ORIGINAL ARTICLE

Rapid Urine Trypsinogen-2 Test for the Early Detection of Pancreatitis in Endoscopic Sphincterotomy Patients

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ABSTRACT

Objective Endoscopic sphincterotomy is more invasive and time-consuming than diagnostic endoscopic retrograde cholangiopancreatography. Abdominal discomfort is also more common, and it is difficult to distinguish pain caused by pancreatitis from other procedural reasons (e.g., gas-related). We used the rapid urine trypsinogen-2 test (UT test) as a screen for early diagnosis of endoscopic sphincterotomy-related pancreatitis while reducing the frequency of taking serum samples. If an early diagnosis was made, early treatment could also be administered. **Method** We collected post- endoscopic sphincterotomy patient data, retrospectively, from April 2014 to November 2014. The UT would be performed 3 hours after the procedure. The serum amylase and lipase would be collected 12 hours after the procedure. The relationship among UT, pancreatic enzymes, and abdominal pain were analyzed. **Results** Thirty-one patients were tested in the study. Sixteen patients (51.6%) received a positive urine trypsinogen test. Ten (32.2%) and 12 (38.7%) people showed abnormal amylase and lipase levels, respectively. Two (6.4%) and 9 (29%) people exhibited amylase and lipase levels that were more than 3 times the upper limit. Six patients (19.4%) experienced post procedural abdominal pain, and 4 patients showed abnormal pancreatic enzymes. UT results were not associated with age (P=0.557), sex (0.081), or abdominal pain (0.17). In patients with elevated amylase, the sensitivity, specificity, positive predictive value, and negative predictive value of the UT were 90.0%, 66.7%, 56.3%, and 93.3% (P=0.006). In patients with elevated lipase, the sensitivity, specificity, positive predictive value, and negative predictive value of the UT were 91.7%, 73.7%, 68.8%, and 93.3% (P<0.001). In patients with amylase levels that were 3 times the upper limit, the sensitivity, specificity, positive predictive value, and negative predictive value of the UT were 100%, 51.7%, 12.5%, and 100% (P=0.484). In patients with lipase levels that were 3 times the upper limit, the sensitivity, specificity, positive predictive value, and negative predictive value of the UT were 88.9%, 63.6%, 50%, and 93.3% (P=0.016). **Conclusion** The rapid urine trypsinogen-2 test had high sensitivity and negative predictive value. It is useful to rule out the procedural pancreatitis with a lower frequency of taking serum samples and a high possibility of early intervention for procedure-related pancreatitis.

INTRODUCTION

Endoscopic retrograde cholangiopancreatography (ERCP) is a valuable procedure for examination and treatment of pancreaticobiliary diseases since it was first reported in 1968 [1]. Although magnetic resonance cholangiopancreatography provides excellent anatomic detail of the biliary and pancreatic ducts and replaces most of the role of diagnostic ERCP, therapeutic ERCP maintains a key role in intervention for biliary and pancreatic diseases. In a systematic review of 21 studies involving 16 855 patients, the incidence rates of ERCP-associated complications and mortality were 6.85% and 0.33%, respectively [2]. Post-ERCP pancreatitis is the most common and major complication of ERCP and occurs in approximately 1% to 10% of patients undergoing ERCP and has a mortality rate of 0.11%. Most episodes are mild to moderate, and severe pancreatitis is reported to occur in 0.5%–7% of patients [3, 4, 5, 6].

Early diagnosis of post-ERCP pancreatitis is based on clinical presentations, laboratory features, and radiological imaging. Detecting the elevation of serum amylase and lipase plays a key role in the early diagnosis of pancreatitis. However, asymptomatic elevation in serum amylase and lipase activities after ERCP occurs in approximately 25% to 75% of all patients [7]. Therefore, serum amylase and lipase are often insufficient for definitively diagnosing pancreatitis. Hence, a more specific and accurate method is necessary for diagnosing and estimating the severity of pancreatic damage during the first few hours after ERCP.

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Abbrevations EST endoscopic sphincterotomy; NPPV negative predictive value; PPV positive predictive value; UT Test urine trypsinogen-2 test
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Trypsinogen, an inactive precursor of trypsin, is secreted from acinar cells into pancreatic juice. Intrapancreatic activation of trypsinogen to trypsin plays a crucial role in the pathogenesis of acute pancreatitis. There are 2 major isoenzymes of trypsinogen, trypsinogen-1 (cationic) and trypsinogen-2 (anionic) [8]. In healthy subjects, the serum concentration of trypsinogen 1 is higher than that of trypsinogen 2, whereas in acute pancreatitis the trypsinogen 2 levels are higher [9]. Several studies have investigated UT strips that utilize monoclonal antibodies and immunochromatography. These studies have shown high sensitivity and negative predictive values, suggesting that the UT can rule out pancreatitis with high probability [10, 11, 12,13].

Endoscopic sphincterotomy (EST) is more invasive and time-consuming than diagnostic ERCP. Post abdominal discomfort was also more common, and it was difficult to distinguish pain caused by pancreatitis from other procedure-related reasons, such as gas. Early diagnosis of post-EST pancreatitis provides the patient with the opportunity for early intervention and intensive care. Few studies have investigated the clinical value of the urinary trypsinogen-2 dipstick test for early diagnosis of post-ERCP pancreatitis. We used the rapid UT screen for early diagnosis of EST-related pancreatitis while reducing the frequency of taking serum samples. If an early diagnosis was made, early treatment could also be administered.

MATERIAL AND METHODS

Patients of all ages, ethnicities, and sexes who underwent EST with a rapid UT screen at the Division of Gastroenterology of Cathy General Hospital from April 2014 to November 2014 were used for this retrospective study. Thirty-one patients, who admitted due to obstructive jaundice and cholangitis, with Sphincter of Oddi dysfunction, pancreatic duct injection, or difficult cannulation were included. No patients with active pancreatitis, end-stage renal disease, or heavy alcohol use were included. The study was approved by the Hospital Ethics Committee of Cathy General Hospital. ERCP was performed by experienced gastroenterologists with an Olympus JF-240 electronic duodenovideoscope (Olympus Optical, Tokyo, Japan) after premedication with local pharyngeal 10% lidocaine spray and an intramuscular injection of 20 mg of hyoscine-N-butylbromide. EST was performed after common biliary duct cannulation. Stone extraction or stent placement was performed as indicated.

All patients were tested with a urinary trypsinogen-2 test strip 3 hours after the procedure. The serum amylase and lipase would be collected routinely 12 hours after the procedure. Additional laboratory tests, imaging studies, and medical treatment were performed as indicated. Complications from EST and clinical information were all recorded.

The Actim© pancreatitis dipstick (MedixBiochemica, Kau- niainen, Finland) strip, an immunochromatographic test, was used for urine trypsinogen-2 detection (threshold 50 mg/L). The tip of the strip was dipped into a urine sample for 20 seconds. The strip was then maintained at room temperature for 5 minutes for observation. Trypsinogen-2 in the sample binds to monoclonal, antibody Y labeled, blue latex particles. The sample fluid with the latex-antibody-Y-trypsinogen-2 complex migrates across the nitrocellulose membrane and a catching zone containing another antibody specific for another epitope on trypsinogen-2. Elevated urinary trypsinogen-2 (>50 mg/L) causes the occurrence of 2 blue stripes (one for trypsinogen-2 and the other as a control). One stripe (as the control stripe) was observed when urinary trypsinogen-2 was within the normal range. If the control line was undetectable, the test was repeated.

Hyperamylasemia was defined as an increase of serum amylase to levels greater than the upper limit of normal (110U/L). Hyperlipasemia was defined as an increase of serum lipase to levels greater than the upper limit of normal (67 U/L). Post-EST pancreatitis was diagnosed according to abdominal pain persistent for at least 24 hours with serum amylase and lipase levels greater than 3 times the upper normal limit.

Data were statistically described according to the mean and standard deviation, number of cases, and percentages, when appropriate. The Student *t* test was used for statistical analysis; $P<0.05$ was defined as statistically significant. Sensitivity, specificity, the positive predictive value, and negative predictive value were calculated.

RESULT

The study included 31 patients who underwent EST. The age of the patients ranged from 26 to 79 years with a mean of 59±1 year; 20 were male (64.5%) and 11 were female (35.5%). Eighteen patients underwent EST because of choledocholithiasis. Three patients with ampulla vater tumor underwent EST and stent implantation. Two patients with distal CBD stricture, one patient with an oddly dysfunctional sphincter, one patient with choleduodenal fistula, and 6 patients with other reasons also underwent EST **(Table 1)**.

Of the 31 patients, 16 received positive results for the urinary trypsinogen-2 dip test. There was no relationship between the trypsinogen-2 dip test and age (P=0.557), sex (P=0.081), Foy use (0.96), or postprocedure abdominal pain (0.17) **(Table 2)**. Six patients complained of abdominal pain after the procedure, and post-EST pancreatitis developed in 4 patients (12.9%). No fatal case was reported. Positive

Table 1. Underwent EST.

Diagnosis	Case no.	(%)	Pancreatitis no.
CBD[1]stone	18	58%	2
Ampulla vater tumor	3	10%	1
CBD stricture	2	6%	1
SOD[2]	1	3%	
Choleduodenal fistula	1	3%	
Others	6	19%	
Total	31	100%	

[1]Common bile duct; [2]Sphincter of Oddi dysfunction

results for the urinary trypsinogen-2 dip test were found in all patients with post-EST pancreatitis, and no pancreatitis patient was noted in the negative trypsinogen-2 test. The sensitivity, specificity, positive predict value, negative predict value of the trypsinogen-2 dip test are 100%, 55.6%, 25%, and 100%. Of those with elevated amylase levels after the procedure (10 patients (32.3%), 9 patients had a positive trypsinogen-2 dip test (90%).

In the positive trypsinogen-2 dip test group, 9 patients (56.3%) had abnormal amylase concentration. Of the 15 patients who received negative trypsinogen-2 dip test results, 14 patients had normal amylase levels (93.3%). There was a statistically significant relationship between the amylase levels and the trypsinogen-2 dip test results (P=0.006). Fourteen of 16 patients with a positive trypsinogen-2 dip test had amylase levels lower than 3 times the upper limit of amylase (87.5%). All patients (2) with amylase levels greater than 3 times the upper limit had a positive trypsinogen-2 dip test. There was no statistically significant relationship in this group (P =0.484) **(Table 3).**

Eleven patients (68.8%) had abnormal lipase concentrations in the positive trypsinogen-2 dip test group. Of the 15 negative trypsinogen-2 dip test patients, 14 had normal amylase levels (93.3%). This relationship was statistically significant (P<0.001). Fourteen (93.3%) of the 15 patients with a negative trypsinogen-2 dip test had no elevated lipase concentration at 3 times the upper limit. Half the patients (8 of 16) with a positive trypsinogen-2 dip test had levels of amylase 3 times the upper limit. This relationship was also statistically significant (P=0.016).

The trypsinogen-2 dip test sensitivity, specificity, positive predictive value, and negative predictive value of amylase and lipase were 90%, 66.7%, 56.3%, 93.3% and 91.7%, 73.7%, 68.8%, 93.3%, respectively. At amylase and lipase levels 3 times the upper limit, the sensitivity, specificity, positive predictive value, and negative predictive value were 100%, 51.7%, 12.5%, 100% and 88.9%, 63.6%, 50%, 93.3% respectively **(Table 4).**

DISCUSSION

In our study, 4 of 31 patients (12.9%) were diagnosed with post-EST pancreatitis. Because all patients underwent EST, it was mildly superior to the ERCP complication rate in the previous study. The high negative predictive value and sensitivity of the urinary trypsinogen-2 test were noted. Early diagnosis of post-EST pancreatitis is critical in clinical practice. Benefits include making early decisions regarding hospital admission and provision of optimal care.

The early markers of post-ERCP pancreatitis can be classified into 3 categories: (1) markers of pancreatic injury-serum or urine amylase/lipase; (2) markers of proteolytic activation-trypsinogen and trypsinogen activation peptide; and (3) markers of systemic inflammation-inflammatory cytokines [14]. However, serum amylase/lipase concentration is commonly elevated, even without pancreatitis, and reveals low specificity. The markers of systemic inflammation-inflammatory cytokines, such as C-reactive protein and interleukins, are also not specific to pancreatitis and could be present under many conditions. In ERCP- induced pancreatitis, serum trypsinogen-2 concentrations may rise within an hour of the insult [15].

Several previous studies have discussed post-ERCP pancreatitis diagnosis by using a urine trypsinogen-2 test. Kemppainen *et al*. [16] tested 106 patients undergoing ERCP with a urinary trypsinogen-2 test strip 6 hours after ERCP. Eleven patients (10.4%) developed post-ERCP pancreatitis. The sensitivity and specificity figures for the urinary trypsinogen-2 test strip results in diagnosing post-ERCP pancreatitis were comparable (81% and 97%, respectively) to those for serum amylase (91% and 96%) and urine amylase measurements (81% and 95%). The test strip showed a good correlation (kappa=0.75) with the quantitative trypsinogen-2 assay. The increase in urinary trypsinogen-2 concentration after ERCP reflects pancreatic injury, and can be detected by the test strip. Early recognition of post procedure pancreatitis is important for the discharge

Table 2. Trypsinogen-2 dip test and age.

		Total		UT[1] (negative)		UT (positive)		P value
Age		No.	(%)	No.	(%)	No.	(%)	
	<40	4	12.9%	1	6.7%	3	18.8%	0.557
	40-49	4	12.9%	2	13.3%	2	12.5%	
	50-59	7	22.6%	3	20.0%	4	25.0%	
	60-69	5	16.1%	4	26.7%	1	6.3%	
	≥70	11	35.5%	5	33.3%	6	37.5%	
Sex								
	male	20	64.5%	12	80.0%	8	50.0%	0.081
	female	11	35.5%	3	20.0%	8	50.0%	
Post-EST[2] abdominal pain	yes	25	80.6%	14	93.3%	11	68.8%	0.17
	no	6	19.4%	1	6.7%	5	31.3%	
Foy use	yes	29	93.5%	14	93.3%	15	93.8%	0.96
	no	2	6.5%	1	6.7%	1	6.3%	

[1]Rapid urine trypsinogen-2 test; [2]Endoscopic sphincterotomy

Table 3. Positive trypsinogen-2 dip test group.

		Total		UT (negative)		UT (positive)		P value
Amylase value	means (sd)	227.6	(457.6)	75.6	(52.2)	360.7	(601.7)	0.078
Amylase test								
	negative	21	67.7%	14	93.3%	7	43.8%	0.006
	positive	10	32.3%	1	6.7%	9	56.3%	
Amylase test (3X)								
	negative	29	93.5%	15	100.0%	14	87.5%	0.484
	positive	2	6.5%	0	0.0%	2	12.5%	
Lipase value	means (sd)	362	(1059.1)	50.1	(69.9)	634.9	(1412.2)	0.119
Lipase test								
	negative	19	61.3%	14	93.3%	5	31.3%	<0.001
	positive	12	38.7%	1	6.7%	11	68.8%	
Lipase test (3X)								
	negative	22	71.0%	14	93.3%	8	50.0%	0.016
	positive	9	29.0%	1	6.7%	8	50.0%	

Table 4. Amylase and lipase test levels.

	Sensitivity	Specificity	Positive predictive value	Negative predictive value
UT test *vs.* amylase test	90.0%	66.7%	56.3%	93.3%
UT test *vs.* amylase test (3X)	100.0%	51.7%	12.5%	100.0%
UT test *vs.* lipase test	91.7%	73.7%	68.8%	93.3%
UT test *vs.* lipase test (3X)	88.9%	63.6%	50.0%	93.3%

management of outpatients undergoing EST. Therefore, we conducted the trypsinogen-2 test 3 hours after the procedure. Similar results for the sensitivity and negative predictive rate were found.

In another small-scale study by Sankaralingam *et al.* [17], 30 patients undergoing ERCP underwent urinary trypsinogen-2 tests at 1 and 4 hours after ERCP. The urinary trypsinogen-2 tests demonstrated 100% sensitivity and a negative predictive value at 1 and 4 hours after ERCP. The specificities at 1 and 4 hours after ERCP were 91% and 96%, respectively. In a study [18] on post-ERCP pancreatitis diagnosis, a urinary trypsinogen-2 test strip was conducted before and 3 hours after ERCP. Of 150 patients, 13 (8.7%) developed post-ERCP pancreatitis. Their urinary trypsinogen-2 strip test 3 hours after ERCP had high sensitivity (84.6%), specificity (97.1%), and a negative predictive value (98.5%). All of the cited studies have focused on ERCP-related complications, and none of them has focused on therapeutic ERCP. We focused on therapeutic ERCP, and similar results were noted. Overall, the urine trypsinogen-2 dip test proved to be an effective screening tool for post-EST pancreatitis because of its high sensitivity. The high negative predictive value of the urinary trypsinogen-2 test provides doctors with a highly reliable tool for excluding post-EST pancreatitis.

LaFerla *et al.* [19] documented elevated serum amylase levels at 2 hours after ERCP. Of the 20 post-ERCP patients evaluated, only 7 went on to develop pancreatitis. In these 7 patients, serum amylase levels rose quickly and were significantly higher than in those patients who did not develop pancreatitis. Thus, they concluded that amylase elevations 2 hours post-ERCP could accurately predict those patients that were at risk of developing pancreatitis. Further studies supported these early findings [20, 21].

The relationship between serum amylase/lipase levels and the urinary trypsinogen-2 test was also analyzed in our study. When the lipase levels were more than 3 times the upper limit, high sensitivity and negative predictive values were observed. These results were statistically significant. When amylase levels were greater than normal, similar conditions could be found. The sensitivity and negative predictive value were both 100%, but these results were not statistically significant because of a small sample size. A urinary trypsinogen-2 test seems to be an effective method for excluding the possibility of serum amylase/lipase elevation. The use of urinary trypsinogen-2 test has an opportunity to early exclude post ERCP pancreatitis.

Several limitations of our study should be noted. First, it was a retrospective study and some data could not be recorded attentively (such as the onset time or the character of abdominal pain). Second, the sample size in our study was somewhat limited. More serial and prospective studies are needed to evaluate the rapid urine trypsinogen-2 test use in the diagnosis of post ERCP pancreatitis.

In conclusion, the rapid urine trypsinogen-2 test has high sensitivity and negative predictive value in elevated pancreatic enzyme to evaluate the post procedure pancreatitis. Lower frequency of serum sample taking is another advantages. A high negative predictive value provides an opportunity to early exclude post ERCP pancreatitis and enables early intervention for procedure-related pancreatitis.

Authors' contribution

Hung CS and Chien NH contributed equally to this work. Chien NH drafted the manuscript. Lee CL proposed the study protocol. Hung CS and Wu CH performed EST and recruited all clinical cases. Lee CL audited all the study details and results.

Conflict of interest

The authors declare that there are no conflicts of interest.

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