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Original Article

Anaesthesia Section

Intra-Operative Fluid Management in Adult Neurosurgical Patients Undergoing Intracranial Tumour Surgery: Randomised Control Trial Comparing Pulse Pressure Variance (PPV) and Central Venous Pressure (CVP)

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ABSTRACT

Introduction: Fluid management in neurosurgery presents specific challenges to the anaesthesiologist. Dynamic parameters like Pulse Pressure Variation (PPV) have been used successfully to guide fluid management.

Aim: To compare PPV against Central Venous Pressure (CVP) in neurosurgical patients to assess hemodynamic stability and perfusion status.

Materials and Methods: This was a single centre prospective randomised control trial at a tertiary care centre. A total of 60 patients undergoing intracranial tumour excision in supine and lateral positions were randomised to two groups (Group 1, CVP n=30), (Group 2, PPV n=30). Intra-operative fluid management was titrated to maintain baseline CVP in Group 1(5-10cm of water) and in Group 2 fluids were given to maintain PPV less than 13%. Acid base status, vital signs and blood loss were monitored.

Results: Although intra-operative hypotension and acid base changes were comparable between the groups, the patients in the CVP group had more episodes of hypotension requiring fluid boluses in the first 24 hours post surgery. {CVP group median (25, 75) 2400ml (1850, 3110) versus PPV group 2100ml (1350, 2200) p=0.03}

The patients in the PPV group received more fluids than the CVP group which was clinically significant. {2250 ml (1500, 3000) versus 1500ml (1200, 2000) median (25, 75) (p=0.002)}. The blood loss was not significantly different between the groups The median blood loss in the CVP group was 600ml and in the PPV group was 850 ml; p value 0.09.

Conclusion: PPV can be used as a reliable index to guide fluid management in neurosurgical patients undergoing tumour excision surgery in supine and lateral positions and can effectively augment CVP as a guide to fluid management. Patients in PPV group had better hemodynamic stability and less post operative fluid requirement.

Keywords: Cerebral, Dynamic indices, Goal directed fluid therapy, Monitoring

INTRODUCTION

In neurosurgical anaesthesia, the emphasis remains on the provision of good operative conditions, assessment and preservation of neurological function, and a rapid, high-quality recovery. Intra-operative fluid management plays a major role in achieving these goals of any major surgery [1]. Candidates presenting for intracranial surgery may be at risk of hypovolemia for various reasons including insufficient fluid intake, physiological compensation for arterial hypertension and osmotic diuretic therapy [2]. Formula based fluid management is inappropriate in these situations. Individualised 'Goal-directed fluid therapy' has been shown to improve outcomes after surgery [3].

Various parameters have been used to guide fluid therapy. Static measurements namely Central Venous Pressure (CVP), Pulmonary Capillary Wedge Pressure (PCWP) have been used to guide fluid therapy. CVP is not fully reliable with wide variations in intra-thoracic pressures. They act as a poor estimate of preload, as preload depends on ventricular volumes and the likelihood that CVP can accurately predict fluid responsiveness was found to be 56% [4, 5]. Pulmonary Artery Occlusion Pressure (PAOP) involves too invasive a procedure and is not recommended for intracranial surgery. To overcome the limitations of these static indices, dynamic indices have been devised and used [6]. These indices are based on the response of the circulatory system to a controlled preload variation by specific manoeuvres redistributing blood volume (e.g., mechanical ventilation and leg raising). Dynamic indices such as pulse pressure variation have been shown to be more reliable than CVP in predicting fluid responsiveness with high sensitivity and specificity [7-9].

The study was aimed to evaluate if an easily established monitoring like PPV can effectively guide fluid therapy in neurosurgical patients and thus replace CVP. The aims were to assess the intra-operative hemodynamic stability, adequacy of tissue perfusion at the end of surgery and post-operative fluid management.

MATERIALS AND METHODS

This study was conducted at a single tertiary medical centre between September 2009-2010.

Sample size calculation: Sample size was calculated based on a similar study done in patients using PPV guided fluid therapy [10]. A sample size of 30 patients in each group was calculated for a 0.05 difference (two-sided) with a power of 80% for the mean outcome of blood pressure.

Randomisation: Randomisation of the groups was done by a statistician not involved in the study, using computer generated random list of 100 numbers with blocks of five. The allocation

concealment was by sequentially numbered opaque envelopes. The envelope was opened when the patient reached the operating room.

Blinding: The patient and the doctor managing the patient in the post operative period were blinded. The statistical analysis was done by a statistician not involved in the study.

Inclusion criteria were patients in the age group 20-80; ASA grade 1 and 2, planned for excision of supra and infratentorial tumours. The exclusion criteria included significant cardiac illness, conditions in which PPV measurement may not be reliable like in arrhythmia, tumours prone to precipitating diabetes insipidus, chronic obstructive airway disease and raised intra-abdominal pressure and those in which acid base measurement may not be reflective of the intra-operative management like sepsis, patients on lactate producing drugs and baseline lactate of more than four. After informed consent the enrolled patients were randomised to one of the two groups, Group 1 Central Venous Pressure (CVP) and Group 2 Pulse Pressure Variance (PPV). The study was approved by the Institution Review Board and Ethics Committee.

Anaesthetic technique: After adequate fasting, all patients received preoperative antibiotics, steroids and anticonvulsants. Diazepam and metoclopramide in the dose of 0.1mg/kg were used as pre-medications. Diazepam was avoided in patients with clinical signs of raised intracranial pressure. Peri-operative anti-hypertensives were continued according to the ACC/AHA guidelines, ACE inhibitors were withheld a day before the proposed surgery [11,12].

Peripheral venous and radial arterial lines were established. Baseline ABG was taken. Monitoring included pulse oximetry, capnography and electrocardiography. Anaesthesia was induced with thiopentone 5mg/kg, Fentanyl 2mcg/kg, and maintained on isoflurane end tidal concentration at 0.9% (MAC 0.8) in air and oxygen. Muscle relaxation was achieved using vecuronium 0.15mg/kg for endotracheal intubation and maintained with an infusion titrated to two twitches on neuromuscular monitoring. All patients were mechanically ventilated with a minimum of 8ml/kg of tidal volume and appropriate respiratory rate to achieve an ETCO2 between 30 and 35 mmHg and thus intra-thoracic pressure variation was avoided in both groups.

Hemodynamic monitoring and management: Post induction, the right internal jugular vein was cannulised using a single lumen 20 gauge (ArrowTM) catheter using ECG guidance and fixed when peaked p waves were observed. Baseline PPV was measured using Philips Intellivue MP50 monitor once mechanical ventilation was ascertained and the tidal volume set at 8ml/kg, in all patients. Normal PPV is 10-13%. Simultaneously a baseline CVP was also measured. All patients had normal baseline CVP (5-10cm H_2O). Based on the randomisation, CVP or PPV monitoring was used intra operatively to guide fluid management. The other corresponding monitor was turned off till the end of surgery and the anaesthetist could not view it. Mannitol was used prior to dural opening in the dose of 0.5mg/kg.

In the CVP group, fluids were given to maintain the normal baseline value in addition to maintenance fluid requirements. In the PPV group fluids were given to maintain the PPV at <13% with boluses when required to bring the PPV back to 13%. Normal saline and ringer lactate were used alternately. If the estimated blood loss exceeded 500ml in both groups, colloid or blood was infused depending on the patient's hemoglobin with the aim of keeping the hemoglobin around 9mg/dl. Blood pressure, heart rate, PPV or CVP readings depending on the group was noted every 5minutes for the first 30minutes of surgery and thereafter every 10minutes. Forced air warming was used to maintain the temperature which was measured with a probe in the nasopharynx. If hypotension (fall in blood pressure, > 20% of baseline systolic blood pressure) persisted despite normal CVP or PPV, this was treated with a vasopressor viz. phenylephrine or ephedrine (50 mcg and 5 mg boluses respectively) [13]. PPV and CVP reading for each patient were taken before discontinuing mechanical ventilation (final PPV or CVP).

The total estimated blood loss was noted down at the end of surgery. Reversal of neuromuscular blockade was done with neostigmine (0.05mg/kg) and glycopyrolate (0.1mg/kg). Patients were extubated when fully awake. Arterial blood gas was repeated at the end of surgery and the vital signs were noted. Post operatively patients were shifted to the intensive care unit. The post operative follow up of the patient was done after the first 24 hours. Post operative fluid management was managed by the intensive care unit doctors who were not aware of which group the patient belonged to. The doctors in the ICU administered fluid boluses when the patient was found to be hypovolemic as evidenced by tachycardia or hypotension (BP fall more than 20% of baseline systolic blood pressure). Fluid boluses were given in 500ml installments and choice of fluid was crystalloids. Colloids or blood was used when patient was hypotensive and having tachycardia, despite previous boluses depending on the post operative hemoglobin. Fluid requirement and blood pressure fluctuations in the post operative period were recorded from the records of the patient.

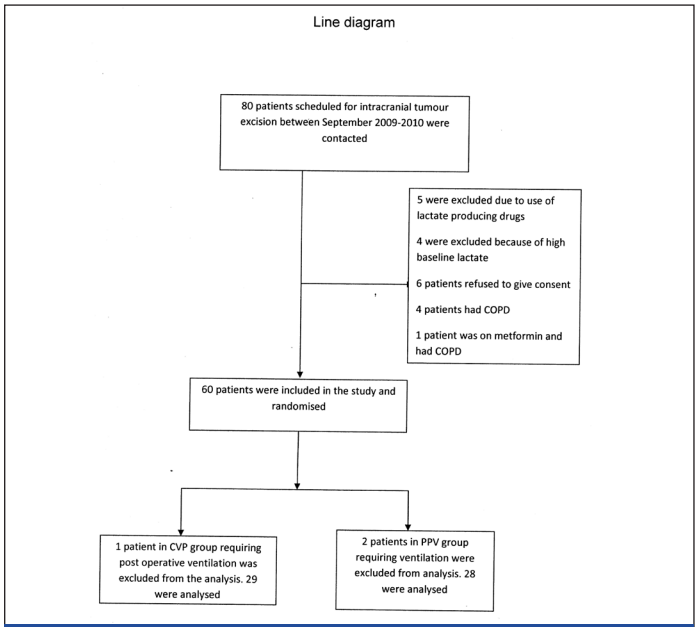
Outcomes: Fall in blood pressure from the baseline and severity of hypotension between the two groups as measured by intra-operative and post-operative serial blood pressure measurements. Adequacy of tissue perfusion as measured by lactate levels and presence of acid base imbalance like metabolic acidosis in both the groups.

STATISTICAL ANALYSIS

All baseline variables were summarized using descriptive statistical methods (mean, standard deviation, frequencies and percentages). The outcome variables were compared between the two groups using Independent two-sample t-test, if they were normally distributed. For variables which were not normally distributed, Mann-Whitney U and Wilcoxan rank sum test was used to compare the medians between the groups. Paired t-test was used for within group comparisons. All statistical analyses were done using SPSS 11.0.

RESULTS

Line diagram showing number of patients in each arm of the study and number analysed [Table/Fig-1].



[Table/Fig-1]: Study design showing number of patients in each group.

Baseline Characteristics	CVP Group Mean (SD)	PPV Group Mean(SD)
Age(in years)	43.44(10.26)	39.96(13.98)
BMI	22.78(2.98)	23.83(3.75)
Sex(M:F)	12:17	11:17
ASA grade 1:2	21:8	21:7
PCV (%)	37.53 (4.89)	37.49 (4.75)
Hb (mg/dl)	12.41(1.79)	12.71(1.97)
S.Creatinine mg/dl	0.878 (0.158)	0.89 (0.15)
Size of tumour (cm)	5.07 (1.4)	5.00 (1.79)
Systolic Pressure (mmHg)	122.38 (26.81)	129.0 (25.94)
Diastolic Pressure (mmHg)	73.06 (10.25)	73.28 (11.3)
Heart Rate/min	83.89 (14.27)	83.93 (13.8)
CVP (mmHg)	7.2(2.8)	6.9(1.8)
PPV	9.8(3.3)	9.5(2.9)
pH	7.45 (0 .05)	7.44 (0.03)
Hco_3 (mmol/L)	25.63(2.30)	24.16 (2.67)
Lactate(mmol/L)	1.95 (0.67)	2.40 (1.65)
Na (mmol/L)	134.76 (3.0)	135.43(2.7)
K (mmol/L)	3.81(1.1)	3.78(0 .33)
Ca (mmol/L)	1.09(.07)	1.11(0 .044)
Cl (mmol/L)	107.9(4.65)	107.88(2.91)

[Table/Fig-2]: Baseline characteristics.

	CVP Group	PPV Group	Significance
Intra-operative			
Lowest Systolic BP (mm Hg)	79.14 (8.10)	80.40 (11.19)	0.63
Lowest Diastolic BP(mm Hg)	46.76 (9.33)	45 (7.14)	0.43
Blood Loss ml Median(IQR)	600(400-800)	850(400-1688)	0.09
Lowest Temperature(Celsius)	35.70 (0.55)	35.71 (0.63)	0.70
Extubation Temperature(Celsius)	36.31 (0.67)	36.25 (0.63)	0.74
Post-operative			
Systolic BP(mm Hg)	125.24 (26.23)	128.68(18.20)	0.57
Diastolic BP(mm Hg)	71.59 (10.51)	75.64 (10.60)	0.15
Heart Rate (beats/min)	96.21 (12.50)	98.5 (15.83)	0.55
CVP (mm Hg)	8.10 (3.42)	6.96 (3.2)	0.20
PPV	9.55 (4.55)	9.143 (3.06)	0.69
PH	7.38 (.05)	7.36 (.05)	0.23
PCo_2 mmHg	38.63 (4.93)	38.56 (5.93)	0.96
Hco_3 (mmol/L)	22.73 (2.52)	22.12 (3.09)	0.42
Lactate (mmol/L)	5.49 (10.17)	3.83 (1.84)	0.40
Base excess	-1.63 (3.82)	-2.89 (3.41)	0.20
Sodium (mmol/L)	137.45 (3.73)	138.18 (3.56)	0.45
Potassium (mmol/L)	3.84 (0.45)	3.85 (0.38)	0.94
Calcium (mmol/L)	1.01 (0.14)	1.023 (0.09)	0.80
Chloride (mmol/L)	111.93 (2.98)	113.31 (2.89)	0.20
Haemoglobin (gm/dl)	9.99 (1.48)	9.75 (1.64)	0.55
24 hours			
Lowest Systolic BP(mm Hg)	97 (18.64)	97.82(10.90)	0.84
Lowest Diastolic BP(mm Hg)	61.79 (13.50)	62.07 (8.21)	0.93
PCV (%)	30.98 (0.87)	31.19 (0.82)	0.86

[Table/Fig-3]: Hemodynamic and acid base parameters.
Significant p-value<0.05

	CVP Group Median (25, 75)	PPV Group Median (25, 75)	p-value
Intra-operative			
Crystalloids (ml)	1500(1200,2000)	2250(1500,3000)	0.002
Colloids (ml)	500(500,500)	500 (250,1000)	0.57
Blood(ml)	0 (0,350)	175 (0,550)	0.14
24 hours post-operative			
Crystalloids (ml)	2400(1850,3100)	2100(1350,2200)	0.03
Blood (ml)	0(0,0)	0(0,0)	0.50

[Table/Fig-4]: Fluid management.
Significant p-value<0.05

Baseline characteristics of patients in the study are shown in [Table/Fig-2]. Both groups were comparable in the baseline data. The groups did not differ in total duration of surgery and requirement of vasopressors.

The hemodynamic and acid base parameters between CVP and PPV group were compared. The fall in blood pressure (>20% from baseline) and heart rate between the groups were comparable in the intra-operative and immediate post-operative period. The blood loss in the PPV group was more though not clinically significant (p=0.09). The post operative hemoglobin was comparable between the two groups.

Hemodynamic and acid base parameters are listed in [Table/Fig-3].

Lactate: The intra-operative change in lactate (post-operative compared to pre-operative) in the CVP group ranged from -0.3 to 4.9 mmol/L with a median of 1.4 (0.9 and 2; 25, 75 percentile) and in the PPV group it ranged from -0.6 to 5.1mmol/L with a median of 1.7 (0.8 and 2.2; 25, 75 percentile) and they were not statistically significant (p=0.992).

Fluid Management: In the post operative period patients in the CVP group had a higher median use of fluids (p=0.03). This was given as boluses of 500ml by intensive care doctors when the patient had hypotension and tachycardia. In the CVP group 17 of 29 patients required fluid boluses of which five patients required three or more boluses of crystalloids. In the PPV group only 10 of 28 patients required boluses and none required more than two boluses [Table/Fig-4].

DISCUSSION

Optimum intra-operative fluid therapy in neurosurgery is an essential pre-requisite for awakening, hemodynamic stability and post operative recovery [14]. Patients with intracranial pathology present special challenges to intensivists and anaesthetists. Large volume of fluids may be needed intra-operatively either to compensate the preoperative restrictive fluid therapy coupled with the use of osmotic diuretics to reduce cerebral edema in addition to replacing intra-operative blood loss.

Fluid requirement in neurosurgery is difficult to assess owing to the occult blood loss under the drapes, irrigating fluids, and unreliability of commonly used indices like urine output due to use of osmotic diuretics. Hence, the anaesthetist has to rely on hemodynamic parameters to guide fluid management and maintain normovolemia in patients.

Anaesthesiologists mostly manage fluid therapy by approximation and in some instances predictors of cardiac preload like CVP are used to guide fluid management. The basis of using CVP is that it reflects the right ventricular end diastolic volume and hence is an indicator of LV preload. In critically ill patients there are changes in the LV and RV compliance, venous tone and intra-thoracic pressures. In these conditions CVP has been proven to be poorly reflective of the fluid responsiveness [5, 15, 16]. However, by convention it is still used as a guide to fluid management [17].

The modern approach to fluid management is based on the concept of Goal-Directed Therapy (GDT), where it is believed that interventions should be performed specifically to affect a meaningful clinical variable. Management of fluids such that stroke volume is optimized is an extremely well-validated approach that has been shown repeatedly to reduce morbidity [18,19]. Three recent prospective, randomized, controlled trials have suggested that optimization of respiratory variation may have the potential to improve outcomes, despite the evidence pointing to use of goal directed fluid therapy it has not been actively used by anesthetists [13, 20-22].

With availability of less invasive methods for monitoring, use of parameters like Stroke Volume Variation (SVV), PPV are being used increasingly to guide fluid management and have been shown to be more useful than CVP in patients presenting for high risk abdominal surgery [4, 5, 15]. PPV has been shown to be reflective of intravascular volume like Systolic Pressure Variation (SPV) in neurosurgical patients [23]. The PPV derived from Datex Ohmeda system has been shown to be reliable [24]. The threshold value of PPV was found to be 13% in a study done comparing delta PPV and delta down and this was used as the cut off value [9, 25]. There are limited studies using PPV in neurosurgical patients and the effect of fluid management and hemodynamic stability and tissue perfusion in comparison to CVP guided treatment has not been studied [26, 27].

In this study the patients included were both ASA grade 1 and 2, to better reflect the actual spectrum of patients in clinical practice. ASA 2 or older patients may have underlying mild cardiac disease or hypertension with hampered RV compliance; but this is not frequent and does not significantly alter post-operative morbidity [28-30]. Moreover, the study design (randomisation) ensures that such potential confounding factors have been adequately dealt with and do not influence the results adversely. This is confirmed by the similar distribution of patients with ASA grade 1 and 2 in both groups [Table/Fig-2].

It was found that there was no significant difference in the fall in blood pressure (>20% fall from baseline) between the groups. Only 38 of 60 patients had a fall in BP which was mostly in the period after induction when surgical preparation of the patient was going on.

The crystalloid use was significantly more in the PPV group. The blood loss though higher in the PPV group was not significant. There was an association between increased crystalloid usage and increased blood loss in patients who received the fluid management on the basis of PPV. Our study was not powered to detect the blood loss and hence, whether this was an association or causation has to be confirmed by a larger study. Patients in the CVP group did not require as much fluids since the value did not change from baseline. Factors like duration of surgery, size of tumour which may influence total fluid administered were compared and no significant difference was found between the groups. The post-operative hemoglobin was also comparable between the groups. Pestel et al., showed that CVP did not change till more than 30% of estimated blood volume was removed in an experimental pig model [31]. Hence using CVP as a guide for fluid management especially intra-operatively in the face of acute blood loss may be erroneous.

Considering that post operative blood loss is minimal in neurosurgery the post operative fluid requirement may reflect adequacy of intra-operative fluid administration unless the patient developed a hematoma. None of the study patients required re-exploration. The postoperative period fluid boluses given in the event of hypotension or tachycardia was significantly more in the CVP group (p=0.03) probably reflecting hypovolemia. Seventeen of 29 patients in the CVP group required fluid boluses of which 10 patients required more than one fluid bolus compared to 10 of 28 patients in the PPV group and only two patients requiring more than one fluid bolus. The intra-thoracic pressure was normal for all patients intra-operatively as measured on the ventilator and there were no clinical signs of hypervolemia and fluid overload in any of the patients.

Studies of perfusion status revealed that the acid base and electrolyte status in the post operative period was comparable between CVP and PPV groups as were the lactate levels. The baseline lactate was higher than normal in both groups probably reflecting other factors in play, 37 of 57 patients had a normal post operative pH between 7.35-7.45 [32]. It is common practice to alternate ringer lactate and normal saline to avoid hyperchloremia and hypotonicity. Despite that there was a tendency for hyperchloremia in both groups.

From this study it can be concluded that PPV can effectively augment CVP as an index to guide fluid therapy. The complications associated with central line insertion like pneumothorax, hemothorax, misplacement of line and catheter related blood stream infections can be avoided [33]. Since most patients undergoing craniotomy for tumour excision are monitored using invasive arterial line, the additional cost of a central line can also be avoided.

LIMITATION

The limitations of the study were that patients were observed post-operatively for only the first 24 hours, factors like duration of hospital stay which varies depending on the type of tumour and type of craniotomy were not studied. Post operative creatinine and renal functions were also not routinely monitored in all patients. The study was confined to patients in supine and lateral position and so the reliability of PPV in other positions cannot be commented upon as with CVP measurements. The effect of vasopressors on PPV and CVP was not studied. The inability of PPV to reflect hypervolemia was another limitation of the study.

CONCLUSION

PPV can be used as a reliable index to guide fluid management in neurosurgical patients undergoing craniotomy in supine and lateral position. PPV monitoring may lead to better post-operative hemodynamic stability. PPV can also augment CVP guided fluid therapy, avoid complications associated with central lines and reduce additional cost. Further studies are warranted to confirm these findings for craniotomies in positions other than supine and lateral.

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