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Evaluating the effects of Desflurane versus Sevoflurane using recent biomarkers of renal functions in laparoscopic cholecystectomy patients

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ABSTRACT

The increased demand for day case laparoscopic procedures mandates a general anesthetic technique with rapid recovery and minimal side effects. Our study aimed at comparing sevoflurane (S) versus desflurane (D) using a more sensitive and specific biomarker of renal functions (Cystatin) in patients undergoing elective laparoscopic cholecystectomy. The study was a prospective randomized study that included 70 patients (D, n = 35 and S, n = 35) undergoing laparoscopic cholecystectomy surgeries. Cystatin-C and standard kidney function tests (BUN and creatinine) were assayed. The cystatin showed early elevations at 1 hour postoperatively in both groups, with no adverse clinical renal effects. Sevoflurane and desflurane both cause comparable elevations of cystatin levels during limited duration laparoscopic procedures. This may indicate an affection of renal integrity, as cystatin is a sensitive and specific biomarker of renal integrity, but there were no adverse clinical manifestations in those patients undergoing laparoscopic cholecystectomy.

1. INTRODUCTION

Nowadays, laparoscopic cholecystectomy is widely used on a day care basis. As with any day case procedure, it requires an anesthetic technique that provides a rapid recovery and minimizes the incidence of side effects. Both desflurane and sevoflurane are currently in widespread clinical use for maintenance of anesthesia in the ambulatory setting [1]. Although such inhalational anesthetics may be appropriate anesthetic choices in patients undergoing abdominal surgeries (including cholecystectomy), major concerns concentrate on their potential for nephrotoxicity [2]. The most common causes of AKI are septic shock, ischemia, and nephrotoxins. AKI has been defined conceptually as a rapid decline in glomerular filtration rate (GFR) that occurs over hours and days. It propels to a clinical syndrome characterized by a rapid decrease in renal excretory function, with the accumulation of products of nitrogen metabolism such as creatinine and urea. Serum creatinine (SCr) and blood urea nitrogen (BUN) display poor sensitivity and

specificity for indicating early rising acute changes in kidney function [3]. Cystatin C is a marker of glomerular filtration rate (GFR) rather than a primary AKI biomarker, yet it can be used to detect AKI. Some studies have considered serum cystatin C as a biomarker for the early diagnosis and long-term outcomes of AKI [4].

1.1 Aim and objectives

To compare sevoflurane (S) versus desflurane (D) using Cystatin C as a more sensitive and specific biomarker of renal functions in patients undergoing elective laparoscopic cholecystectomy.

2. Subjects and methods

Technical design: The study was a prospective randomized study that included 70 patients (D, n = 35 and S, n = 35). Inclusion criteria involved patients undergoing elective laparoscopic cholecystectomy surgeries, of both sexes, aged 25-55 years with ASA (American Society of Anesthesiologists) Class: I&II, BMI of 18.5-24.9 km2/kg and with duration of surgery not exceeding two hours. Patients of extremes of age with abnormal hepatic function by ALT and AST values outside the normal range, abnormal renal function by BUN and creatinine above the normal ranges, hypertension, unstable angina pectoris or myocardial infarction within the last six months or bronchial asthma were excluded. Pregnant and lactating women, alcohol or drug addicts, patients having drug allergies or received general anesthesia within the last three months, were also excluded.

2.1 Methods

All patients received midazolam 0.05 mg kg-1 and 4mg ondansetron intravenously before the induction of anesthesia. Five-lead ECG Monitor, non-invasive blood pressure, pulse oximetry, peripheral nerve Stimulator, ventilatory alarms, ETCO2 estimation (Capnography), and Multi gas Analyzer was used in monitoring. Venous blood samples (5 ml) for the assessment of Cystatin-C and standard kidney function tests (BUN and creatinine) were taken at the following times: preoperatively at T0, 1 hour after induction at T1, 6 hours after induction at T2, 24 hours postoperatively at T3. Administrative considerations: Written informed consent was obtained from all participants after clear explanation of the study and the study was approved by the research ethical committee of our institute (Institutional Research Board IRB). The work has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for studies involving humans. Informed written consents were obtained from 70 patients scheduled for laparoscopic cholecystectomy.

2.2 Statistical Analysis

Results are expressed as means ± standard deviation of the means (SD) or number (%). Comparison between mean values of different parameters was performed using either the unpaired t test or the Mann Whitney test when appropriate. Comparison relative to the baseline within the same group was performed using either the paired t test or the Wilcoxon Signed Ranks test whenever appropriate. Comparison between categorical data was performed using the Chi squared test. Correlation between the different parameters was performed using either the Pearson or the Spearman's rho correlation coefficient test, whenever it was appropriate. The Statistical Package for Social Sciences (SPSS) computer program (version 19 windows) was used for data analysis. A P value ≤ 0.05 was considered significant and < 0.01 was considered highly significant.

3. Results

Table (1) reveals the demographic data of the included patients. It showed no statistically significant differences in age and gender between the two studied groups. There were no differences significant

differences between the 2 groups regarding BMI and duration of the procedure. The hemodynamic data of the two groups involved in our study was showed in Table (2). The average intraoperative mean arterial pressure in both groups was within 20 % of the baseline levels. There is no statistically significant difference in the average MAP between the desflurane group and the sevoflurane group. Although the desflurane group had a higher statistically significant rise in the heart rate than the sevoflurane group, it was within the clinically acceptable range.

Serial post-operative biomarker comparison of alterations between both groups were assessed as demonstrated in Table (3) and Figure (3).

On comparing both groups, serial measurements of CST showed a significant rise from baseline levels in both groups as early as 1 hour. In the desflurane group, the levels continued to rise until 6 hours postoperatively, while in the sevoflurane group, the levels started to decline before 6 hours. Although at 24 hours, the level dropped in both groups, yet it was still statistically significantly higher than the baseline. However, there were no statistically significant differences between the two groups (Table (3)).

Regarding standard renal functions, the levels increased within each group in a statistically significant manner than the baseline levels, but the elevations did not reveal kidney injury according to standard criteria. On comparing the groups together, although desflurane showed a statistically significant higher mean of urea and creatinine (Table 4) than the sevoflurane group in the first 24 hours, its values were within acceptable ranges.

4. Discussion

The current study aimed at evaluating the effect of desflurane and sevoflurane on renal functions of patients undergoing laparoscopic cholecystectomy using the more specific and early diagnostic biomarker, cystatin (CST) for renal integrity assessment. Our study showed that sevoflurane and desflurane are both comparable regarding renal integrity during limited duration laparoscopic procedures. Cystatin is a 13.3-kDa nonglycosylated cysteine protease inhibitor produced by all nucleated cells of the body, and which is released into the intravascular compartment at a constant rate (serum level: 0.8–2.04 mg/L). Serum CST levels seem to be independent of gender, race, muscle mass, and hydration status [5]. Standard criteria for the diagnosis of acute kidney injury based on serum creatinine and urine output include the RIFLE criteria (2002), the AKIN criteria (2004) and the KDIGO criteria (2012). KDIGO defines AKI as an increase in serum creatinine by 0.3mg/dL or more within 48 hours, or an increase in serum creatinine to 1.5 times baseline or more within the last 7 days, or urine output less than 0.5 mL/kg/h for 6 hours [6].

However, as these criteria depend on creatinine, they are affected by its limitations. One limitation is the difference in creatinine half life depending on GFR. At normal GFR, the half life is 4 hours, whereas the half life increase at low GFR, achieving a new steady state concentration after 24 - 72 hours [3 to 5 half lives] [5]. Other limitations of serum creatinine include its affection by dietary factors, as meat consumption or malnutrition. Fluid overload causes dilution of serum creatinine, and renal disease can cause secretion of creatinine. Furthermore, drugs like corticosteroids, salicylates and active vitamin D metabolites can increase serum creatinine. In addition, high blood pressure, diabetes mellitus, congestive heart failure, and diseases of the transplant kidney can all affect creatinine levels [7]. In addition to the limitations of creatinine, studies performed in the last decade indicate that the more specific and sensitive biomarker Cystatin C displays more accurate outcomes in the assessment of renal functions. According to colleagues, Cystatin-C is a biomarker that is preferred because it reveals the changes in renal functions at an early and mild stage particularly in critical patients in the intensive care unit. Showed that CST is useful in oliguric ARF WITH

CVVH. CST makes it possible to determine residual renal function in CRRT, as CRRT clears urea and creatinine more than CST. Performed a meta-analysis correlation of CST accuracy to a gold reference standard of GFR. Showed that serum cst increased 2 days before serum creatinine. [8] showed that at GFR<80 ml/m2, CST increases by 88% versus creatinine which only increases by 48%. [9] showed that CST was a better parameter compared to creatinine in detecting AKI. [10] Glomerular filtration rate calculation is more accurate by cystatin-based equations than creatinine-based equations [11].

Accordingly, this study used cystatin-C to compare the renal integrity after sevoflurane and desflurane anesthesia.

On comparing both groups, serial measurements of CST showed a significant rise from baseline levels in both groups as early as 1 hour. In the desflurane group, the levels continued to rise until 6 hours postoperatively, while in the sevoflurane group, the levels started to decline before 6 hours. Although at 24 hours, the level dropped in both groups, yet it was still statistically significantly higher than the baseline. However, there were no statistically significant differences between the two groups (Table (3).

The elevations of cystatin-C may indicate the presence of a renal insult due to the alterations in renal perfusion in laparoscopy, rather than acute kidney injury due to toxic effects of the anesthetics.

This is evident as there were no clinically adverse renal effects during the study in either group, as shown by the clinically insignificant elevations of standard renal functions. The levels of creatinine increased within each group in a statistically significant manner than the baseline levels, but the elevations did not reveal kidney injury according to standard criteria. On comparing the groups together, desflurane showed a statistically significant higher mean of urea and creatinine (Table 4) than the sevoflurane group in the first 24 hours. Currently, there are no studies performed comparing sevoflurane and desflurane using CST-C in laparoscopic cholecystectomy procedures. Other studies that used standard renal functions tests showed comparable results to the current study. These include. Neither agent caused deterioration in serum BUN or creatinine [12- 15].

Another aspect of interest regarding the comparison between the drugs is the cost of consumption of the inhalational anesthetics, especially in low-income hospitals. As the average cost of consumption of desflurane is more expensive than sevoflurane, insignificant differences between both drugs on renal and hepatic function in short day case procedures can help manage hospital budgets more efficiently in favor of sevoflurane.

One of the limitations of the study is the absence of urine output monitoring. This was decided for ethical purposes, due to the short and day-case nature of the surgical procedure.

Further studies with more lengthy procedures are recommended for better assessment of renal integrity and more close monitoring of the urine output.

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6. Disclosure statement
The authors declare that they have no conflict of interest.

7. Funding
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8. Conclusion and recommendations
Sevoflurane and desflurane are both comparable regarding renal integrity during limited duration laparoscopic procedures. Both anesthetics elevated cystatin, a sensitive and specific biomarker, but had no adverse clinical manifestations in those patients undergoing laparoscopic cholecystectomy. However, the initial rise of cystatin in both groups may indicate sub-clinical renal affection, although not manifested in acute kidney injury. Wide scale studies comprising larger numbers of patients in longer procedures should be performed to assess the microscopic effects on renal integrity using sevoflurane and desflurane during longer periods of exposure to pneumoperitoneum and volatile anesthetics.

Table (1): Demographic data of both groups.

		Sevoflurane group (n=35)		Desflurane group (n=35)		Test value	P value
Age (mean±SD) (years)		37.1±7.6		35.7±6.8		0.832	0.408[1]
Gender	M	9	25.7%	6	17.1%	0.764	0.382[2]
	F	26	74.3%	29	82.9%		

Values are mean ± SD.
1.Independent t test used; 2. Chi square test used.
*Statistically significant as p<0.05.

Table (2): Average hemodynamic measurements of both groups.

	Sevoflurane group (n=35)		Desflurane group (n=35)		P value
	Mean	SD	Mean	SD	
Baseline MAP (avg) (mmHg)	98.6	7.29	97.06	8.16	0.399
Average of all intraoperative MAP values (mmHg)	96.3	13.3	104.4	10.23	0.06
Baseline HR (avg) (bpm)	82.5	7.64	80.6	8.56	0.306
Average of all intraoperative HR values (bpm)	76.6	18.7	87.7	10.3	0.03*

Values are mean ± SD.
1.Independent t test used.
*Statistically significant as p<0.05. Abbreviations: MAP; mean arterial pressure, HR; heart rate.

Table (3): Serial post-operative biomarker comparison of alterations between both groups.

	Sevoflurane group (n=35)		Desflurane group (n=35)		Test value	P value
CST mg/l at baseline	3.99	1.96	4.24	2.45	0.466	0.610[1]

CST 1 hr	97.80	74.77	77.19	83.89	1.085	0.282[1]
CST 6 hr	90.71	64.11	105.92	83.64	0.854	0.396[2]
CST 24 hr	57.77	52.42	48.84	56.48	0.681	0.498[1]

Values are mean ± SD (Standard Deviation).
1.Independent t test used; 2. Man Whitney test used.
*Statistically significant as p<0.05.
Abbreviations: CST; Cystatin C,
Units: CST: mg/l,

Table (4): Comparison of 24 hour measurements with baseline.

	Sevoflurane (n=35)		Desflurane (n=35)		P value (between groups)
	Mean	SD	Mean	SD	
Urea 0	23.403	5.82	21.434	6.679	
Urea 24 h	22.14	5.64	31.43	5.56	<0.001**[1]
$P^{(w)}$ value	0.034*[1]		< 0.06*[1]		
Creat. 0	0.586	0.12	0.571	0.113	
Creat. 24 h	0.514	0.12	0.734	0.111	<0.001**[1]
P [(w)]value	0.003*[2]		< 0.001**[2]		

1.Paired t test used; 2. Wilcoxon signed rank test used. 3. Mann Whitney test used P (w) = P value within the group. Creat. = Creatinine, *statistically significant as p<0.05. **highly statistically significant as p<0.01
Units: Urea: mg/dl, Creatinine: mg/dl

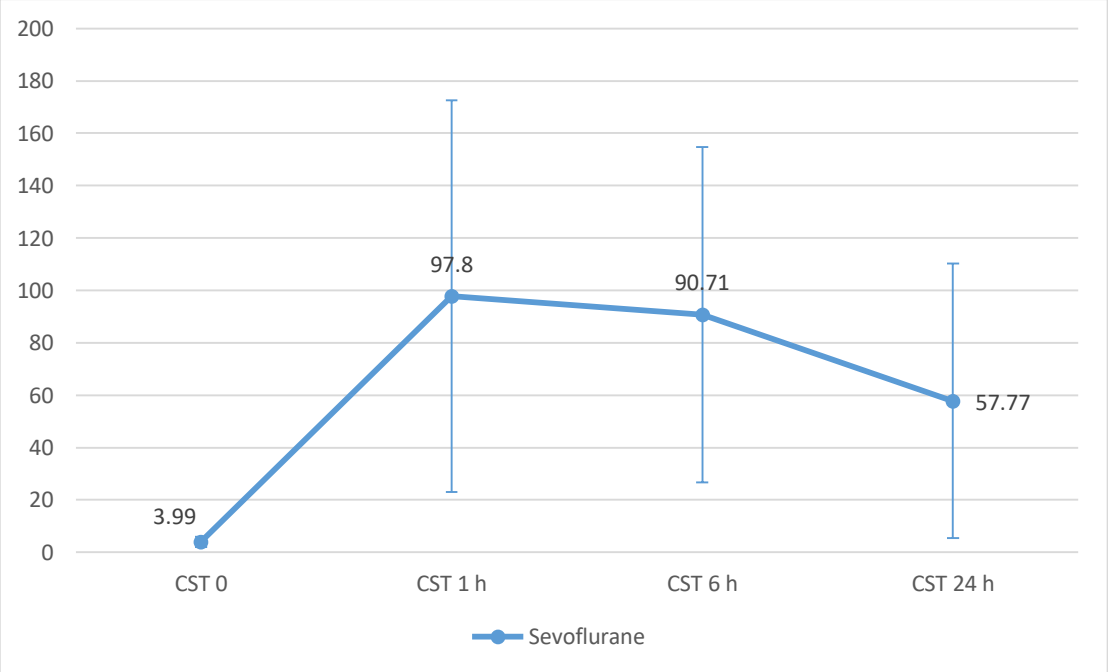

Figure (1): CST (ng/ml) serial measurements in sevoflurane group.

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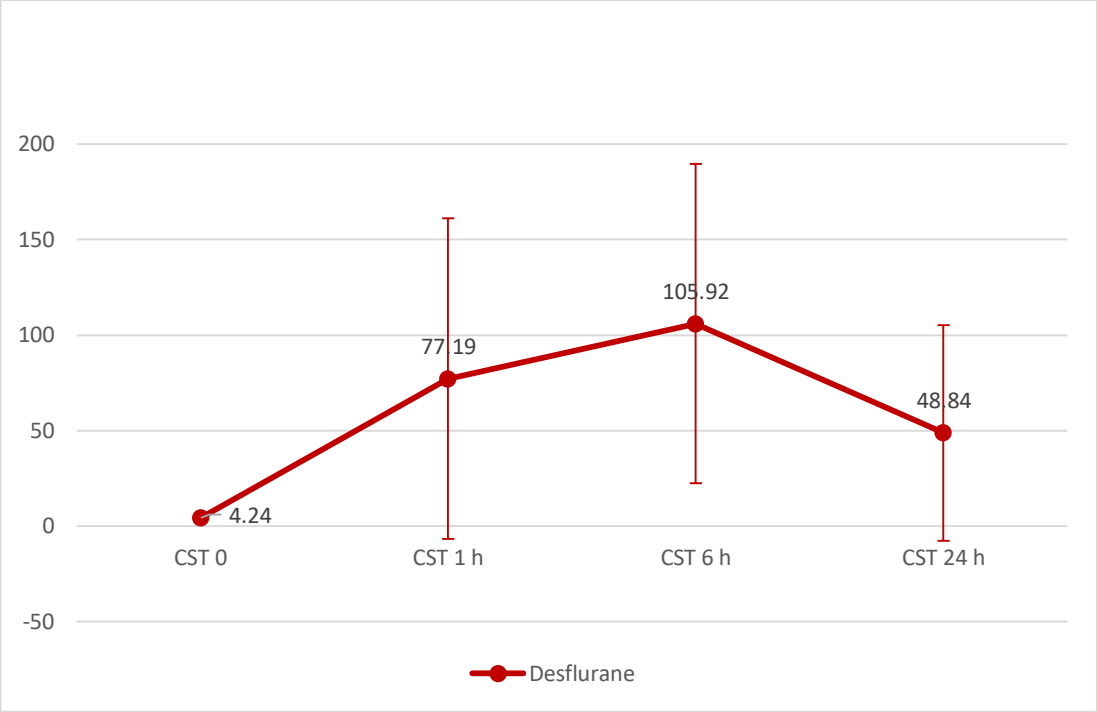

Figure (2): CST (mg/ml) serial measurements in desflurane group.

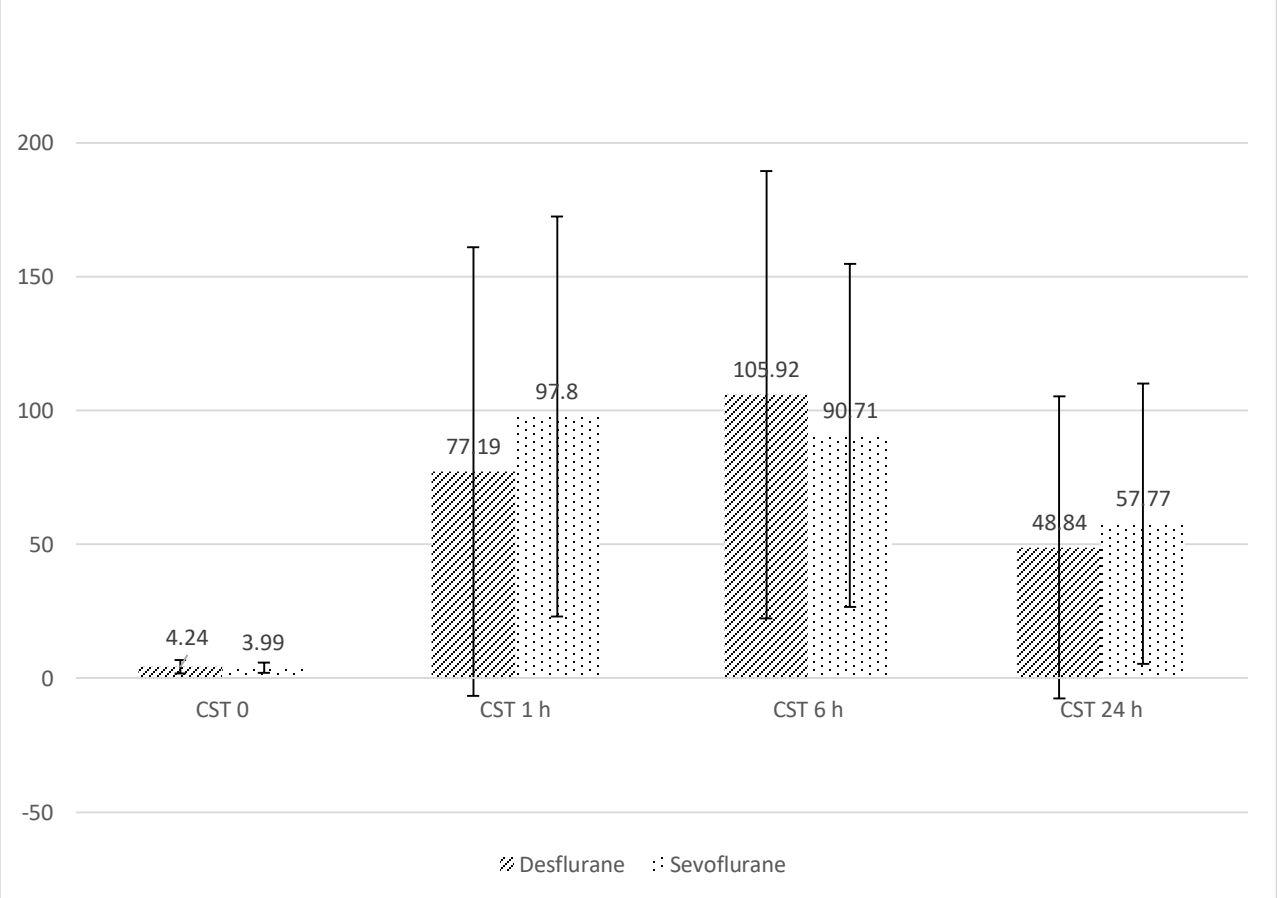

Figure (3): CST (mg/ml) comparison of measurements between both groups (*statistically significant as $p<0.05$).

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