Role of 4-H Serum Lipase Level in Predicting Postendoscopic retrograde Cholangiopancreatography Pancreatitis

Abstract

Introduction: Serum amylase level can rise asymptptomatically after endoscopic retrograde cholangiopancreatography (ERCP). Thus, its assay can lead to overprediction of post-ERCP pancreatitis (PEP). Lipase assay is used to diagnose other forms of pancreatitis but usually not for PEP. Objectives: The aim of this study was to predict whether lipase may be of better use for the early prediction of PEP. Methods: One hundred and twenty-five consecutive ERCPs performed over a period of 1 year and 9 months were observed. On admission (baseline) and after ERCP at 4 and 24 h, serum amylase and lipase were measured. Based on sensitivity and specificity from the receiver operator characteristic (ROC) curve, optimal cutoff levels for the enzyme, serum lipase, and amylase levels were employed to predict PEP. Results: Out of 125 patients, 26 (20.8%) developed PEP. In multivariate analysis, young age, suspected sphincter of Oddi dysfunction, recurrent pancreatitis, and needle papillotomy were significant risk factors. Considering the optimum cutoff level (single value with the best sensitivity and specificity), both the enzyme amylase and lipase evaluated at 4 h were significant (Chi-square test: $P=0.0001$ for both the enzymes). However, multivariate regression analysis and levels of enzymes at different cutoff values in the ROC found that 4-h lipase levels were more (about 4 times) increased of the upper limit of normal range than amylase levels (1.19 times). Conclusion: The enzyme, serum amylase, and lipase evaluated at 4 h after ERCP were satisfactory predictors for PEP. However, when compared, serum lipase was more reliable than amylase.

Keywords: Endoscopic retrograde cholangiopancreatography, lipase, pancreatitis

Introduction

Endoscopic retrograde cholangiopancreatography (ERCP) has widely been used in treating biliary and pancreatic disorders as a diagnostic and therapeutic procedure since its first introduction in 1968.[1,2] However, this modality of the procedure is not without complications. After ERCP commonly occurred, adverse events include pancreatitis, hemorrhage, and infection.[2,3] A careful literature search found that post-ERCP pancreatitis (PEP) is to occur in <1%–40% cases (1%–4% among low-risk cases and 8%–40% in high-risk cases) with a mortality rate ranging between 0.05% and 1%.[4,6] Among these complications, PEP, although usually mild, is potentially the most severe complication that results in substantial morbidity and occasional mortality.[7-9] The most commonly encountered risk factors for PEP are previous PEP, needle papillotomy, suspected sphincter of Oddi dysfunction (SOD), female gender, and young age.[10-12]

The widely used criteria to define PEP in a consensus paper proposed by Cotton et al. in the year 1991 was 24 h post-procedure amylase level at least 3 times above the upper level of the standard value along with the characteristic of newly developed abdominal pain consistent with pancreatitis and severity of symptoms demanding hospital admission or extending the hospital stay of already hospitalized.[7] In 1996, Freeman et al. added serum lipase level instead of serum amylase and a new-onset or worsening of preexisting abdominal pain as the clinical definition of pancreatitis.[10]

Serum amylase assay at 4 h after ERCP is preferred for the diagnosis of PEP because its level can be compared with 24-h assay level. However, PEP can be overpredicted using a 4-h amylase assay because serum amylase value might be increased asymptptomatically starting from 1½ to 4 h after ERCP. On the other hand,
serum lipase level starts to rise between 4 and 8 h after the onset of PEP, reaches to peak at 24 h, and declines within 8–14 days. Considering this, lipase levels measured at 4 h can be a good and valid alternative investigation for the early prediction of PEP. Very few studies have shown the comparison between serum lipase and amylase assay as an early predictor of PEP pancreatitis.[9,13,14]

The early detection of PEP is very crucial to reduce not only the hazards and expenditure but also allows prompt admission and timely rapid commencement of the necessary supportive care of patients at risk of developing PEP and safe discharge of others. This prospective single-centered study has evaluated both the enzymes serum lipase and amylase at 4 h for the prediction of PEP with special attention to serum lipase if it could be a better than serum amylase for the early prediction.

Methods

Considering expected proportion of event 40% (incidence rates of PEP have been reported to vary from <1% to 40%)[6] and a margin of error of 10% with 95% confidence interval (CI), we calculated a sample size of at least 92. Using a cross-sectional study design and a nonprobability convenience sampling approach, we investigated on 125 ERCPs conducted during a 1-year and 9-month period. Adult patients (age >18 years) having baseline serum lipase and amylase level <3 times the upper range of standard value were studied, but those having a stent in situ or having any contraindication for ERCP were excluded. This research has been approved by the institutional review board of the author’s affiliated institutions.

A predesigned structured questionnaire was filled up containing information regarding clinical history focusing on risk factors for PEP and necessary baseline investigations, including serum lipase and amylase levels. Follow-up data were recorded with serum amylase and lipase level during the procedure and 4 h and 24 h (next morning) after the procedure. Serum amylase and lipase, were measured according to the laboratory standards [Table 1].[15,16]

Statistical analyses were carried out using the SPSS (Statistical Package for the Social Sciences) for Windows, Version 23.0 (IBM Corporation, Armonk, New York). “Chi-square” test, binary logistic regression test, and multivariate regression analysis were used for statistical analysis where applicable. Based on sensitivity and specificity from the receiver operator characteristic (ROC) curve, optimal cutoff levels for the enzyme, serum lipase, and amylase levels were employed to predict PEP. \( P \leq 0.05 \) was considered statistically significant, and the CI was 95%.

Results

Among the patients who underwent ERCP, 125 who satisfied the inclusion criteria were studied. Patients’ ages ranged from 21 to 80 years with a mean of 55.76 ± 13.57 years. Among them, 58.4% were male [Table 2]. In the present study, 26 (20.8%) cases developed PEP [Figure 1]. Multivariate analysis found a significant association between young age, suspected SOD, recurrent pancreatitis, needle papillotomy,

| Reactive ingredients | Concentration | Reactive ingredients | Concentration |
|----------------------|---------------|----------------------|---------------|
| 2-chloro-4-nitrophenyl-α-D-maltotrioside (mmol/L) | 2.25 | Cholic acid (mmol/L) | 5.34 |
| Sodium chloride (mmol/L) | 350 | 1,2-diglyceride (mmol/L) | 1.1 |
| Calcium acetate (mmol/L) | 6 | Monoglyceride lipase (U/mL) | ≥0.86 |
| Potassium thiocyanate (mmol/L) | 900 | Glycerol kinase (U/mL) | ≥1.34 |
| Sodium azide (%) | <0.1 | Glycerol-3-phosphate oxidase (U/mL) | ≥4.0 |
| - | - | Peroxidase (U/mL) | ≥1.34 |
| - | - | Colipase (U/mL) | ≥4.0 |
| - | - | TOOS (%) | 0.068 |
| - | - | ATP (mmol/L) | 0.66 |
| - | - | Deoxycholate (mmol/L) | 36.0 |
| - | - | 4-aminoantipyrine (%) | 0.12 |

TOOS=N-ethyl-N-(2-hydroxy- 3-sulfopropyl)-m-toluidine, ATP=Adenosine triphosphate

![Figure 1: Pie diagram showing the frequency of postendoscopic retrograde cholangiopancreatography pancreatitis](image)
and PEP [Table 3]. The enzyme amylase level at 4 h in the ROC curve found a test result of 149 IU/L (area under the curve [AUC] of 0.967) where the optimal cutoff levels were 1.19-fold increase of the highest level of the standard range, showing the highest sensitivity and specificity of 88 and 92, respectively [Figure 2a]. On the other hand, serum lipase level at 4 h also showed good test result (AUC of 0.963) where the optimal cutoff levels were 3.82-fold (298 IU/L) increase of the highest level of standard range, showing the highest sensitivity and specificity of 96 and 89, respectively [Figure 2b]. Again, the enzyme serum amylase level at 24 h in the ROC curve found to have good test performance (AUC of 0.998) where the optimal cutoff levels were 3.10 times (388 IU/L) the highest level of the standard range, showing the highest sensitivity and specificity of 96 and 99, respectively [Figure 2c]. On the other hand, serum lipase level at 24 h also showed good test performance (AUC of 0.991) where the optimal cutoff levels were 3.60 times (281 IU/L) the upper level of the normal range, showing the highest sensitivity and specificity of 96 and 97, respectively [Figure 2d]. When the ROC curve summarized in a tabulated form, 4-h lipase level showed good test performance (AUC of 0.963), where the cutoff value 298 U/L was 3.82 times the highest level of the standard range, showing the highest sensitivity and specificity of 96 and 89, respectively [Table 4]. In multivariate regression analysis, both the amylase and lipase are significantly increasing while ERCP with PEP (P < 0.001); but the change in lipase was greater than amylase [Table 5].

Discussion

Pancreatitis after ERCP can be a substantial threat that often results in notable morbidity and occasional mortality.[8,9] Although its reported incidence has varied among studies, when considering low-risk and high-risk groups together, it occurs after <1%–40% of procedures.[6] In this study, we diagnosed PEP by measuring the enzyme, lipase, and amylase values following the consensus paper of Cotton et al. (1991). To the best of our knowledge, this is the pioneer paper from Bangladesh on the early diagnosis of PEP using serum lipase or amylase.

In the present study, 26 (20.8%) out of 125 patients developed PEP. A study on 238 subjects in Indonesia reported PEP to occur in 63 (26%) cases.[17] Another study in Ohio, USA, found 23% PEP.[18] Another recent study on 300 cases reported 11.7% of PEP.[19] The incidence of PEP varies due to the wide variation of cases, overall follow-up, the definition of the PEP, associated risk factor, comorbid conditions, and expertise of the intervening endoscopist.[20] Regarding risk factors, young age, suspected SOD, recurrent pancreatitis, and needle papillotomy have been identified as a significant risk factor for PEP in multivariate analysis. Cheng et al. similarly found age, suspected SOD, and history of PEP as a significant risk factor.[9]

Plotted in the ROC curve, both the enzyme assay (lipase or amylase) at 4 h after ERCP showed good test performance with AUC of 0.967 and 0.963, respectively. Again, levels at 24 h were also able to demonstrate good test performance, with AUC of 0.998 and 0.991 found, respectively. Enzyme level increment at 24 h has confirmed the diagnosis of PEP and has also justified the acceptability of lipase values measured at 4 h for the early diagnosis of PEP.[7,10] Nishino et al., in their study, reported that lipase assay after ERCP at 4 h was useful for predicting pancreatitis.[9]

Considering optimum cutoff levels, the performance test of both 4-h serum amylase and lipase in this study found to be significant (P < 0.0001 for both enzymes). However,
a careful observation of the cutoff levels showed that the level at 4 h lipase was on an average nearly 4 times the upper level of the standard range, which might be very useful for early detection of pancreatitis compared to 4-h amylase (nearly 4-times versus only slightly more than 1-time increase), the same observation explained by Cotton et al. (1991) in his consensus paper previously.

Unadjusted and adjusted multivariate regression analysis found that both 4-h serum amylase and lipase level were significantly increasing \( (P < 0.001) \) while ERCP with PEP. But, if we look at the estimate of change where lipase level had a greater change than amylase, which is the same reflection of more increase of 4 h lipase cutoff value found in ROC. When taking all these issues into account, 4-h serum lipase level is a more reliable indicator in predicting PEP than amylase and for same-day discharge.

**Conclusion**

Both the enzyme lipase and amylase assay at 4 h after ERCP were satisfactory predictors for PEP. However, the change in the upper level of the normal range of serum lipase was greater than that of amylase. Thus, serum lipase assay at 4 h would allow the early prediction of PEP with less possibility of overprediction than amylase. Thereby, it would allow prompt admission of those at risk and early safe discharge of others.

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**Conflicts of interest**

There are no conflicts of interest.

**References**

1. Adler DG, Baron TH, Davila RE, Egan J, Hirota WK, Leighton JA, et al. ASGE guideline: The role of ERCP in diseases of the biliary tract and the pancreas. Gastrointest Endosc 2005;62:1-8.
2. Coelho-Prabhu N, Shah ND, Van Houten H, Kamath PS, Baron TH. Endoscopic retrograde cholangiopancreatography: Utilisation and outcomes in a 10-year population-based cohort. BMJ Open 2013;3:e002689.
3. Cotton PB, Garrow DA, Gallagher J, Romagnuolo J. Risk factors for complications after ERCP: A multivariate analysis of 11,497 procedures over 12 years. Gastrointest Endosc 2009;70:80-8.
4. Freeman ML, Guda NM. Prevention of post-ERCP pancreatitis: A comprehensive review. Gastrointest Endosc 2004;59:845-64.
5. ASGE Standards of Practice Committee, Anderson MA, Fisher L, Jain R, Evans JA, Appalaneni V, et al. Complications of ERCP. Gastrointest Endosc 2012;75:467-73.
6. Pekgöz M. Post-endoscopic retrograde cholangiopancreatography pancreatitis: A systematic review for prevention and treatment. World J Gastroenterol 2019;25:4019-42.
7. Cotton PB, Garrow DA, Gallagher J, Romagnuolo J. Risk factors for complications after ERCP: A multivariate analysis of 11,497 procedures over 12 years. Gastrointest Endosc 2009;70:80-8.
8. Freeman ML, Guda NM. Prevention of post-ERCP pancreatitis: A comprehensive review. Gastrointest Endosc 2004;59:845-64.
9. ASGE Standards of Practice Committee, Anderson MA, Fisher L, Jain R, Evans JA, Appalaneni V, et al. Complications of ERCP. Gastrointest Endosc 2012;75:467-73.
10. Pekgöz M. Post-endoscopic retrograde cholangiopancreatography pancreatitis: A systematic review for prevention and treatment. World J Gastroenterol 2019;25:4019-42.
11. Cotton PB, Garrow DA, Gallagher J, Romagnuolo J. Risk factors for complications after ERCP: A multivariate analysis of 11,497 procedures over 12 years. Gastrointest Endosc 2009;70:80-8.
12. Freeman ML, Guda NM. Prevention of post-ERCP pancreatitis: A comprehensive review. Gastrointest Endosc 2004;59:845-64.
prediction of post-ERCP pancreatitis by 4-hr serum lipase levels than amylase levels. Dig Endosc 2008;20:169-77.
10. Freeman ML, Nelson DB, Sherman S, Haber GB, Herman ME, Dorsher PJ, et al. Complications of endoscopic biliary sphincterotomy. N Engl J Med 1996;335:909-18.
11. Christoforidis E, Goulimiras I, Kanellos I, Tsalis K, Demetriades C, Betsis D. Post-ERCP pancreatitis and hyperamylasemia: Patient-related and operative risk factors. Endoscopy 2002;34:286-92.
12. Wang P, Li ZS, Liu F, Ren X, Lu NH, Fan ZN, et al. Risk factors for ERCP-related complications: A prospective multicenter study. Am J Gastroenterol 2009;104:31-40.
13. Papachristos A, Howard T, Thomson BN, Thomas PR. Predicting post-endoscopic retrograde cholangiopancreatography pancreatitis using the 4-h serum lipase level. ANZ J Surg 2018;88:82-6.
14. Sutton VR, Hong MK, Thomas PR. Using the 4-hour Post-ERCP Amylase Level to Predict Post-ERCP Pancreatitis. J Pancreas 2011;12:372-76.
15. Abbott Laboratories Clinical Chemistry. Amylase Assay on the ARCHITECT cSystems, Abbott Park, IL 60064, USA: Abbott diagnostics; February 2007. Available from: https://www.ilexmedical.com/files/PDF/Amylase_ARC_CHEM.pdf. [Last accessed on 2021 Jun 28].
16. Abbott Laboratories Clinical Chemistry. Lipase assay on the ARCHITECT cSystems, Abbott Park, IL 60064, USA: Abbott diagnostics; March 2009. Available from: https://www.ilexmedical.com/files/PDF/Lipase_ARC_CHEM.pdf. [Last accessed on 2021 Jun 28].
17. Makmun D, Abdullah M, Syam AF, Fauzi A. Post-ERCP pancreatitis and its related factors: A prospective study in Cipto Mangunkusumo National General Hospital. J Dig Endosc 2019;6:163-8.
18. Kaw M, Singh S. Serum lipase, C-reactive protein, and interleukin-6 levels in ERCP-induced pancreatitis. Gastrointest Endosc 2001;54:435-40.
19. Minakari M, Sebghatollahi V, Sattari M, Fahami E. Serum amylase and lipase levels for prediction of postendoscopic retrograde cholangiopancreatography pancreatitis. J Res Med Sci 2018;23:54.
20. Nishino T TFe. Prediction of Post-ERCP Pancreatitis. In: Rodrigo L, editor. Pancreatitis Treatment and Complications. 1st ed. London, UK: Intech Open Limited; 2012. p. 131-44.