *et al.* utilized a non-invasive method of assessing stroke volume for GDFT.[12] The Starling SV monitor is completely non-invasive and is based on the principle of bio-impedance. Furthermore, it does not require any external calibration. As per the meta analysis by Peyton and Chong, bio-impedance-based methods can be compared to invasive monitors in terms of accuracy.[22] Thus, non-invasive cardiac output monitors can also prove to be useful as a tool for perioperative GDFT.

Luo *et al.* observed that in the GDFT group, the ICU expenses were significantly lower than in the conventional group.[16] The authors linked this reduction in expenses to the decreased length of ICU stay and lesser complications in the GDFT cohort. A cost-effectiveness analysis of the large scale OPTIMISE trial also found that perioperative cardiac output-guided hemodynamic therapy algorithm was associated with an average cost reduction of £400.[23] A similar reduction in total hospital cost in the GDFT group was reported by Hand *et al.* in cases of head and neck cancer.[9] These findings indicate that not only clinically, GDFT might help in reducing the economic burden.

However, our systematic review had few limitations. The study population was heterogeneous. Sae-Phua *et al.* included only elderly patients aged more than 60 years, unlike the rest of the studies.[24] The type of neurosurgical lesion also was not homogenous in all the studies which can have an impact on the outcomes parameters. Only qualitative analysis of the studies was done. No statistical meta-analysis was performed. The brain relaxation scores assessed can be subjective. Different authors also varied the approach and targets to achieve GDFT. Finally, all the included trials in our review were single centered.

The strength of our systematic review is that all the included studies were relatively new, that is, within the year 2016–2023. No other review has been done in the literature exclusively assessing GDFT in the neurosurgical patient population.

CONCLUSION

Perioperative optimal fluid management plays an important role in neurosurgical patients. GDFT, when compared to conventional regime in neurosurgery showed that the total volume of fluids administered was lesser in the GDFT group with no increase in serum lactate levels. However, there was no difference in the hemodynamics, urine output, brain relaxation, urine output, length of stay, and biochemical parameters. More large scale trials should be done with a homogeneous cohort to establish an optimal perioperative fluid management regime in neurosurgical patients.

Ethical approval

The Institutional Review Board approval is not required.

Declaration of patient consent

Patient's consent was not required as there are no patients in this study.

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Conflicts of interest

There are no conflicts of interest.

Use of artificial intelligence (AI)-assisted technology for manuscript preparation

The authors confirm that there was no use of artificial intelligence (AI)-assisted technology for assisting in the writing or editing of the manuscript and no images were manipulated using AI.

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