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Goal-directed fluid therapy in craniotomy surgery: a prospective, randomized controlled trial

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Abstract : We studied the use of goal directed fluid therapy (GDFT) in a population of patients undergoing elective craniotomy surgery for intracranial lesion (cerebral tumor, metastasis or abscess), epilepsy surgery, or Chiari I malformation. The study was a prospective, single-blinded, randomized controlled trial. Fifty-six (56) ASA Class I to IV patients were enrolled. The subjects were randomized into one of two groups: a control group, and an intervention group where a GDFT algorithm was used. In order to evaluate the effectiveness of GDFT, data analysis was focused on patients who experienced hypotension to pre-defined parameters. In these patients, the mean intraoperative fluid administered in the GDFT group was less than in the control group; however, there was no statistical difference [2766 ± 1134 mL vs. 4238 ± 2915 mL, respectively (mean ± SD), p = 0.152]. Mean ICU length of stay in the GDFT group was longer, but the difference was not statistically significant (5 ± 13 days vs. 2.5 ± 2 days, respectively, p = 0.256). There were no differences in the length of hospital stay, evidence of under-resuscitation, or neurological complications for 30 days after the surgery. We conclude that GDFT in elective craniotomies does not lead to a significant reduction in intraoperative fluid administration or improved perioperative outcomes.

Keywords : Craniotomy ; Pulse wave analysis ; Stroke volume variation ; Cardiac index; intraoperative blood pressure management ; Intraoperative goal-directed fluid management ; Arterial pressure waveform analysis.

Introduction

Intraoperative goal-directed fluid therapy (GDFT) has been utilized to optimize tissue perfusion and hemodynamic stability while minimizing excessive fluid administration (1). Stroke volume variation (SVV) and cardiac index (CI) derived from arterial pressure waveform analysis (APWA) have been used to guide GDFT. A body of literature has accumulated evaluating the usefulness of such monitoring for fluid optimization in the perioperative period (2, 3).

Few studies address whether GDFT is beneficial in a neurosurgical context, where a restrictive fluid management is often adopted (4). In intracranial surgery, excessive IV fluids may increase intracranial pressure (ICP) through increased cerebral blood volume (CBV) and by exacerbating cerebral edema through hydrostatic pressure and osmotic forces. Conversely, excessive fluid restriction may result in hypotension, which may reduce cerebral perfusion pressure (CPP) and lead to poor tissue perfusion (5-7).

The objective of this study was to examine the ability of our GDFT algorithm to restrict fluid administration, while maintaining safe hemodynamic parameters, in a prospective, randomized, controlled clinical trial. The total amount of fluid administered was compared between a control group (a standard IV fluid administration group based on clinical judgment), and a GDFT group with a fluid management algorithm based on CI and SVV derived from APWA. The algorithm was triggered

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Table 1

Subject inclusion and exclusion criteria

Inclusion Criteria	Exclusion Criteria
Male or female patients ≥ 18 years of age	Uncontrolled hypertension with preoperative SBP > 160 or MAP > 110 mmHg
ASA Class I-IV	Patients in NYHA Class III or IV heart failure, or who have had at least one episode of CHF in the past 6 months requiring admission
Non-emergent craniotomy surgery	Patients with antecedent EF < 30%
	Patients with End Stage Renal Disease on hemodialysis
	Patients in Acute Renal Failure
	Patients with liver disease with evidence of ascites
	Patients with antecedent diabetes insipidus
	Patients with atrial fibrillation
	Pregnant women
	ASA status > IV
	Traumatic brain injury
	Intracranial hematoma

NYHA : New York Heart Association ; CHF : congestive heart failure ; EF : left ventricular ejection fraction ; SBP : systolic blood pressure ; ASA : American Society of Anesthesiologists.

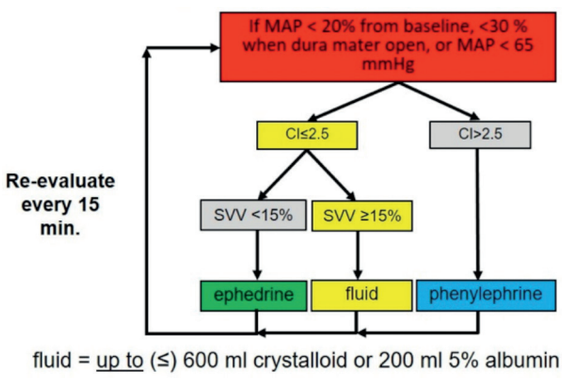
by pre-determined hypotension cut-offs. Our hypothesis was that use of a GDFT algorithm might result in safe restriction of IV fluid administration and potentially affect other outcomes in a favorable way.

Methods

Study approval/ethics

The study was conducted between January 2012 and November 2014 in a tertiary healthcare center. After institutional review board (IRB) approval (study number 11-059), we enrolled 56 neurosurgical cases by approaching patients listed on the operating room schedule. All subjects provided written informed consent.

Fig. 1. – GDFT algorithm



GDFT : goal-directed fluid therapy ; MAP : mean arterial blood pressure ; CI : cardiac index ; SVV : stroke volume variation.

Patient selection

The patients enrolled were adult ASA I-IV patients at least 18 years old and scheduled to undergo an elective craniotomy. In order to minimize hemodynamic variability due to preexisting conditions, comorbidities such as significant or decompensated heart failure or renal failure were excluded (Table 1). Traumatic brain injury patients were excluded.

Randomization and groups

Study subjects were randomly assigned to a standard fluid management group (Control) or to a GDFT group using a 1:1 computer-generated randomization table. In the GDFT group, fluid management was based on an algorithm (Fig. 1) were the SVV and CI were measured by using a FloTrac™ Vigileo monitor (Edwards Lifesciences Corporation, Irvine, CA, USA; software version 3.0). The randomization table was maintained by a non-clinician investigator who was not involved in the enrollment of the subjects, and the group assignments were revealed individually after the subject had provided signed informed consent for participation in the study. The anesthesia providers were not blinded to group assignment, but the surgeon and the patient were blinded.

Outcome variables

The primary outcome was the amount of IV fluid administered intraoperatively to the patients who experienced at least one hypotensive episode

according to the GDFT algorithm. Secondary outcomes included: use of phenylephrine and ephedrine, serum lactate levels, ICU length of stay (LOS), hospital LOS, and neurological complications up to 30 days after the surgery. Quantitative variables included: demographic data (age, height, weight), surgical time, furosemide or mannitol administration, urine output, estimated blood loss, serum lactate and intraoperative mean arterial pressure (MAP).

Intraoperative anesthetic management

The intraoperative anesthetic management was standardized for all subjects entering the study. The patients were monitored with 5-lead ECG, radial arterial line, non-invasive blood pressure, pulse oximetry, capnography, inspired and expired gas analysis, and esophageal temperature. Muscle relaxation was monitored with a standard train of four monitor stimulating the ulnar nerve. A bispectral index (BIS) monitor was applied when the sensor strip did not interfere with the surgical field.

The arterial line was placed before or after induction of anesthesia at the discretion of the anesthesiologist. A FloTrac™ arterial line sensor was used in all study subjects but was connected to the Vigileo monitor in the GDFT group only. The arterial line was zeroed at the level of the right atrium. No central venous catheter was placed or transduced in any of the subjects for purposes of the study. All of the surgeries were performed in the supine position except for four patients in the prone position.

Total intravenous anesthesia (TIVA) was used. Anesthesia was induced with propofol 2-2.5 mg Kg^{-1} and either fentanyl 2-6 µg Kg^{-1} or sufentanil 0.5-1µg Kg^{-1}. Tracheal intubation was facilitated with vecuronium 0.08-0.1 mg Kg^{-1} or rocuronium 0.5-0.6 mg Kg^{-1}. Anesthesia was maintained with a continuous infusion of propofol 100-200 µg Kg^{-1} min^{-1} and remifentanil 0.05-0.5 µg Kg^{-1} min^{-1}. After intubation of the trachea, the lungs were mechanically ventilated with 50 % oxygen in air, and tidal volumes of 8 to 10 mL Kg^{-1} were used. The IRB-approved study protocol allowed for the end-tidal carbon dioxide concentration to be kept between 25-40 mmHg. In the subjects in the study, minute ventilation was adjusted to a level between 30-35 mmHg.

Depth of anesthesia was targeted to a BIS of 40 to 60. Serum lactate was obtained from arterial blood samples after induction of anesthesia and at 2 hour intervals thereafter. A final serum lactate level was measured 2 hours after the end of the operation. Postoperatively, all patients were transferred to the ICU and hemodynamic management continued based on the surgeon's ICU protocol.

Intraoperative fluid management and algorithm

Both groups

We aimed for a pragmatic trial where fluid management in both groups followed the standard of care (8) prevalent in the United States, with the addition of the GDFT algorithm to the intervention group. Pre-operative fluid deficits, maintenance fluid requirements, surgical and urinary losses were replenished with lactated Ringer's solution (LR). Blood loss, if substantial, was replenished with banked blood products or 5% human albumin, in conference with the neurosurgeon. Administration of platelets was allowed if deemed necessary to treat non-specific oozing in the surgical field. The blood pressure targets were the same in both groups. In both groups, if a BIS monitor was not available, the anesthesiologist of record was instructed to make sure that depth of anesthesia was adjusted prior to initiating the GDFT algorithm or treating low blood pressure empirically, in order to ensure that too deep a plane of anesthesia was not the cause of hypotension. This was achieved by reducing the infusion rate of remifentanil to the lowest possible rate at which the patient did not respond with tachycardia or hypertension to surgical stimulation. Once the lowest rate of remifentanil was reached, the same was done with the infusion rate of propofol. If a BIS monitor was available, the BIS was adjusted to a level of 40 to 60.

GDFT group

The GDFT algorithm is shown in figure 1. The level of hypotension was pre-defined as MAP < 20% from baseline, < 30 % when dura mater was open, or when MAP was < 65 mmHg. The algorithm was based on the premise that hypotension in the setting of an acceptable cardiac index (CI > 2.5) required no additional IV fluid administration. Hypotension was treated with phenylephrine. In the setting of CI ≤ 2.5, stroke volume variation (SVV) was considered in the management of IV fluids. Stroke volume variation ≥ 15% (9) triggered administration of fluid alone (crystalloid or colloid), whereas SVV<15, suggesting euvolemia with vasodilation or low inotropic state, triggered the

use of ephedrine, an agent with both inotropic and vasopressor properties. The crystalloid used was lactated Ringer's solution. The colloid used was 5% albumin. The patient's hemodynamics were re-evaluated every 15 minutes with reference to the algorithm, and the algorithm was triggered as many times as its conditions were met. The precise amount and type of fluid administered was recorded in our electronic anesthesia record.

Tissue hypoperfusion or hypovolemia that would call for the abandonment of the algorithm was judged by a urine output < 0.5 mL Kg^{-1} h^{-1} for > 2 hours or a doubling of serum lactate during the course of the operation. This situation did not arise in any of the study subjects. The study design allowed for additional inotropic or vasoactive medications (e.g. epinephrine) if the need arose; however, no such interventions were required.

Table 2

Characteristics of the subjects experiencing an intraoperative hypotension episode (defined according to the algorithm – Fig. 1). All surgeries are craniotomies (the indications are listed in Table 1)

	GDFT group (N=16)	Control group (N=10)	p value
Gender			0.4279[1]
Male	8	7	
Female	8	3	
Coronary artery disease			1.000[1]
Yes	1	0	
No	15	10	
Hyperlipidemia			0.7015[1]
Yes	8	4	
No	8	6	
Hypertension			0.4279[1]
Yes	8	7	
No	8	3	
COPD			1.000[1]
Yes	2	1	
No	14	9	
GERD			0.1358[1]
Yes	4	0	
No	12	10	
Seizure			0.5385[1]
Yes	1	2	
No	15	8	
Stroke or transient ischemic attack			n/a
Yes	0	0	
No	16	10	
Trigeminal neuralgia			1.000[1]
Yes	1	0	
No	15	10	
Diabetes mellitus			0.3846[1]
Yes	0	1	
No	16	9	
History of smoking			0.1213[1]
Yes	5	0	
No	11	10	
Neurosurgical (admission) diagnosis:			0.0541[3]
Primary brain neoplasm	4 (25%)	7 (70%)	
Metastasis to brain	4 (25%)	1 (10%)	
Epilepsy	2 (12.5%)	2 (20%)	
Other[4]	6 (37.5%)	0 (0%)	
Mean age	55	56	0.7716[2]
Mean BMI	25	31	0.0810[2]
Surgical positioning			1.000[1]
Supine	15	10	
Prone	1	0	

GDFT : Goal Directed Fluid Therapy ; COPD : chronic obstructive pulmonary disease ; GERD : gasteroesophageal reflux disease ; BMI: body mass index. A p value < 0.05 was considered statistically significant.

[1] Fisher's Exact Test ; [2] Wilcoxon two-sample test ; [3] Chi-Square ; [4] e.g., cerebral abscess.

Table 3

Main results for the subjects who experienced hypotension according to the algorithm. Wilcoxon rank sums two-sample test (Control vs. GDFT) was used

VARIABLE	CONTROL (N=10)			GDFT (N=16)			
	MEAN	STD DEV	95% CI	MEAN	STD DEV	95% CI	p
SURGICAL TIME (minutes)	303	225	142 - 464	215	94	165 - 264	0.580
CRYSTALLOID (milliliters)	4170	2923	2079 - 6261	2719	1113	2126 - 3312	0.159
COLLOID (milliliters)	68	205	-79 - 214	47	136	-26 - 119	0.648
TOTAL FLUID (milliliters)	4238	2915	2153 - 6322	2766	1134	2161 - 3370	0.152
PHENYLEPHRINE (micrograms)	1890	3088	-319 - 4099	486	435	254 - 718	0.482
EPHEDRINE (milligrams)	8	13	-1 - 17	7	11	0.9 - 12.9	0.749
HOSPITAL LOS (days)	7	3	4 - 9	11	14	4 - 19	0.601
ICU LOS (days)	2.5	2	1 - 4	5.0	13	-2 - 12	0.256
TIME TO EXTUBATION (minutes)	40	55	0.26 - 79	36	81	- 7 - 80	0.120

Sample size justification and statistical analysis

A statistical power analysis showed that 29 subjects were required per treatment group in order for the study to have 80 % power to detect an estimated ≥ 15 % difference in mean intraoperative fluid administration between the groups. The sample size was determined using a power analysis for a one way fixed effects analysis of variance with 2 levels. The criterion for significance (alpha) was set at 0.05 and the analysis of variance was non-directional. Differences between groups were analyzed using Fisher's exact test for categorical variables and Wilcoxon rank sum test for non-parametric data. Multiple measurements of continuous variables were analyzed using analysis of variance (ANOVA) for repeated measures with an autoregressive covariance structure. Data were transformed into normalized ranks prior to analysis. All data analysis was carried out using SAS v.9.4 software (SAS Institute, Cary, NC).

Results

Analysis of all 56 subjects

Thirty-one (31) patients in the GDFT group and 25 patients in the control group were analyzed. There were no significant differences in the baseline characteristics of the groups. The total fluid administered was 2702 ± 1155 mL in the GDFT group and 2863 ± 2179 mL (mean ± SD; p = 0.5442) in the control group (N=25). No statistically significant differences for any of the outcome variables were found.

Analysis of the subjects who experienced hypotension

The subjects who experienced at least one hypotensive episode according to the algorithm are presented in Table 2 (Characteristics of the subjects), Table 3 (Main results), Table 4 (Comparison of lactate, mean arterial pressure (MAP), mannitol and furosemide), and Table 5 (Complications). Sixteen of the 31 patients in the GDFT group (51 %) and 10 of the 25 patients in the control group (40 %) developed at least one intraoperative hypotension episode according to the predefined criteria (Fig. 1). On average, the control group had 1.19 potential triggers of the algorithm per hour, and the GDFT group had 0.96 triggers of the algorithm per hour, which was not significantly different.

The intraoperative course in the groups was not significantly different judging by MAP, surgical time, and amount of furosemide administered. The mean amount of mannitol administered in the GDFT group was larger than that in the control group [0.51 ± 0.31 g Kg^{-1} vs. 0.24 ± 0.23 g Kg^{-1} (mean ± SD; p = 0.0275)]. The total fluid administration in the GDFT group was 2766 ± 1134 mL, and 4238 ± 2915 mL in the control group (mean ± SD; p = 0.152). The breakdown between crystalloid and albumin in the GDFT was 2719 ± 1113 mL and 47 ± 136 mL respectively, and in the control group 4170 ± 2923 mL vs. 69 ± 205 mL, respectively (mean ± SD). ICU

Table 4

Comparison of lactate, mean arterial pressure (MAP), mannitol and furosemide between the control and GDFT groups. Shown is data from subjects experiencing intraoperative hypotension according to the study algorithm

VARIABLE	CONTROL				GDFT				
	N	MEAN	STD DEV	RANGE	N	MEAN	STD DEV	RANGE	p
LACTATE[1] (millimol/liter)	35	2.6	1.3	0.7 - 6.5	51	1.8	1.1	0.6 - 4.7	0.212
MAP[1] (mmHg)	163	76	11	50 - 117	244	79	11	57 - 147	0.986
MANNITOL[2] (grams/kg)	10	0.24	0.23	0 - 0.57	16	0.51	0.31	0 - 0.97	0.0275
FUROSEMIDE[2] (milligrams/kg)	10	0.08	0.06	0 - 0.19	16	0.12	0.10	0 - 0.38	0.2721

[1]Analysis of variance (ANOVA) with repeated measures was used. N= total number of data points entered into the analysis of variance. Each data point represents a 15 minute time interval starting with surgical incision. Since the cases were of different length, the number of data points varied. In the case of lactate, the number of data points represents the number of discrete samples drawn and analyzed.
[2]Wilcoxon two-sample test.
GDFT : goal directed fluid therapy group ; MAP : mean arterial pressure. A p value < 0.05 was considered statistically significant.

Table 5

Complications

Control Group (N=10)	GDFT Group (N=16)
Subject 4 : sixth and seventh nerve palsy ; vocal cord palsy ; difficulty closing eye ; dysphagia secondary to tenth cranial nerve palsy ; aspiration pneumonia ; sepsis	Subject 8 : left upper extremity hemiparesis with slight left pronator drift
Subject 42 : left upper extremity numbness and weakness	Subject 36 : SIADH secondary to CNS bleed/mass. Treated with fluid restriction, hyponatremia.
Subject 53 : Non-occlusive left greater saphenous vein thrombus	Subject 41 : Left arm weakness and left facial droop, mild residual tumor along medial peripheral border of corpus callosum.

SIADH: syndrome of inappropriate antidiuretic hormone secretion; CNS: central nervous system

length of stay in the GDFT group was 5 ± 13 days, and in the control group was 2.5 ± 2 days (mean ± SD; p = 0.256).

No significant differences were found between the groups for crystalloid and colloid administration, hospital LOS, ICU LOS, time to extubation, administration of phenylephrine or ephedrine, lactate levels, neurological complications, or other complications. Twenty percent of subjects in the control group developed post-operative neurological complications as opposed to 19 % in the GDFT group (p = 1.0, Fisher's exact test). None of the complications were related to the anesthesia management or the study. Twenty percent of subjects in the control group and 0 % in the GDFT group developed non-neurological complications (p = 0.1385). There were no deaths within the 30-day post-operative follow-up period.

Discussion

In patients undergoing non-emergent craniotomy surgery, the present study showed that the use of a GDFT algorithm is not related to a significant decrease in intraoperative fluid administration. There was no difference in the outcome data that could favor restriction or more liberal administration of fluids in this patient population. A substantially larger sample would be required to demonstrate a statistically significant difference between the groups. Since the conclusion of our study, others have published results from a study examining a similar hypothesis (4). They found a significant reduction in the amount of fluid used in their intervention group. However, in that study intravenous fluids were administered at a fixed rate of 3 mL Kg^{-1} h^{-1}.

The known limitations of AWPA in estimating CI and SVV did not apply to our patient population (10-15). Colloid (5 % albumin) was allowed as an option because LR is mildly hypotonic relative to plasma (7), and this might be disadvantageous in our patient population. If only LR were used as the intraoperative fluid, the resulting reduction in plasma osmolality may theoretically increase brain water content and ICP. In patients receiving mannitol, any acute reduction in plasma osmolality would be reversed for a period of time (16, 17).

Experimental data involving mild brain injury has shown that a reduction in colloid oncotic pressure (COP) may aggravate brain edema (18). In our surgical population, the state of the blood brain barrier (BBB) could not be known with certainty. The possibility was present that the BBB was damaged to the point of being unable to maintain a sufficient osmotic gradient, but may still be able to maintain an oncotic gradient. It was therefore prudent to manage those patients by making certain that serum osmolality and COP were not lowered simultaneously, by allowing the use of albumin as needed.

The level of hypotension triggering the use of the algorithm was selected with the intention to secure adequate CPP and to not breach the lower limit of cerebral autoregulation. Controversy still exists about the acceptable CPP and lower limit of cerebral autoregulation (19-21). We took into account the patient's baseline MAP, recorded at the time of the patient's pre-operative visit, by setting the lower limit of acceptable MAP at 20% below baseline while the dura was closed, and 30% below baseline while the dura was open. In both cases, a floor of 65 mmHg MAP was used to ensure that CPP would remain at an acceptable level in all cases. Identical MAP levels were targeted in both the control and GDFT groups.

The main limitation of this study is its limited sample size. The small sample size is likely the reason we found an unexpected difference in the amount of mannitol used between the groups. The variability in the amount of fluid administered could have been reduced if a formal fluid administration algorithm had been used for baseline fluid repletion in both groups. However, we did not wish to be overly prescriptive with respect to the baseline fluid management. We aimed at a pragmatic study design where a new monitoring modality was introduced in addition to standard management. This more closely represents the way new technologies become incorporated in clinical practice. The standard of care does allow some leeway for fluid administration in patients with normal cardiovascular function, based on clinical judgment. We were careful not to create a non-representative sample by "artificially" reducing the variability in fluid administration that results from clinical judgment. A large prospective trial could definitively answer whether GDFT leads to a reduction in fluid administration in craniotomies that is clinically meaningful with respect to outcomes.

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