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Role of White Test in Prevention of Bile Leakage after Liver Surgery

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Abstract

Background: Post-operative bile leakage is a troublesome complication following liver surgery, with a reported incidence ranging from 3 to 27% in different series. Bile leak may be prevented by per-operative leakage test. Some studies have shown that bile leakage test using fat emulsion (White Test) is safe and effective. So this study was done to assess the effect of White Test on per-operative detection and post-operative prevention of bile leakage after liver surgery. **Methods:** This prospective analytic study was conducted in the Department of Hepatobiliary Pancreatic & Liver Transplant Surgery (HBPLTS), Bangabandhu Sheikh Mujib Medical University (BSMMU) from September' 2018- August 2019. Data is presented in the form of tables, figures and graphs, as necessary. Statistical analyses of the results were done by using statistical software SPSS version 25. Means, standard deviations, percentage frequencies were determined as indicated. **Results:** Fifty (50) patients of liver surgery for different liver diseases were included, 4 patients were excluded. So, 46 patients were assigned either in Group A (Bile leak test not performed) (n23) or in Group B (White Test performed) (n23). Data of main outcome variables - WT result, number of BL site identified during operation, incidence of post-operative BL, post-operative hospital stay (day) were recorded. Demographic variable and surgical procedure types were similar in both groups. White Test was well tolerated by all patients of Group B. Per-operative identification of bile leak site was significantly higher in Group B (82.60% vs. 30.43%) (p=.001). Incidence of post-operative bile leak was significantly lower in Group B (8.70% vs. 34.87%) (p=.032). Post-operative hospital stay was also significantly higher in Group A {7.09 (± 2.46) vs. 11.78 (± 7.44) days} (p=.006). **Conclusion:** There was no significant difference of post-operative complications between two groups. White Test was effective in per–operative detection of bile leaks. It can effectively prevent post-operative bile leakage after liver surgery.

Keywords*:* White Test, Prevention, Bile Leakage, Liver Surgery.

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INTRODUCTION

Bile leakage (BL) is a common complication of liver surgery and in different studies its incidence range from 3 to 27%.[1] Most of BL resolve spontaneously but some may persist for a long period of time, which may hamper the outcome of liver surgery.[2] BL remains a major cause of infection, intra-abdominal abscess formation, severe sepsis & liver failure after hepatectomy.[3,4] According to International Study Group of Liver Surgery (ISGLS) BL is the fluid with an increased bilirubin concentration (3 or > 3 times greater than the serum bilirubin) in the abdominal drain or intra-abdominal fluid at or after 3rd post- operative day (POD).[5] Bile may leaks from a transected liver surface or form partially closed hepatic duct stump or from injured extra-hepatic biliary tree.[6,7] Post-operative BL may be prevented if leak site can be identified and closed during operation. To detect leakage sites, intra-operative cholangiography or bile leak tests are performing in different center. BL tests are performing using several fluids and dyes like normal saline, methylene blue, indocyanine green and fat emulsion (White Test).[8,9] Each method has its own limitations.[10] Main problem of intra-operative cholangiography is its logistical difficulties, 2-dimensional view & radiation exposure.[11] The BL test by using normal saline is less costly, nontoxic and can be repeated as many times as needed.[8] But saline is difficult to detect, because it is colorless.[12] Methylene blue stains the entire resection surface, so repetition of the procedure is not possible.[10]These limitations can overcome by indocyanine green but it requires special equipment and there is a risk of allergic reaction.[8,13] White Test (WT) by using diluted fat emulsion is a new technique.[11] Fat emulsion is compatible with body fluid, harmless to the tissue, not allergic to body, easil visualized on the cut surface due to its white color and can be washed easily wit tissue staining and thus the procedure can be repeated.[8,10]Even after bile leak test, still there is chance of bile leak from small bile ducts that have no direct communication with the main bile duct. That's why debates on effect of BL test on postoperative BL are stillcontinuing. Several studies revealed that, WT can reduce the incidence of postoperative BL.[9,14] But some studies are arguing the effectiveness of BL test.[7,15] Moreover, the additional procedure may increase the risk of cholangitis.[9] So the clinical significance of BL test remains inconsistent. That's why we did this study to evaluate the impact of WT on per-operative detection and post-operative prevention of BL after liver surgery.

MATERIALS AND METHODS

This prospective analytic study was conducted in the Department of Hepatobiliary Pancreatic & Liver Transplant Surgery (HBPLTS), Bangabandhu Sheikh Mujib Medical University (BSMMU) from September' 2018- August 2019. All patients of who underwent liver surgery during the

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study period were included but patient who had Child- Pugh Class C disease, required duct rebuilding, needed resection of other organs in addition to liver surgery and who had serious heart or pulmonary disease were not included to the study. Total fifty (N=50) patients were included by purposive sampling method. According to admission sequence patients were assigned in Group A (BL test not performed) (n=25) or in Group B (WT performed) (n=25). Valid consent was taken. All patients were carefully evaluated and prepared pre-operatively, according to their diagnosis, general condition and assessment findings. The main outcome variables – WT result, number of BL site identified during operation, operation time (minutes), incidence of post-operative BL (ISGLS), duration of persistence of BL (day), grading of BL (ISGLS), post-operative hospital stay (day) were recorded. Data is presented in the form of tables, figures and graphs, as necessary. Statistical analyses of the results were done by using statistical software SPSS version 25. Means, standard deviations, percentage frequencies were determined as indicated. Hypothesis testing was done by using student t-test for quantitative variables. Chi- Square test and Fisher Exact test was used for qualitative variables. Statistical significance was set at $p \leq 0.05$ and confidence interval at 95% level.

Surgical procedures:

All the operations were done by an expert hepatobiliary surgeon of the Department of HBPLTS. The type of operation performed on a particular patient depends on the type, location and the extent of the disease. Under general anesthesia with all aseptic precaution incision was given according to the type of surgery. After proper exposure liver resection was done by combination of bipolar and mono-polar electro-coagulation devices with clamp crush method or by Cavitron Ultrasonic Surgical Aspirator (CUSA). Appropriate measures were applied to prevent bleeding during parenchymal transaction. After full control of bleeding a white gauge was placed on the transected surface and any bile leak was tried to identify. If any spontaneous bile leak was found, the site was closed with prolene suture. Then, in Group A, fibrin sealant was put on the raw cut surface of the liver. A wide bore drain was kept near the operative area.

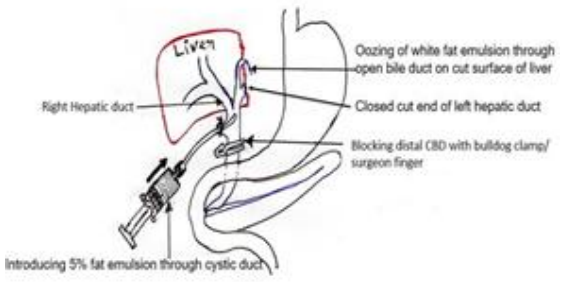

Image 1: Procedure of White Test

In Group B at the end of all steps as in Group A, the WT was performed. A cannula or feeding tube was inserted into the cystic duct or in common bile duct (depending upon the procedure). Then about 10 to 30 milliliter of sterile 5% fat emulsion was introduced through the cannula with gentle pressure, at that time the distal

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common bile duct was occluded by the surgeon's finger.

Image2 (a,b): Showing leakage site on cut surface of liver (Courtesy – HBPLTS Department of BSMMU)

In case of biliary leakage, extra-vasation of white fluid through the cut surface was detected and the number of leakage was recorded. The leaks were closed by prolene suture. Fat emulsion was washed with saline and the test was repeated if needed. After that fibrin sealant was put on the raw cut surface of the liver. A wide bore drain was kept near the operative area. Post-operatively all patients were treated under standard protocol. At 3rd POD serum and drain fluid bilirubin was checked.

RESULTS

Total 50 patients were included, 25 in each group. But in 2 patients of Group A and 1 patient of Group B, operation was cancelled due to in-operability and these 3 patients were excluded from the study. 1 patient of Group B denied doing WT on the day of operation, that patient was also excluded from the study. 4 patients were excluded. So, 46 patients were assigned either in Group A (Bile leak test not performed) (n23) or in Group B (White Test performed) (n23). Data of main outcome variables - WT result, number of BL site identified during operation, incidence of post-operative BL, post-operative hospital stay (day) were recorded. Demographic variable and surgical procedure types were similar in both groups. White Test was well tolerated by all patients of Group B. Per-operative identification of bile leak site was significantly higher in Group B (82.60% vs. 30.43%) (p=.001). Incidence of post-operative bile leak was significantly lower in Group B (8.70% vs. 34.87%) (p=.032). Post-operative hospital stay was also significantly higher in Group A {7.09 (± 2.46) vs. 11.78 (± 7.44) days} (p=.006). There was no significant difference of post-operative complications between two groups.

Table 1: Demographic difference between two groups of respondents (N = 46)

Variables	Group A (n = 23)		Group B (n = 23)		(p-value)
	N	%	N	%	
Gender Distribution					
Male	13	56.52	7	30.43	0.074a
Female	10	43.48	16	69.57	
Age (Year)					
Mean	46.39(± 16.87)		47.39 (± 13.39)		0.825b
Range	4-76		22 - 70		

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Table – II: Difference of pre-operative functional status of the liver, Liver parenchymal status, Liver resection type, Type of liver surgery, Operation time (Minutes) (N =46)

Variables	Group A (n = 23)		Group B (n = 23)		(p-value)
	N	%	N	%	
Child Pugh class					
A	22	95.65	22	95.65	1.000a
B	1	4.35	1	4.35	
C	0	0.00	0	0.00	
Liver parenchymal status					
Normal	19	82.61	19	82.61	1.000a
Cirrhotic	4	17.39	4	17.39	
Liver resection type					
Major	6	26.09	9	39.13	0.345a
Minor	17	73.91	14	60.87	
Type of liver surgery					
Left lobectomy	4	17.39	5	21.74	0.495a
Left hepatectomy	3	13.04	7	30.43	
Right hepatectomy	3	13.04	2	8.70	
Segmentectomy	4	17.39	1	4.35	
De-roofing of cyst	2	8.70	0	0.00	
Endo-cystectomy	3	13.04	2	8.70	
Non Anatomical Resection	1	4.35	2	8.70	
Extended cholecystectomy	3	13.04	4	17.39	
Operation time (Minutes)					
Mean (± SD)	183.61(±37.79)		186.65 (±27.08)		0.755b
Range	110 – 250		145 - 266		

Table –III: Tolerance of White Test (n = 23)

Hypersensitivity Para-meters	N	Mean (± SD)	(p value)
Pulse (beats/minute)	23	79.22 (± 6.11)	0.545b(Test value = 80)
Systolic BP(mm of hg)	23	132.61 (± 14.30)	0.391b (Test value = 130)
Diastolic BP(mm of hg)	23	79.13 (± 7.48)	0.583b (Test value = 80)
O2 saturation (%)	23	99 .26 (± 0.81)	0.137b (Test value = 99)
Allergic rash	23	0	0

Table – IV: Difference of bile leak site identification at operation, post-operative BL between two groups, Difference of post-operative BL between two groups, duration of persistence of post-operative BL :(N =46)

Variables	Group A (n = 23)		Group B (n = 23)		(p-value)
	N	%	N	%	
Bile leak identified					
Yes	7	30.43	19	82.61	0.001[a]
Not	16	69.57	4	17.39	
No. of bile leak site identified					
Without BL test	9		7		0.812[b]

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With WT	0		22		0.000[b]
Total leak site	9		29		0.000[b]
Post-operative bile leakage					
Present	8	34.78	2	8.70	0.032[a]
Absent	15	65.22	21	91.30	
Grading of bile leak					
A	3	37.5	2	100	0.444[c]
B	5	62.5	0	0	
C	0	0	0	0	
Duration of persistence of BL (Day)					
Mean(±SD)	16.38 (± 10.58)		6.50 (± 0.70)		0.243[b]
Range	6 – 38		6 – 7		

Table – V: Differences of post -operative complications between two groups, post-operative hospital stay between two groups (N=46)

Variables	Group A (n = 23)		Group B (n = 23)		(p-value)
	N	%	N	%	
Post-operative complications					
Minor SSI	3	13.04	5	21.74	0.681[a]
RTI	2	8.70	1	4.35	
UTI	0	0.00	1	4.35	
Transient hepatic insufficiency	1	4.35	1	4.35	
Post-Operative hospital stay (Day)					
Mean(±SD)	11.78 (± 7.44)		7.09 (± 2.46)		0.006[b]
Range	5 – 39		3 – 11		

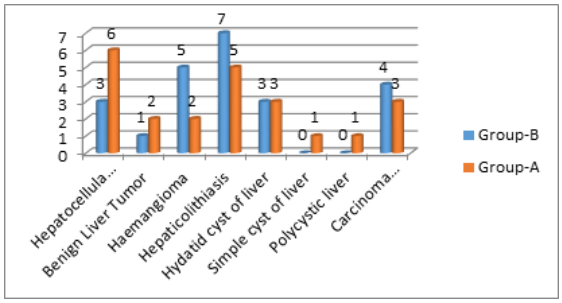

Figure – I: Pre-operative Diagnosis (N = 46)

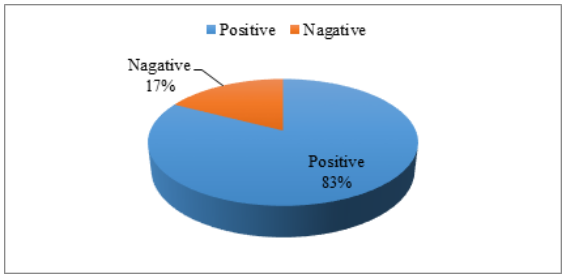

Figure – II: Finding of White test (n =23)

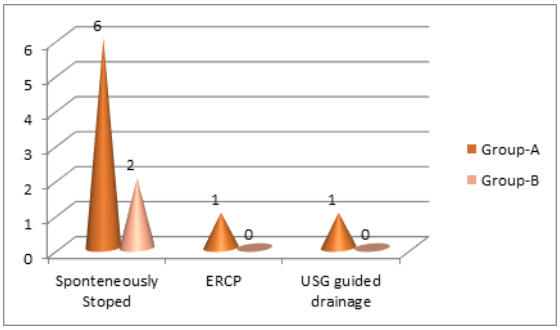

Figure – III: Difference in management of post-operative bile leakage (N = 46)

DISCUSSION

BL after liver resection is common and difficult to avoid. It can impair the postoperative course of patients and also can lead to hospital death.[2,16] Incidence of post-operative BL might be reduced by per-operative bile leak

site identification and closing. Bile leak site can be identified by WT. So this study was carried out on 46 patients {Group A (n23) & Group B (n23)}. Both group had similar demographic characteristics. Also had no significant (p = 0.648) difference in pre-operative diagnosis. In this study, patients who underwent WT had significantly lower post-operative BL (P = 0.032) {Group A - 8 (34.78%) Vs Group B - 2 (8.70%)}.We also found that the patients who did not undergo WT had higher incidence (62.5%) of intractable (Grade B) BL. A prospective cohort study at Germany found post-operative BL 22.9% in the control group and 5.3% in the WT group, (p<0.01).[10] Another systematic review on 4 publications found significant (p = 0.002) reduction of post-operative BL in WT group.[14] In a study at 2013 got higher incidence of intractable (Grade B) BL in non-leakage test group.[16] A randomized trial did not find any difference in BL between test group and control group [3(6%) vs. 2 (4%)].[7] But in that trial normal saline was used for BL test. Probably for this reason they did not find any advantages of BL test. Functional & parenchymal condition of liver has influence on BL. In a study at 2002 found BL in 4.5% (6/132) of cirrhotic patient and in 8.7% (20/231) of non-cirrhotic patients18. Incidence of BL is less in cirrhotic patient, because less extensive procedures were performed to prevent post- operative liver failure.[17] To avoid the effect of functional status on post-operative BL, in our study liver was assessed pre-operatively using Child – Pugh Class and liver parenchymal condition. There was no significant difference regarding functional status of the liver between two groups of this study (p = 1.000). In case of major liver resection chance of BL is more. A study by Capussotti et al. found significantly higher BL rate after major hepatectomy (p = 0.03).[18] Probable causes of higher BL are increasing chance of leakage from large cut surface area, leakage from partially closed hepatic duct and from extra-hepatic duct injury. In our study, major (≥3 liver segment) or minor (<3 liver segment) liver resection type or surgical procedure type, statistically had no influence (p= 0.345) on post-operative BL, because in both group more or less equal types of surgical procedure was performed.On cut surface of liver bile duct may remain unopened, because normal biliary pressure is low (10 to 15 cm of H2O). So, it is difficult to identify leak site without doing BL test. In a study BL was identified in 8 (26.7%) patients without doing BL test, whereas in 19 (63.3%) patients per-operative BL was identified by WT (P< 0.001).[12] In our study, per- operative bile leak site identification was significantly (p=0.001) high when WT done{Group A - 7 (30.43%) Vs Group B -19 (82.60%)}. BL test can be done by several materials like normal saline, methylene blue, indocyanine green and fat emulsion. Most of materials have some limitations. But fat emulsion can overcome these limitations. Its well tolerated and no patient of this study developed any hypersensitivity to WT. Because, it is the fat emulsion, that normally used for parenteral nutrition. But by doing WT, operation time was

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little increased in our study (p = 0.755). In a study by Yamashita et al. also had higher (334 ± 14 minutes) surgical time in BL test group than no BL test group (294 ± 4 minutes) (p < 0.01).[19] If we compare this little difference of operation time with impact of BL, we can realize the benefit of WT.Though most of the BL of both groups healed spontaneously (Group A - 75% Vs Group B -100%), but in 2 cases of Group A BL persisted longer duration and required surgical interventions like ERCP and USG guided drainage. Probable cause of this longer persistence is chance of leakage from large ducts was high when WT was not done. In Liu et al. study 70% post-operative BL healed without additional treatment.[2] Carrying drain tube for longer period of persistence of BL is troublesome for patients and it also increases hospital stay. In our study Mean (± SD) post – operative hospital stay was significantly (p = 0.038) high when WT was not done. Another study also found higher post-operative hospital stay in control group 18 (12-41) days than in test group 17 (13-47) days.[7] Other than BL, WT had no added post-operative complication. Because others post-operative complications were similar in two groups of this study.

Limitations of the study:

All type of liver diseases and surgeries were included in this study. This heterogeneity may have relation with post-operative outcome. This was not addressed in this study.

CONCLUSION

Per-operative WT is safe, improve the per-operative BL site identification and can effectively reduce the incidence of post – operative BL, without increasing the incidence of other complications.

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