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The effect of low-flow and high-flow sevoflurane anaesthesia on renal and liver function: a comparative study

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ABSTRACT

Background and Aims: Sevoflurane degradation products can affect liver and renal functions. The study was undertaken to assess the safety of low- flow sevoflurane anaesthesia and high- flow sevoflurane anaesthesia by comparing their effects on renal and liver functions. **Material and Methods:** The study was conducted in 100 adult patients of American Society of Anaesthesiologists physical status I or II, who underwent elective surgery under general anaesthesia. Patients were selected randomly into two groups to receive either low-flow Sevoflurane (n=50) or high-flow Sevoflurane (n=50) anaesthesia. In all these patients, preoperative renal function tests (RFT) & liver function tests (LFT) were done. RFT included blood urea, serum creatinine, creatinine clearance, urinary protein & LFT included serum bilirubin, SGOT, SGPT, ALP. The patients were induced by intravenous thiopentone [4-7 mg/kg] and succinylcholine [1-2 mg/kg] was given to facilitate tracheal intubation. Trachea was intubated with appropriate size cuffed endotracheal tube. Anaesthesia was maintained with either high-flow Sevoflurane with fresh gas flow of 4.5- 7 Liters/minute or low-flow Sevoflurane with fresh gas flow of 1- 3 L/min. Blood samples were collected before operation and at 0 hour, 06 hr, 24 hr, 48 hr & 72 hr postoperatively to measure Blood urea, Serum creatinine, Creatinine Clearance (CL), serum bilirubin, Serum Glutamic Oxaloacetic Transaminases (SGOT), Serum Glutamic Pyruvic Transaminases (SGPT), Alkaline phosphatase (ALP). Urine samples were collected at 24 hrs preoperatively & every 24 hrs for up to 72 hrs postoperatively to measure urine protein. **Results:** This study shows alterations in renal & hepatic functions in low-flow sevoflurane anaesthesia as well as high-flow sevoflurane anaesthesia. However, the alterations in renal & hepatic functions were within upper normal limit in both groups as assessed using conventional measures of hepatic & renal functions. **Conclusion:** We conclude that there were no statistically significant differences in the hepato-renal function by the effect of low flow and high flow sevoflurane anaesthesia and both seem to be equally safe.

Key words: High- flow, kidney function, low-flow, liver function, sevoflurane

INTRODUCTION

Sevoflurane was first synthesized in 1968 by Regan[1] and described in 1972, but FDA approved the use of sevoflurane in June 1995 with caution that it should not be used at fresh gas flow of <2lit/min[2]. Sevoflurane has gained popularity over halothane and isoflurane due to its property of low solubility in blood which results in rapid wash in and wash out from blood[2]. This allows faster inhalational induction and rapid and smooth recovery in comparison to traditional inhalational anaesthetics.

Studies have shown that sevoflurane reacts with sodalime

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and baralyme resulting in the generation of several degradation products (Compound A), which is reported to be a possible cause of organ toxicity[3].Its concentration in circle absorber system increases with increase in absorber temperature, increase in sevoflurane concentration and with decrease in fresh gas flow rate. Although compound A has a dose dependent nephrotoxic effect in rats, but there have been no cases of renal toxicity reported in humans and hence, sevoflurane use has been recommended[4]. Concentration of compound A is higher in closed circuit or low flow sevoflurane (SL) than in high flow sevoflurane (SH) with a flow rate of 6L/min. Therefore, there has been debate regarding the safety of low flow anaesthesia. The safety of sevoflurane anaesthesia in a closed circuit or low flow system has not yet been clarified.[4]

MATERIALS AND METHODS

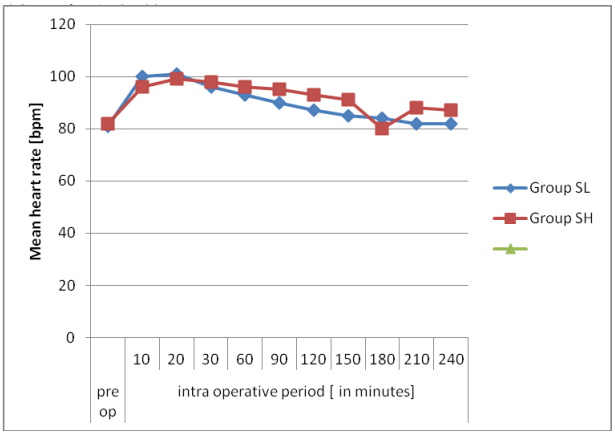
This prospective, randomized, controlled, double blind study was conducted after getting approval from institutional ethics committee and obtaining written, informed consent from patient/patient's relative. This was a double blind study in which neither patient, research nurse, investigator, or any other medical or nursing staff in the OT was aware of the treatment assignments for the duration of the study. All statistical analysis was also done with masking maintained. Randomisation authorities were instructed to report any suspected breach of the masking procedures. No report was filed. Patients with pre-existing renal and liver dysfunction, other metabolic disorders, on nephrotoxic or hepatotoxic drugs, hypersensitivity to sevoflurane, known or suspected susceptibility to malignant hyperthermia were excluded. All patients were randomly allocated to one of the two groups (n=50) to receive either low-flow sevoflurane (SL) or high-flow sevoflurane (SH) anaesthesia, applying closed envelope technique. In all these patients, preoperative Renal Function Test (RFT) and Liver Function Test (LFT) were done. RFT included blood urea, serum creatinine (S.Cr), creatinine clearance (CL), urinary protein. LFT included serum bilirubin, Serum Glutamic Oxaloacetic Transaminases (SGOT), Serum Glutamic Pyruvic Transaminases (SGPT), & Alkaline Phosphatise (ALP). Prior to induction of anaesthesia patients were preoxygenated with 100% oxygen with face mask for 3-5 min, premedicated with intravenous (i.v) glycopyrrolate 0.005-0.01milligram/kilogram (mg/kg) and pentazocine 0.5mg/kg. All patients were induced by i.v. thiopentone 4-7 mg/kg, loss of eyelash reflex being the end point of induction, then 1.-2 mg/kg i.v. succinylcholine was given to facilitate tracheal intubation. Anaesthesia was maintained with either SH with Fresh Gas Flow (FGF) of 4.5-7 L/min according to the patient's body weight or SL with FGF of 1- 3 L/min according to the group assigned by randomization. Loading dose of i.v. atracurium 0.3 mg /kg and maintenance dose dose of 0.1 mg / kg was given to facilitate surgical procedure. In SL anaesthesia, FGF of 3L/min was gradually decreased to 2 L/min then to 1 L/min after one hour. In all groups the carrier gas was nitrous oxide and oxygen in the ratio of 70:30 adjusted to ensure FiO_2 of > 0.3. Fresh soda lime was used in the low flow and high flow sevoflurane. Blood samples were collected preoperatively and at 0 hr, 06 hr, 24 hr, 48 hr & 72 hr postoperatively to measure serum bilirubin, SGOT, SGPT, ALP, blood urea, S Cr, CL.[4,7,8] Urine sample was collected 24 hrs preoperatively & every 24 hrs for up to 72 hrs postoperatively to measure urine protein.

A sample size of 100 patients of either sex of age group between 15- 70 years, weight range from 35-65 kgs with ASA physical status I or II undergoing elective surgery under general anaesthesia was selected. Calculations were based upon standard deviation {SD}, which was derived from PILOT STUDY done prior to the study. The mean bilirubin level after sevoflurane between the two groups was statistically significant, and the estimated difference between mean bilirubin levels of two groups was 3%. And with the help of estimated SD we derived sample size of 50 each in both the groups.

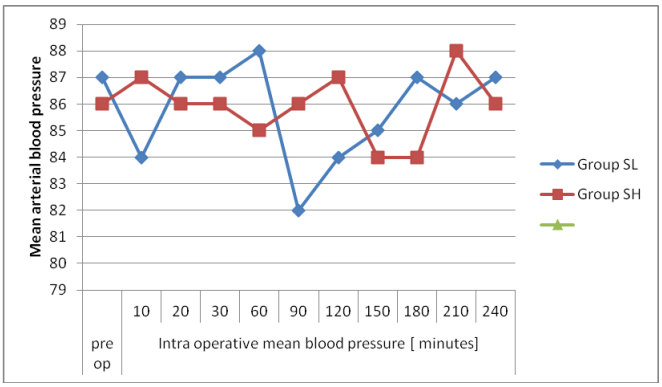
RESULTS

All patients in two groups were comparable with respect to demographic profile and duration of surgery. (Table – 1). Preoperative mean value of blood urea was 19.36 ± 4.3 mg/dl in group SL and 18.3 ± 3.6 mg/dl in group SH. The statistically significant rise in blood urea level was found at 48 hr and 72 hr in postoperative period in both the groups ($p = 0.0002$, $p = 0.0034$ in SL group and $p = 0.0019$, $p = 0.0035$ in SH groups, respectively) that was within normal limit. The difference in blood urea levels between the groups was also found to be statistically insignificant ($p > 0.05$). S Cr was raised at 72hr in SL group but the rise was within normal limit & statistically insignificant ($p = 0.6680$). There was slight decrease in CL in both the groups in postoperative period, but that was not statistically significant ($p > 0.05$).Preoperative mean values for urine protein was 84.18 ± 7.2 mg/24 hr in group SL and 85 ± 5.56 mg/24 hr in group SH. Urine protein was raised at 1st, 2nd& 3rd postoperative day that was statistically highly significant in both the groups ($P < 0.0001$). The difference between the groups was also found to be statistically insignificant ($p > 0.05$).(Table 2a & 2b).

The preoperative mean value of serum bilirubin was 0.04 ± 0.14 mg/dl in group SL & 0.4 ± 0.15 mg/dl in group SH and the difference between the two values was statistically not significant (p>0.05) Serum bilirubin increased in postoperative period in both the groups in comparison to preoperative bilirubin & was found to be statistically highly significant [p = 0.0001] but it was within the upper normal limit. The difference in serum bilirubin levels between the groups was found to be statistically insignificant at various time intervals postoperatively (p >0.05). Preoperative mean value of SGOT was 25.38 ± 4.9 U/L in group SL & 25.72 ± 4.9 U/L in group SH. SGOT was found to be elevated but remained within upper normal limit in postoperative period compared to the preoperative value in both the groups which was statistically significant at 6 hr in SL group & at 48 hr in SH group (p = 0.0307). Raised SGOT was highly significant at 24 hr & 48 hr in only SL group (p < 0.001). The difference in SGOT levels between the groups was found to be statistically insignificant at 0 hr, 6 hr, 24 hr, 48 hr & 72 hr postoperatively (p >0.05).No statistically significant rise in SGPT & ALP was observed in postoperative period in both the groups (p > 0.05). (Table-3a & 3b). The preoperative mean heart rate was 81 ± 6.6 beats/ minute (bpm) and 82 ± 4.1 bpm, mean blood pressure was 87±5 mmHg and 86.2 ± 6.2 mmHg and SPO_2 was 99.5±0.82% and 99.76 ± 0.62 % in group SL and group SH, respectively. Intraoperative mean heart rate, mean blood pressure and SPO_2 at various time intervals was comparable between the groups and no statistically significant changes were observed [p> 0.05].



Graph 1. Mean heart rate at various time intervals [bpm].



Graph 2. Mean blood pressure at various time intervals[mmHg].

Table 1: Patient characteristics annd Duration of surgery

Group (n=50)	Low-flow Sevoflurane	High–flow Sevoflurane	p-value
Age [yrs]	29.36±12.72	31.2±13.81	0.49
Weight [kg]	47.68±7.61	47.82±7.51	0.93
Sex [M:F]	27:23	26:24	>0.05
Mean duration of surgery [hr]	2.8±0.267	2.85±0.38	0.45

Table 2 (a): Renal Functions

	Blood urea[mg/dl]					Sr. creatinine [mg/dl]				
Time	SL		SH		SL VS SH	SL		SH		SL vs SH
	Mean±SD	p-value*	Mean±SD	p-value*	p value**	Mean±SD	p-value*	Mean±SD	p-value*	p value**
Pre-op	19.36±4.3		18.3±3.6		0.3208	0.65±0.14		0.7±0.12		0.2946
Pop- 0hr	19.22±2.5	0.7947	18.64±2.4	0.7168	0.3743	0.64±0.11	0.7403	0.7±0.09	0.9999	0.0975
Pop- 6 hrs	19.54±3.2	0.8146	18.86±3.1	0.5820	0.2283	0.64±0.11	0.8573	0.7±0.08	0.8654	0.0870
Pop- 24 hrs	20.6±2.4	0.0879	19.76±2.7	0.0317	0.3631	0.64±0.11	0.7360	0.7±0.086	0.8583	0.1189
Pop- 48 hrs	21.16±3.05	0.0034	20.82±3.6	0.0019	0.0577	0.65±0.10	0.7597	0.72±0.08	0.2720	0.0980
Pop- 72 hrs	21.58±3.1	0.0034	20.66±3.5	0.0035	0.1676	0.8±1.04	0.6680	0.72±0.09	0.2878	0.0895

*- intragroup comparison, **- intergroup comparison

Table 2 (b): Renal Functions

	Creatinine Clearance [ml/min.]					Urine protein[mg/24 hrs]				
Group	SL		SH		SL VS SH	SL		SH		SL vs SH
	Mean	p-value*	Mean	p-value*	p value**	Mean	p-value*	Mean	p-value*	p value**
Pre-op	108.23±25.78		109.14±8.80		0.1770	84.18±7.2		85±5.52		0.2167
Pop- 0hr	107.40±26.79	0.8675	108.49±27.72	0.5793	0.2851	-	-	-	-	-
Pop- 6 hrs	107.36±26.45	0.9105	108.23±25.78	0.3270	0.3068	-	-	-	-	-
Pop- 24 hrs	107.36±26.45	0.6160	107.40±26.79	0.5872	0.1824	297±33.58	<0.0001	310±32.4	<0.0001	0.0731
Pop- 48 hrs	107.36±21.90	0.9110	107.36±26.45	0.8010	0.2995	401±43.34	<0.0001	413±41.88	<0.0001	0.1607
Pop- 72 hrs	108.49±27.72	0.8963	107.72±25.37	0.2544	0.7857	499±61.02	<0.0001	524±45.65	<0.0001	0.1920

*- intragroup comparison, **- intergroup comparison

Table 3 (a): Liver Functions

	Sr. Bilirubin [mg/dl]					SGOT [U/L]				
Time (hrs)	SL		SH		SL vs SH	SL		SH		SL vs SH
	Mean	p-value*	Mean	p-value*	p value**	Mean	p-value*	Mean	p-value*	p value**
Pre-op	0.4±0.14		0.4±0.15		0.999	25.38±4.9		25.72±4.9		0.6421
Pop- 0	0.5±0.2	0.0003	0.55±0.13	0.0001	0.13	25.82±4.55	0.7734	25.82±4.53	0.9832	0.9169
Pop- 6	0.55±0.17	0.0001	0.54±0.17	0.0001	0.76	27.56±7.1	0.0267	26.38±5.38	0.9517	0.0922
Pop- 24	0.57±0.16	0.0001	0.57±0.16	0.0001	0.999	28.74±6.34	0.0078	26.32±5.3	0.6426	0.1779
Pop- 48	0.58±0.15	0.0001	0.58±0.15	0.0001	0.999	30.46±4.8	0.0001	27.98±4.83	0.0307	0.0829
Pop- 72	0.57±0.29	0.0001	0.57±0.20	0.0001	0.999	27.08±4.6	0.0664	26.22±3.95	0.6717	0.2840

*- intragroup comparison, **- intergroup comparison

Table 3 (b): Liver Functions

	SGPT [U/L]					ALP [U/L]				
Group	SL		SH		SL VS SH	SL		SH		SL vs SH
	Mean	p-value*	Mean	p-value*	p value**	Mean	p-value*	Mean	p-value*	p value**
Pre-op	18.58±4.4		19.92±5.64		0.1885	71±29.1		66.96±12.04		0.8500
Pop- 0hr	19.14±6.4	0.4581	19.44±6.67	0.7459	0.9928	73.18±27.3	0.7339	70.31±26.80	0.7268	0.6130
Pop- 6 hrs	20.8±7.4	0.0556	20.45±6.93	0.7284	0.5082	73.5±25.2	0.6767	72.15±24.32	0.7953	0.9516
Pop- 24 hrs	19.6±7.7	0.3726	19.72±7.3	0.8312	0.9932	79.5±25.9	0.1405	76.74±23.96	0.1368	0.8595
Pop- 48 hrs	19.5±7.9	0.3881	19.66±7.26	0.8065	0.9937	80.1±29.1	0.1096	76.94±25.16	0.2257	0.6714
Pop- 72 hrs	20.22±8.4	0.1774	20.21±7.73	0.9295	0.8367	80.3±29.1	0.1207	76.94±25.16	0.1955	0.7314

*- intragroup comparison, **- intergroup comparison

DISCUSSION

Sevoflurane anaesthesia appears to be the most effective of the inhaled anaesthetic for maintaining both blood flow and oxygen delivery, thus theoretically it is less likely to induce liver injury than halothane and enflurane and is no more toxic than desflurane and isoflurane. However some studies report that sevoflurane, but not desflurane , caused small post anaesthetic increases in serum alanine aminotransferase denoting mild and transient hepatic injury suggesting that its caused by compound A.[5]

Sevoflurane is transformed to inorganic fluoride ions and degraded to compound A, (fluoromethyl 2,2- difluoro-1 (trifluoromethyl 1) vinyl ether 6,7) in presence of sodalime or baraylime and it is nephrotoxic in rats.[6,7] . However whether it is toxic in humans has been the subject of several studies.[8]

Renal function in our study was measured by blood urea & S. Cr, which remain the gold standard for clinical assessment because they are widely available, inexpensive and have been clinically validated. We also measured CL and Urine protein to measure renal function. Liver function was measured by serum bilirubin, SGOT, SGPT and ALP.

In our study, there was statistically significant rise in blood urea level at 48 hr and 72 hour postoperatively in both the groups. Raised postoperative mean values of blood urea at 0 hr, 6 hr, 24 hr, 48 hr & 72 hr in both groups were comparable [$p > 0.05$]. However there were no significant differences in pre and postoperative S Cr and CL between the groups. Urine protein was raised significantly at 1st, 2nd& 3rd postoperative day in both the groups [$p < 0.0001$], but the difference in rise of urine protein between the groups at these time intervals was statistically insignificant [$p > 0.05$].Rise in blood urea level and transient proteinuria

postoperatively could be due to transient injury to the glomerulus and any renal function variable. No evidence for low-flow Sevoflurane toxicity was observed and might not be unique for one anaesthetic agent. There could be contribution of other non-anaesthetic factors such as antibiotics, surgical stress & surgical site. Rise in blood urea level postoperatively in our study is comparable with the findings observed by Sahin SH et al [2011][9] and Kim Ji Wook et al [2013][10]. Similarly Nishiyama T et al [1998], and Kharash Evan D et al [2001][12] have observed transient proteinuria in both low flow as well as high flow sevoflurane anaesthesia.

In our study, Serum bilirubin was increased in postoperative period at 0, 6, 24 , 48 & 72 hr in SL & SH group in comparison to preoperative bilirubin and was found to be statistically highly significant [p = 0.0001]. Postoperative mean values at various intervals in both groups were comparable and statistically insignificant [p > 0.05]. In SL group postoperative rise in SGOT was found to be significant at 6 hrs and & highly significant at 24 hr & 48 hr [p < 0.001], while postoperative rise in SGOT value in SH group was statistically significant only at 48 hr [p = 0.0307] although the rise in SGOT was within normal limit in both the groups. However there were no significant differences in SGPT and ALP in this study groups. Results in our study correlates well with the finding observed by Bito H et al [1996][4], Nishiyama T etal [1998][11], Obata R et al [2000][13], Ebert Thomas J et al [2000][14], Lin I Hua et al [2013][15].

The increase in total bilirubin and SGOT in postoperative period in both the group could be due to administration of antibiotics [Ceftriaxone, Metronidazole] during surgery and other drugs, fluid infusion and surgical trauma. However inhalational anaesthetics induces hepatic dysfunction by reduction in hepatic blood flow during anaesthesia, increasing cytosolic calcium ion concentration in hepatocytes and generation of toxic metabolites [Compound-A & TFA], so contribution of these agents cannot be ruled out.

CONCLUSION

We conclude that both low flow and high flow sevoflurane anaesthesia seem to be equally safe because the observed alterations in renal & hepatic functions were within upper normal limit in both groups as assessed using conventional measures of hepatic & renal functions.

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