Original Article

A pilot randomised clinical trial comparing desflurane anaesthesia vs total intravenous anaesthesia, for changes in haemodynamic, inflammatory and coagulation parameters in patients undergoing hyperthermic intraperitoneal chemotherapy

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ABSTRACT

Background and Aims: Cytoreduction and hyperthermic intraperitoneal chemotherapy (CRS+HIPEC) cause numerous pathophysiological changes. The objective of this study was to compare the effect of two anaesthetic techniques on haemodynamic changes, inflammatory and coagulation parameters during this procedure. **Methods:** Twenty-one consenting adults undergoing CRS+HIPEC procedure, were block randomised to receive desflurane (V, $n = 9$) or TIVA (T, $n = 12$). After epidural catheter placement and intravenous induction of anaesthesia in both groups with fentanyl, propofol and rocuronium, anaesthesia was maintained with propofol or with desflurane, based on group allocation. Haemodynamic and temperature changes were assessed intra-operatively and variance was analysed. Inflammatory and coagulation markers were measured and compared at five time-points in the peri-operative period. Categorical variables were analysed using Chi square or Fisher exact test. Continuous variables were compared using t-test or Wilcoxon rank sum test. **Results:** Changes in core body temperature and haemodynamic variables during the hyperthermic intraperitoneal chemotherapy (HIPEC) phase were comparable between the two groups; except mean variance of mean arterial pressure, which was significantly higher ($P = 0.0056$) in group V (receiving desflurane) (58.98 ± 36.74) than TIVA group (27.51 ± 14.22). Inflammatory markers in both groups were comparable at five defined time points in the peri-operative period. On post-hoc analysis, pairwise comparisons with baseline, between levels of inflammatory markers within each group showed increased post-operative inflammation in group V. Mean prothrombin time was comparable. **Conclusion:** Desflurane group suffered greater mean arterial pressure (MAP) instability during the HIPEC phase. Inflammation in both groups was highest during the first 24 h after surgery. Prolonged inflammation was noted in patients receiving desflurane.

Key words: Desflurane, hyperthermic intraperitoneal chemotherapy, induced hyperthermia, inflammation, propofol, temperature

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INTRODUCTION

Peritoneal carcinomatosis (PC) characterises an extensive metastatic spread throughout the abdomen and pelvis of various organ-based malignancies. Hyperthermic intraperitoneal chemotherapy (HIPEC) permits the administration of intraperitoneal chemotherapy following cytoreductive surgery (CRS) to attain higher local concentrations of the cytostatic agents, combined with hyperthermia, to eliminate any microscopic residual disease.[1]

Numerous pathophysiological changes in the patients' systemic parameters occur during this procedure.[2,3] Initially, these changes are secondary to CRS and later due to hyperthermia, increased intra-abdominal pressure and the cytostatic, immune-modulating and toxic effects of the perfused chemotherapeutic drug. Surgical stress leads to metabolic and neuroendocrine changes causing significant depression of cell-mediated immunity.[4,5] There exists a large lacuna in the literature regarding the role of anaesthetic drugs in this interplay.

Anaesthetic agents may inhibit neutrophil phagocytosis, induce lymphocytosis and modulate the hypothalamic-pituitary-adrenocortical, neural-immunoregulatory and anti-inflammatory pathways. Previous studies have shown a benefit of total intravenous anaesthesia (TIVA) over inhalational anaesthesia in non HIPEC surgeries.[6] Numerous studies have investigated the influence of anaesthetic techniques on the immune function and their biological effect on malignant tumours.[7] However, no prospective studies have evaluated the effects of anaesthesia techniques during HIPEC. The primary objective of this study was to compare the effect of two anaesthetic techniques on haemodynamic changes during HIPEC surgery. The secondary objective was to study and compare inflammatory and coagulation parameters in the two groups.

METHODS

This is a single centre, pilot randomised parallel-group clinical trial to compare desflurane anaesthesia vs TIVA, for changes in haemodynamic, inflammatory and coagulation parameters of patients undergoing CRS and HIPEC. This study was approved by the Institutional Ethical Committee and prospectively registered with the Clinical Trial Registry of India [CTRI/2017/11/010520]. After obtaining informed written consent, 27 patients [American Society of Anesthesiologists (ASA) I, II, III], aged 18–70 years, admitted for CRS and HIPEC, with a diagnosis of peritoneal carcinomatosis without distant metastasis were consecutively enrolled and block randomised into two groups; Group T (n = 9) receiving TIVA and Group V (n = 12) receiving desflurane-based balanced anaesthesia [Figure 1]. Six patients were excluded due to the inoperability of the disease. Exclusion criteria were: contraindications to epidural block or propofol, desflurane, or local anaesthesia, liver and/or kidney impairment, or coagulopathy, asplenia or splenectomy.

Epidural catheter was placed in awake patients followed by the induction of anaesthesia with propofol (1–3 mg/kg) and fentanyl (2 mcg/kg), preceded by an intravenous injection of lignocaine (0.5 mg/kg) followed by 0.6 mg/kg rocuronium. After intubation, patients were mechanically ventilated with a tidal volume of 8 mL/kg ideal body weight, at a rate enough to maintain normocapnia (end-tidal CO_2 of 30–35 mm Hg) with 1.0 l/min O_2 and 1.0 l/min air. Anaesthesia maintenance was with propofol or with desflurane, based on group allocation, and adjusted to maintain the bispectral index (BIS) between 40 and 60. Analgesia in both groups included a combination of intravenous opioids and epidural infusions (bupivacaine 0.125% with fentanyl 2mcg/mL). Advanced haemodynamic monitoring was performed with: estimated continuous cardiac output (esCCO) technology. Fluid and inotrope requirement was managed according to the Goal Directed Fluid Therapy. HIPEC was performed as an open procedure with the coliseum technique with a peritoneal and outflow thermal plateau of 41.5°C. Residual neuromuscular blockade was reversed with neostigmine (50 μg/kg) and glycopyrrolate (10 μg/kg) IV if patient was a candidate for extubation. Patient was extubated if patient demonstrated good respiratory effort and airway reflexes. All patients were transferred to the intensive care unit (ICU) for further management.

The following information: patient characteristics, peritoneal cancer index (PCI), histological type, ASA score, intra-operative haemodynamic heart rate (HR), mean arterial pressure (MAP), pulse pressure variation (PPV), cardiac Index (CI), systemic vascular resistance index (SVRI), central venous pressure (CVP), and peripheral oxygen saturation (SpO_2), electrocardiography (ECG), capnography, temperature, BIS and urine output were collected.

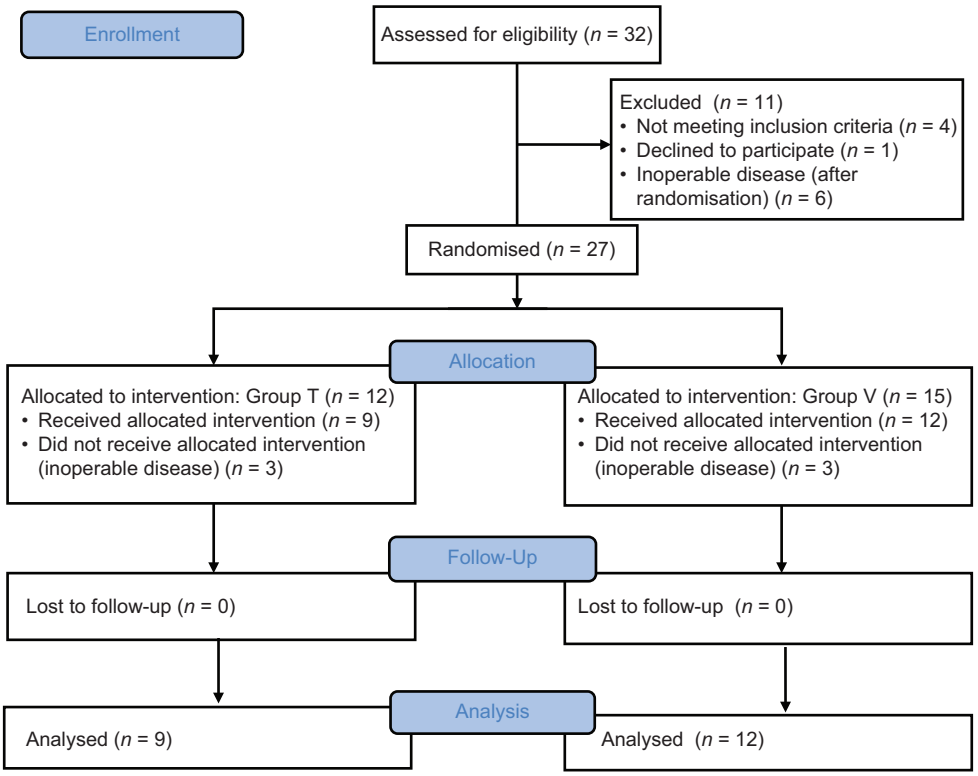

Figure 1: Flow diagram of the study population- Among the 32 patients who were assessed for inclusion, 27 patients were consecutively enrolled and block randomised into two groups; Group T (*n* = 9) receiving TIVA and Group D (*n* = 12) receiving desflurane. Six patients were excluded due to inoperability of the disease

Further, five time-points were defined in the peri-operative period: baseline (t1, before induction of anaesthesia); after incision (t2, 30 min after skin incision), end of HIPEC phase (t3, 30 min after warm chemotherapeutic circulation stopped), post-operative day 1 (t4), and post-operative day 3 (t5). At every time point, blood specimens (5 mL) were drawn for the measurement of inflammatory markers, which were measured in the laboratory by personnel blinded to patients' group allocation. Total leucocyte count (TLC), absolute neutrophil count (ANC), neutrophil-lymphocyte ratio (NLR), platelet-lymphocyte ratio (PLR) and prothrombin time (PT) were analysed. NLR and PLR were calculated by dividing, respectively, the absolute neutrophil and platelet counts by the absolute lymphocyte count. Blood loss, fluid requirement, blood products administered and complications if any were documented.

Each qualitative variable was expressed as frequency and percentage. Continuous variables were organised as mean (SD) and/or median (range). Further, to assess the variability during CRS and HIPEC, the mean of variance for each haemodynamic variable and temperature was calculated and reported. For the association between two categorical variables, Chi square or Fisher exact test was used. However, continuous variables with normal distribution were compared between two groups, using t-test; and those with non-normal distribution were analysed by Wilcoxon rank sum test. For more than two groups, analysis of variance (ANOVA) was used with Bonferroni correction. A probability value (*P* value) of less than 0.05 was considered as statistically significant. Statistical Software STATA 14.2 was used for the analysis. A post-hoc analysis within each group was performed for pairwise comparisons of the levels of inflammatory markers with baseline.

RESULTS

Patient characteristics and surgical factors were comparable between the groups [Table 1]. Haemodynamic parameters: During CRS core body temperature and haemodynamic variables were compared between the groups and no statistically significant differences were observed [Table 2].

During the HIPEC phase, no significant differences were observed in the mean and variance of the parameters between the two groups, except for the variance of MAP. Mean variance of MAP was significantly

Table 1: Patient characteristics and peri-operative details (data as mean (SD))

Mean (SD)	TIVA (*n*=9)	Desflurane (*n*=12)	*P* (TIVA-TCI vs. BAL)
Age (yrs.)	52 (16.23)	52.75 (9.1)	0.89
Sex, *n* (%)	6	15	0.33
Males	4 (44.44%)	2 (16.67%)	
Females	5 (55.56%)	10 (83.33%)	
Histologic diagnosis of Cancer, *n* (%)			
Ovary	4 (44.44%)	8 (66.67%)	
Appendiceal	2 (22.22%)	1 (8.33%)	
Rectum	2 (22.22%)	0	
Peritoneal Mesothelioma	0	2 (16.67%)	
Pseudomyxoma peritonei	1 (11.11%)	0	
Colon	0	1 (8.33%)	
ASA, *n* (%)			0.38
ASA I	5 (55.56%)	3 (25%)	
ASA II	3 (33.33%)	8 (66.67%)	
ASA III	1 (11.11%)	1 (8.33%)	
ECOG, *n* (%)			0.83
ECOG 0	3 (33.33%)	2 (16.67%)	
ECOG I	5 (55.56%)	8 (66.67%)	
ECOG II	1 (11.11%)	2 (16.67%)	
Chemotherapeutic drug, *n* (%)			0.204
Cisplatin	5 (55.56%)	10 (83.33%)	
Mitomycin	3 (33.33%)	1 (8.33%)	
Oxaliplatin	1 (11.11%)	0	
Melphalan	0	1 (8.33%)	
Weight (kg)	60.44 (10.9)	67.92 (13.48)	0.19
BSA (m^2)	1.64 (0.2)	1.64 (0.16)	0.95
Time duration of Surgery (min)	409.44 (50.34)	362.5 (86.64)	0.16
Time duration of HIPEC (min)	56.67 (10)	57.5 (6.22)	0.82
PCI	6.44 (5.17)	8.58 (5.37)	0.21
Post-op duration of stay (days)	11 (4.92)	10.5 (5.07)	0.86
Blood Loss (mL)	744.44 (678.44)	529.17 (232.05)	0.91
Total Fluids (mL)	4883.33 (1130.82)	5562.5 (2486.25)	0.64
Fluid CRS (mL)	3266.67 (806.23)	3666.67 (2120.28)	0.6
Fluid HIPEC (mL)	1250 (651.44)	1420.83 (525.04)	0.5
Total UO (mL/kg/h)	2.43 (1.36)	1.6 (0.86)	0.18
HIPEC UO (mL/kg/h)	5.55 (4.95)	2.31 (1.34)	0.14

Table 2: Haemodynamic parameters during CRS and HIPEC

Haemodynamic Parameter (Mean (SD))	Haemodynamics during Cytoreduction			Haemodynamics during HIPEC		
	Group T	Group V	*P*	Group T	Group V	*P*
Mean HR (beats/min)	75.54 (12.38)	81.88 (12.81)	0.27	93.22 (14.58)	92.63 (13.35)	0.93
HR Variance	97.07 (77.15)	90.93 (105.18)	0.78	22.07 (21.08)	27.67 (16.56)	0.48
MAP mean (mm Hg)	79.89 (7.22)	80.81 (6.51)	0.76	83.39 (15.82)	76.08 (6.57)	0.12
MAP Variance	108.9 (71.34)	149.62 (71.05)	0.10	27.51 (14.22)	58.98 (36.74)	0.01
PPV Mean	17.78 (8)	17.37 (5.87)	0.83	14.11 (8.05)	16.89 (7.43)	0.57
PPV Variance	49.26 (36.05)	38.05 (36.81)	0.43	17.62 (26.4)	30.85 (28.56)	0.13
CI Mean (L/min/m^2)	2.62 (0.62)	2.69 (0.31)	0.74	3.47 (0.92)	3.14 (0.68)	0.35
CI Variance	0.35 (0.41)	0.42 (0.43)	0.43	0.09 (.07)	0.11 (0.1)	1.00
SVRI Mean (dyn·s·cm^{-5}/m^2)	2387 (611.57)	2239 (357.84)	0.49	1793.54 (558.39)	1829.81 (516.10)	0.88
SVRI Variance	258040.5 (212817.4)	511470 (842297.3)	0.48	65646.73 (123214.3)	105055 (103909.3)	0.44
CVP Mean (mm Hg)	7.37 (1.51)	9.21 (2.63)	0.08	10.01 (2.18)	9.18 (2.94)	0.30
CVP Variance	9.71 (7.78)	8.19 (9.76)	0.39	1.14 (.80)	5.08 (7.09)	0.12
Temp Mean (Celsius)	35.6 (0.46)	35.67 (0.54)	0.76	37.08 (0.48)	37.10 (0.42)	0.89
Temp Variance	0.11 (0.12)	5.69 (19.38)	0.94	0.24 (0.24)	0.47 (0.40)	0.15

higher ($P = 0.0056$) in desflurane group (58.98 ± 36.74) than TIVA group (27.51 ± 14.22) [Table 2].

Vasoactive drug support was required in 7 (77.8%) patients in group T and for 9 (75.0%) patients in

group V suggesting no significant association between inotrope use and treatment groups.

The mean HR at start of HIPEC was 89.67 ± 17.41 in Group T and 87.08 ± 14.79 in Group V, which showed a gradual rise during the procedure. At the end of HIPEC, the mean HR in Group T was 100.57 ± 7.16, and in Group V it was 97.09 ± 11.56 [Figure 2].

The mean MAP at the start of HIPEC was 82.67 ± 12.67 in group T and 77.42 ± 8.07 in Group V. MAP in both the groups increased and peaked at 15 min from the initiation of HIPEC and was 87.00 ± 16.84 in group T and 79.92 ± 13.51 in group V. At the end, the mean MAP in group T was 84.86 ± 16.19; and in group V it was 71.55 ± 9.63 [Figure 3].

The mean SVRI at the start of HIPEC was 1780.67 ± 265.01 in group T and 1822.41 ± 353.16 in group V. SVRI in both the groups decreased and reached the lowest value near the end of HIPEC and was 1581.71 ± 392.94 in group T and 1590.03 ± 363.46 in group V.

The mean PPV at the start of HIPEC was 15.00 ± 9.71 in group T and 18.83 ± 10.20 in group V. The PPV showed fluctuations during HIPEC, which gradually decreased to 13.57 ± 11.57 in group T and 15.18 ± 9.62 in group V at the end of HIPEC.

The mean CI at the start of HIPEC was 3.24 ± 0.66 in group T and 2.83 ± 0.59 in group V. The CI in both groups gradually increased during this phase. At the end of HIPEC, the mean CI in group T was 3.82 ± 1.04; and in group V it was 3.26 ± 0.73.

Inflammatory parameters [Table 3]: Mean TLC, ANC, NLR, PLR, serum albumin levels in both groups were comparable ($P > 0.05$) at five defined time points in the peri-operative period. The mean TLC, mean ANC and mean NLR in both groups showed an increasing trend during the peri-operative period and peaked at t4 and thereafter decreased at t5. The mean PLR in both groups exhibited an initial decrease at t2. PLR then increased to reach the highest value at t3 in group T, and t4 in group V. It decreased at t5 in both groups. The albumin in both groups gradually decreased and reached the lowest value at t3 and began to increase in the post-operative period but remained significantly low at t5. On post-hoc analysis, pair wise comparisons with baseline, between the levels of inflammatory markers within each group was performed. In group T, ANC at t5 was found to be significantly higher as compared with t1. In group V, mean TLC and ANC on t4 and t5, and NLR on t5 were significantly higher than t1 [Table 3]. Mean PT in both groups were comparable ($P > 0.05$) at all the five defined time points in the peri-operative period, which peaked at t4 and decreased at t5.

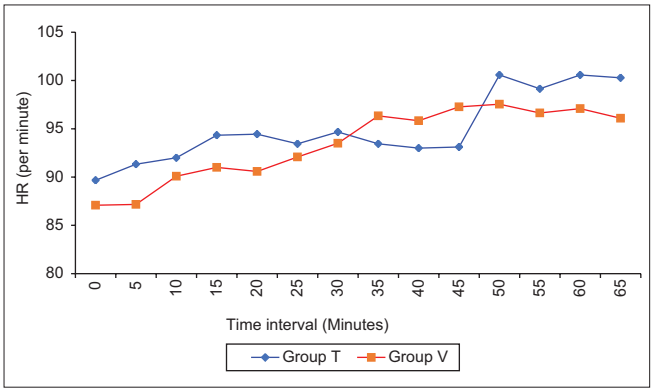

Figure 2: Mean heart rate in both groups increases during HIPEC and peak towards the end, in response to increasing temperature and decreasing SVR

DISCUSSION

There is not much literature available on haemodynamic parameters and systemic alterations associated with CRS and HIPEC. Society of onco-anaesthesia and peri-operative care has recently published consensus guidelines for anaesthesia protocol, use of TIVA vs inhalational anaesthesia, coagulation, haemodynamic, temperature monitoring and fluid therapy. This guideline also emphasised the use of cardiac output monitoring.[8] During extensive cytoreductive surgery, factors such as pain, heat loss, blood loss, tissue handling and positioning can cause fluctuations in haemodynamics. However, during HIPEC body temperature rises due to the circulation of the heated solution, significantly increasing the metabolic rate.[9]

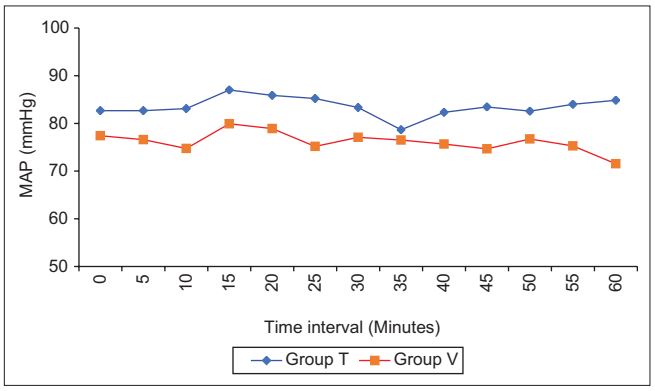

Figure 3: Mean arterial pressures rise during the initial part of HIPEC

Table 3: Inflammatory markers measured at Baseline (t1, before induction of anaesthesia); After incision (t2), End of HIPEC phase (t3), Post-operative day 1 (t4), and Postoperative day 3 (t5)

	All patients (*n*=21)	TIVA-TCI (*n*=9)	Desflurane (*n*=12)	*P* (TIVA vs. DES)
TLC (Mean (SD)				
t1	6122.86±2306.71	5502.22±1611.94	6588.33±2689.46	0.52
t2	7734.76±4589.94	7037.78±3188.95	8257.5±5496.66	0.94
t3	8463.81±4850.04	7947.78±2902.73	8850.83±6021.6	0.86
t4	11449.52±5401.22	11337.78±4641.77	11533.33±6111.83*	0.52
t5	9780.95±3607.83	9242.22±2684.21	10185±4243.91*	0.43
ANC (Mean (SD)				
t1	3646.19±1691.5	3165.56±963.63	4006.67±2048.42	0.57
t2	4600.48±3171.59	3934.44±2163.48	5100±3774.89	0.52
t3	5588.1±3278.88	5194.44±2354.72	5883.33±3910.62	0.89
t4	8425.71±4417.06	8050±3896.89	8707.5±4922.11*	0.72
t5	7209.05±3372.39	6744.44±2117.38*	7557.5±4136.26*	0.94
NLR (Mean (SD)				
t1	2.00±0.95	1.96±1.05	2.03±0.92	1.00
t2	1.96±0.71	1.68±0.75	2.17±0.63	0.12
t3	2.89±1.12	2.85±1.33	2.92±1.00	0.57
t4	5.8±5.34	4.31±2.55	6.91±6.63	0.62
t5	4.88±3.18	4.51±3.10	5.16±3.33*	0.89
PLR (Mean (SD)				
t1	95.02±40.48	96.26±44.85	94.09±38.92	0.89
t2	81.12±29.28	70.62±24.33	88.99±31.15	0.16
t3	108.87±48.70	106.64±43.46	110.54±54.14	0.94
t4	96.74±64.48	67.18±21.18	118.91±77.34	0.14
t5	80.67±37.77	72.22±26.9	87.01±44.34	0.48
Albumin (Mean (SD)				
t1	3.82±0.63	3.71±0.48	3.9±0.74	0.51
t2	3.54±0.48	3.39±0.39	3.66±0.52	0.21
t3	2.49±0.54	2.54±0.62	2.45±0.5	0.70
t4	2.61±0.49	2.67±0.43	2.58±0.54	0.68
t5	2.74±0.45	2.82±0.3	2.68±0.53	0.49

*Significant as compared to Pre-anaesthesia within group

The mean PPV was found to be comparable during CRS, the fluid responsiveness was also expected and found to be comparable between the groups. These findings differ from a previous study, which concluded that haemodynamic and neuroendocrine responses to surgical stress were better controlled with TIVA compared with inhalation anaesthesia.[6]

During the HIPEC phase, the variance of MAP was significantly higher ($P = 0.0056$) in the desflurane group as compared to TIVA. Changes in MAP in response to HIPEC are variable, with few studies showing stable MAP and others showing a significant decrease.[3,10-12] MAP variations are also governed by the use of vasopressors (norepinephrine), intravascular volume and changes in SVR. But in the present study, the use of vasoactive drug support, blood loss and administered fluids in both groups were comparable.

The HR variance was comparable in both groups. An increase in HR has been reported in previous studies also attributed to the body's initial responses to hyperthermia, to maintain CO in the face of decreasing SVR, splanchnic heating or abdominal distention.[2,10-14]

The mean SVRI decreases and reached the lowest value near end of HIPEC in both groups. During the cooling phase, SVRI begins to increase. These findings were similar to those of previous studies, wherein SVR decreased during HIPEC in response to systemic hyperthermia.[2,11,13]

In the present study, there were fluctuations in PPV during HIPEC, which gradually decreases at the end. The decrease in PPV could be attributed to the absence of blood loss during this period and therefore minimal changes in preload, along with intravenous infusion of cold crystalloids. Mean PPV and variance of PPV during HIPEC was comparable. However, PPV is unable to predict fluid responsiveness after intra-abdominal hypertension

induction. Hence, the significance of PPV during HIPEC is yet to be studied and therefore cannot be remarked upon.[15]

CI of patients in both the groups showed an increase during HIPEC and peaked towards the end of HIPEC. This trend was mirrored by the changes in HR during HIPEC. In the event of hyperthermia, the initial response of the body is dilatation of the peripheral vasculature to augment the loss of heat from the core to the environment. With the occurrence of decreasing SVR, cardiac output is maintained by an increase in HR[2,11,13,14] CVP was found to increase after the onset of HIPEC in the present study, which coincides with the findings of previous studies.[3,11,12,16]

Inflammatory parameters: Owing to acute inflammation and altered immune function during cancer surgery, individual inflammatory biomarkers and composite scores have been proposed to predict oncological outcomes.[12,17] Previous studies comparing anaesthesia techniques for specific markers of inflammation have revealed conflicting results.[18,19]

NLR during HIPEC was found to be a prognosticator for risk stratification, overall survival and progression-free survival.[17,20,21] PLR has been reported to be more closely associated with the recurrence risk and survival of PC patients undergoing CRS-HIPEC than NLR.[22] The peri-operative inflammation, predicted by mean TLC, ANC, NLR and PLR in both groups peaked during the immediate peri-operative period. Thus, inflammation was highest in the 24 h following HIPEC. Inflammatory parameters were comparable in both groups, consistent with the findings presented in a retrospective study, where TIVA did not impact NLR and PLR profiles of patients undergoing HIPEC.[23]

On post-hoc analysis, in comparison within the groups, 'peak levels' of inflammatory markers in group T were comparable to baseline. On the other hand, significantly higher levels in group V on t4 and t5, suggest amplified inflammation in patients receiving inhalational anaesthesia. These findings have important implications in peri-operative outcomes in any major oncological procedure including HIPEC.

Synthesis of albumin, a 'negative' acute-phase protein, decreases as part of the acute inflammatory response.[24] The mean albumin levels in both groups showed a similar trend reciprocal to change in the 'positive' inflammatory markers. It is also likely that albumin leaves the plasma compartment and extravasates into the tissue, secondary to increases in vascular permeability.

Various studies have reported coagulopathy during and after HIPEC.[24,25] In the present study, no statistical difference was observed in mean PT between both groups at five defined time points in the perioperative period. It showed an increasing trend after incision and peaked on the 1st post-operative day and decreased on the 3rd post-operative day. These findings are consistent with a previous study, which reported that coagulation reached normality only 3–4 days after CRS and HIPEC.[26]

The study is limited by small sample size and being a single centre study, has an inherent bias towards its presenting population. Thromboelastometry could not be performed for all patients due to technical problems, and therefore was excluded from the analysis.

CONCLUSION

The findings of the study are suggestive of greater instability with respect to MAP during the HIPEC phase, in patients who receive inhalational anaesthesia as compared to TIVA. However, no statistical difference was observed between the two groups with respect to other haemodynamic variables such as HR, CI, SVRI or CVP. Inflammation in both groups was highest during the first 24 h after the surgery. Post-hoc analysis of the pattern of inflammation within each group is suggestive of prolonged inflammation in patients receiving desflurane-based anaesthesia.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patients have given their consent for their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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