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ANTICANCER CHEMOTHERAPEUTIC AGENTS AND VOLATILE ANESTHETIC INTERACTION: COMPARISON BETWEEN SEVOFLURANE AND DESFLURANE

Anaesthesiology

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ABSTRACT

Context: Cancer is a leading cause of death worldwide. Chemotherapy forms an important aspect of cancer treatment. The toxicity of chemotherapy drugs and their relevance to perioperative anesthesia management relates to the specific agents used, their cumulative dosage and drug toxicity. Volatile agents have remained the mainstay of general anesthesia for decades. Volatile anesthetic agent can produce toxic metabolites and lead to varying degree of renal or hepatic dysfunction. To prepare the best perioperative management, the knowledge of acute and long-term side effects of chemotherapeutic agents is required by the anaesthesiologists.

AIM: To evaluate the hepatic and renal effect of inhalational agents on oncosurgery patients receiving chemotherapeutic agents.

Setting and design: prospective observational study was conducted on ASA grade 1 and 2 patients posted for oncosurgery under inhalational anesthetics.

MATERIAL AND METHODS: Patients were allocated to two groups, based on chemotherapy received, then divided into subgroups according to inhalational agent used (sevoflurane versus desflurane)

Group 1 - patients who have not received chemotherapy.

Group Is- sevoflurane (NCS)

Group Id- desflurane (NCD)

Group 2 – patients who have received chemotherapy

Group II s– sevoflurane (CS)

Group IId – desflurane (CD)

STASTICAL ANALYSIS: The statistical analysis was done using SPSS (Statistical Package for Social Sciences) Version 15.0 statistical Analysis Software. The values were represented in Number (%) and Mean±SD.

RESULTS: Groups were comparable with regard to demographic data. Elevation in liver enzymes was more pronounced in the chemotherapy group as compared to non-chemotherapy group. There was no significant difference in renal function in either group at any time interval.

CONCLUSION: Sevoflurane was found to have more elevate liver enzyme in comparison to desflurane though elevation in liver enzymes was for transient period. Considering the side effects of chemotherapeutic agents, vigilant monitoring of hepatic and renal function test are required in oncosurgery patients exposed to inhalational anesthetics.

KEYWORDS

Chemotherapeutic agents, inhalational Anesthetics, Hepatic and Renal function

INTRODUCTION

Cancer is a leading cause of death worldwide.

Chemotherapy forms an important aspect of cancer treatment. These patients, when posted for surgical intervention may pose serious interaction and complication during anesthesia.

The toxicity of chemotherapy drugs and their relevance to perioperative anesthesia management relates to the specific agents used, their cumulative dosage and drug toxicity. The most common toxicities to chemotherapeutic agents include cardiac, pulmonary, hematologic, bone marrow and gastrointestinal. Coagulopathies, thrombocytopenia and anemia with ulceration and bleeding of the gastrointestinal tract may often occur.[1]

Abnormal liver function tests are a common problem in the cancer patient with possible causes including hepatic metastases, infections, liver disease (e.g. alcoholic liver disease), hepatotoxic medications and Chemotherapy-related liver damage [2]. Several chemotherapy drugs are nephrotoxic, causing either acute or chronic renal failure.

Volatile agents have remained the mainstay of general anesthesia for decades. Volatile anesthetic agent can produce toxic metabolites and lead to varying degree of renal or hepatic dysfunction [3]. Liver damage ranging from mild increase in serum aminotransferases to massive hepatic necrosis can occur after inhalational agents. These effects may be more pronounced in patients with various anticancer treatments.

To prepare the best preoperative, intraoperative and postoperative management plans for patients with a history of cancer, the knowledge of acute and long-term side effects of chemotherapeutic agents is required by the anaesthesiologists[4]

This study is conducted to evaluate the interaction of chemothera peutic agents with inhalational anesthetic agents on oncosurgery patients and their hepatic and renal effect.

MATERIAL AND METHODS

After getting approval from our institutional ethical committee, this prospective observational study was conducted on 40 oncology patients posted for elective surgery. The patients with normal liver and renal function test (LFT and KFT), who received chemotherapy 6 month to 1 year before surgery were included in the study.

ASA grade III and IV patients with preoperative deranged liver and renal function test, history of previous surgery in general anesthesia within last 6 months and post operative exposure to chemotherapy and radiotherapy within 21 days were excluded from the study.

STUDY GROUP–

Patients were allocated to two groups, patients who have received chemotherapy and patients who have not received chemotherapy then divided into subgroups according to inhalational agent used (sevoflurane versus desflurane)

Group 1 - patients who have not received chemotherapy.

Group Is- sevoflurane (NCS)

Group Id- desflurane (NCD)

Group 2 – patients who have received chemotherapy

Group II s– sevoflurane (CS)

Group IId – desflurane (CD)

All patients were subjected to the pre anesthetic checkup that included medical history, physical examination, treatment history,

chemotherapy history (chemotherapy agent, number of cycles of chemotherapy), history of radiotherapy, history of previous surgery and exposure to general anesthesia, all routine investigation, preoperative LFT (Serum bilirubin total,

s. bilirubin direct, SGOT/AST, SGPT/ALT, serum alkaline phosphatase), and RFT (serum urea and serum creatinine).

On arrival in the operation theatre patient's baseline parameters like blood pressure (BP), heart rate (HR), ECG and oxygen saturation (SpO2) were monitored at 5 min intervals. Intravenous access was established and an intravenous fluid started.

Patients were induced with injection midazolam (1 – 2 mg), fentanyl (1-2 microgram/kg), propofol (1-2 mg/kg) & ventilated with 100 % oxygen before administration of injection Vecuronium (0.08-0.12mg/kg). Tracheal intubation was performed by either direct laryngoscopy or with the aid of fiberoptic guidance as indicated. Anesthesia was maintained in all cases with O2 (oxygen) & N2O (nitrous oxide) gaseous mixture along with use of any of the volatile anesthetic agent sevoflurane, desflurane as per allotted group. Fresh gas flow rate was kept between 2-2.5 litres in every group. Minimal alveolar concentration (MAC) of both inhalational agents were maintained between 1-2. Bolus of vecuronium was given every 30miutes to body weight for muscle relaxation and fentanyl was given if required for analgesia. All the hemodynamic parameters (BP, HR, SpO2) were noted at various intervals before induction, intra operatively and after extubation. The inhalational agents were discontinued immediately after skin closure and the residual neuromuscular blockade reversed at the end of surgery. After extubation patients were shifted to postoperative ward.

Blood samples were taken at one day before surgery and post operatively on day 1(POD1), day 3(POD3), day 21(POD21) and analyzed for LFT and RFT. The normal ranges of these biomarkers are aforementioned.

Patient data is presented as mean and standard deviation range. Results were evaluated and analysed using various statistical test.

STATISTICAL TOOLS EMPLOYED-

The statistical analysis was done using SPSS (Statistical Package for Social Sciences) Version 15.0 statistical Analysis Software. The values were represented in Number (%) and Mean±SD.

OBSERVATION AND RESULTS

A total of 40 patients selected using purposive sampling designs were enrolled in the study. 20 patients were allocated to each sevoflurane and desflurane groups. Each group was then further bifurcated into two on the basis of chemotherapy status. Thus a total of four subgroups (n=10) were formed *i.e.* NCS (non-chemotherapy sevoflurane), CS (Chemotherapy sevoflurane), NCD (non-chemotherapy Desflurane) and CD (Chemotherapy Desflurane) respectively.

Table 1 shows the demographic profile and baseline characteristics of patients in different groups. Statistically, there was no significant difference among groups with respect to gender of patients. ASA grade and duration of surgery is also comparable in all groups.

On comparing the total bilirubin, the difference among groups was not significant statistically. (Table 2).

Serum bilirubin direct levels (Table 3) were found to be significantly elevated in CS group at POD 1 and POD 3. There was no significant change in direct bilirubin in desflurane group.

On comparing SGOT and SGPT (table 4 and 5) for the difference between chemotherapy and non-chemotherapy subgroups. Significant difference was observed at day 1in both the groups, and on day 3 in CS group ($p<0.05$). At all these time intervals, mean value in NCS subgroup was significantly lower as compared to that in CS subgroup.

Serum urea levels were comparable at baseline among all groups (Table 6). Serum urea levels were decreased significantly at day 21st day in NCD Group while in CD groups at 3rd and 21st day. On intergroup comparison significant differences were noticed in CS vs CD groups at different time interval (21st day).

Serum creatinine levels were comparable in all groups at base line levels (Table 7)

On intergroup comparison serum creatinine values were not found to be statistically significant.

DISCUSSION

Cancer patients are increasing day by day and thus the numbers of patients for scheduled surgery are also increasing.

Anaesthesiologist plays a major role in the perioperative management of patients on antichemotherapeutic agents posted for surgery because of several pathophysiological changes in their body[5-6]

Volatile anesthetic are administered to virtually all patients subjected to general anesthesia and are an integral part of the peri-operative period. Inhalational agents, which are traditionally used for maintenance of general anesthesia, have varying degree of renal and hepatic toxicities. Chemotherapeutic agents adversely affect most of the organ systems of body, and thus the patients require specific anesthetic considerations[7]

In our study majority of patients were of carcinoma breast that received multiple cycles of 5- fluorouracil, etoposide & cyclophosphamide. Cancer buccal mucosa & cancer tongue patients received cisplatin and paclitaxel.

The present study was carried out with an aim to evaluate the impact of volatile anesthesia and chemotherapy status on liver and renal functions of cancer patients undergoing surgical procedures.

Statistically, there was no significant difference among groups with respect to gender of patients. ASA grade and duration of surgery is also comparable in all groups.

No statistically significant difference is seen in serum bilirubin total in any of intergroup comparison and no significant changes at different time interval**.**

I-Hua Lin etal. found no change in serum bilirubin total concentration at different time interval in both desfluane and sevoflurane group.[8]

Serum bilirubin direct levels were found to be significantly elevated in CS group at POD 1 and POD 3. There was no significant change in direct bilirubin in desflurane group. Increase in serum bilirubin direct level found may be due to hepatotoxicity of chemotherapy drugs [9].

Lin J etal. [10] in their study suggested that about a quarter of patients with drug induced liver injury who had exposure of volatile anesthetic drug developed significant liver injury.

In our study hepatic enzymes were found elevated in chemotherapy groups.

On comparing SGOT and SGPT mean value in Non chemotherapy subgroup was significantly lower as compared to that in Chemotherapy subgroup.

Akuyam SA etal. in their study found that the levels of serum SGOT, SGPT, ALP were significantly higher in cancer patients than in controls both before and after chemotherapy, with more pronounced elevations after chemotherapy.[11]

Elevated liver enzymes occurring during chemotherapy is more likely due to hepatic toxicity of the drugs.

Many chemotherapy drugs are metabolized by the liver and, as such, require dose reductions if liver function is impaired. Usual precautions for anaesthetic drug dosing in patients with hepatic disease should be applied.

Volatile anesthetic produce similar dose related decrease in renal blood flow, glomerular filtration rate, and urine output. Preoperative hydration attenuates many of changes in renal function associated with volatile anesthetics. Volatile anesthetics appear to induce a protective activity on the kidney similar to that of the heart via spingosine kinase and spingosine-1-phosphate generation.[12]

Serum urea levels were comparable at baseline among all groups. Serum urea levels were decreased significantly at day 21st day in NCD Group while in CD groups at 3rd and 21st day. On intergroup comparison significant differences were noticed in CS vs CD groups at different time interval (21st day).

This is seen in contrast to many other studies in which no significant difference is noted in serum urea levels post operatively. These changes in serum urea levels may be multifactorial or may be due to better fluid status of patients post operatively or due to decrease in catabolism after resection of tumor. This result needs further evaluation.

Serum creatinine levels were comparable in all groups at base line levels. . On intergroup comparison serum creatinine values were not found to be statistically significant.

Ebert and coworkers found no change in BUN and serum creatinine concentration after 4-hour exposure of sevoflurane anesthesia. [13]

Smiley and colleagues in their study concluded that desflurane is not nephrotoxic. [14]

CONCLUSION

In our study, sevoflurane was found to have more elevate liver enzyme in comparison to desflurane though elevation in liver enzymes was for transient period. Hepatic damage was more pronounced in the chemotherapy group in comparison to non-chemotherapy group. Inspite of elevation in liver enzymes no patient of both chemotherapy and non-chemotherapy group developed overt hepatotoxicity.

In our study there was lack of relevant nephrotoxicity after inhalational exposure. Renal function changes were not much affected by any of volatile anesthetic.

This study needs further evaluation with large sample size to get conclusive results.

Considering the acute and long term side effects of chemotherapeutic agents, vigilant monitoring of hepatic and renal function test are required in oncosurgery patients exposed to inhalational anesthetics.

Table 1: Demographic Profile and Baseline characteristics of patients in different study groups

SN	Characteristic	Sevoflurane (n=20)		Desflurane (n=20)	
		NCS	CS	NCD	CD
1.	N	10	10	10	10
2.	Chemotherapy	N	Y	N	Y
3.	M:F	4:6	2:8	4:6	2:8
4.	Mean Age ±SD (Years)	42.4± 8.1	47.0± 7.8	43.0± 9.0	51.7± 9.7
5.	Duration of surgery±SD (hrs)	1.79± 0.64	1.81± 0.47	1.81± 0.60	1.64± 0.51
5.	ASA I:II	6:4	6:4	7:3	5:5
6.	Diagnosis				
	Ca BM	1	2	3	0
	Ca Breast	6	8	6	8
	Ca Tongue	3	0	1	2
7.	Type of Surgery				
	BCS	0	0	0	0
	Commando	1	2	3	0
	MRM	6	8	6	8
	SOND	0	0	0	0
	WE	2	0	1	2
	WE+SOND	1	0	0	0

Table 2: S. Bilirubin Levels (Total) in different groups at different time intervals

Time interval	Sevoflurane				Desflurane					
	NCS (n=10)		CS (n=10)		NCD (n=10)		CD (n=10)		NCS vs NCD	CS vs CD
	Mean	SD	Mean	SD	Mean	SD	Mean	SD		
Baseline	0.44	0.20	0.47	0.28	0.51	0.13	0.56	0.29	NS	NS
Day 1	0.46	0.21	0.66	0.35	0.58	0.20	0.62	0.22	NS	NS
Day 3	0.44	0.20	0.57	0.24	0.54	0.15	0.51	0.17	NS	NS
Day 21	0.40	0.17	0.52	0.23	0.46	0.13	0.45	0.17	NS	NS
BL vs Day 1	NS		NS		NS		NS			
BL vs Day 3	NS		NS		NS		NS			
BL vs Day 21	NS		NS		NS		NS			

Table 3: S. Bilirubin (Direct) Levels in different groups at different time intervals

Time interval	Sevoflurane				Desflurane					
	NCS (n=10)		CS (n=10)		NCD (n=10)		CD (n=10)		NCS vs NCD	CS vs CD
	Mean	SD	Mean	SD	Mean	SD	Mean	SD		
Baseline	0.14	0.07	0.21	0.12	0.17	0.05	0.18	0.17	NS	NS
Day 1	0.23	0.11	0.34	0.16	0.23	0.09	0.23	0.13	NS	NS
Day 3	0.21	0.11	0.29	0.12	0.19	0.07	0.19	0.07	NS	NS
Day 21	0.18	0.10	0.20	0.11	0.15	0.07	0.17	0.06	NS	NS
BL vs Day 1	NS		*		NS		NS			
BL vs Day 3	NS		*		NS		NS			
BL vs Day 21	NS		NS		NS		NS			

Table 4: SGOT Levels in different groups at different time intervals

Time interval	Sevoflurane				Desflurane					
	NCS (n=10)		CS (n=10)		NCD (n=10)		CD (n=10)		NCS vs NCD	CS vs CD
	Mean	SD	Mean	SD	Mean	SD	Mean	SD		
Baseline	22.20	6.34	28.40	10.99	27.00	8.03	27.70	8.97	NS	NS
Day 1	26.90	8.32	44.40	11.95	33.70	7.56	42.60	14.55	NS	NS
Day 3	26.60	7.50	40.40	12.11	31.50	11.89	37.40	11.69	NS	NS
Day 21	23.30	7.17	35.20	11.96	26.90	10.09	29.60	10.39	NS	NS
BL vs Day 1	*		*		*		*			
BL vs Day 3	NS		*		NS		NS			
BL vs Day 21	NS		NS		NS		NS			

Table 5: SGPT Levels (Total) in different groups at different time intervals

Time interval	Sevoflurane				Desflurane					
	NCS (n=10)		CS (n=10)		NCD (n=10)		CD (n=10)		NCS vs NCD	CS vs CD
	Mean	SD	Mean	SD	Mean	SD	Mean	SD		
Baseline	21.60	7.31	29.20	10.15	27.90	11.53	23.70	6.63	NS	NS
Day 1	26.10	9.73	40.10	10.84	26.50	11.21	28.10	7.06	NS	NS
Day 3	24.80	9.93	37.40	10.09	21.20	9.15	27.00	8.08	NS	NS
Day 21	22.80	10.35	34.40	15.58	17.70	7.86	20.00	8.97	NS	NS
BL vs Day 1	*		*		NS		*			
BL vs Day 3	NS		*		NS		NS			
BL vs Day 21	NS		NS		NS		NS			

Table 6: S. Urea Levels in different groups at different time intervals

Time interval	Sevoflurane				Desflurane					
	NCS (n=10)		CS (n=10)		NCD (n=10)		CD (n=10)		NCS vs NCD	CS vs CD
	Mean	SD	Mean	SD	Mean	SD	Mean	SD		
Baseline	23.80	10.37	26.70	10.32	43.90	29.20	22.60	8.69	NS	NS
Day 1	24.80	9.20	34.90	14.00	33.90	19.21	22.50	10.49	NS	NS
Day 3	24.30	9.98	32.20	9.07	32.40	15.16	19.20	9.73	NS	NS
Day 21	22.40	10.28	30.20	7.67	24.80	8.85	17.40	9.35	NS	*
BL vs Day 1	NS		NS		NS		NS			
BL vs Day 3	NS		NS		NS		*			
BL vs Day 21	NS		NS		*		*			

Table 7: S. Creatinine Levels in different groups at different time intervals

Time interval	Sevoflurane				Desflurane					
	NCS (n=10)		CS (n=10)		NCD (n=10)		CD (n=10)		NCS vs NCD	CS vs CD
	Mean	SD	Mean	SD	Mean	SD	Mean	SD		
Baseline	0.51	0.10	0.51	0.15	0.52	0.18	0.47	0.24	NS	NS
Day 1	0.50	0.11	0.47	0.15	0.53	0.22	0.55	0.36	NS	NS
Day 3	0.47	0.11	0.42	0.10	0.50	0.25	0.40	0.23	NS	NS
Day 21	0.44	0.12	0.36	0.13	0.43	0.22	0.36	0.23	NS	NS
BL vs Day 1	NS		NS		NS		NS			
BL vs Day 3	NS		NS		NS		NS			
BL vs Day 21	NS		NS		*		NS			

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