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Comparison of Effects of Isoflurane And Nacetyl Cysteine with Isoflurane on Liver Function in Laparoscopic Surgery Patients Under General Anaesthesia

Dr.S.Madhana Gopalan,M.D[1] , Dr.S.M.Senthilnathan M.D[2]

Abstract
Aim : *To study the effects of n-acetyl cysteine on hepatic function during isoflurane anaesthesia .* ***Material and methods*** *: ASA I and II patients between 18-60 yrs scheduled for elective laparoscopic surgery under general anaethesia were eligible for the study. 60 patients were randomized into two groups.In a randomized manner 30 patients were given N-acetyl cysteine 150mg/kg in 250 ml 0.9% normal saline(Group N) while 30 patients received only 250 ml of 0.9% normal saline before induction.Group N received 12.5mg/kg/hr of N-acetyl cysteine throughout the operation. These parameters observed in preoperative period, postoperative 1st hr and postoperative 24th hr from peripheral venous blood are Serum bilirubin,Aspartate aminotransferase ,Alanine aminotransferase ,Lactate dehydrogenase ,Prothrombin time. Perioperative side effects were also noted.* ***Result:*** *Bilirubin and prothrombin time did not significantly change in the two groups at postoperative period. Alanine aminotransferase levels showed a little decrease in both groups at postoperative 1st hour but not statistically significant. Lactate dehydrogenase levels did not show any significant difference in both the groups. Aspartate aminotransferase levels were increased in both the groups at the postoperative period but was not statistically significant.*
Conclusion : *Liver functions are well preserved when N acetyl cysteine is used with isoflurane and when isoflurane is used alone in general anaesthesia for laparoscopic surgeries.*

I. Introduction

The general anesthetics were introduced into clinical practice over 150 years ago. It is one of the greatest milestone achieved in the field of medicine. This discovery revolutioned the branch of anaesthesiology. It has helped the speciality of modern surgery to flourish beyond imagination.

General anesthesia can broadly be defined as a drug-induced reversible depression of the central nervous system resulting in the loss of response to and perception of all external stimuli. A dynamic balance between the level of hypnosis, analgesia and stimulation is general anaesthesia. It is usually defined as a triad of amnesia, analgesia and muscle relaxation.

Inhalation anaesthetics are the most common drugs used for general anesthesia. A state of unconsciousness and amnesia is achieved by adding inhaled anaesthetic to inspired oxygen. A fraction of inhaled agent is enough to produce anaesthesia. A balanced anesthethesia is achieved when combined with intravenous anaesthetic agents, opioids and benzodiazepines and results in still more deeper plane . Ease of administration and monitoring the clinical effects of inhaled agents and reliable measurement of their end tidal concentration has given way to the widespread use of inhaled anaesthetics . In addition , volatile anesthetic gases are relatively inexpensive in terms of the overall cost.

Inhaled volatile anesthetics remain the most widely used drugs for maintenance of general anesthesia because of their predictable intraoperative and recovery characteristics. Management of haemodynamic stability and early recovery is the most important part of a standardized balanced technique.

Rapid induction and recovery may lead to faster operating room turnover times, shorter recovery room stays, and earlier discharges to home.

Various organ and system toxicities are seen with volatile anaesthetics since they have become operational.Since they are metabolized in the liver, hepatic toxicity is one of the most vital adverse effect . Halothane anaesthesia is related to postoperative hepatitis ranging from mildly elevated bilirubin levels to fatal fulminant hepatic necrosis. Isoflurane is metabolized very little in liver (0.17%) and is safer than halothane. There are some reports of hepatitis due to isoflurane anaesthesia but not severe as in halothane cases. These agents are not toxic themselves, their by-products or end products of metabolism are toxic. Isoflurane is halogenated ether and an isomer of enflurane. Its anaesthetic induction is faster and is nearly insoluble in blood. Only 0.17% of isoflurane is metabolized in liver and produce trifluoroacetic acid. Trifluoroacetic acid is a reactive metabolite and main reason for hepatic toxicity. Trifluoroacetic acid binds to hepatocyte proteins and acts like a hapten. These antigens are attacked by patients antibodies.

The toxicity of volatile anaesthetics can be seen after biodegradation. Biodegradation causes lipid peroxidation and depletion of antioxidants like glutathione**.** The purpose of this study is to assess the antioxidant effects of N acetyl cysteine which replaces the depleted glutathione stores caused by biodegradation in patients undergoing surgery with isoflurane anaesthesia.

Aim Of The Study

This study was undertaken with the aim of prospectively comparing the effects of isoflurane and N acetyl cysteine with isoflurane on liver functions in patients undergoing laparoscopic surgeries under general anesthesia.

Materials And Methods

After instituitional ethical committee approval the study was conducted in 60 patients. ASA I and II Patients scheduled for elective laparoscopic surgeries under general anaethesia were eligible for the study. After getting consent , the anaesthetic technique was performed. It was a randomized controlled study.

Selection of patients

The patients selected for this study were of age group from 18 to 60 yrs, ASA I and II Patients of both sexes are included in the study. Patients undergoing laparoscopic appendicectomy and hernioplasty were included in the study.

The patients exhibiting the following are excluded from the study

- Patients with severe cardiovascular,pulmonary,renal,hepatic,endocrine,neuropsychiatric diseases.
-History of using Coumadin recently.
-Patient on aspirin,NSAIDS,corticosteroids,immune depressants.
-Patient with history of asthma.
-Patient with history of drug or alcohol abuse.
-Patient with history of Hepatitis B or C
-Patient with history of abdominal surgery in past 5 yrs.
-Patient's refusal.

Preoperative Preparation

All patients are premedicated with injection Glycopyrrolate 10 µg/kg 15 minutes prior to induction.The patients were allocated into two groups

Group p -Placebo group (Isoflurane with normal saline)

Group n –N acetyl cysteine group (N acetyl cysteine with isoflurane)

Procedure details:

After shifting the patient inside the operating room, they are monitored with standard 3 lead electrocardiogram, pulseoximetry, and automatic cuffed non invasive blood pressure were connected. Basal values of heart rate, systolic blood pressure, diastolic blood pressure, mean arterial pressure and oxygen saturation are noted. After securing a intravenous line , in a randomized manner 30 patients in Group N were given N-acetyl cysteine 150mg/kg in 250 ml 0.9% normal saline while 30 patients in Group P received only 250 ml of 0.9% normal saline before induction. All patients are preoxygenated with 100% oxygen. All patients are induced with injection thiopentone sodium 5mg/kg, injection fentanyl 2µg/kg and injection succinyl choline 1.5 mg/kg. Patients were intubated and connected to ventilator after 3 minutes. Anaesthesia was maintained with 50% nitrous oxide and 50% oxygen with 1-2% isoflurane in fresh gas flow of 6l/min. Tidal volume delivered was about 8-10ml/kg with a frequency of 10-12/min. Neuromuscular blockade was maintained with injection atracurium.

Volatile anaesthetic concentration was adjusted to maintain the mean arterial blood pressure and heart rate within 20% of preinduction values. In case of signs of light anaesthesia(lacrimation,sweating or flushing) isoflurane concentration is increased by 0.5% to 2%.Atropine 0.6mg was given intravenously if heart rate dropped less than 45 beats per minute. In case of hypotension not responding to intraoperative replacement of fluids,treatment of bradycardia then isoflurane concentration is reduced.Blood pressure was maintained above 80mmhg throughout the procedure to prevent liver damage.

After the last skin suture, nitrous oxide and isoflurane were discontinued.Injection neostigmine 40µg/kg and injection Glycopyrrolate 10 µg/kg were used to reverse the residual neuromuscular blockade. Trachea was extubated when the regular spontaneous breathing pattern was returned and when the patients were able to open their eyes on command. Perioperative complications like nausea , vomiting ,flushing,rash, urticaria,cough and hypotension were noted.

Parameters Monitored:

These parameters were observed in preoperative period, postoperative 1st hr and postoperative 24th hr from peripheral venous blood.

Serum bilirubin,Aspartate aminotransferase ,Alanine aminotransferase ,Lactate dehydrogenase ,Prothrombin time ,Perioperative side effects were also noted.

Statistical Method

Descriptive analysis was done in terms of proportions for categorical variables and in terms of mean and standard deviation for continuous variables. Baseline characteristics between the two groups was compared using chi square test for categorical variables and using independent samples t test for continuous variables.

The difference between baseline value and 1 hour value for LFT was calculated and the differences between the two groups were tested by unpaired t test. Similarly the difference between baseline value and 24 hour value for all LFT parameters was calculated and the difference between the two groups was compared using unpaired t test. This method is called testing the difference in differences. A p value of <0.05 was considered statistically significant. All data were entered in Microsoft Excel and analyzed using Stata version 12.

II. Results

A:Profile Of Cases Studied

Table 1 : Age Distribution

Age Group	**Group P (N = 30)**		**Group N (N = 30)**	
	N	**%**	**N**	**%**
21-30 Years	16	53.3	17	56.7
31-40 Years	9	30.0	10	33.3
41-50 Years	5	16.7	3	10.0
Total	**30**	**100**	**30**	**100**
P Value	0.747			
	Not Significant			

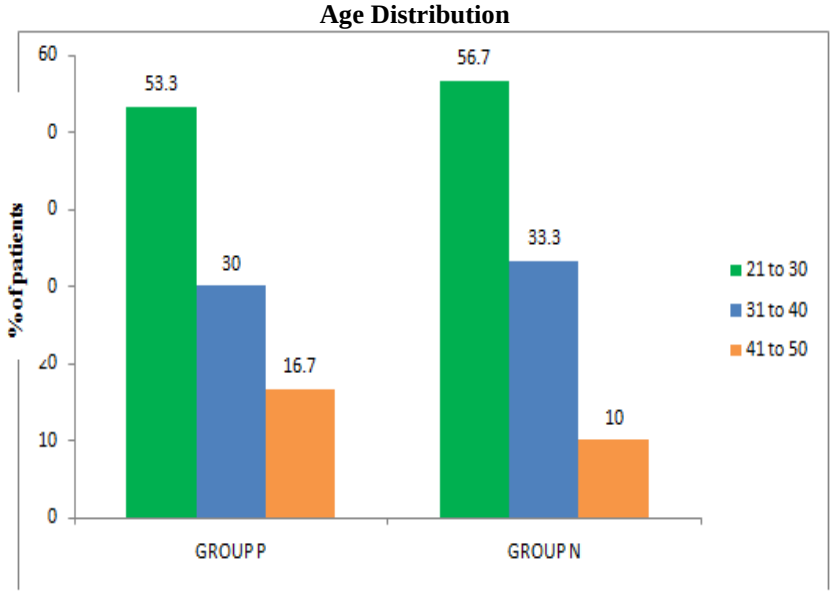
There was no statistically significant difference in age between the two groups.

Table 2 : Sex Distribution

Sex	**Group P (N = 30)**		**Group N (N = 30)**	
	N	**%**	**N**	**%**
Male	20	66.7	21	70
Female	10	33.3	9	30
Total	**30**	**100**	**30**	**100**
P Value	0.781			
	Not Significant			

The sex composition of the two groups was identical without any significant difference.

Age Distribution



Sex Distribution

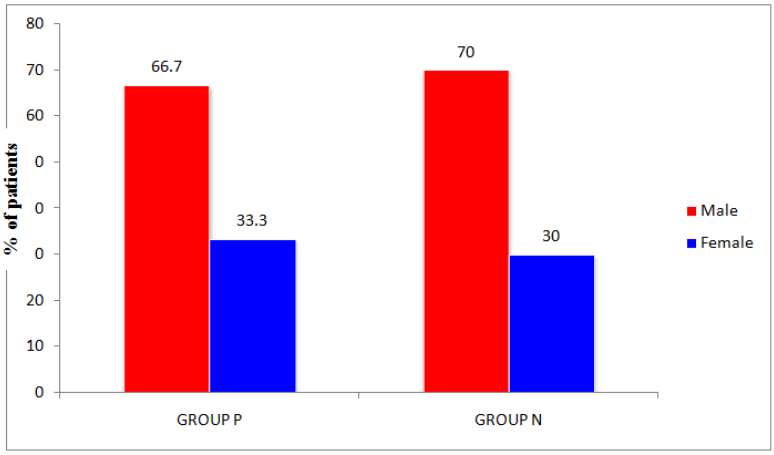


Table 3 : Type Of Surgery

Type Of Surgery	**GROUP P (N = 30)**		**GROUP N (N = 30)**	
Lap Appendicectomy	24	80.0	25	83.3
Lap Hernioplasty	6	20.0	5	16.7
TOTAL	**30**	**100**	**30**	**100**
P VALUE	0.739			
	Not Significant			

There was no any difference in the type of surgery between placebo group and N acetyl cysteine group.

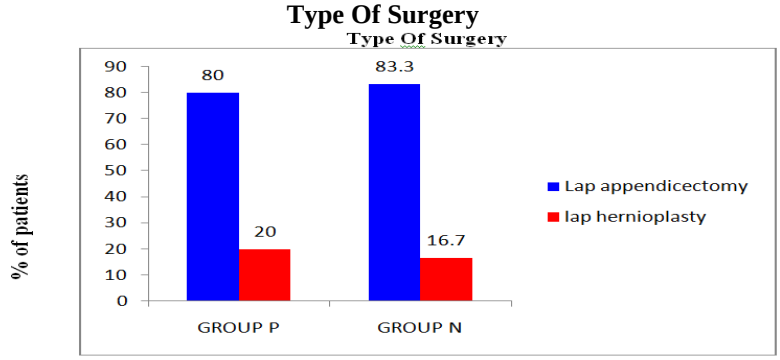


Table 4 : Asa Status

Asa	**Group P (N = 30)**		**Group N (N = 30)**	
I	24	80	26	86.66
Ii	6	20	4	13.33
Total	**30**	**100**	**30**	**100**
P Value	0.488			
	Not Significant			

There was no significant difference in the ASA status of the two groups. (P value>0.05)

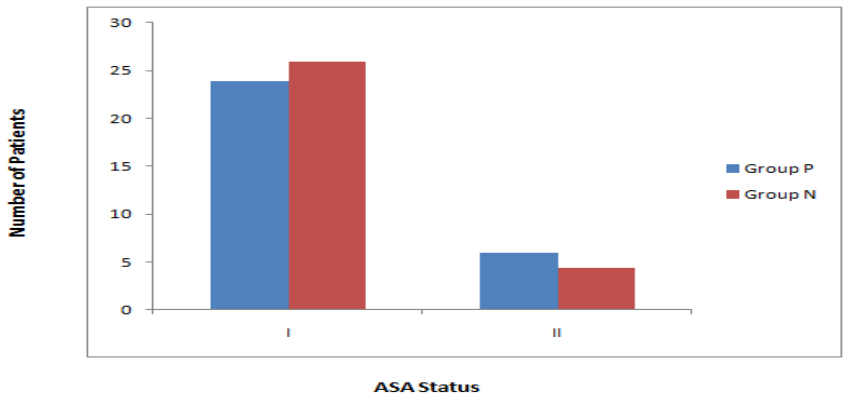


Table 5 : Weight

Parameter Weight	**Group P (Kg)**	**Group N (Kg)**
Mean	53.53	53.53
Sd	7.81	7.51
P Value	**0.712 Not Significant**	

There was no difference in weight of the patients between the two groups.

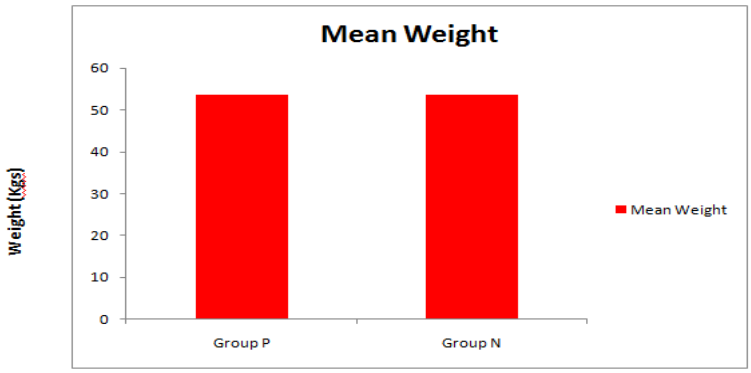
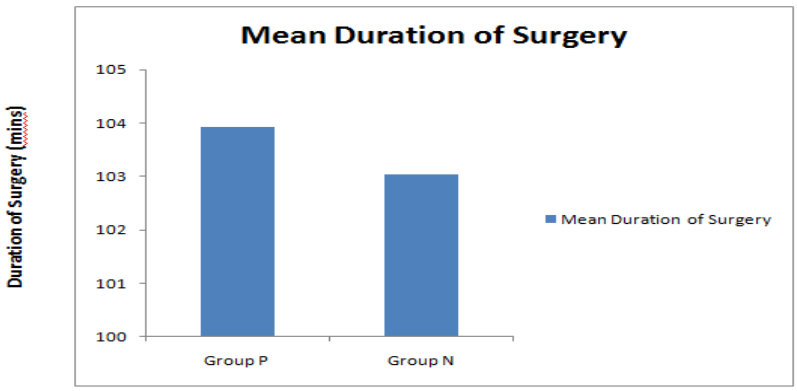


Table 6 : Duration Of Surgery

Parameter Duration of surgery	**Group p (minutes)**	**Group n (minutes)**
Mean	103.93	103.03
Sd	13.64	12.86
P value	**0.793 Not significant**	

Duration of surgery between the two groups does not show any significant difference .(p>0.05)



B : Parameters Monitored

Table 7a : Bilirubin

Parameter Bilirubin	Group P (Placebo Group)		Group N (N Acetyl Cysteine Group)	
	Mean	Sd	Mean	Sd
Preinduction Level	0.86	0.1	0.83	0.1
Postoperative 1st Hr Level	0.863	0.1	0.84	0.1
P Value	0.470 Not Significant			

Statistically there is no any significant difference in bilirubin levels between Group P and Group N at postoperative 1st hour.

Table 7b : Bilirubin

Parameter Bilirubin	Group P (Placebo Group)		Group N (N Acetyl Cysteine Group)	
	Mean	Sd	Mean	Sd
Preinduction Level	0.86	0.1	0.83	0.1
Postoperative 24th Hr	0.876	0.1	0.843	0.1
P Value	0.550 Not Significant			

Bilirubin levels after 24 hours postoperative period does not show any significant difference between two groups.

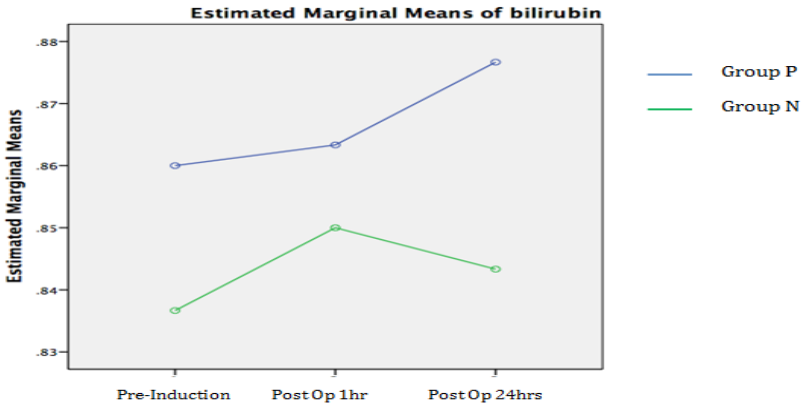


Table 8a : Aspartate Aminotransferase

Parameter Aspartate Aminotransferase	Group P (Placebo Group)		Group N (N Acetyl Cysteine Group)	
	Mean	Sd	Mean	Sd
Preinduction Ast Level	26.16	10	24	10
Postoperative 1 Hr Ast Level	29.66	12	25	10
P Value	0.094 Not Significant			

There is no significant difference in AST levels postoperatively after one hour between the two groups and the P value is insignificant.

Table 8b : Aspartate Aminotransferase

Parameter Aspartate Aminotransferase	Group P (Placebo Group)		Group N (N Acetyl Cysteine Group)	
	Mean	Sd	Mean	Sd
Preinduction Levels	26.16	10	24	10
Postoperative 24th Hr Levels	31.23	13	25.2	10
P Value	0.059 Not Significant			

There is no statistically significant difference in AST levels between two groups in postoperative 24th hour.

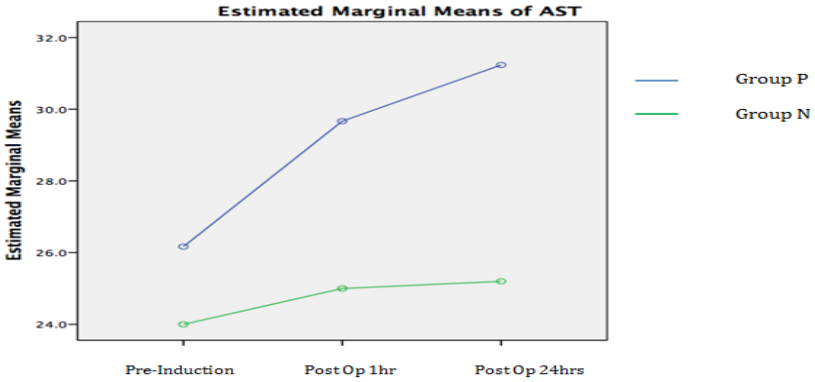


Table 9a: Alanine Aminotransferase

Parameter Alanine Aminotransferase	Group P (Placebo Group)		Group N (N Acetyl Cysteine Group)	
	Mean	Sd	Mean	Sd
Preinduction Level	21.5	11	22.43	11
Postoperative 1st Hr Level	21.1	11	22.1	9
P Value	0.954 Not Significant			

ALT levels show a decrease at postoperative 1st hour in both groups it is not stastistically significant.

Table 9b : Alanine Aminotransferase

Parameter Alanine Aminotransferase	Group P (Placebo Group)		Group N (N Acetyl Cysteine Group)	
	Mean	Sd	Mean	Sd
Preinduction Level	21.5	11	22.43	11
Postoperative 24th Hr Level	21.86	14	22.83	10
P Value	O.064 Not Significant			

Alanine aminotransferase levels after postoperative 24 hours in group P and group N does not show any stastistically significant difference.(P value > 0.05).

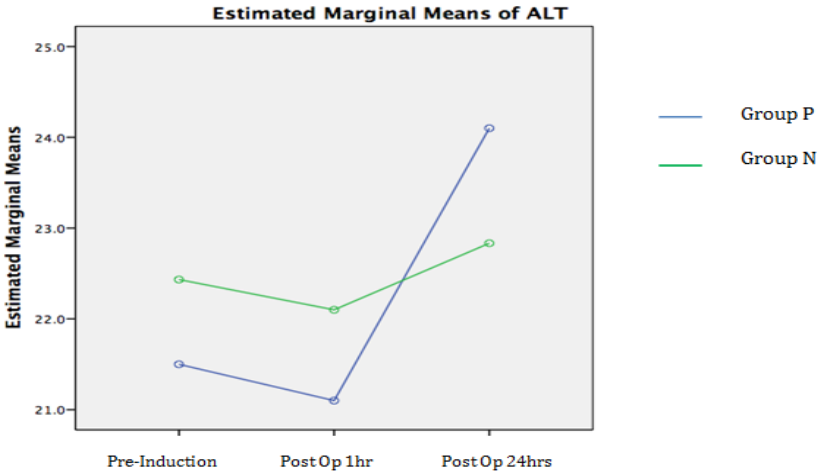


Table 10a : Lactate Dehydrogenase

Parameter Lactate Dehydrogenase	Group P (Placebo Group)		Group N (N Acetyl Cysteine Group)	
	Mean	Sd	Mean	Sd
Preinduction Level	177.6	54	160.5	62
Postoperative 1st Hr Level	188.2	64	171.2	70
P Value	0.901			

	Not Significant

Lactate dehydrogenase levels in both groups show a rise after 1 hour of postoperative period which is not statistically significant.

Table 10b : Lactate Dehydrogenase

Parameter Lactate Dehydrogenase	Group P (Placebo Group)		Group N (N Acetyl Cysteine Group)	
	Mean	Sd	Mean	Sd
Preinduction Level	177.6	54	160.5	62
Postoperative 24th Hr Level	184.7	57	163.96	62
P Value	0.734 Not Significant			

There is no any stastistically significant difference between postoperative level of lactate dehydrogenase

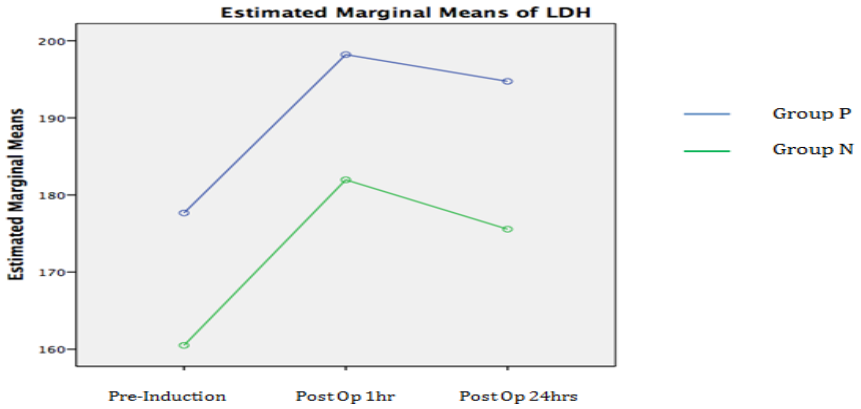


Table 11a: Prothrombin Time

Parameter Prothrombin Time	Group P (Placebo Group)		Group N (Nac Group)	
	Mean	Sd	Mean	Sd
Preinduction Level	12.83	1	12.9	1
Postoperative 1st Hr Level	12.8	1	12.66	1
P Value	0.419 Not Significant			

There is no significant difference in prothrombin time between the placebo group and N acetyl cysteine group after first hour of postoperative period.

Table 11b: Prothrombin Time

Parameter Prothrombin Time	Group P (Placebo Group)		Group N (Nac Group)	
	Mean	Sd	Mean	Sd
Preinduction Level	12.83	1	12.9	1
Postoperative 24th Hr Level	12.9	1	12.5	1
P Value	0.556 Not Significant			

There is no significant difference in prothrombin time between the placebo group and N acetyl cysteine group after 24 hrs postoperative period.

Estimated means of prothrombin time

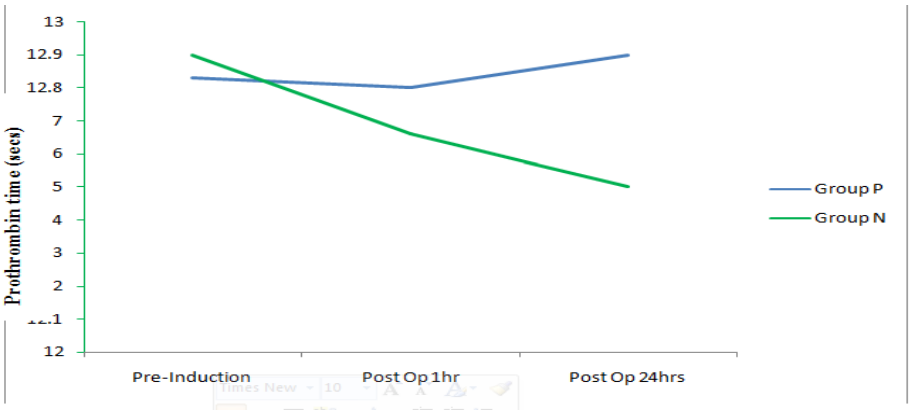


Table 12 : Complications

Complication	Group P	Group N
Nausea	5	4
Rash	0	2
Urticaria	0	1
Hypotension	4	5
Anaphylactoid Reaction	0	0

Complications like nausea and hypotension are comparable between the two groups. Rash and urticaria occurred only in two patients and one patient in N acetyl group respectively which was treated with antihistaminic medication.

III. Discussion

The common organ to be affected by drug toxicity is liver. Because, it is where the drug get metabolized. In this study with isoflurane no adverse effect on liver was seen.

Preoperative liver function tests are usually not indicated, unless there is some history related to hepatic injury or any clinical signs during examination related to it. Hence, pre-operative liver function tests are not done routinely. It should be based on history and physical examination.

Nishiyama et tal in their study found that there is postoperative decrease in AST, ALT levels after usage of volatile agents. Wissing H and Kuhr I showed insignificant decrease in level of ALT and AST postoperatively in children anaesthetized with desflurane.

In a study conducted by Beyez et al there was stastistically significant decrease in levels of AST,ALT,GGT,LDH at postoperative 1st hour and 24th hour in patients who underwent laparoscopic gynaecological procedures with isoflurane anaesthesia. There was significant increase in prothrombin time at postoperative 1st hour and 24th hour. Significant increase in levels of glutathione S transferase is seen in N acetyl cysteine group compared to isoflurane group proving the antioxidant effects of N acetyl cysteine.

In this study ALT and LDH levels show a decrease in post-operative period which is similar to above mentioned studies. But AST levels in post-operative period showed non-significant rise which is contradictory to the results of previous studies.

In another study conducted by Yokoyama T and Nishiyama T comparing the effects of sevoflurane and isoflurane on neurosurgical patients had found in isoflurane group there is a peak increase in AST, ALT, GGT and LDH levels on 7th day after surgery. But this increase is not statistically significant.

In both sevoflurane and isoflurane group prothrombin time showed significant increase at post-operative 1st hour and post-operative 24th hour. PTT levels were within normal range.

In our study, rise in aspartate transaminase levels correlates with the result of above mentioned study. Prothrombin time did not show any significant change as happened in above mentioned study.

An imbalance between endogenous antioxidant mechanisms and free oxygen radicals is the cause for oxidative stress. N acetyl cysteine is a commonly used antioxidant against this oxidative stress. N acetyl cysteine has both direct antioxidant effect and indirect action by increasing glutathione stores.

It reacts directly with hydroxyl ions and deactivates them. A study conducted by Tepel M et al showed that glutathione significantly decreases contrast induced nephrotoxicity in high risk patients undergoing computerized tomography.

Hepatic blood flow is decreased in a dose dependant manner by all volatile agents. An important mechanism is raised sympathetic tone of the vena canal system, due to controlled ventilation. Isoflurane partially decreases portal blood flow but increases hepatic arterial flow.

Hypoxic environment can increase the risk of hepatic injury. But in this study the mean arterial pressure was maintained above 80mmhg to prevent hypoxic liver damage.

IV. Summary

The aim of the study is to prospectively compare the effects of isoflurane and N-acetyl cysteine with isoflurane on liver function in laparoscopic surgery patients during general anaesthesia. 60 ASA 1 and 2 patients were randomized into two groups.In a randomized manner 30 patients were given N-acetyl cysteine 150mg/kg in 250 ml 0.9% normal saline(Group N) while 30 patients received only 250 ml of 0.9% normal saline(Group P) before induction.Both the groups were induced with a standard intravenous induction technique. Anaesthesia was maintained with 50% nitrous oxide and 50% oxygen with 1-2% isoflurane in fresh gas flow of 6l/min. Tidal volume delivered was about 8-10ml/kg with a frequency of 10-12/min. Neuromuscular blockade was maintained with injection atracurium. The mean arterial pressure was maintained above 80mmhg to prevent hypoxic liver damage. Atropine 0.6mg was given intravenously if heart rate dropped less than 45 beats per minute. In case of hypotension not responding to intraoperative replacement of fluids and treatment of bradycardia then isoflurane concentration is reduced. After the last skin suture, nitrous oxide and isoflurane were discontinued. Injection neostigmine 40µg/kg and injection and glycopyrrolate 10 µg/kg were used to reverse the residual neuromuscular blockade.Trachea was extubated when the regular spontaneous breathing pattern was returned and when the patients were able to open their eyes on command. Perioperative complications like nausea, vomiting , flushing, urticaria,cough,bradycardia and hypotension were noted.
Parameters monitored were serum bilirubin, aspartate aminotransferase, alanine aminotransferase, lactate dehydrogenase, prothrombin time before induction and in postoperative period at 1st and 24th hour.

The following results were obtained of the two groups compared,

1.Patient characteristics were comparable in both the groups.
2.Bilirubin and prothrombin time did not significantly change in the two groups at postoperative period.
3.Alanine aminotransferase levels showed a little decrease in both groups at postoperative 1st hour but not statistically significant.
4.Lactate dehydrogenase levels did not show any significant difference in both the groups.
5.Aspartate aminotransferase levels were increased in both the groups at the postoperative period but was not statistically significant.

V. Conclusion

In conclusion liver functions are well preserved when N acetyl cysteine is used with isoflurane and when isoflurane is used alone in general anaesthesia for laparoscopic surgeries.

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