Original Research Paper

Volume - 14 | Issue - 03 | March - 2024 | PRINT ISSN No. 2249 - 555X | DOI : 10.36106/ijar

Hepatobiliary Surgery

A PROSPECTIVE SINGLE BLIND RANDOMIZED CONTROL TRIAL TO COMPARE THE OUTCOMES AFTER LIVER RESECTION WITH OR WITHOUT INTERMITTENT PORTAL INFLOW CONTROL (PRINGLE'S MANOEUVRE)"-LIPINCOT TRIAL -CTRI/2016/04/006816

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ABSTRACT

Background: Liver resection, a crucial surgical intervention for hepatic conditions, involves removing a portion of the liver, addressing benign and malignant lesions. The Pringle's maneuver, an intermittent portal inflow control, is frequently used perioperatively during liver resection. **Aim:** To assess whether Pringles maneuver during liver resection as a method of inflow control has any influence on operative outcome. **Patients and Methods** Between July 2013 and March 2015, 80 liver resection cases were randomly divided into Group A (Pringle's maneuver) and Group B (Non-Pringle's). Both groups received selective low CVP anesthesia. After excluding 14 cases, the remaining 66 cases underwent minor or major hepatectomy (≥3 segments). Assessments included blood lactate, Neutrophil-to-Lymphocyte Ratio, liver enzymes tests, and bilirubin levels on days 1, 3, and 5. **Results:** In Group A, major and right hepatectomies showed increased blood loss, higher transfusion needs, and prolonged hospital stays. Elevated liver enzymes, lactate levels, and Neutrophil-to-Lymphocyte ratio on day one was observed in Group A. Group A experienced significantly higher-Grade B & C liver failure, postoperative hyperglycaemia, and mortality (five deaths attributed to liver failure). Univariate analysis revealed age, comorbidity, liver condition, resection type, bloodless procedure, duration, N/L ratio, lactate level, and 50-50 criteria significantly correlated with morbidity and mortality ($p<0.05$). **Conclusion:** Pringle's manoeuvre in liver resection extends hospital stay, heightens transfusion requirement, and raises complications, particularly in diseased livers. Elevated blood lactate and Neutrophil-to-Lymphocyte ratio reliably predict postoperative liver failure and mortality.

KEYWORDS : Pringle's manoeuvre, Neutrophil Lymphocyte ratio, Post-operative liver failure.

INTRODUCTION

In the past decades, bleeding during liver surgery is routinely controlled by the Pringle maneuver consisting in the temporary clamping of hepatic artery, portal vein, and bile duct.[1] There are pros and cons in using Pringles maneuver during liver resections.[3] Though it is proved to be better in controlling excessive bleeding during liver resection there are potential side effects like ischemia reperfusion injury which severely affects the outcome after surgery. Normothermic ischemia of the normal liver is well-tolerated for periods as long as 90 minutes.[4] Operative mortality and morbidity after liver resections are not modified by the duration of hepatic vascular inflow occlusion within these limits. Then after introduction of intermittent clamping and ischemic preconditioning it was proved that intermittent clamping appears to be safe. Hence if clamping is necessary during complex resections or in abnormal liver parenchyma, IPM is advised.

Several studies have investigated the impact of different clamping techniques during liver resection. In 1997, Man et al. conducted a study involving 93 patients, comparing intermittent clamping to non-clamping.[5] Subsequently, in 2003, the same authors extended their research with 40 patients, still evaluating intermittent clamping. Chouker et al. explored the comparison between intermittent (n=25) and continuous (n=25) clamping in a study involving 75 patients in 2004.[6] Additionally, Capussotti et al. investigated intermittent clamping in a larger cohort of 126 patients in 2006.[7] These studies contribute to the understanding of the effects of clamping techniques on liver resection outcomes, providing valuable insights for clinical considerations and potential improvements in surgical practices.

There is no evidence supporting the routine use of IPM, during liver resection. As there are still so many conflicts of recommendations of use of IPM to prove the situations in which it is more deleterious when it is to be recommended we have started this study.

Aim and Objective

The study aimed to identify situations where IPM can be safely employed and circumstances where it may be advisable to avoid its use, particularly in consideration of potential tissue hypoxia. The objective of this study was to assess the impact of Intermittent Pringle's maneuver (IPM) during liver resection on blood loss and operative outcomes in comparison to procedures without inflow control.

MATERIAL AND METHODS

Study Design and Duration

This is a single-blinded parallel-armed randomized controlled trial conducted for a period of 2 years in the Institute of Surgical Gastroenterology, Rajiv Gandhi Govt. General Hospital, Madras Medical College, Chennai.

Study Population

Patients meeting the following inclusion criteria were enrolled: individuals with various benign or malignant liver conditions, good Eastern Cooperative Oncology Group (ECOG) status (0, 1), and age >13 years. Preoperative baseline investigations, ultrasound (USG), multidetector computed tomography (MDCT), magnetic resonance imaging (MRI), and positron emission tomography-CT (PET CT) for malignant disorders were performed.

Exclusion Criteria

Patients with advanced disease on radiology and diagnostic laparoscopy, poor ECOG status (2, 3, 4), and those unwilling to participate were excluded.

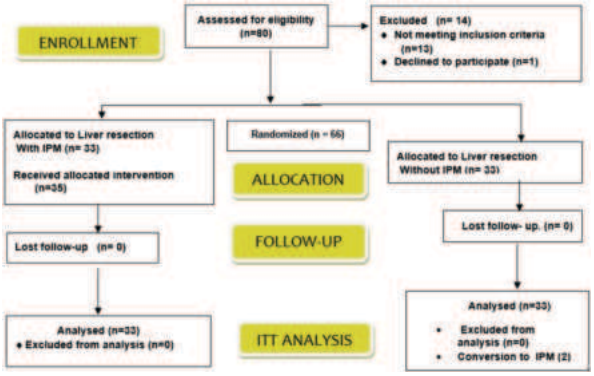
Sampling

A total of 66 patients were enrolled to achieve an 80% confidence interval using purposive sampling.

Randomization Procedure

Randomization was done at the time of surgery using random number tables after ruling out inoperability through exploration/diagnostic laparoscopy in cases of malignancy. The study employed a single-blinded parallel-armed randomized design.

A total of 80 participants were initially assessed for eligibility. Among them, 14 individuals were excluded from the study, with 13 not meeting the inclusion criteria and one declining to participate. The remaining 66 participants were randomized into two groups: one undergoing Liver resection Without IPM (n=33) and the other undergoing Liver resection with IPM (n=33). All 66 participants were allocated and analysed according to their respective groups. In the Liver resection Without IPM group, none of the participants were excluded from the analysis, but two underwent conversion to IPM during the course of the study. Similarly, in the Liver resection with IPM group, none of the participants were excluded from the analysis.



Consort Diagram For The Study. IPM, Intermittent Pringle Maneuver: ITT, Intention To Treat Analysis

Interventions

In both groups, selective low central venous pressure (CVP) anesthesia and restricted volume replacement were employed during parenchymal transactions to minimize bleeding. In Group 2 (intermittent Pringles), total occlusion time did not exceed 45 minutes.

Parameters Analyzed

Demographic profile, duration of surgery, amount of blood loss, transfusion requirements, blood lactate levels, and Neutrophil-to-Lymphocyte ratio on the first postoperative day, liver function tests (LFT) levels on days 1, 3, and 5, duration of ICU and postoperative hospital stay, morbidity, and 90 day- mortality were analyzed.

Definitions

- Major Hepatectomy: Removal of 3 or more liver segments.
- Liver failure: Classified according to the International Study Group of Liver Surgery (ISGLS) criteria (Grade A, Grade B, Grade C).

Statistical Analysis

Appropriate statistical tests, such as independent t-tests and chi-square tests, were employed for the analysis of demographic profiles, surgery duration, blood loss, transfusions, and other relevant parameters. The significance level was set at $p<0.05$.

RESULTS

Baseline Characteristics

The mean age in GROUP 1 was 45.78 ± 13.78, while in GROUP 2, it was 50.03 ± 11.34, with no statistically significant difference observed (p = 0.177). Sex distribution revealed 15 males and 18 females in GROUP 1, compared to 17 males and 16 females in GROUP 2, with a non-significant p-value of 0.629. Disease condition, categorized as benign or malignant, showed an equal distribution in both groups (p = 1.0). Comorbidity status exhibited a non-significant difference (p = 0.202), with 4 participants having comorbidities in GROUP 1 and 8 in GROUP 2.

Table 1: Baseline Clinical Characteristics

Baseline Characteristics		Group 1	Group 2	p- value
Age		45.78±13.78	50.03±11.34	0.177
Sex	Male	16	17	0.629
	Female	18	15	
Disease condition	Benign	17	17	1.0
	Malignant	16	16	
Comorbidity	Yes	4	8	0.202
	No	29	25	
Hepatectomy class	Major	20	18	0.618
	Minor	13	15	
Additional procedure	Yes	8	5	0.353
	No	25	28	
Status of Liver	Cirrhosis	3	4	0.608
	Fibrosis	2	3	
	Steatosis	2	2	

Hepatectomy class (Major or Minor) demonstrated no significant difference between the groups (p = 0.618). The presence of additional procedures also did not significantly differ between GROUP 1 (8 – yes, 25 – no) and GROUP 2 (5 – yes, 28 – no; p = 0.353). The status of the liver in terms of cirrhosis, fibrosis, and steatosis did not show significant group differences (p = 0.608). Regarding surgical parameters, the mean surgery time was 3.65 ± 1 in GROUP 1 and 3.27 ± 0.9 in GROUP 2 (p = 0.125). Blood loss (1263.63 ± 870.99 vs. 968.18 ± 509.72, p = 0.097) and transfusion requirements (2.57 ± 1.71 vs. 1.78 ± 1.47, p = 0.05).

Table 2: Disease Status And Procedure Done

	Group 1	Group 2	P - value
Procedure			
Right hepatectomy	13	8	0.186
Left hepatectomy	7	8	0.769
Left lateral segmentectomy	8	13	0.186
Seg 4,5 (radical cholecystectomy)	3	2	1.000
Non anatomical resection	2	2	1.000
Disease status			
HCC	11	9	0.535
Hemangioma	10	9	0.786
Hepatolithiasis	4	6	0.492
Carcinoma GB	1	3	0.613
Metastasis			
Colon	1	3	0.613
GIST	0	1	1.000
NET	1	0	1.000
Rare tumours			
angiomyolipoma	0	1	1.000
Biliary cystadenoma	1	0	1.000
IHCC	1	0	1.000
Adenomatosis	2	0	0.492
Hepatoblastoma	1	0	1.000
Rhabdomyosarcoma	0	1	1.000

Disease Status and Procedure Done

In the comparative analysis between Group 1 (Liver resection Without IPM) and Group 2 (Liver resection with IPM), specific surgical procedures demonstrated comparable distribution: right hepatectomy (13 vs. 8, p = 0.186), left hepatectomy (7 vs. 8, p = 0.769), and left lateral segmentectomy (8 vs. 13, p = 0.186). Disease statuses, including hepatocellular carcinoma (11 vs. 9, p = 0.535), haemangioma (10 vs. 9, p = 0.786), hepatolithiasis (4 vs. 6, p = 0.492), and gallbladder carcinoma (1 vs. 3, p = 0.613), exhibited no significant differences between the groups. Similarly, metastasis occurrences from the colon (1 vs. 3, p = 0.613), gastrointestinal stromal tumour (0 vs. 1, p = 1.000), and neuroendocrine tumour (1 vs. 0, p = 1.000) were comparable. Rare tumours such as angiomyolipoma, biliary cystadenoma, intrahepatic cholangiocarcinoma, adenomatosis, hepatoblastoma, and rhabdomyosarcoma also showed no significant group differences (p > 0.05 for all comparisons).

Table 3: Intra-operative Findings In The Study Participants

Variables	Group 1	Group 2	P value
Surgery Time	3.65 ± 1	3.27±0.9	0.125
Parenchymal Transection time	2.23±0.8	1.7±0.7	0.003
Blood Loss	1263.63 ±870.99	968.18 ± 509.72	0.097
Transfusion	2.57 ± 1.71	1.78 ± 1.47	0.05

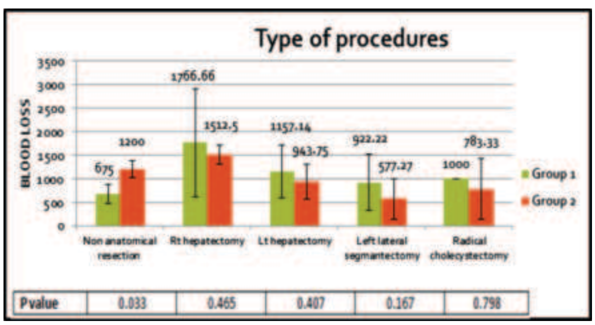


Figure 1: Comparison Of Blood Loss With Different Types Of Procedure

Table 4: Post-operative Findings In The Study Participants

Variables	Group 1	Group 2	P value
Hospital stays	15.42±6.29	11.15±3.60	0.001
ICU Stay	5.3±3.42	2.4±1.5	<0.0001

Table 5: Liver Enzymes

Variables	Group 1		Group 2		P value
	Mean	SD	Mean	SD	
SGOT	131.51	46.35	51.39	9.81	<0.0001
SGPT	101.9	37.68	48.27	10.39	<0.0001
ALP	164.12	43.33	131.45	37.23	0.002
Bilirubin Day1	2.58	1.25	1.47	0.81	<0.0001
Day 5	2	1.19	1.29	0.61	0.004
PT/INR					
Day 1	1.39	0.24	1.26	0.26	0.05
Day 5	1.26	0.32	1.22	0.31	0.62

Table 6: Morbidity In The Study Participants

Variables	Group 1	Group 2	P value
Liver failure			
Grade A	3	7	0.037
Grade B	7	1	0.041
Grade C	3	1	0.063
Bile leak	8	5	0.353
Wound infection	12	6	0.041
Pulmonary complication	1	3	0.613
Post-operative hyperglycemia	4	2	0.672

Mortality Correlation

In Group 1, five cases experienced liver failure, whereas only one case in Group 2 faced a similar outcome, yielding a statistically significant p-value of 0.027. Regarding metastatic disease, Group 1 had one mortality case compared to two in Group 2, with no significant difference observed (p = 1.000). Additionally, comorbidity-related mortality occurred in one case in Group 2, while Group 1 had none, resulting in a non-significant p-value of 0.615.

Table 7: Correlation Analysis Of Laboratory Parameters With Spearman's Rho Test

Variables	Correlation coefficient	P value
Bile leak		
SGOT	-0.031	0.805
SGPT	0.058	0.641
ALP	-0.006	0.962
Bilirubin	-0.231	0.062
PT/INR	-0.190	0.126
Lactate	-0.345	0.005
NL ratio	-0.460	<0.0001
Renal failure		
SGOT	-0.089	0.486
SGPT	-0.004	0.973
ALP	-0.075	0.552
Bilirubin	-0.442	<0.0001
PT/INR	-0.399	0.001
Lactate	-0.470	<0.001
NL ratio	-0.394	0.001

Table 8: Correlation Analysis Of Variables And Mortality With Spearman's Rho Test

Variables	Correlation Coefficient	P value
Bilirubin and Mortality	-0.525	<0.001
PT/INR and Mortality	-0.502	<0.001
N/L Ratio and Mortality	-0.299	0.015
Liver failure and Mortality	0.5	<0.001
Duration of stay and mortality	-0.016	0.896
Surgery time and mortality	-0.293	0.017
Blood loss and mortality	-0.404	<0.001
Transfusion and mortality	-0.23	0.063
Lactate and mortality	-0.239	0.053

The correlation analysis revealed significant associations between clinical variables: a strong negative correlation between cirrhosis and blood loss (correlation coefficient = -0.579), a positive correlation between cirrhosis and mortality (correlation coefficient = 0.329), and a positive correlation between hepatectomy class and blood loss (correlation coefficient = 0.505).

DISCUSSION

The research conducted a prospective single-blind randomized controlled trial, denoted as the "LIPINCOT TRIAL CTRI/ 2016/ 04/ 006816," to evaluate the impact of Pringle's maneuver on liver resection outcomes. The primary objective was to determine whether the use of Pringle's maneuver as a method for inflow control during liver resection influences surgical outcomes. The trial enrolled 80 participants, randomly assigned to Group A (Pringle's maneuver) and Group B (Non-Pringle's).

Baseline characteristics revealed no significant differences in age, sex distribution, disease condition, comorbidity status, hepatectomy class, additional procedures, or liver status between the two groups. Surgical parameters, including mean surgery time, blood loss, and transfusion requirements, were comparable, with trends toward significance in blood loss and transfusion observed.

Intra-operative findings indicated that major and right hepatectomies in Group A exhibited increased blood loss, higher transfusion needs, and prolonged hospital stays compared to Group B. Elevated levels of liver enzymes, lactate, and Neutrophil-to-Lymphocyte ratio on day one was noted in Group A. Additionally, Group A experienced significantly higher Grade B and C liver failure, postoperative hyperglycemia, and mortality. Univariate analysis identified various factors significantly correlated with morbidity and mortality.

Numerous randomized controlled trials (RCTs) have investigated the effectiveness and safety of Pringle's maneuver.[7-9] the initial RCT by Man et al. in 1997 found comparable mortality but less blood loss and shorter transection time in patients undergoing Pringle's maneuver. Capussoti L et al.'s 2006[7] RCT showed no differences in postoperative complications or death.[7] However, Lee KF et al.'s[8] 2012 RCT reported higher postoperative problems with Pringle's maneuver, and a 2018 RCT suggested increased ascites and pleural effusions in cirrhotic patients but improved overall survival in HCC patients.[9]

Ischemia-reperfusion injury following Pringle's maneuver leads to microcirculatory disruption and inflammatory cytokine release, potentially causing hepatocyte damage and liver dysfunction.[10] the study emphasizes the importance of hemi-hepatic vascular inflow blockage when feasible. Contradictory evidence exists regarding Pringle's maneuver and cancer recurrence, with retrospective analyses yielding mixed results.[11]

Hester et al.'s analysis of NSQIP data identified cirrhotic liver texture as an independent risk factor for post-hepatectomy liver failure.[12] the study's conclusion highlights that Pringle's maneuver prolongs hospital stays, increases transfusion requirements, and raises complications, particularly in diseased livers. Elevated blood lactate and Neutrophil-to-Lymphocyte ratio emerged as reliable predictors of postoperative liver failure and mortality.

CONCLUSION

The implementation of Pringle's maneuver during liver resection is associated with prolonged hospitalization, heightened transfusion needs, and increased complications, particularly evident in the context of liver pathologies. This maneuver induces elevated levels of blood lactate and Neutrophil-to-Lymphocyte (N/L) ratio following hepatic resection, serving as precise indicators for predicting postoperative liver failure and mortality. Consequently, it is advisable to refrain from employing Pringle's maneuver in cases involving cirrhotic livers, as well as in minor and left lobe resections. However, its application may be considered in selective scenarios involving non-cirrhotic livers, non-anatomical resections, and extensive vascular right lobe and central tumors, particularly when an anterior approach is preferred.

Conflict of Interest Disclosure: The authors declare no conflict of interest.

Funding: This research didn't receive grants from any funding agency in the public, commercial or not-for-profit sectors

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