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Pulse Pressure Variance (PPV)-Guided Fluid Management in Adult Patients Undergoing Supratentorial Tumor Surgeries: A Randomized Controlled Trial

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Abstract

Objective Appropriate fluid management in neurosurgery is critical due to the risk of secondary brain injury. Determination of volume status is challenging with static variables being unreliable. Goal-directed fluid therapy with dynamic variables allows reliable determination of fluid responsiveness and promises better outcomes. We aimed to compare the intraoperative fluid requirement between conventional central venous pressure (CVP)-guided and pulse pressure variance (PPV)-guided fluid management in supratentorial tumor surgeries.

Materials and Methods This prospective, randomized, double-blind, single-center trial was conducted with 72 adults undergoing supratentorial tumor surgery in a supine position. Patients were divided into two groups of 36 patients each receiving CVP- and PPV-guided fluid therapy. The CVP-guided group received boluses to target CVP greater than 8 mm Hg along with hourly replacement of intraoperative losses and maintenance fluids. The PPV-guided group received boluses to target PPV less than 13% in addition to maintenance fluids. Total intraoperative fluids administered and the incidence of hypotension was recorded along with the brain relaxation score. Postoperatively, serum lactate levels, periorbital and conjunctival edema, as well as postoperative nausea and vomiting were assessed.

Statistical Analyses All statistical analyses were performed with Statistical Package for Social Sciences, version-20 (SPSS-20, IBM, Chicago, Illinois, United States). To compare the means between the two groups (CVP vs. PPV), independent samples *t*-test was used for normal distribution data and Mann–Whitney *U* test for nonnormal distribution data. The chi-square test or Fischer's exact test was used for categorical variables.

Keywords
- central venous pressure (CVP)
- fluids
- goal-directed fluid therapy (GDFT)
- neurosurgery
- pulse pressure variance (PPV)
- supratentorial

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Results The CVP group received significantly more intraoperative fluids than the PPV group ($4,340 \pm 1,010$ vs. $3,540 \pm 740$ mL, $p < 0.01$). Incidence of hypotension was lower in the PPV group (4 [11.1%] vs. 0 [0%], $p = 0.04$). Brain relaxation scores, serum lactate levels, periorbital and conjunctival edema, and incidence of postoperative nausea and vomiting were comparable between the groups.

Conclusion The requirement for intraoperative fluids was less in PPV-guided fluid management with better hemodynamic stability, adequate brain conditions, and no compromise of perfusion.

Introduction

Craniotomies for supratentorial tumors pose unique anesthetic challenges. The main objectives for anesthetic management include optimizing intracranial pressure and maintaining cerebral perfusion pressure. This ensures adequate oxygen delivery to the cerebral tissues and thereby avoids secondary insults to the brain.[1] Perioperative fluid therapy is an important predictor of postoperative outcomes. The amount of fluid administered depends on factors like preoperative hydration, associated comorbidities, intraoperative blood loss, hemodynamic stability, and institutional practice. A change in fluid management alone on the day of surgery has been shown to reduce perioperative complications by 50%.[2–6]

Conventionally, fluid management is based on the calculation of various losses during the intraoperative period and replacement by mere approximation. Volume status can be assessed with continuous intraoperative monitoring of various static and dynamic variables. Regardless of the monitoring methods employed, accurate determination remains uncertain. This is attributed to unknown intravascular volume status, continuously changing cardiovascular responses to anesthetic drugs, blood loss under drapes that are often difficult to quantify, as well as the manifestations of the normal physiological responses to surgery. Estimation of preload of patients thereby becomes an arduous task for anesthesiologists. Thus, the decision to administer fluid should be supported by a definitive predictor for volume deficit without causing additional risk.[7]

To determine cardiac preload, static parameters like central venous pressure (CVP), pulmonary artery occlusion pressure, and pulmonary capillary wedge pressure are often used, yet found to be unreliable.[8] The magnitude of respiratory variation in preload, helps predict fluid responsiveness in mechanically ventilated patients with greater accuracy. Such dynamic variables like stroke volume variance (SVV) and pulse pressure variance (PPV) provide reliable indicators of fluid responsiveness.[9]

Too much or too little fluid is detrimental to patient outcomes and algorithm-based fluid regimes have proved efficacious. The use of dynamic variables is worthwhile in various surgical populations. PPV is frequently considered a gold standard to compare other new dynamic variables.[10] However, neurosurgical patients represent a unique population with a high risk of morbidity and mortality in the perioperative period. To the best of our knowledge, very few studies have suggested the efficacy of PPV in the neurosurgical population.[11–14]

Hence, this study aimed to compare the effect of PPV-guided fluid management with the conventional CVP-guided method in patients undergoing supratentorial tumor surgeries. The primary outcome was to compare the intraoperative fluid requirement between CVP- and PPV-guided management. Secondary outcomes were to compare the effects of CVP- versus PPV-guided fluid management on the incidence of intraoperative hypotension and consequences of inefficient fluid therapy in the form of serum lactate levels, brain relaxation score (BRS), conjunctival and periorbital edema at the end of the surgery, as well as postoperative nausea and vomiting (PONV).

Materials and Methods

Type and Setting

This prospective randomized trial was conducted at a tertiary care teaching hospital in North India, between December 2019 and January 2021. The trial was registered with the Clinical Trials Registry, India (CTRI/2019/04/018746), and approval from the Institutional Ethics Committee (IEC: 2018-188-MD-107) was sought. Patients were briefed about the study protocol and written and informed consent was obtained before enrollment. They were also informed that they can withdraw from the study at any time without stating a reason. All research participants were treated with appropriate ethical standards, as per Helsinki's Declaration.

Recruitment

Adult patients aged 18 to 60 years, belonging to the American Society of Anesthesiologists (ASA) I and II status, undergoing elective supratentorial tumor surgery in supine position were included. Exclusion criteria included significant cardiac illness, tumors prone to precipitate diabetes insipidus, chronic obstructive airway disease, peripheral vascular disease, raised intra-abdominal pressure, patients in sepsis, consumption of lactate-producing drugs like metformin, antiretroviral drugs, etc., massive intraoperative blood loss (more than 50% of blood volume within 3 hours), and patients requiring ventilatory support postoperatively.

Randomization and Blinding

Using computer-generated random numbers, 97 patients were divided into two groups depending on the intraoperative fluid management strategy. Patients in group 1 received conventional CVP-guided fluids while those in group 2 received PPV-guided fluids. The allocation was concealed using opaque envelopes, which were opened only when the patient entered the operating room. The patients, surgeons, and nursing staff were blinded to group allocation. Intraoperative management and data collection were done by the attending anesthesiologist who was aware of the group allocation, but not involved in further study.

Anesthetic Management

Each patient was assessed a day before surgery and was advised to fast as per the ASA protocol.[15] Preoperative drugs like antibiotics, steroids, diuretics, and anticonvulsant medications were continued as indicated. Premedication in the form of tablets ranitidine 150 mg and alprazolam 0.25 mg was advised a night before surgery.

Intraoperative Management

After shifting the patients to the operation theatre, standard ASA monitoring in the form of electrocardiogram, pulse oximetry probe (SpO_2), and noninvasive blood pressure (BP) cuff were attached along with a train-of-four (TOF) monitor and bispectral index (BIS) electrodes. A peripheral venous line (18 gauge or larger) was established. Anesthesia was induced with midazolam 0.01 to 0.02 mg/kg, fentanyl 1 to 2 mcg/kg, and propofol 1.5 to 2 mg/kg. Tracheal intubation was facilitated with vecuronium bromide 0.08 to 0.1 mg/kg followed by intermittent maintenance doses titrated to two twitches on TOF monitoring. Anesthesia was maintained with sevoflurane, air, and oxygen mixture (FiO_2 50%) titrated to maintain a BIS of 40 to 60. Analgesia was obtained with intermittent boluses of 1 mcg/kg fentanyl. Patients were ventilated with a tidal volume of 8 mL/kg, with a respiratory rate of 10 to 15 breaths/min to maintain end-tidal carbon dioxide of 32 ± 2 mm Hg. Postinduction, an arterial catheter was inserted into the radial artery of the nondominant hand for invasive BP monitoring. A triple-lumen central venous catheter (Arrow International, Reading, Pennsylvania, United States) was inserted in the internal jugular vein for CVP monitoring. Both CVP and PPV were measured by Mindray BeneView T9 monitor (Mindray Bio-Medical Electronics Co. Ltd, Shenzhen, China). Baseline values of CVP, PPV, and serum lactate were noted in both groups. Mannitol 1 g/kg was given before the opening of the dura mater as per institutional practice. BRS reported by the subjective assessment of the senior operating neurosurgeon, at the time of exposure of dura mater was noted. A four-point scoring system was used: grade 1—perfectly relaxed, grade 2—satisfactorily relaxed, grade 3—firm brain, and grade 4—bulging brain.[16] Fluid management protocol is described subsequently.

Intraoperative parameters including heart rate, mean arterial pressure, CVP, or PPV were recorded. Serum lactate was measured at the end of surgery. All patients received injection ondansetron 0.1 mg/kg before extubation. Patients were reversed with neostigmine 0.05 mg/kg and glycopyrrolate 0.01 mg/kg, extubated on fulfillment of the usual clinical extubation criteria, and shifted to the neurosurgical intensive care unit. Patients were examined for conjunctival and periorbital edema after extubation.

Fluid Management Protocol

Based on the group allotted, CVP or PPV was used to guide fluid management intraoperatively. After noting the baseline CVP and PPV values in both groups, the alternate monitor, that is, the one not used for fluid management, was removed from the further display so that the anesthetist could not view it. Balanced salt solution Plasmalyte-A (Baxter India Pvt. Ltd, Gurgaon, Haryana, India) and 0.9% normal saline were administered alternatively in both groups.

All patients received maintenance fluid as per the Holliday–Segar 4-2-1 rule.[17] In group 1, fluid management was done using the conventional method of calculating cumulative losses accounting for vasodilation during anesthetic induction, estimated blood loss, and urine output every hour. In addition, 100 mL fluid boluses were given whenever CVP was less than 8 mm Hg. In group 2, the conventional calculation-based fluids were avoided. Only 100 ml fluid boluses were administered to maintain PPV less than 13% in addition to the maintenance fluids (►**Fig. 1**).

Hypotension was defined as a fall in mean arterial pressure of more than 20% from the baseline. Vasopressors were used when hypotension occurred despite maintaining CVP or PPV in the normal range. Intravenous mephentermine was given in increments of 6 mg up to a maximum of 30 mg. If hypotension persisted, intravenous noradrenaline infusion was started at the rate of 0.1 mcg/kg/min. Blood loss was managed in both groups according to the institutional protocol. The total fluid given, the number of fluid boluses required, and the incidence of hypotension in both groups were noted.

Postoperative Management

Patients were postoperatively managed in the neurosurgical intensive care unit. Fluid management was done at the discretion of the surgeon. Serum lactate levels were measured at the end of 24 hours in addition to two other time points, that is, baseline and end of surgery. The presence of PONV at the end of 24 hours was noted.

Statistical Analysis and Sample Size Calculation

The sample size was estimated using software G Power version 3.1.9.2 (Düsseldorf University, Germany) based on a previous study using PPV-guided fluid therapy for high-risk surgeries.[18] Assuming an alpha error of 0.05, we calculated that 33 patients would be required in each group to detect a difference of 613 mL in the volume of intraoperative fluid infused with a power of 80%. Allowing for 20% exclusion, we increased the sample size to 40 subjects in each group.

To compare the means between the two groups (CVP vs. PPV), independent samples *t*-test was used for normal distribution data and Mann–Whitney *U* test for nonnormal distribution data. Chi-square test or Fischer's exact test was

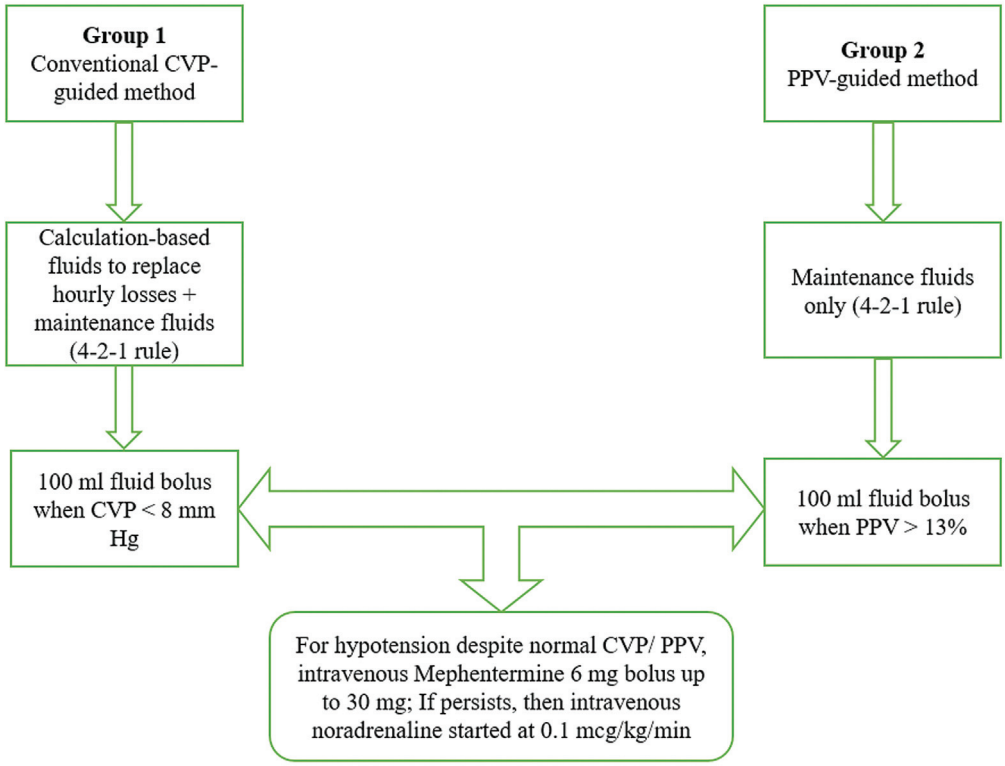

Fig. 1 Fluid management protocol.

used as suitable for categorical variable comparisons among groups. A *p*-value of less than 0.05 was considered statistically significant. Statistical Package for Social Sciences, version-20 (SPSS-20, IBM, Chicago, Illinois, United States) was used for analyzing the data.

Results

During the study period, 136 patients of supratentorial tumors were evaluated for eligibility, of which 64 patients were excluded and a total of 72 patients underwent final analysis (►**Fig. 2**).

Demographic Data

Both groups were comparable with respect to demographic data and baseline characteristics (►**Table 1**).

Primary Outcome

Fluid management was based on the group allotted. The CVP group had a significantly higher requirement of fluids compared to the PPV group (4,340 ± 1,010 vs. 3,540 ± 740 mL, $p < 0.01$) (►**Fig. 3**). The number of fluid boluses required in each group (3.11 ± 2.62 vs. 2.25 ± 2.13, $p = 0.13$) was comparable (►**Table 2**).

Secondary Outcomes

The incidence of intraoperative hypotension was significantly more in the CVP group as compared to the PPV group (4 [11.1%] vs. 0 [0%]; $p = 0.04$), although blood loss and requirement for vasopressors among groups were similar (►**Fig. 4**). Comparison of urine output between the two groups, CVP versus PPV (1,283.75 ± 783.51 vs. 1,008.13 ± 477.59 ml, $p = 0.04$) was statistically significant with the CVP group

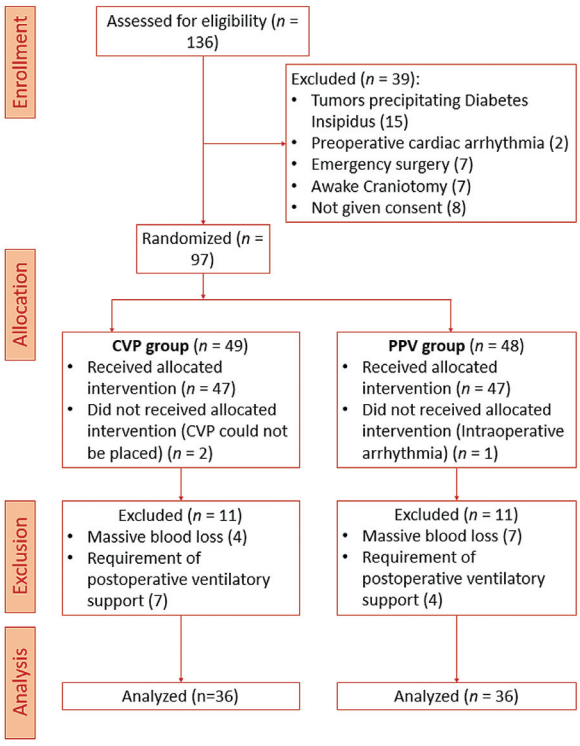

Fig. 2 Consort diagram.

Table 1 Baseline characteristics

Patient characteristics	Group 1 (CVP) $n = 36$	Group 2 (PPV) $n = 36$	*p*-Value
Age (y)[a]	39.94 ± 13.89	36.19 ± 12.71	0.24
Gender (male:female) [b]	19:17	23:13	0.34
BMI (kg/m^2)[a]	23.86 ± 2.26	23.70 ± 1.96	0.75
ASA grading (1, 2) [b]	22, 14	20, 16	0.64
Comorbidities (%)[b]	14 (38.9)	16 (44.4)	0.64
Duration of surgery (min)[a]	265.83 ± 50.45	247.22 ± 42.33	0.94
Baseline heart rate[a]	82.44 ± 10.76	80.75 ± 8.74	0.47
Baseline MAP[a]	83.67 ± 5.08	82.17 ± 4.63	0.20
Baseline CVP[a]	9.89 ± 1.74	9.94 ± 1.97	0.89
Baseline PPV[a]	10.17 ± 2.47	10.53 ± 2.47	0.54
Baseline serum lactate (mg/dL)[a]	11.61 ± 4.90	11.97 ± 5.22	0.77

Abbreviations: ASA, American Society of Anesthesiologists; BMI, body mass index; CVP, central venous pressure; MAP, mean arterial pressure; PPV, pulse pressure variance; SD, standard deviation.
[a]Independent *t*-test used, values presented as mean ± SD.
[b]Chi-square test or Fisher's exact test used, values presented as number or number (%).

having a greater urine output. No significant difference was found in serum lactate levels at any point between the two groups. The BRS was comparable among groups. The incidence of conjunctival and periorbital edema as well as PONV were also similar (►**Table 2**).

Discussion

Fluid management in neurosurgery is primarily aimed at maintaining adequate cerebral perfusion. These patients often receive brain dehydrating measures predisposing them to severe hypovolemia. Appropriate intraoperative fluid therapy paves the way to better postoperative recovery.[6] In our study, PPV-guided therapy resulted in less intraoperative fluid requirement with better hemodynamic stability compared to the conventional CVP-guided regime (4,340 ± 1,010 vs. 3,540 ± 740 mL, $p < 0.01$). Conventionally, anesthesiologists are accustomed to giving fluids derived by approximate calculation that accounts for fasting, maintenance, and intraoperative losses. CVP has been used for a long time to guide fluid therapy. Multiple studies have proved that static indices like CVP are not a reliable estimate of the preload status.[19] Of late, the concept of goal-directed fluid therapy (GDFT) has come up focusing on restricted fluid management. GDFT, based on dynamic variables, is a strategy to optimize preload by monitoring parameters derived from cardiorespiratory variations. A few such variables include SVV, PPV, systolic pressure variation, and

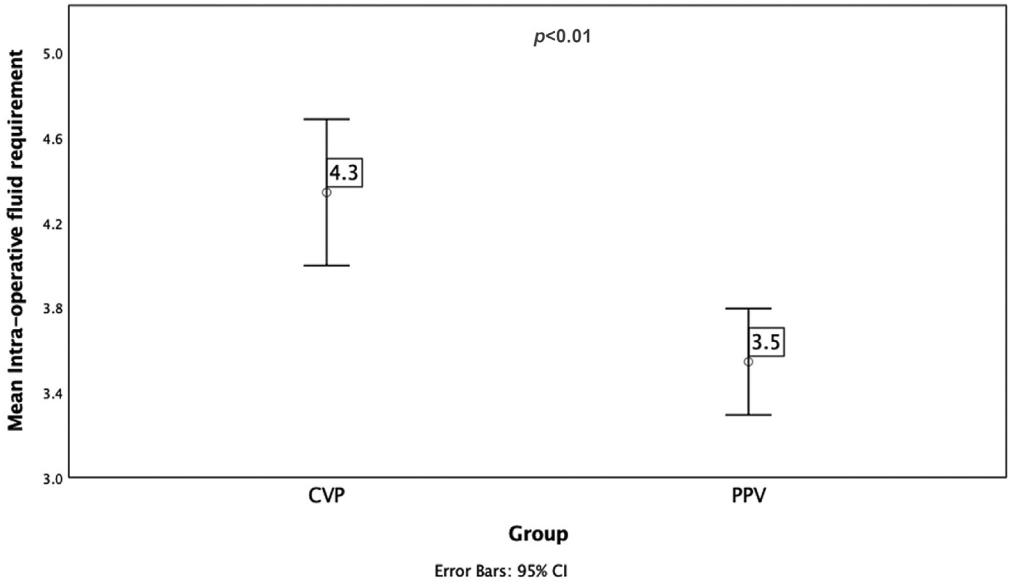

Fig. 3 Error bars comparing intraoperative fluid requirement (liters) between the two groups.

Table 2 Summary of outcomes

Patient characteristics	Group 1 (CVP) $n = 36$	Group 2 (PPV) $n = 36$	*p*-Value
Intraoperative fluid requirement (mL)[a]	4,340 ± 1,010	3,540 ± 740	< **0.01**[c]
Baseline serum lactate (mg/dL)[a]	11.61 ± 4.90	11.97 ± 5.22	0.77
Serum lactate at end of surgery (mg/dL)[a]	17.69 ± 8.90	16.74 ± 7.66	0.61
Serum lactate 24 hours after surgery (mg/dL)[a]	17.52 ± 8.23	16.77 ± 9.38	0.70
Rise in serum lactate at end of surgery from baseline (%)[a]	63.0 ± 9.97	42.92 ± 6.79	0.09
Rise in serum lactate 24 hours after surgery from baseline (%)[a]	63.83 ± 70.57	42.72 ± 47.07	0.12
Urine output (mL)[a]	1,283.75 ± 783.51	1,008.13 ± 477.59	**0.04**[c]
Blood loss during surgery (mL)[a]	629.17 ± 321.67	531.94 ± 219.14	0.14
Intraoperative hypotension (%)[b]	4 (11.1)	0 (0)	**0.04**[c]
Vasopressor requirement (%)[b]	1 (2.8)	0 (0)	0.31
Conjunctival and periorbital edema (%)[b]	5 (13.9)	3 (8.3)	0.45
Brain relaxation score (1: 2: 3: 4)[b]	2: 32: 2: 0	3: 32: 0: 1	0.36
PONV (%)[b]	5 (13.9)	4 (11.1)	0.72

Abbreviations: CVP, central venous pressure; PONV, postoperative nausea and vomiting; PPV, pulse pressure variance; SD, standard deviation.
[a]Independent *t*-test used, values presented as mean ± SD.
[b]Chi-square test or Fisher's exact test used, values presented as number or number (%).
[c]$p < 0.05$ was considered significant.

plethysmography variability index. These variables are believed to predict the accurate position on Frank–Starling's curve proportional to the degree of preload dependency.[20] Earlier studies on GDFT have proven to provide better postoperative outcomes.[21] Although various studies have been conducted to determine the ideal parameter to guide intraoperative fluid administration, the most appropriate method is still a matter of contention.[22]

Knowledge of fluid responsiveness is beneficial over a gross estimation of volume status. Hence, such dynamic indices are particularly suitable in the neurosurgical population as there is a narrow margin of safety to prevent secondary brain injury and organ damage.[6] Literature on GDFT in the neurosurgical population is limited with contradictory results.[11–13,23–25]

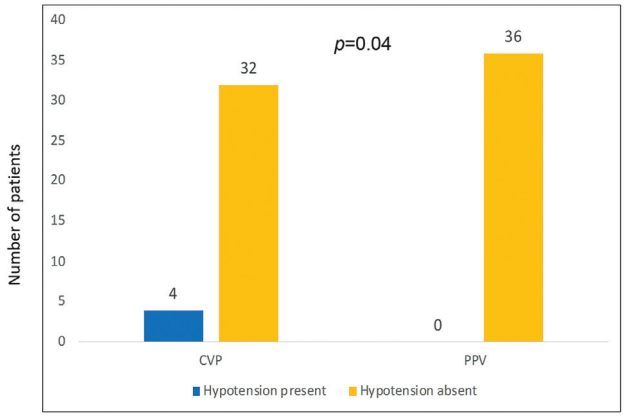

Fig. 4 Bar graph showing comparison of intraoperative hypotension between the two groups.

Akin to our study, estimation of fluids by GDFT has led to a lesser intraoperative fluid requirement than conventional CVP-guided regimen in studies on renal transplant recipients.[26–28] De Cassai et al used PPV to guide fluid management to achieve adequate urine output and found it to be as effective as liberal fluid therapy.[26] Another randomized controlled trial (RCT) reported decreased intraoperative crystalloid requirement using PPV as compared to CVP-guided fluid therapy with similar outcomes.[27] Although we studied neurosurgical patients, the efficacy of PPV-guided fluid therapy appears evident.

Appropriate intraoperative fluid strategy in patients undergoing supratentorial surgery has been previously studied.[11,12] Sundaram et al compared PPV with CVP in these patients to assess hemodynamic stability and perfusion status. Fluids were administered to keep CVP around 5 to 10 cm H_2O along with maintenance fluid. However, we used fixed-volume boluses for the targeted CVP or PPV.[11] In another RCT by Hasanin et al, all patients received 5 mL/kg colloid bolus after induction. PPV-guided GDFT group received restricted fluid at a rate of 1 ml/kg/h compared to 4 ml/kg/h in the control group. In addition, fluid boluses of 3 mL/kg were given as deemed necessary for the required CVP or PPV.[12] Both these studies resulted in the PPV group receiving significantly higher fluids compared to the conventional group. On the contrary, in our study, the PPV group required lesser intraoperative fluids. This can be attributed to heterogeneity in fluid management strategy among studies.

Our study did not use weight-based fluid boluses and we preferred to keep them uniform in all patients. No difference was found in the number of fluid boluses among groups (3.11 ± 2.62 vs. 2.25 ± 2.13, $p = 0.13$). A significantly higher urine output was seen in the CVP group (1,283.75 ± 783.51

vs. 1,008.13 ± 477.59 mL, $p = 0.04$). As per the conventional calculation-based fluid strategy, hourly urine output was replaced in the CVP group whereas it was not a part of the protocol in the PPV group. This could have been a possible cause for the higher fluid requirement in the CVP group. We did not collect data on preoperative diuretic usage which could be a confounding factor in this context. Hence, the requirement of more fluids with higher urine output was an association or causation, needs to be studied further.

Four patients in the CVP group developed intraoperative hypotension as compared to none in the PPV group ($p = 0.04$). These four patients also had higher mean blood loss as compared to other patients in this group (1,000 ± 697.62 vs. 567 ± 217.62 mL), though this was statistically insignificant ($p = 0.30$). Anticipating blood loss among these patients to be a confounding factor, a repeat analysis was done, excluding these four patients in the CVP group. The new analysis (CVP:PPV, 32:36), however, yielded similar results in terms of intraoperative fluid requirement (4,450 ± 1,010 vs. 3,540 ± 740 mL; $p = 0.00$), BRS, serum lactate levels, conjunctival and periorbital edema, and PONV.

This again implies that the CVP-guided strategy underestimates the volume status resulting in unwarranted fluid administration probably because of the inability of CVP to accurately predict the position of the patient on the Frank–Starling's curve. In contrast to our study, Sundaram et al and Hasanin et al found the study groups (CVP vs. PPV) comparable in terms of intraoperative hypotension.[11,12] Differences in study protocols and fluid administration strategies make explicit comparisons challenging.

In our study, the BRS was comparable among groups (2: 32: 2: 0 vs. 3: 32: 0: 1, $p = 0.36$). Hasanin et al studied the effect of fluid management on BRS as their primary outcome and found no difference between the two groups.[12] We could not find any other study investigating the effect of PPV on the BRS. Nevertheless, few studies using SVV-guided GDFT have proved fruitful in improving intraoperative brain condition compared to conventional fluid therapy in supratentorial surgeries.[23,24]

The present study revealed no significant difference in serum lactate levels at any time point between the two groups (►**Tables 1** and **2**). Lactate levels serve as an indirect but sensitive estimate of tissue hypoxemia.[29] Elevated perioperative lactate levels are correlated with prolonged morbidity and mortality.[30,31] Our study results, matched the previous study by Sundaram et al.[11] Since serum lactate levels were measured as the adequacy of perfusion, we avoided lactate-containing fluids in our study. Though the two groups had comparable lactate levels, the fact that mean postoperative serum lactate levels and the percentage rise in serum lactate levels from baseline, were lower in the PPV group, despite receiving less intraoperative fluids, suggests the benefit of administering just the optimal amount of crystalloids without compromising peripheral perfusion.

We found no significant difference between the two groups ($p = 0.45$) concerning postoperative conjunctival edema and periorbital edema. All the patients were operated on in a supine position and those with preexisting fluid overload or organ failure were excluded at the time of recruitment.

Association between hypovolemia and PONV is well described.[32] Our analysis revealed no difference in the incidence of PONV between the two groups ($p = 0.72$). In our study, PONV was assessed just once, at the end of 24 hours. Moreover, postoperative hydration was at the discretion of the surgeon and hence uniformity could not be ensured.

Deng et al in their meta-analysis on intraoperative fluid therapy in high-risk surgeries suggested improved outcomes with GDFT-guided management in combination with cardiac output or cardiac index than GDFT alone.[21] Despite proving to be a reliable marker of fluid responsiveness, PPV does have a gray area of 9 to 13% with different studies using variable cutoffs for fluid responsiveness. The real-time evaluation of an actual optimization goal like stroke volume, cardiac output, or cardiac index in combination with PPV is a road not taken in neurosurgery. Further research in this regard might assist in setting a clear PPV target as well as provide a better perspective to see if optimization goals in combination with PPV could provide favorable outcomes over PPV alone.

Limitations

Our study had a few limitations, of which a small sample size is of note. We assessed the efficacy of PPV only in the supine position. The ability of PPV to effectively determine fluid responsiveness in other positions requires further research. Besides, our study protocol was based on the use of only crystalloids. Despite trying to match both groups based on age, sex, and comorbidities, we did not classify patients based on tumor size, preoperative diuretic usage, and duration of therapy. We included only ASA 1 and 2 patients and hence results could not be extrapolated to higher ASA grades.

Conclusion

Succinctly, PPV can be an effective, less invasive, and reliable modality to guide fluid therapy in patients undergoing supratentorial tumor surgeries in the supine position, with significantly better hemodynamic stability.

Authors' Contributions

J.G. contributed to the enrolment of patients, acquisition of data, analysis, interpretation of data, drafting, critical revision of the manuscript, and approval of final manuscript. S.S. contributed to the study concept and design, analysis, interpretation of data, drafting and critical revision of the manuscript, study supervision, and approval of final manuscript. N.S. contributed to the analysis, interpretation of data, drafting and critical revision of the manuscript, and approval of final manuscript. R.H. contributed to the study concept and design, study supervision, drafting and critical revision of the manuscript, and approval of final manuscript. R.V. contributed to the study concept and design, enrolment of patients, analysis, interpretation of data, drafting and critical revision of the manuscript, study supervision, and approval of final manuscript. D.G. contributed to the study concept and design, drafting and critical revision of the manuscript,

approval of final manuscript, and study supervision. P.M. contributed to the study concept and design, statistical analysis and interpretation of data, critical revision of the manuscript, and approval of final manuscript.

Prior Presentation

This paper was presented as a poster (virtual) at the International Anesthesia Research Society (IARS) 2022 annual meeting, March 17–20, 2022, in Hawaii, USA.

Ethical Approval

This study received the Institutional Ethics Committee approval under the following ID: 2018-188-MD-107. All research participants were treated with appropriate ethical standards, as per the Helsinki declaration. Clinical Trials Registry, India registration number: CTRI/2019/04/018746.

Conflict of Interest

None declared.

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