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Original Article

Hydrogen peroxide test for intraoperative bile leak detection

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ABSTRACT

Background: Bile leakage (BL) is a common complication following liver surgery, ranging from 3 to 27% in different series. To reduce the incidence of post-operative BL various BL tests have been applied since ages, but no method is foolproof and every method has their own limitations. In this study we used a relatively simpler technique to detect the BL intra-operatively. Topical application of 1.5% diluted hydrogen peroxide (H₂O₂) was used to detect the BL from cut surface of liver and we compared this with conventional saline method to know the efficacy.

Methods: A total of 31 patients included all patients who underwent liver resection and donor hepatectomies as part of Living Donor Liver Transplantation. After complete liver resection, the conventional saline test followed by topical diluted 1.5% H₂O₂ test was performed on all.

Results: A BL was demonstrated in 11 patients (35.48%) by the conventional saline method and in 19 patients (61.29%) by H₂O₂ method. Statistically compared by Wilcoxon signed-rank test showed significant difference ($P = 0.014$) for minor liver resections group and ($P = 0.002$) for major liver resections group.

Conclusion: The topical application of H₂O₂ is a simple and effective method of detection of BL from cut surface of liver. It is an easy, non-invasive, cheap, less time consuming, reproducible, and sensitive technique with no obvious disadvantages.

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Introduction

Bile leakage (BL) following liver surgery is quite common that results in increase in post-operative morbidity like peritonitis, septicemia, and even liver failure.^{1,2} These days hepatic resections are being performed with increasing frequency because of recent advancement in operative technology. The post-operative mortality rate after liver resections is decreasing, but post-operative BL still remains a most common complication following liver resection and it ranges from 3 to 27% in different series.^{2–5} To reduce the incidence of post-operative BL various BL tests have been applied since ages, but no method is foolproof and every method has their own limitations.

In this study, we used a relatively simpler technique to detect the BL intra-operatively. Topical application of 1.5% diluted hydrogen peroxide (H_2O_2) was used to detect the BL from liver parenchymal transaction surface and compared this with conventional saline method to know the efficacy.

Materials and methods

A total of 31 patients including all patients who underwent elective liver resection and donor hepatectomies as part of Living Donor Liver Transplantation (LDLT) were included. The period of study was for 2 years, from June 2013 to May 2015. Operations are classified according to the Brisbane terminology proposed by Strasberg et al.⁶

Intervention

The liver parenchymal transection was done with Cavitron Ultrasonic Surgical Aspirator (CUSA). The bleeding and BL points from the cut surface of liver is controlled and secured with sutures. The conventional normal saline test and the hydrogen peroxide test are performed on the same patient. To carry out the conventional test, a catheter is inserted through the cystic duct into the common bile duct and 20 mL of isotonic sodium chloride solution is injected via the catheter under pressure while occluding the distal common bile duct with a clamp. The transected liver surface is inspected by two

Picture 1 – Performing 1.5% diluted hydrogen peroxide test.

Picture 2 – Bile leak gets highlighted in white background with H_2O_2 .

surgeons for the leakage of any sodium chloride solution. The total number of BL sites are counted. 1.5% diluted H_2O_2 is then applied over the cut surface of the liver (Picture 1). H_2O_2 on contact with the cut surface decomposes into water and active oxygen radicals, which bleaches the blood and liver tissues creating a vigorous white froth against which the yellow bile gets highlighted at the cut surface of liver (Picture 2). The number of BL site is again counted. After completing the tests, the detected BL sites are closed with 5-0 polydioxanone suture. Drainage of the operative field is performed with a subhepatic tube drain.

Outcome

Post-operative BL is defined as per definition given by International Study Group of Liver Surgery (ISGLS)⁷ i.e. bilirubin concentration in the drain fluid is three times the serum bilirubin level on or after post-operative day 3.

Statistical analysis

Sample size is calculated on the basis of an expected difference of 2.0 between the mean number of BL sites detected by the conventional method and the diluted H_2O_2 , with an estimated standard deviation of 2.0. Using a significance level of 0.05 (two sided) and a power of 0.95, at least 18 hepatectomized patients are required for the study. We have done 31 cases in a period of 2 years. The continuous variables are expressed as the mean $\pm$ SD. A Wilcoxon signed-rank test is used to compare the number of BL sites identified by the conventional method and the diluted H_2O_2 in each patient. Differences at $P < 0.05$ is considered statistically significant.

Results

A total of 31 patients who have undergone hepatic resection including LDLT in 2 years were included. The indications of liver resection are as shown in Fig. 1. Out of 31 patients, 20 (65%) were male and 11 (35%) were female. The mean age of

Fig. 1 – Indications for liver resection in 31 patients.

Fig. 2 – Different types of liver resection in 31 patients.

patients were 44.12 years with range between 1 and 79 years. 16 patients underwent major liver resection (>3 segment resection) including 10 patients of LDLT donors and 15 underwent minor liver resection (<3 segment resection). Various surgical procedures performed are as shown in

Fig. 2; mean blood loss was 717 mL (± 587 mL) with mean operative time of 270 min (± 75 min).

Intraoperative identification of BL

In our study the BL was demonstrated in 11 patients (35.48%) by the conventional normal saline method and in 19 patients (61.29%) by hydrogen peroxide method.

In addition, the H_2O_2 has identified all 11 leaks which were identified by conventional saline method with additional 8 leaks by topical H_2O_2 .

Results showed that the topical diluted H_2O_2 identified a significantly higher number of BL sites than the conventional method in both after minor and major hepatic resection as depicted in Table 1. The median (min–max) in the conventional method and H_2O_2 method was 0 (0–2) and 1 (0–4) respectively and it was statistically significant (P -value = 0.001) as depicted in Box-and-whisker plots in Figs. 3 and 4. There was no operative mortality nor serious morbidity, but post-operative BL were present in three cases (9.6%) which were classified as per ISGLS. There was one case of LDLT donor who underwent right hepatectomy without middle hepatic vein (MHV). He developed transient BL i.e., drain fluid bilirubin was more than three times the serum bilirubin level on third post-operative day (grade A BL as per ISGLS). The drain was kept for 7 days without any other complication. One case had grade B BL in a patient of echinococcus multilocularis. He had left hepatectomy with CBD excision and Roux-en-Y hepaticojejunostomy with the right hepatic duct. He continued to have drain fluid bilirubin >3 times the serum bilirubin level for 7 days. He underwent MRCP then ERCP which showed intrahepatic BL. He underwent biliary stenting to decrease the biliary pressure and aid in stoppage of leak. Subsequently resolution of drain occurred gradually over 3 weeks without any additional intervention. One patient of carcinoma gall bladder underwent extended cholecystectomy with segment IVb and V liver segment resection. She started having bilious drain on first post-operative day with features suggestive of biliary peritonitis. She was taken up for exploratory laparotomy (grade C BL) and found leak from cut surface of liver, which was secured with 5-O PDS. Post-operative period was then uneventful and she was discharged on post-operative day 7. The identification of BL intraoperatively by conventional saline and H_2O_2 method and subsequently post-operative BL and their management is summarized in Table 2.

Table 1 – Comparing bile leak sites by conventional saline and H_2O_2 method.

Type of liver resection	No. of bile leakage sites (mean ± SD)				P-value
	Conventional method		H ₂ O ₂		
	Mean ± SD	Median (min–max)	Mean ± SD	Median (min–max)	
Major (n = 16)	0.5 ± 0.63	0 (0–2)	1.25 ± 1.18	1 (0–4)	0.002
Minor (n = 15)	0.33 ± 0.62	0 (0–2)	0.73 ± 0.79	1 (0–2)	0.014
Total (n = 31)	0.42 ± 0.62	0 (0–2)	1 ± 1.03	1 (0–4)	0.001

The median (min–max) in the conventional method and H_2O_2 method was 0 (0–2) and 1 (0–4) respectively and it was statistically significant (P -value = 0.001).

Fig. 3 – Box-and-Whisker plots comparing bile leak sites by conventional and H₂O₂ method.

Fig. 4 – Box-and-Whisker plots comparing bile leak sites by conventional and H₂O₂ in major and minor liver resection.

Discussion

Hepatic resections including LDLT are being performed with increasing frequency. With the advancement of surgical techniques, high quality equipments, overall mortality rate after liver resection are decreased but post-operative BL is still

a surgical challenge. After liver resection, the possible BL sites are: (1) stump of cystic duct or bile duct, (2) exposed hilar plate, and (3) cut surface of liver. Standard use of gauze method is good enough for an experienced surgeon for detection of BL from hilar plate or bile duct stump but problem comes from minor BL sites from cut surface of liver.

In the recent past, various BL tests have been proposed, but none gaining wide acceptance. Standard intraoperative cholangiography is the gold standard test for detection of BL intraoperatively from hilar plate or cut surface of liver, but it is time-consuming with disadvantage of radiation exposure to patient and OT staff.⁸ The conventional normal saline injection under pressure through the catheter in the cystic duct into CBD is a low-cost, easily reproducible technique with no obvious disadvantages, but the transparent nature of normal saline makes this technique inadequate for detecting minor BL from cut surface of liver. The injection of various dye solutions (e.g., methylene blue) has also been recommended. The related disadvantages of this approach includes staining of the field of interest and masking of additional BL sites.⁹ There was a publication from Japan where transductal injection of indocyanine green was used while performing a fluorescent cholangiography using an infrared camera, which turned to be quite sensitive in detection of BL during liver resection, but this also has various limitations like requiring special contrast material which is not available in most of the developing countries like India, specialized complex equipment, and extended operative time.¹⁰

The other method is the intraoperative use of air leak test (ALT). The study was done at MD Anderson Cancer Center,¹¹ where about 103 patients were taken on which ALT was performed and found 62.1% detection of BL sites which is comparable with our study also where we found 61.29% of detection of BL intraoperatively using topical application of diluted H₂O₂. The problem with ALT is requirement of intraoperative ultrasound to see pneumobilia which confirms the bile duct patency before performing this test.¹² The relative new BL test is “White Test,” reported from Thailand at HPB Surgery in 2012¹³ based on the intraductal injection of 5% fat emulsion. A BL was demonstrated in 26.7% by the conventional method, which was 35.48% in our study and 63.3% by the White test and 61.29% by topical H₂O₂ in our study. Currently Wang et al.¹⁴ published a review and meta analysis of all available BL tests in 2013 and found that White test is the most promising tool to detect BL intraoperatively from cut surface of liver, but no BL test is without limitations like fat emboli, immunosuppressive effects, and fungal infections have been mentioned in literature with White test.

Table 2 – Post-operative bile leaks and management.

Diagnosis	Surgery performed	Normal saline method	H ₂ O ₂ method	Post-operative drain fluid bilirubin	Post-operative period	Intervention
LDLT donor	RT hepatectomy without MHV	2	2	7.5 mg/dl (serum bilirubin 1.7 mg/dl)	Transient bile leak	Drain kept for 7 days
Echinococcus multilocularis	Left hepatectomy	1	2	17 mg/dl (serum bilirubin 2.3 mg/dl)	Bile leak persistent	ERCP + stenting and pig tail for 21 days
CA gall bladder	Extended cholecystectomy	0	0	12 mg/dl (serum bilirubin 2.3 mg/dl)	Redo surgery	Re-explored on 1 POD

In our study, a BL was demonstrated in 35.48% by normal saline method and in 61.29% by the topical H₂O₂ which is statistically significant (Wilcoxon signed-rank test; $P < 0.001$). As no BL test is foolproof in detection of BL intraoperatively so shown in our study also. In our study post-operative BL was still found in three patients (9.6%). One patient had type A BL as per ISGLS which was managed conservatively; second patient had type B BL which was managed with ERCP with biliary stenting. Third patient had type C leak for which we had to re-explore, but overall there was no mortality and no major post-operative morbidity.

Conclusion

The topical application of H₂O₂ is a novel method in intraoperative detection of minor BL from cut surface of liver which is a non-invasive, cheap, less time consuming, simple to execute, and reproducible with no obvious disadvantages.

Conflicts of interest

The authors have none to declare.

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