

Optimizing Management of Cirrhotic Patients Who Need Colorectal Surgery: Role of Neoadjuvant TIPS

Bion AL¹, Alves A^{1,2}, Fohlen A³, Mulliri A¹, Lubrano J^{1,2} and Menahem B^{1,2*}

¹Department of digestive surgery, University hospital of Caen, France

²Normandie Univ, Unicaen, Inserm, Anticipe, 14000 Caen, France

³Department of radiology, University hospital of Caen, France

*Corresponding author:

Benjamin Menahem,
University Hospital of Caen,
Avenue de la côte de Nacre,
14033 Caen cedex, France,
Tel +33231063221; Fax+33231064535,
E-mail: menahem-b@chu-caen.fr

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1. Abstract

1.1. Purpose: Colorectal resection in cirrhotic patients is associated with high mortality and morbidity related to portal hypertension. The aim of this study was to evaluate the impact of neoadjuvant transjugular intrahepatic portosystemic shunt (TIPS) on postoperative outcomes.

1.2. Material and Methods: From 2003 to 2015, 42 consecutive cirrhotic patients who underwent colorectal resection were included. Main outcomes (i.e., postoperative mortality and morbidity at 90 days) were analyzed in patients with or without neoadjuvant TIPS.

1.3. Results: both groups with (TIPS-group, n=15) and without TIPS (no-TIPS group n=27) were comparable according to sex ratio, ASA class and body mass index. Main outcomes such as 90-day postoperative mortality rate (20% vs 18%, p=0.9) and major postoperative morbidity rates (33% vs 39%, p=0.77) were comparable in Both groups.

1.4. Conclusion: The present study suggests that a “two-step strategy” (i.e. neoadjuvant TIPS followed by surgery) allows to perform colorectal resection in cirrhotic patients despite severe portal hypertension, without increasing both postoperative mortality and morbidity.

2. What Do This Paper Add to The Literature?

Despite multidisciplinary improvements in perioperative manage-

ment, colorectal resection stills remain a surgical challenge in cirrhotic patients, especially with portal hypertension. This paper focused on the opportunity to use a two-step promising strategy including neoadjuvant transjugular intrahepatic portosystemic shunt which allows to perform colorectal resection without increasing both postoperative mortality and morbidity.

3. Introduction

Despite improvements in surgical techniques and preoperative management, colorectal surgery remains a major challenge in patients with cirrhosis with a mortality rate ranged from 6% to 30% [1-4]. The severity of liver disease according to Child-Turcotte-Pugh (CTP) class and/or model for end stage liver disease (MELD) score, plays a role, as well as age, emergency operation, and co-morbidities (ASA class) [5]. Irrespective of liver disease, colorectal surgery is also considered to be at high risk of morbidity and mortality. According to two recent French prospective multicenter studies, colorectal resection was associated with a 3.4% mortality and a 35% morbidity rates [6]. Age older than 70 years, neurologic comorbidity, underweight (body weight loss of >10% in the last 6 months), and emergency surgery determine the four-item predictive score of postoperative mortality (the AFC score), which was prospectively validated [6, 7].

To our knowledge, there are limited data available on specific management of cirrhotic patients in colorectal surgery. Studies are generally limited due to institutional volume [8-11] and the majority of the

data available provided from retrospective studies of large database using surrogate markers for liver disease rather than a true diagnosis [1-3, 12].

Severe portal hypertension leads to poor outcomes in elective colorectal resection, with a mortality rate ranged from 16% to 40% [1]. Then, preoperative optimization and management of comorbidities are very important for the improvement of outcomes [13]. We have recently reported a preliminary study (8 patients) about neoadjuvant Transjugular Intrahepatic Portosystemic Shunt (TIPS) placement before colorectal surgery with an acceptable mortality (25%) and morbidity (75%) rate [15]. Like Azoulay et al, we agreed that this “two-step strategy” achieve portal decompression, and limit intraoperative bleeding and decompensated cirrhosis [14]. The aim of this retrospective was to evaluate postoperative morbidity and mortality rates in consecutive cirrhotic patients with and without neoadjuvant TIPS undergoing colorectal resection in our institution.

4. Materials and Methods

4.1. Study Population

Between July 2003 and December 2015, all consecutive cirrhotic patients who underwent colorectal surgery were included. Demographic data of the patients included age, sex, body mass index, medical comorbidities according to ASA class. Details of the cirrhosis included specifically cirrhotic etiology (alcoholic, viral or else), mode of diagnosis (pathologic, biologic, based on imaging, upon discovery of esophageal varices or hepatic macroscopic aspect during surgery), evolution of cirrhosis (portal hypertension and its complications). The severity of liver disease according to CTP class and MELD score was reported. Portal hypertension is defined as a portosystemic gradient larger than 6 mm Hg, severe portal hypertension with a gradient ≥ 12 mm Hg. Pressure gradient before surgery or TIPS placement was reported.

Surgical data included the context of surgery (elective or emergency), indication (cancer or other), type of procedure (limited resection e.g restoration of digestive continuity, right colectomy) or extended resection (e.g left hemicolectomy, subtotal colectomy, anterior resection with or without anastomosis).

4.2. TIPS Placement

Since 2005, cirrhotic patients complicated by severe portal hypertension underwent neoadjuvant TIPS placement in our institution. We have previously reported our TIPS procedure [15]. In summary, the right hepatic vein is catheterized with a C2 4F catheter, a transhepatic puncture to the right portal vein is performed with a Transjugular Liver Needle 15G, 9F (RMT-15-51.0-TJL) (Cook Medical, Bloomington, IN, USA), under general anesthesia. Portal venography is performed to evaluate the portal anatomy. A portocaval pressure measurement is systematically performed before dilatation of the transhepatic track with an 8-mm diameter semi-Compliant-Wanda™

PTA-Balloon (Boston Scientific, Natick, MA, USA). A nitinol stent, E-Luminexx® (Bard, Tempe, AZ, USA) is placed from the hepatic vein to the portal vein, 10 mm diameter length 80-100mm. This endoprosthesis is completed by a covered 10mm diameter length 60-80mm stent Fluency® (Bard, Tempe, AZ, USA) through the transhepatic track to prevent TIPS thrombosis. Intra stent dilatation is performed after stent placement with the 8mm diameter semi compliant stent (Wanda). Splanchnic varices are selectively embolized if necessary with permanent embolic material (Plug, coils or glue).

4.3. Delay Between TIPS Placement and Surgical Treatment Was Reported

Shunt's functionality was systematically checked 24 hours after the procedure using Doppler ultrasonography. We did not perform anticoagulative measures after the procedure. Prophylactic broad-spectrum antibiotics was systematically administered according to the CIRSE Krajina 2012 guidelines [16]. The porto-systemic gradient after TIPS placement was measured and reported. Successful of TIPS placement was considered if end point gradient was < 12 mm Hg or reduction of at least 20%. All patients were followed up after their TIPS procedures until their colorectal surgery with a Doppler Ultrasonography exam of the TIPS, the day before surgery. Clinical success is defined as cessation of variceal bleeding, decrease of ascites and improvement of liver function [16]. Hepatic encephalopathy as a TIPS complication was reported.

4.4. End Points

The primary end point was post-operative mortality rate, including in-hospital death or death occurring within 90 days of surgery. The secondary end points were the incidence of post-operative surgical and medical complications graded according to the Dindo-Clavien classification [17]. They included surgical complications (*i.e.*, anastomotic leakage, surgical site infection, reoperation) and medical complications (especially edemato-ascitic decompensation, gastro-intestinal bleeding, hepatic encephalopathy, or delirium tremens). Post-operative complications grade 1 and 2 were considered minor complications, and grade 3-4 complications were considered major.

4.5. Statistical Analysis

Continuous variables were expressed as the mean +/- Standard Deviation (SD) or median and interquartile range (IGR) with skewed distribution. Categorical variables were expressed in percentages. Linear association were analyzed with χ^2 , or Fisher's exact test, if necessary. P value less than 0.05 were considered significant.

5. Results

5.1. Patients and Procedures

There were 31 men and 11 women with a mean age of 65.9 +/- 10.0 years. Both groups with (n=15) and without TIPS (n=27) were comparable according to age, sex ratio, ASA class and body mass

index (Table 1). The etiology of cirrhosis was alcoholic in 36 patients and cryptogenic/unknown in 6 patients. Preoperative cirrhosis was significantly more known in patient with TIPS than without TIPS (93% vs 52%, $p=0.01$). Severity of cirrhosis was significantly higher in patients with TIPS before TIPS procedure than without TIPS, according to CTP B/C class (87% vs 15%, $p=0.02$) and portal hypertension such as esophageal varices (87% vs 30%, $p=0.001$). Median MELD score was 5.8 (range 3-30) without difference in both groups.

5.2. TIPS Procedures

Neoadjuvant TIPS placement was used in 15 patients (36%) due to severe portal hypertension [6], refractory ascites [4] or hemorrhage [4] (sometimes from the colo-rectal cancer [2]). Varices embolization was performed in 9 patients (60%). The mean porto-systemic gradient was 13.6 before TIPS [range: 7-20]; 8 patients had a pressure gradient > 12mm Hg. The mean-porto systemic gradient after TIPS was 9.8 [range: 4-11], with a mean gradient decrease 7.5 [range: 3-12]. Successful of TIPS placement was 100%: all the gradient pressure decrease more than 20% and were less than 12 mm Hg after procedure. In 7 patients, complications occur after TIPS. Hepatic encephalopathy after TIPS occurs in 2 patients, stent thrombosis occurred in 1 patient, 2 patients had resolute post-TIPS liver insufficiency and 2 patients had infectious issues (one lung infection and one urinary infection). Ultrasound examination after procedure was done between POD 1 and 2 post-TIPS. The mean delay between TIPS and surgery was 42 days [range: 16-103].

5.3. Post-Operative Course

Colorectal resection for carcinoma was significantly performed in pa-

tients with TIPS as compared without TIPS (60% vs 29.6%, $p=0.04$). Nine patients (2 with TIPS and 7 without TIPS required emergent surgery for bowel obstruction ($n=3$) and 6 for peritonitis ($n=6$). Although not significant, TIPS allows to perform more complex colorectal resection (67% vs 53%, $p=0.23$), that leading significantly more protective stoma (67% vs 32%, $p=0.04$). both group were comparable according to blood loss, intraoperative technical difficulties and mean operative time (Table 2).

At 90-day postoperative, five patients (18.6%) died, of whom four underwent emergent surgery. The causes of death included anastomotic leak ($n=4$, 1 in TIPS group and 3 in no-TIPS group), hemorrhage ($n=2$ in no-TIPS group) and liver insufficiency ($n=2$ in no TIPS group). Patients in no-TIPS have several complications that might explain cause of death. There was no significant difference between both groups.

Postoperative complications and their severity according to Dindo-Classification were comparable between both groups. Fifteen patients (37.2%) suffered from one or more complications Dindo-Clavien grade >2. Postoperative outcomes were comparable between both groups, whatever ascites, encephalopathy, blood transfusion and mean hospital stay (Table 3). After a mean follow-up of 25 months, 14 patients (seven in each group) underwent stoma closure. Restoration of digestive continuity was performed more frequently in patients with preoperative TIPS than in patients without even if this result was not statistically significant (8 patients (57.4%) vs 14 (50%), $p=0.75$). No patient died and four patients experienced major post-operative complications.

Table 1: preoperative features of the patients with and without transjugular intrahepatic portosystemic shunt(TIPS)

Legend: OV= oesophageal varices, *= Fisher Test, MELD= Model for End Liver Disease, BMI= Body Mass Index, ASA: American society of anaesthesiologists.

	TIPS	Non TIPS n = 27 (%)	p
Sex			
Men	11	20	0.6*
Women	4	7	
ASA class			
2	5	9	0.91*
3	10	15	
BMI			
< 30	12	17	0.48*
> 30	3	10	
Weight Loss			
< 10%	13	24	0.92*
> 10%	2	3	
Colorectal cancer			
Yes	9	8	0.04
No	6	19	
History of Cirrhosis			
Cirrhosis			
known	15	14	0.01*
Peroperative diagnosis	0	13	
Cause			
ethylic	14	22	0.47*
Other(viral hepatitis)	1	5	

Child			
A	2	23	0.02*
B/C	13	4	
MELD			
< 13	14	22	0.6*
> 13	1	5	
OV			
Yes	13	8	0.001*
No	2	19	

Table 2: perioperative characteristics of the patients with and without transjugular intrahepatic portosystemic shunt (TIPS)

Legend *= Fisher test, **=missing datas ; SD : standard deviation.

	TIPS n = 15 (%)	No TIPS n = 27 (%)	Global population n = 42 (%)	p value
Emergency surgery	2 (13)	7 (25)	9 (21)	0.45*
Previsional surgery	13 (87)	20 (75)	33 (79)	
Colorectal resection				
<i>Right colectomy</i>	5 (33)	12 (47)	17 (42)	0.46
<i>Left colectomy (ie hartmann, anterior resection and subtotal colectomy)</i>	10 (67)	15 (53)	25 (58)	
Drainage				
Yes	11 (73)	17 (61)	28 (64)	0.73*
No	4 (27)	10 (39)	14 (36)	
Stoma				
Yes	10 (67)	9 (32)	19 (45)	0.04*
No	5 (33)	18 (68)	23 (55)	
Blood loss > 500ml				
Yes	0 (0)	1 (3,5)	1 (3)	0.58*
No	15 (100)	26 (96,5)	41 (97)	
Surgeon difficult feeling**				
Yes	7 (47)	9 (32)	16 (36)	0.51
No	8 (53)	18 (68)	26 (64)	
Mean operative time (mean, +/- SD)	141 +/-46	137+/-42	139+/-37	0.67

Table 3: Post-operative characteristics of the patients with and without transjugular intrahepatic portosystemic shunt (TIPS)

** missing datas

	TIPS N=15(%)	No-TIPS N=27(%)	p-value
Post-operative ascitis			
Yes	5 (33)	11 (43)	0.9
No	10 (67)	16 (57)	
Encephalopathy			
Yes	1 (7)	2 (7)	0.9*
No	14 (93)	25 (93)	
Digestive Bleeding			
Yes	2 (14)	3 (11)	0.9*
No	13 (86)	24 (89)	
Anastomotic leak			
Yes	5 (33)	4 (14)	0.34*
No	10 (67)	23 (86)	
Clavien-Dindo Classification			
1	5 (33)	10 (39)	0.94
2	5 (33)	6 (21)	
3	1 (7)	4 (14)	
4	3 (21)	2 (7)	
5	1 (7)	4 (14)	
Major complication (Clavien-Dindo \geq 2)			
< 2	10 (67)	17 (61)	0.77*
\geq 2	5 (33)	10 (39)	
Reoperation			
Yes	5 (33)	8 (29)	0.74*
No	10 (67)	19 (71)	

Blood Transfusion**			0.9*
Yes	2 (14)	3 (11)	
No	26	12	
Lenght hospital stay (mean +/- SD)**	21,9 +/-12.1	14,5 +/-11.7	0.11
90-day postoperative mortality			0.9*
Yes	3 (20)	5 (18)	
No	12 (80)	22 (82)	

6. Discussion

The present study suggests that a “two-step strategy” (i.e. neoadjuvant TIPS followed by surgery) allows to perform safety colorectal resection in cirrhotic patients despite severe portal hypertension. Although the patients in the TIPS group had more severe liver disease, they underwent colorectal resection with comparable postoperative outcomes as compared with patients in the non-TIPS group, probably due to preoperative TIPS creation. Our study reported a 90-day

postoperative mortality rate of 18.6% which is similar to results published by several authors (Table 4). Unlike our study, the majority of previous studies assessed only in-hospital and 30-day mortalities in liver disease patients, ranging from 6% to 29% after colorectal surgery (Table 4). However, some patients in those studies might have discharged from the hospital before potential death. That's why we choose to report 90-day postoperative mortality in order to better understand the prognosis effect of liver disease in patients undergoing colorectal resection.

Table 4: Review of the literature of colorectal surgery in cirrhotic patients.

NA: not available; PHT: portal hypertension; TIPS: transjugular intrahepatic portosystemic shunt;

Authors	N° patients	Colorectal	PHT	Child	Mortality	Morbidity	Dindo-Clavien ≥ 3
		Cancer %	%	A/B/C	%	%	%
Sabbagh (8)	40	100	2 TIPS	25/15/0	22.5	82.5	57.5
Artinyan (4)	838	100	NA	NA	8.8	NA	NA
Csikesz (3)	4764	100	-	NA	6	NA	NA
	1341		+		17		
Martinez (10)	17	82.3	0	12/5/2000	6*	29	11.7
Gervaz (11)	72	100	0	31/31/10	13	46	NA
Meunier (10)	43	83.7	67.4	17/21/5	26	77	NA
Lian (17)	23	0	21.7	14-Sep	10	82.6	30.4
Nguyen (1)	2909	NA	-	NA	14	43	NA
	1133		+		29	55	
Ghaferi (2)	1565	NA	NA	NA	21.5	50.4	41.9
Montomoli (12)	158	100	NA	NA	24.1	NA	NA
Metcalf (18)	24	48.1	NA	NA	24	48	DM
Lee bion	43	17					
TIPS	15	9	+	26/7/10	20*	66.7	33
Non-TIPS	27	8	-		17.8*	57.1	39

Although cirrhotic patients are to be at increased risk in major colorectal resections, the scientific literature is scarce in this topic. According to large prospective cohort study, cirrhotic patients have a 6 times increased risk of death as compared to non-cirrhotic patients [2]. Furthermore, patients with portal hypertension experienced worse outcomes than those with compensated cirrhosis. According to Nguyen et al, portal hypertension increased twofold in-hospital mortality compared to compensated liver disease [1]. Most interestingly, the real impact of the portal hypertension on in-hospital death was most prominent among elective colorectal resections [1]. Eighty-three patients suffered from portal hypertension, of whom 15 had a preoperative TIPS. This procedure was introduced in our hospital since 2006. Among the 8 patients died, 3 underwent a « two-step strategy » and 5 did not of whom 2 had PHT.

Previous studies suggested that severity of liver disease according to CTP class, (MELD) score, age, co-morbidities and emergency sur-

gery, increased postoperative mortality [2, 4]. We did not perform a multivariate statistical analysis of mortality due to the limited small sample study.

We reported a postoperative morbidity rate of 62.7% which is almost equal that reported previously in the literature. According to a large multi-institutional prospective cohort study, cirrhotic patients have a 2- to 3-fold increased risk of complications compared to non-cirrhotic patients [13]. Furthermore, more than one third of our patients experienced major postoperative complications according to Dindo-Clavien which is similar to previous published results ranged from 30.4 to 57.5% (Table 4). However, cirrhotic patients had nearly 2.3 times the risk of dying after a major complication [2]. Among our 8 postoperative deaths, 6 patients died after a major complication (i.e Clavien-Dindo>IIIb). The failure to rescue rate was higher for prolonged-mechanical ventilation, postoperative bleeding, deep wound infections and organ space infection. Not only major postoperative

complication but also failure to rescue were significantly increased by the severity of liver diseases measure by MELD score ≥ 15 [2]. For other authors, cirrhosis is still associated with an increased risk of postoperative morbidity up to 14.3-fold in case of portal hypertension. In our study, not only overall morbidity but also major postoperative complications were comparable in patients with and without portal hypertension, probably due to preoperative TIPS.

The study's main limitations were its retrospective design, the small number of patients reported, and the twenty-year span from 1997 to 2016. Nevertheless, our patient's clinical information and treatment's factors are not limited unlike population-based study and allows to measure liver disease severity such as CTP and MELD scoring systems. Furthermore, since 2006, all consecutive cirrhotic patients despite severe portal hypertension were included, except those with contraindications to TIPS placement (ie portal vein thrombosis, right cardiopathy). To conclude, cirrhotic patients with portal hypertension, without contraindications to TIPS placement and who need an elective colo-rectal surgery should be discuss to underwent a neoadjuvant TIPS procedure before their colorectal surgery. Literature on the topic is poor and further studies should be undergone in order to answer this topic.

The indications for colorectal surgery in cirrhotic patients have recently been broadened, mostly due to better understanding and multidisciplinary management of cirrhosis (*i.e.*, perioperative period and postoperative complications. If colorectal resection can be safely performed electively in patients with low MELD scores or CTP A cirrhosis, without portal hypertension, it is essential to optimize the others cirrhotic patients in the preoperative setting. According to our results, preoperative TIPS placement represents a promising strategy which need to be validated in a large prospective randomized study.

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