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ORIGINAL ARTICLE

Perioperative Carbon Dioxide Gap Following Crystalloid and Colloid Therapy in Neurosurgical Patients: A Randomised Comparative Study

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Abstract

Background: The carbon dioxide gap (CO_2, gap) is a flow-dependent variable inversely related to cardiac output and has emerged as a potential marker of circulatory adequacy. **Aim:** This randomized comparative study aimed to evaluate perioperative CO_2, gap behaviour following intraoperative crystalloid and colloid fluid therapy in neurosurgical patients. The primary objective was to assess variation in the CO_2, gap after administration of crystalloid and colloids. Secondary objectives included evaluation of haemodynamics and correlation of CO_2, gap with serum lactate and central venous oxygen saturation ($ScvO_2$,). **Methods:** Forty-four adult, ASA-PS I-II patients, 18-60 years, of either sex, planned for neurosurgical intervention under general anaesthesia were included in the study.Patients were randomly allocated to Crystalloid (CR) or colloid (CO) group .Fluid replacement for blood loss was performed using the allocated study fluid according to the predefined protocol. **Results:** Baseline parameters were comparable between groups. The CO_2, gap values were comparable between the crystalloid and colloid group (p value > 0.05 at T1, T2, T3). Macro-hemodynamic parameters were largely similar between groups, except for a higher heart rate in the crystalloid group at 6 hours. No significant correlation was found between CO_2, gap and lactate or $ScvO_2$, (CO_2, gap vs Lactate, $\rho = 0.03$, $p = 0.700$) (CO_2, gap vs $ScvO_2$, $r = 0.06$, $p= 0.404$). **Conclusion:** The perioperative CO_2, gap was comparable between crystalloid and colloid groups in neurosurgical patients.

Key Words

Perfusion, Colloids, Lactates, Neuroanaesthesia

Introduction

Neurosurgical procedures are accompanied by significant fluid shifts, blood loss, exposure to vasoactive drugs, and position-related physiological alterations. Surgical manipulation, bleeding, anaesthetic exposure, vasopressor administration, and fluid therapy may induce significant alterations in microcirculatory flow, even when hemodynamic parameters are stable. The macrocirculatory stability, assessed by conventional parameters such as mean arterial pressure and heart rate, may not reliably reflect the adequacy of tissue perfusion.[1]

The carbon dioxide gap (CO_2 gap) is the difference between venous and arterial carbon dioxide tensions.It is a flow-dependent variable inversely related to cardiac output and has emerged as a potential marker of circulatory adequacy.[2] CO_2 gap values greater than 6

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mmHg are associated with impaired CO_2 clearance in low-flow states and are predictive of postoperative complications in high-risk surgical patients.[3,4] A strong inverse correlation between the CO_2 gap and cardiac index was observed, suggesting that CO_2 gap may serve as a reliable surrogate of cardiac performance.[5] Elevated CO_2 gap values have been demonstrated even in the presence of normal lactate and $ScvO_2$ levels, suggesting its ability to detect occult hypoperfusion not captured by traditional markers.[3]

Fluid therapy is a critical component of haemodynamic management .Crystalloids and colloids differ in their intravascular retention, oncotic properties, and effects on preload and cardiac output.[6] These differences influence venous return, cardiac output, and hence, the clearance of metabolically produced CO_2.

The physiological importance of CO_2 gap has been explored in critical care. The haemodynamic effects of crystalloid and colloid fluids have been studied independently, but the perioperative behaviour of CO_2 gap in relation to intraoperative fluid strategy has not been evaluated in neurosurgical patients.It is unclear whether different fluid regimens affect CO_2 gap dynamics differently in neurosurgical patients. We hypothesised that the intraoperative fluid strategy influences perioperative CO_2 gap values, and that colloid therapy would be associated with lower CO_2 gap values than crystalloid therapy.

This study aimed to evaluate perioperative CO_2 gap behaviour following intraoperative crystalloid and colloid fluid therapy in neurosurgical patients. The primary objective was to assess variation in the CO_2 gap after administration of crystalloid and colloid solutions. Secondary objectives included evaluation of haemodynamic parameters and correlation of CO_2 gap with serum lactate and central venous oxygen saturation ($ScvO_2$).

Material and Methods

This prospective, randomised, single-centre comparative study was conducted in the Department of Anaesthesiology of a tertiary care hospital. Ethical clearance was obtained from the institutional ethical committee (EC/NEW/INST/2022/HR/0189 on 29/09/2023), followed by registration with the Clinical Trials Registry-India (CTRI/2023/12/060550). The study was conducted in accordance with the Declaration of Helsinki. Written informed consent was obtained from all patients.

44 adult, ASA-PS I-II patients, 18-60 years, of either sex, planned for neurosurgical intervention under general anaesthesia requiring arterial line and central line placement were included. Patients with history of cardiac illness, chronic kidney illness, allergy to any fluid used in the study, diabetes mellitus, coagulation disorder, or deranged liver function tests were excluded. All patients underwent pre-anaesthetic evaluation as per institutional protocol. Patients were fasted according to standard guidelines.

Patients were randomly allocated in 1:1 ratio to Crystalloid (CR) or colloid (CO) group using a computer-generated randomisation sequence prepared by an independent investigator. Allocation concealment was ensured using sequentially numbered, opaque, sealed envelopes, which were opened only after patient enrolment. Due to the nature of the intervention, blinding of the treating anaesthesiologist was not feasible.

In both groups, baseline maintenance fluid was administered using balanced salt solution at 2 mL/kg/h throughout the intraoperative period. Fluid replacement for blood loss was performed using the allocated study fluid according to the predefined protocol described below.

For blood loss up to the calculated Maximum Allowable Blood Loss (MABL), volume replacement was performed using 250 mL boluses of the allocated study fluid administered over 3–5 minutes.Patients in the CR group received balanced salt solution (Plasmalyte). Patients inthe CO group received 6% hydroxyethyl starch (130/0.4). When blood loss exceeded the calculated MABL, transfusions of packed red blood cells were initiated. If mean arterial pressure (MAP) decreased below 65 mmHg despite protocolized fluid replacement and blood transfusion, intravenous noradrenaline infusion was started at 0.05 mcg/kg/min and titrated to maintain MAP of 65 mmHg.

Samples of arterial and central venous blood were obtained simultaneously at predefined time point: before surgical incision (T0), two hours after incision (T1), at the commencement of skin closure (T2), 30 minutes after transfer to the post-anaesthesia care unit (PACU) or intensive care unit (ICU) (T3).

The following parameters were recorded: Arterial partial pressure of carbon dioxide ($PaCO_2$), Central venous partial pressure of carbon dioxide ($PcvCO_2$), lactate concentration, Central venous oxygen saturation ($ScvO_2$).

The CO, gap was calculated as the difference between central venous and arterial partial pressures of carbon dioxide: CO_2 gap = $PcvCO_2$ - $PaCO_2$.

Systolic blood pressure (SBP), diastolic blood pressure

(DBP), mean arterial pressure (MAP), heart rate (HR), and urine output were recorded hourly during surgery and in the early postoperative period in the post-anaesthesia care unit or intensive care unit.

Sample size calculation

The sample size was calculated based on a previous study by Mahrous and Ismail *et al*.[7] which reported mean CO_2 gap of 5.09 ± 0.92 mmHg in the CR group and 4.57 ± 0.87 mmHg in the CO group. Using these values, the required sample size was calculated with a two-sided alpha error of 0.05 and a power of 80%. The minimum sample size required was 48 patients. As the study was conducted at a single centre with a fixed recruitment period and a limited eligible patient population, finite population correction was applied. Based on anticipated patient availability during the study period, the final sample size was adjusted to 44 patients, with 22 in each group.

Statistical Analysis

Data were recorded in Microsoft Excel and analysed using SPSS v23 (IBMCorp.) software**.** The distribution of continuous variables was assessed using Shapiro–Wilk test. Normally distributed data are presented as mean ± standard deviation (SD). Non-normally distributed data are presented as median (interquartile range, IQR). Categorical variables are expressed as a number (percentage). For between-group comparisons, the independent Student's t-test was used for normally distributed continuous variables. Mann–Whitney U test was used for non-normally distributed variables. Chi-square test was used for categorical variables.

Between-group differences in CO_2 gap at each time point were estimated using unadjusted mean differences and baseline-adjusted mean differences, calculated using linear regression (ANCOVA approach) with the CO_2 gap at the respective time point as the dependent variable and study group as the main predictor, adjusting for baseline CO_2 gap. Correlation between variables was assessed using Pearson's correlation coefficient for normally distributed variables. Spearman's rank correlation coefficient was used when at least one variable was not normally distributed. p-value< 0.05 was considered statistically significant.

Results

44 patients were included, with 22 patients in each group. Baseline demographic characteristics were comparable between the groups (Table 1).

CO_2 gap was significantly higher in the CR group compared with the CO group at all predefined perioperative time points in the unadjusted analysis (Table 2). After adjustment for baseline CO_2, gap, the adjusted mean difference between the groups was reduced at subsequent time points. Although the direction of the effect remained unchanged, adjusted analyses demonstrated loss of statistical significance at 2 hours after incision, at skin closure, and in the early postoperative period. HR and MAP were comparable between the CR and CO groups at most time points. (Table 3). No meaningful correlation was found between CO_2 gap and lactate or $ScvO_2$ (Table 4).

Table 1 : Baseline demographic and clinical characteristics of the study population.

Characteristic	CR group (n = 22)	CO group (n = 22)	Test statistic	p-value
Age (years)	40.23 (12.8)	44.27 (10.5)	t = -1.145	0.259
Gender Male n (%) Female n(%)	 13(59.1%) 9 (40.9 %)	 10 (45.5%) 12 (54.5%)	$\chi 2$ = 0.820	0.365
BMI (kg/m²)	23.19 (3.0)	24.14 (3.8)	t = -0.914	0.366
ASA -PS I n (%) II n (%)	 6 (27.3%) 16 (72.7%)	 9 (40.9%) 13 (59.1%)	$\chi 2$ = 0.91	0.340
Duration of surgery (hours)	4.8 (1.42)	4.1 (1.17)	W = 302.500	0.144
Total Baseline Fluid (ml)	588.64 ± 159.57	532.64 ± 185.73	W = 313.500	0.095
Total Bolus Volume (ml)	875.00 ± 168.15	863.64 ± 148.95	W = 235.500	0.914
Total Input (ml	1463.64 ± 252.51	1396.27 ± 222.23	W = 235.500	0.391

Table 2 : Comparison of carbon dioxide gap values between crystalloid and colloid groups at predefined timepoints.

Timepoint	CR group (mmHg) Mean ± SD	CO group (mmHg) Mean ± SD	Unadjusted Mean difference (95%CI)	p-value	Baseline Adjusted mean difference* (95%CI)	p-value
T0	6.60 ± 1.72	4.50 ± 1.62	−2.10 (−3.12 to −1.09)	<0.001	NA	<0.001
T1	6.88 ± 1.90	4.36 ± 1.75	−2.52 (−3.63 to−1.41)	<0.001	−1.00 (−2.00 to 0.00)	0.051
T2	7.26 ± 2.40	4.77 ± 1.53	−2.49 (−3.72 to −1.26)	<0.001	−1.01 (−2.21 to 0.19)	0.09
T3	7.20 ± 2.33	4.74 ± 1.32	−2.47 (−3.63 to −1.31)	<0.001	−1.03 (−2.14 to 0.08)	0.069

Table 3 : Comparison of macro-hemodynamic parameters between crystalloid and colloid groups at different time points.

Parameter	Time point	Group CR	Group CO	p value
Heart Rate (BPM)	Baseline	77.45 ± 21.84	78.59 ± 10.91	0.897
	2 h	82.45 ± 16.54	78.41 ± 11.04	0.346
	4 h	82.68 ± 16.73	76.88 ± 13.19	0.327
	6 h	86.14 ± 3.76	74.33 ± 5.13	0.037
	PACU	81.50 ± 11.52	77.41 ± 12.69	0.269
MAP (mmHg)	Baseline	87.09 ± 11.72	83.55 ± 9.91	0.285
	2 h	81.91 ± 11.93	85.55 ± 11.22	0.304
	4 h	82.32 ± 9.98	84.38 ± 10.92	0.568
	6 h	83.71 ± 8.60	85.67 ± 18.34	0.874
	PACU	86.20 ± 11.97	85.09 ± 9.98	0.796

Table 4 : Correlation of carbon dioxide gap with serum lactate levels and central venous oxygen saturation.

Variable pair	Correlation coefficient	p-value
CO_2 gap vs Lactate	ρ =0.03	0.700
CO_2 gap vs $ScvO_2$	r = 0.06	0.404

Discussion

In the present study, CO_2 gap values were higher in the crystalloid group than in the colloid group throughout the perioperative period. Although the patients were randomly allocated, a significant imbalance in the baseline CO_2 gap was observed. This could be attributed to the study's relatively small sample size.To account for the baseline difference, statistical adjustment for baseline CO_2 gap was applied, and after the adjustment, between-group differences did not remain statistically significant.

CO_2 gap greater than 6 mmHg indicates inadequate tissue perfusion and reduced cardiac output.[8] Despite lack of significance after baseline adjustment, a clinical observation was that CO_2 gap in the CR group remained above 6 mmHg during most perioperative time points, whereas values in the CO group remained below this threshold. The observed difference in CO_2 gap should be interpreted cautiously and may, at least in part, reflect the initial baseline imbalance rather than a true independent effect of fluid type.

Mahrous *et al*.[7] evaluated the effect of crystalloid and colloid fluid therapy on CO_2 gap during major orthopaedic procedures. CO_2 gap was found comparable between the groups during the early intraoperative period.Significant differences emerged at the fourth and fifth hours and at PACU admission, with the crystalloid group showing higher CO_2 gap than the colloid group. Despite these differences, the absolute CO_2 gap in both groups remained within the physiological range and did not exceed 6 mmHg threshold. The differences between their results and current study may be related to differences in surgical population and perioperative physiology. They included ASA I–III patients undergoing major orthopaedic procedures rather than neurosurgical patients. Various factors affect CO_2 gap measurements, including cardiac output, microcirculatory alterations, metabolic activity, ventilatory parameters, inotropes, hemoglobin oxygenation.[8] Therefore, variability in these determinants may contribute to differences in CO_2 gap observed across studies.

Change from supine to sitting position in neurosurgical patients is associated with deterioration in cardiac index. CO_2 gap shows a strong inverse relationship with cardiac index.$ScvO_2$ correlates weakly with cardiac index.[5] These findings support the physiological relevance of CO_2 gap in neurosurgical patients and suggest that an increased CO_2 gap in this setting may reflect reduced cardiac performance and impaired adequacy of blood flow relative to metabolic demand.

A possible explanation for the relatively lower CO_2 gap values observed with colloid therapy is the greater intravascular persistence of colloid solutions, which may provide more effective plasma volume expansion and better maintenance of systemic blood flow than crystalloids.[6] Mahrous *et al***.**[7] attributed lower CO_2 gap values with colloid therapy to better intravascular volume expansion and hemodynamic stability. However, this interpretation should remain cautious in current study because both groups maintained broadly acceptable conventional hemodynamic parameters, and direct cardiac output monitoring was not performed.

Maintenance of adequate arterial pressure is important in neurosurgical patients because cerebral perfusion is vulnerable to systemic hemodynamic fluctuations. Similar macro-hemodynamic profiles observed in both groups in current study suggest that numerical differences observed in the CO_2 gap were not fully explained by conventional systemic hemodynamic variables.

Although colloids have traditionally been considered superior for maintaining intravascular volume, evidence for a clinically meaningful macrohemodynamic advantage remains inconsistent. In present study, conventional hemodynamic variables were comparable between groups. This is in line with larger perioperative data suggesting minimal differences in cardiac index and arterial pressure variability between colloid- and crystalloid-based goal-directed strategies,[9] although studies such as Mahrous et al**.**[7] have reported lower CO_2 gap and better late perfusion indices with colloids despite limited differences in routine hemodynamic parameters. Markovic-Bozic et al.[10] found that although patients receiving crystalloids required significantly higher phenylephrine doses, perioperative outcomes, including lactate levels and hospital stay, did not differ significantly from those receiving colloids when hemodynamic management was protocol driven.

The CO_2 gap primarily reflects the adequacy of blood flow relative to tissue CO_2 production and is influenced by cardiac output and systemic perfusion.[11]In contrast, serum lactate is considered a marker of anaerobic metabolism and typically increases when tissue oxygen delivery becomes insufficient to meet metabolic demands.[12] $ScvO_2$ reflects the global balance between oxygen delivery and consumption.[13] Because these parameters represent distinct physiological processes, a direct correlation between them may not always be observed, particularly in patients with relatively preserved systemic hemodynamics.

Mahrous *et al*.[7] reported no significant correlation between the CO_2 gap and HR, MAP, central venous pressure, blood loss, serum lactate, and $ScvO_2$. Thiehoff *et al* [14] also reported that there is no significant correlation between the CO_2 gap and lactate levels.The relative hemodynamic stability in the current study also explain the absence of significant correlation between CO_2 gap and lactate or $ScvO_2$, as global oxygen delivery was likely maintained in both groups. Under such conditions, lactate levels may remain within normal limits, and $ScvO_2$ values may remain relatively preserved despite minor variations in blood flow reflected by the CO_2 gap. CO_2 gap provides complementary information on tissue perfusion and may not necessarily correlate directly with traditional markers such as lactate or $ScvO_2$.[11,13]

This study was conducted at a single centre with a relatively small sample size.Cardiac output was not directly measured; therefore, the relationship between the CO_2 gap and systemic blood flow could not be objectively evaluated. Future studies incorporating direct cardiac output monitoring along with additional microcirculatory perfusion markers may help further clarify the utility of the CO_2 gap in the perioperative setting.

Conclusion

In this randomized comparative study, there was no significant difference in perioperative CO_2 gap between crystalloid and colloid groups. Conventional hemodynamic parameters were comparable and CO_2 gap showed no significant correlation with lactate or $ScvO_2$.

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Conflict of Interest: Nil

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