

**Comparison of Total Intravenous Anesthesia versus Inhalation Anesthesia on Postoperative Liver Function in Patients with Non-Alcoholic Steatohepatitis Undergoing Laparoscopic Sleeve Gastrectomy: A randomized Clinical Trial****Tamer M. Allam<sup>a</sup>, Mahmoud M. Elnady<sup>a</sup>, Ramy Mousa Saleh<sup>a\*</sup>**

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**Abstract**

**Background:** Cases with high levels of liver enzyme may experience a decline in liver function as a result of anesthesia and surgery; consequently, it may be crucial to select anesthetics that exhibit minimal hepatotoxicity.

**Objectives:** We aimed to compare the effect of INHA and TIVA on the liver function in patients with NASH after LSG.

**Patients and methods:** The cases were randomly assigned to two equal groups; In Group I (TIVA group), propofol and fentanyl were used to induce and maintain an anesthesia, propofol and fentanyl were used to induce anesthesia in Group II (SEVO group) and sevoflurane was used to maintain it. A comprehensive history, vital signs, and laboratory tests were conducted on all cases.

**Results:** Regarding the liver function tests, in group I (TIVA group), ALT and AST were insignificantly different between baseline and postoperative day 1 and postoperative day 2 and between POD1 and POD2. In group 2 (SEVO group), both ALT and AST at POD 1 and 2 were higher to baseline values ( $P<0.05$ ) and were significantly higher at POD 2 compared to POD 1 ( $P<0.05$ ). When comparing between both groups, TIVA group had lower levels of ALT and AST in comparison to SEVO group at POD 1 and 2 ( $P<0.05$ ).

**Conclusion:** We concluded that TIVA was superior and safe compared to SEVO in maintaining the liver enzymes (ALT and AST) postoperatively, unlike SEVO which showed elevation in ALT and AST levels. Moreover, TIVA showed less postoperative pain and analgesic consumption, with higher satisfaction rate compared to SEVO.

**Keywords:** Total Intravenous Anesthesia; Inhalation Anesthesia; Liver Function; Non-Alcoholic Steatohepatitis; Laparoscopic Sleeve Gastrectomy .

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## Introduction

The pandemic of obesity has become a serious issue of public health worldwide as the size of the obese population has almost tripled over the last four decades and continues to rise (Chauhan et al., 2022). The prevalence of non-alcoholic fatty liver disease (NAFLD) has significantly increased as a result of the obesity pandemic. Presently, NAFLD is the most prevalent chronic liver disease, with 25–30% estimated global prevalence. In morbidly obese individuals, this prevalence can reach 90% (Ahmed et al., 2022). Worldwide, obesity and obesity-related disorders have experienced an alarming surge due to unhealthy lifestyles and eating habits (Alsulami et al., 2023).

Obese individuals who are unable to achieve appropriate weight loss with lifestyle modifications and pharmaceutical therapies may consider bariatric surgery as an alternative. Bariatric surgery can help obese individuals achieve recommended weight reduction and thus improve the course of NAFLD. Resolving or improving hypertension, type 2 diabetes, and hyperlipidemia as well as reducing cardiovascular risk and mortality, are among the extra advantages of bariatric surgery (Diemieszczyk et al., 2021; Doumouras et al., 2021).

Laparoscopic sleeve gastrectomy (LSG) is one of the most frequently performed worldwide bariatric operations (Vitiello et al., 2023).

Cases with high levels of liver enzyme may experience a decline in liver function as a result of anesthesia and surgery; consequently, it may be crucial to select anesthetics that exhibit minimal hepatotoxicity. Halothane, a conventional inhalational anesthetic, is recognized for its liver and renal toxicity. Eventhough rare instances of acute liver injury have been recorded with the most recent anesthetic drugs, such as desflurane and

sevoflurane (SEVO), there is a lower incidence of hepatotoxicity (Oh et al., 2020).

Propofol (2,6-diisopropylphenol) is an intravenous anesthetic. Its pharmacokinetic profile makes it very suitable for total intravenous anesthesia (TIVA) and this is a widely used technique in many centres. It is particularly advantageous in the ambulatory context because to its early onset and reduced susceptibility to side effects, such as postoperative nausea and vomiting (Chan et al., 2016).

Additionally, propofol is an exceptional anesthetic drug for cases with hepatic illness due to its brief half-life, which is applicable even in decompensated cirrhosis (Jeong et al., 2020). Consequently, it is probable that TIVA with propofol is considerably safer for cases with preoperatively high values of liver transaminase, which may indicate hepatic injury. Nevertheless, the postoperative hepatic function of these individuals has been the subject of just a handful of studies that have compared the effects of TIVA to those of inhalation anesthesia (INHA) (Oh et al., 2020).

We aimed to compare the effect of INHA and TIVA on the liver function in patients with non-alcoholic steatohepatitis (NASH) after LSG.

## Patients and methods

This prospective randomized clinical trial was performed on 80 obese patients, had American Society of Anesthesiologists (ASA) physical status I-III diagnosed with NASH hepatic disease in abdominal ultrasound preoperatively and undergoing laparoscopic sleeve gastrectomy at Benha University Hospital during the period from July 2022 to July 2023. This manuscript adheres to the CONSORT guidelines. Informed written consent was acquired from the patients. The research was done in accordance with the institutional ethics

committee's authorized standards at Benha University Hospitals (Approval code: RC 3-4-2024) and registered on clinical trial (NCT06423846) from January 26, 2023 to May 12, 2024.

Inclusion criteria were obese patients aged >18years, diagnosed with NASH based on abdominal ultrasound with elevated liver enzymes and no additional procedures during LSG.

Exclusion criteria was procedures that were conducted utilizing anesthetic drugs that were not explicitly labelled as INHA or TIVA, including cesarean section or cardiac operations, and neuromuscular diseases as the results might be confounded by the potential leakage of AST and ALT from the injured muscles.

**Randomization:** Participants were randomly assigned to two equal groups on a 1:1 scale utilizing a computer-generated list of random numbers that were sealed in an opaque envelope. In Group I (TIVA group), propofol and fentanyl were used to induce and maintain an aesthesia, Propofol and fentanyl were used to induce anesthesia in Group II (SEVO group) and SEVO was used to maintain it.

**Preoperatively:** All patients were evaluated by complete history taking including age, sex, ASA physical status, comorbidities (hypertension, ischemic heart disease from myocardial infarction to stable angina, cerebrovascular disease, pulmonary disease, diabetes mellitus, and cancer), body mass index (BMI; kg/m<sup>2</sup>), and preoperative use of any hepatoprotective agents. Vitals and laboratory examinations, which included a complete blood profile and renal function testing, were implemented (Selewski et al., 2011; Balakumar et al., 2017).

All patients were premedicated with 0.05 mg/kg midazolam (Dormicum®), Roche, Switzerland) and 50 mg ranitidine (Urantac™, Whanin, Korea) for 30 min before undergoing anesthesia. Venous

access was secured with an 18G needle, and lactated Ringer's solution was infused at 2 ml/kg/hr. For anesthesia induction, spontaneous breathing with 100% oxygen was performed for 2 min for denitrogenation.

Anesthesia was administered in the TIVA group using fentanyl 1 ug/kg, propofol 2 mg/kg, and fentanyl 0.1ug/kg/min, propofol 200 ug/kg/min, dexmedetomidine 1 ug/kg/hour for maintenance. Propofol 2 mg/kg and fentanyl 1 ug/kg were administered to patients in the SEVO group to produce general anesthesia. Thereafter, SEVO in air and oxygen, as well as dexmedetomidine 1 ug/kg/hour, were administered to maintain the anesthesia. If the heart rate and/or mean arterial blood pressure exceeded the baseline by 20%, all cases were administered an intraoperative IV bolus of fentanyl at a rate of 1 ug/kg. In order to assist tracheal intubation, rocuronium 0.6 mg/kg was given.

The neuromuscular blockade was reversed with atropine neostigmine 0.05 mg/kg and 0.02 mg/kg once the surgical operations were completed, and tracheal extubation was performed. Vitals such as oxygen saturation (SpO<sub>2</sub>), blood pressure, and heart rate were monitored in the post-anesthesia care unit (PACU). The visual analogue scale (VAS) score was employed to evaluate pain (10—the most severe imagined pain, 0—absolutely no pain) (Delgado et al., 2018). A 3 mg bolus of IV morphine was administered as a rescue analgesia if the pain was > 3. An IV infusion of 1 gram of paracetamol was administered every six hours.

Patient satisfaction was evaluated using 5-point Likert scale, (5=extremely satisfied; 1=extremely dissatisfied) at 24 hrs postoperatively (Chyung et al., 2017). Assessments were done by anesthesiologist not involved in the

administration of block or intraoperative management of cases.

**Outcomes:** Primary outcome: included the assessment of postoperative pain by VAS and postoperative liver function (ALT and AST) in the first 48 hrs postoperatively. Secondary outcome: included the assessment of operative time, anesthetic time, intraoperative and postoperative analgesic requirements, incidence of intraoperative and postoperative side effects (as intraoperative hypotensive events, intraoperative vasopressor use, PONV and Dizziness or delirium), hospital stay, and patients' satisfaction.

**Sample size:** G. power 3.1.9.2 (Universität Kiel, Germany) was utilized for calculating the sample size. The VAS values were used to determine the sample size, which were significantly reduced in the TIVA group than in the inhalational (Desflurane) group at all measurement points ( $P < 0.0001$ ), based on a prior research (Elbakry et al., 2018). Based on the following considerations: 90% power of the study and 0.05  $\alpha$  error, allocation ratio is 1:1. In order to overcome dropout, eight cases were added. Consequently, 80 patients were assigned.

### Statistical analysis

SPSS v28 (IBM©, Armonk, NY, USA) was used for analyzing the data. Data normality was assessed utilizing the histograms and Shapiro-Wilks test. Qualitative data analysis was performed utilizing Chi-square test or Fisher's exact test when applicable, and were provided as number and percentage. The unpaired student t-test was employed to analyze the quantitative parametric variables, which were reported as mean and standard deviation (SD). The Mann Whitney-test was employed to analyze quantitative non-parametric variables, which were reported as the median and interquartile range (IQR). Statistical significance was defined as a two-tailed P value that was  $< 0.05$ .

### Results

An assessment of eligibility was conducted for 117 cases in this study. Of these, 8 cases declined to participate, and 29 cases did not match the requirements. The 80 cases that remained were randomly assigned to two groups (40 cases in each). All cases that were allocated were statistically analyzed and followed up on (Fig.1).

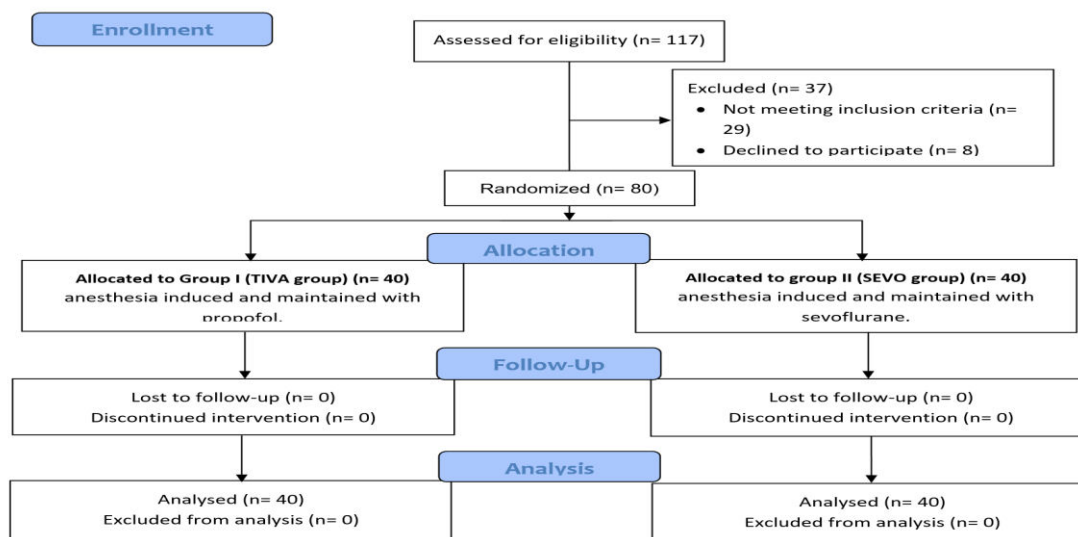


Fig.1. CONSORT flowchart of the enrolled patients

Baseline characteristics (age, sex, weight, height, BMI and ASA), comorbidities (DM, HTN and IHD) and

liver steatosis grades were insignificantly different between both groups, (Table. 1).

**Table 1. Baseline characteristics, comorbidities, and liver steatosis of the studied groups**

Variables		Group I (TIVA group) (n=40)	Group II (SEVO group) (n=40)	P value
Age (years)		52.5 ± 7.67	54.0 ± 8.05	0.404
Sex	Male	22 (55%)	19 (47.5%)	0.502
	Female	18 (45%)	21 (52.5%)	
Weight (Kg)		115.7 ± 15.73	117.2 ± 14.73	0.672
Height (m)		1.67 ± 0.05	1.70 ± 0.06	0.088
BMI (Kg/m <sup>2</sup> )		41.4 ± 5.91	40.9 ± 5.57	0.676
ASA	ASA I	6 (15%)	8 (20%)	0.637
	ASA II	18 (45%)	14 (35%)	
	ASA III	16 (40%)	18 (45%)	
Comorbidities	DM	7 (17.5%)	4 (10%)	0.518
	HTN	9 (22.5%)	11 (27.5%)	0.606
	IHD	3 (7.5%)	5 (12.5%)	0.456
Liver steatosis	Grade 1	15 (37.5%)	18 (45%)	0.550
	Grade 2	14 (35%)	15 (37.5%)	
	Grade 3	11 (27.5%)	7 (17.5%)	

Data presented as mean ± SD or frequency (%), BMI: body mass index, ASA: American society of Anesthesiologists, DM: diabetes mellitus, HTN: hypertension, IHD: ischemic heart disease.

Regarding the liver function tests, in group I (TIVA group), ALT and AST were insignificantly different between baseline and POD1 and POD 2 and between POD1 and POD2. In group 2 (SEVO group), both ALT and AST at POD 1 and POD 2 were significantly higher to baseline values (P<0.05) and were significantly higher at POD 2

compared to POD 1 (P<0.05). When comparing both groups, group I (TIVA group) had significantly lower levels of ALT and AST in comparison to group 2 (SEVO group) at POD 1 and POD 2 (P<0.05), with insignificant variation between both groups regarding baseline ALT and AST, (Table. 2).

**Table 2. Assessment of liver function tests of the studied groups**

Variables		Group I (TIVA group) (n=40)	Group II (SEVO group) (n=40)	P value
ALT (U/L)	Baseline	42.2 ± 0.9	41.8 ± 1.06	0.116
	POD 1	42.6 ± 1.65	46.7 ± 2.47	<0.001*
	POD 2	42.5 ± 1.63	48.6 ± 2.78	<0.001*
	P value within group	P1= 0.149, P2= 0.302, P3= 0.702	P1<0.001*, P2<0.001*, P3=0.004*	
AST (U/L)	Baseline	43.4 ± 1.24	43.7 ± 1.14	0.351
	POD 1	43.9 ± 1.63	46.6 ± 2.91	<0.001*
	POD 2	43.7 ± 1.39	48.3 ± 3.25	<0.001*
	P value within	P1= 0.104, P2= 0.424,	P1<0.001*,	

	<b>group</b>	P3= 0.553	<b>P2&lt;0.001*, P3=0.028*</b>
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Data presented as mean  $\pm$  SD, ALT: alanine aminotransferase, AST: aspartate aminotransferase, POD 1: first postoperative day after surgery, POD 2: second postoperative day after surgery, \*: statistically significant as p value <0.05. P1: p value between baseline and POD1, P2: p value between baseline and POD2, P3: p value between POD1 and POD2.

(Table.3) shows insignificant the operative time, anesthesia time and variation between both groups as regard hospital stay.

**Table 3. Operative time, anesthetic time and hospital stay of the studied groups**

Variables	Group I (TIVA group) (n=40)	Group II (SEVO group) (n=40)	P value
<b>Operative time (min)</b>	113.2 $\pm$ 34.78	107.9 $\pm$ 32.16	0.481
<b>Anesthetic time (min)</b>	128.1 $\pm$ 40.41	137.03 $\pm$ 37.96	0.311
<b>Hospital stay (day)</b>	2.4 $\pm$ 0.5	2.2 $\pm$ 0.7	0.145

Data presented as mean  $\pm$  SD, \*: statistically significant as p value <0.05.

In group 1 (TIVA group), VAS at POD1 and POD 2 were significantly lower in comparison to VAS at baseline (P<0.001, <0.001) and VAS at POD 2 was significantly lower in comparison to VAS at POD1 (P=0.001). In group 2 (SEVO group), VAS at POD 2 was significantly lower in comparison to VAS at baseline and at POD 1 (P<0.001, <0.001), with insignificant difference between VAS at POD 1 and at baseline. Group 1 (TIVA group) had significantly lower VAS at POD1 and POD 2 in comparison to Group II (SEVO group) (P<0.001, 0.006), with insignificant variation regarding VAS at baseline between both groups, (Table. 4).

**Table 4. Assessment of postoperative pain by visual analogue scale (VAS) of the studied groups**

Variables	Group I (TIVA group) (n=40)	Group II (SEVO group) (n=40)	P value
<b>Baseline</b>	4 (3-5)	4 (4-5)	0.180
<b>POD 1</b>	3 (2-4)	4 (3-5)	<0.001*
<b>POD 2</b>	2 (1-2.25)	3 (2-3)	0.006*
<b>P value within group</b>	<b>P1&lt;0.001*, P2&lt;0.001*, P3=0.001*</b>	P1= 0.191, <b>P2&lt;0.001*, P3&lt;0.001*</b>	

Data presented as median (IQR), POD 1: first postoperative day after surgery, POD 2: second postoperative day after surgery, \*: statistically significant as p value <0.05. P1: p value between baseline and POD1, P2: p value between baseline and POD2, P3: p value between POD1 and POD2.

(Table.5) shows that group I (TIVA group) had significantly lower intraoperative bolus fentanyl consumption and total morphine consumption in comparison to group II (SEVO group) (P<0.001, <0.001).

**Table 5: Intraoperative and postoperative analgesic requirements of the studied groups**

Variables	Group I (TIVA group) (n=40)	Group II (SEVO group) (n=40)	P value
<b>Total intravenous bolus fentanyl consumption (mcg)</b>	119.4 $\pm$ 2.62	134.5 $\pm$ 2.86	<0.001*
<b>Total morphine consumption (mg)</b>	9.9 $\pm$ 1.2	14.4 $\pm$ 3.1	<0.001*

Data presented as mean  $\pm$  SD, \*: statistically significant as p value <0.05.

(Table.6) shows that intraoperative hypotensive events occur in 22 (55%) cases in group I (TIVA group) and 17 (42.5%) cases in group II (SEVO group), intraoperative vasopressor use was recorded in 16 (40%) cases in group I (TIVA group) and 13 (32.5%) cases in group II (SEVO group). Postoperative PONV occurred in 2 (5%) cases in group I

(TIVA group) and 4 (10%) cases in group II (SEVO group), and dizziness or delirium occurred in 1 (2.5%) case in group I (TIVA group) and 2 (5%) cases in group II (SEVO group). Insignificant variation was reported as regard the incidence of intraoperative and postoperative side effects between both groups.

**Table 6. Incidence of intraoperative and postoperative side effects of the studied groups**

Variables	Group I (TIVA group) (n=40)	Group II (SEVO group) (n=40)	P value
Incidence of intraoperative hypotensive events	22 (55%)	17 (42.5%)	0.263
Intraoperative vasopressor use	16 (40%)	13 (32.5%)	0.485
PONV	2 (5%)	4 (10%)	0.675
Dizziness or delirium	1 (2.5%)	2 (5%)	1.00

Data presented as frequency (%), PONV: postoperative nausea and vomiting.

(Table.7) shows that group I (TIVA group) showed significantly higher satisfaction compared to group II (SEVO group) (P<0.001).

**Table 7. Satisfaction of the studied groups**

Variables	Group I (TIVA group) (n=40)	Group II (SEVO group) (n=40)	P value
Very dissatisfied	0 (0%)	4 (10%)	<0.001*
Dissatisfied	1 (2.5%)	10 (25%)	
Neutral	4 (10%)	16 (40%)	
Satisfied	16 (40%)	10 (25%)	
Very satisfied	19 (47.5%)	0 (0%)	

Data presented as frequency (%), \*: statistically significant as p value <0.05.

## Discussion

The global prevalence of morbid obesity has resulted in the implementation of metabolic/bariatric surgery, as a result of the significant rise in obesity throughout modern nations (Courcoulas et al., 2023). Bariatric surgery is believed to have a therapeutic impact that extends beyond weight loss to enhance the prognosis of obesity-related disorders (Chandrakumar et al., 2023).

The relationship between the kind of anesthetic drugs and postoperative hepatic function in hepatic procedures has been the subject of certain studies; nevertheless, their conclusions are still

subject to debate (Soliman et al., 2020; Koraki et al., 2020). According to a prior investigation, individuals with cirrhosis who had partial hepatectomy were reported to experience less postoperative hepatocellular damage when administered isoflurane anesthesia than when administered TIVA (Oladimeji et al., 2022). Surgical trauma, hepatic mass reduction, ischemia, stress response, and hepatic oxygen deprivation are all potential causes of postoperative liver dysfunction in hepatic surgery. (Ocak et al., 2020). Furthermore, temporary ischemia may occur as a consequence of hepatic inflow blockage during resection

of the liver. This has the potential to result in liver damage and postoperative hepatic function impairment. (Settmacher et al., 2023).

There is a lack of research that has examined the impact of various types of anesthetics, particularly IV vs INHA, on postoperative hepatic function in NASH patients after non-hepatic procedures. Eventually, blood transaminase levels are elevated as a result of liver damage, regardless of whether it is acute or chronic. The liver is the site of significant concentrations of both AST and ALT. AST is also widespread in the skeletal muscles, heart, brain, red blood cells, and kidneys, while ALT is found in modest amounts in the kidneys and skeletal muscles. Consequently, liver damage is more specifically associated with an elevation in ALT levels (Vaja and Rana, 2020). This explains why the primary outcome in a prior research was the ALT level (Oh et al., 2020).

Regarding the liver function tests, in group I (TIVA group), ALT and AST were insignificantly different between baseline and POD1 and POD 2 and between POD1 and POD2. In group 2 (SEVO group), both ALT and AST at POD 1 and POD 2 were significantly higher to baseline values ( $P < 0.05$ ) and were significantly higher at POD 2 compared to POD 1 ( $P < 0.05$ ). When comparing both groups, group I (TIVA group) had significantly lower ALT and AST in comparison to group 2 (SEVO group) at POD 1 and POD 2 ( $P < 0.05$ ), with insignificant variation as regard baseline ALT and AST between both groups.

The retrospective research conducted by Oh *et al.* examined the impact of TIVA versus INHA in patients with preoperatively increased levels of liver enzymes on the postoperative liver function. The TIVA group (TIVA:  $n=138$ )

had significantly lower AST and ALT changes than in the INHA group (INHA:  $n=592$ ) (Oh et al., 2020).

Sahin *et al.* conducted a comparison of the effects of TIVA and INHA on cases who underwent lumbar discectomy. They discovered no variations between the two groups and that postoperative liver function remained unaffected (Sahin et al., 2011). Yoon *et al.* discovered no variations in liver function following laparoscopic cholecystectomy surgery with either INHA or propofol anesthesia (Yoon et al., 2005).

Kim *et al.* studied 200 cases, scheduled for an elective thyroidectomy were randomly assigned into two groups. The SEVO group (Group S) maintained anesthesia with remifentanyl and SEVO 1-2%, whereas the TIVA group (Group T) maintained anesthesia with remifentanyl 2-5 ng/ml and propofol 2-5 ug/ml at the effect site, utilizing a target controlled infusion pump for maintaining BIS of 40-60. In comparison to the preoperative value in Group S, the AST was elevated at POD1 and POD3, and at POD1 in Group T. However, the results were within the normal range. ALT remained unaltered in both groups following anesthesia (Kim et al., 2013).

Regarding VAS, in group 1 (TIVA group), VAS at POD1 and POD2 were significantly reduced in comparison to VAS at baseline and VAS at POD2 was significantly reduced in comparison to VAS at POD1. In group 2 (SEVO group), VAS at POD2 was significantly reduced in comparison to VAS at baseline and at POD 1. Group 1 (TIVA group) had significantly reduced VAS at POD1 and POD 2 in comparison to Group II (SEVO group) ( $P < 0.001, 0.006$ ).

Propofol was initially designed as a sedative and anesthetic medication, and the possible analgesic action is a



fascinating and surprising finding (Wong et al., 2022).

A retrospective research was conducted by Chan *et al.* The records of cases who underwent liver surgery were examined. TIVA group had reduced NRS pain scores during coughing on POD1 and 2 but not 3 ( $p = 0.0127$ ,  $p = 0.0472$ ,  $p = 0.4556$  respectively). In comparison to the SEVO group, they also consumed significantly less total morphine ( $p=0.03$ ) (Chan et al., 2016).

Cheng *et al.* conducted a research that shown that propofol was linked with reduced postoperative pain and self-administered morphine in the first day following open uterus surgery, in comparison to isoflurane. This was particularly the case with acute pain (Cheng et al., 2008). Tan *et al.* reported that at immediate postoperative 4-hour duration, the SEVO group had significantly elevated pain scores in comparison to the propofol group (Tan et al., 2010).

**Limitations:** The sample size was small. Also, the study was single centered with short follow-up duration. As a result, more large-scale, multicenter studies are necessary to verify the impact of anesthetics on liver function and long-term clinical outcomes.

### Conclusion

We concluded that TIVA was superior and safe compared to SEVO in maintaining the liver enzymes (ALT and AST) postoperatively, unlike SEVO which showed elevation in ALT and AST levels. Moreover, TIVA showed less postoperative pain and analgesic consumption, with higher satisfaction rate in comparison to SEVO.

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**Conflict of Interest:** Nil

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