Diagnostic and Prevention Approach in Post Endoscopic Retrograde Cholangiopancreatography Pancreatitis

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ABSTRACT

Obstructive jaundice (icterus) was an emergency situation in gastroenterology. Endoscopic retrograde cholangiopancreatography (ERCP) was a nonsurgical approach to release obstruction, mostly in common bile duct. Nowadays, this procedure was become frequently used in daily practice, but several complications also emerging. One of the severe complication was Post-ERCP Pancreatitis (PEP). Since it has a high mortality and morbidity, and also reduce patient quality of life, several approaches have been developed to reduce its incidence. In general, approaches consist of patient identification, efficient procedure, until pharmacological agent prevention. Although there were still contradiction among these, careful approach should be considered for each patients for a better outcomes.

Keywords: *post-endoscopic retrograde cholangiopancreatography (post-ERCP), pancreatitis, prevention*

ABSTRAK

Ikterus obstruktif merupakan masalah darurat di bidang gastroenterology. Endoscopic retrograde cholangiopancreatography (ERCP) merupakan prosedur non-bedah untuk melepas sumbatan yang sering ditemukan pada duktus biliaris. Saat ini, prosedur tersebut menjadi rutin dilakukan pada praktik keseharian, namun beberapa komplikasi juga terjadi. Salah satu komplikasi yang parah adalah pankreatitis post-ERCP. Oleh karena tingginya mortalitas dan morbiditas, juga menurunkan kualitas hidup pasien, beberapa upaya telah dikembangkan untuk mengurangi insidensi pankreatitis ini. Secara umum, upaya dilakukan melalui identifikasi pasien, tindakan prosedur yang efisien, serta medikamentosa. Walaupun masih ada kontradiksi di antara hal tersebut, upaya yang hati-hati seharusnya dapat dipertimbangkan untuk setiap pasien untuk hasil yang lebih baik.

Kata kunci: *post-endoscopic retrograde cholangiopancreatography (post-ERCP), pankreatitis, pencegahan*

INTRODUCTION

Obstructive jaundice (icterus) was still an important emergency in gastroenterology. Both acute and chronic bile obstruction could lead to several complications such as cholangitis and sepsis. Endoscopic retrograde cholangiopancreatography (ERCP) was a non-surgical approach to release obstruction in common bile duct. Nowadays, this procedure was become frequently used

in daily practice, but severe complication was still present from mild to severe. Among the complications was acute pancreatitis that raise mortality and morbidity in patients.

Post ERCP pancreatitis was related to difficulty, technique, and skills of the endoscopist. Post ERCP pancreatitis (PEP) incidence was about 2-9% and in several center could as high as 30% because of different definition of pancreatitis.[1] PEP could be mild (90%) to severe (pancreatitis necroticans, multiorgan failure, and death). Yet, there were several definition of PEP with different severity of pain and duration as its factors.

Some therapy was used to prevent the developing of PEP, such as right patient selection, pancreatitis prophylaxis, and more advanced skills during procedure. Early detection of PEP was also studied to develop a better outcomes in patients management. This review will discuss about diagnosis and prevention of post ERCP pancreatitis comprehensively from pharmacological to various ERCP technique.

Epidemiology and Diagnosis of Post-ERCP Pancreatitis

Pancreatitis was a severe complication of ERCP procedure in obstructive jaundice patients. In general, pancreatic enzymes increase after procedure but could not be classified as pancreatitis. Based on Atlanta Criteria, PEP could be diagnosed if (1) New and progressive abdominal pain; (2) New or longer hospitalization; (3) Increase serum amylase by 3 times or more from upper norma limit in 24 hours after ERCP procedure.[2]

Based on diagnostic criteria above, PEP incidence in a Meta Analysis study involving 21 prospective study was about 1,6-15% (mean 3,5%).[3] On the other hand, Cotton et al proposed another diagnostic criteria: (1) Increase serum amylase more than 3 times from upper normal limit; (2) Typical abdominal pain for pancreatitis; (3) Abdominal pain more than 24 hours; (4) A severe pain that need hospitalization.[4] Cotton et al also classified patients into several pancreatitis grading based on its severity, as shown in Table 1. Pancreatitis severity based on Atlanta Criteria was shown in Table 2.

Table 1. Post-endoscopic retrograde cholangiopancreatography (PEP) severity grading[4]

Mild	Moderate	Severe
– Elevation in serum amylase concentration more than three times upper normal level – At least 24 hours after the procedure – Requiring admission or prolongation of planned admission to two to three days	– Hospitalization of four to ten days	– Hospitalization for more than ten days, – Patients with hemorrhagic pancreatitis, – Patients with newly developed phlegmon or pseudocyst, or – Patients who require intervention such as percutaneous drainage or surgery

Table 2. Post- endoscopic retrograde cholangiopancreatography (PEP) severity grading based on Atlanta classification[4]

Mild	Moderate	Severe
– Lacking both organ failure and local or systemic complications	– Transient organ failure (organ failure < 2 days) – Local complications*, and/or exacerbation of co-existent disease	– Presence of persistent organ failure (≥ 2 days)

*Local complications include acute peripancreatic fluid collections, pseudocyst, acute pancreatic or peripancreatic necrotic collection, and walled-off necrosis

Post-ERCP Pancreatitis Pathogenesis

Until nowadays, the exact mechanism of PEP development was still unknown. Several hypothesis have been proposed by experts, such as mechanical trauma in papillae orificium, hydrostatic damage, and enzymatic damage caused by proteolytic enzyme activated form duodenum.[4] Mechanical trauma damaging papilla orificium that lead to Oddi sphincter spasm or pancreatic orificum edema, so that pancreatic duct obstruction happened and lead to increase in pancreatic enzyme and finally inflammation. This damage could occur as a result from difficult-canulation ERCP that need a longer time, or a recanulation procedure. Beside that, thermal trauma from electrocautery during spinchterectomy could also lead to those damage.[5]

Hydrostatic damage was possible in overinjection in pancreatic duct that disrupt cell membrane and tight junction. As a result, a backflow of intraductal secrete to interstitial tissue cause pancreatitis.[6] Chemical trauma from ionic contrast with high osmolarity was another cause of pancreatic tissue damage. Otherwise, there were no meta analysis yet to show the relation between contrast and non-contrast media. This chemical trauma cause premature proteolytic enzymes activation that cause pancreatic cell autodigestion with reduced protective effect of acinar cell secretion, so that pancreatitis was developed.[4]

Risk Factors of Post-ERCP Pancreatitis

Several risk factors was present in PEP, involving patient, procedural, and operator factors. Based

on meta analysis by Masce et al from 15 studies, it can be concluded that those risk factors was:[7] (1) patient factors: women (RR = 2.23), SOD (RR = 2.23), previous pancreatitis (RR = 2.46), young age (< 60 years old), normal bilirubin (OR = 1.89); (2) Procedural factors: sphinchterectomy precut (RR = 2.71), pancreatic duct injection (RR = 2.21), balloon dilatation in intact sphincter , pancreatic sphicnterectomy, difficult cannulation (6-15 x try, OR = 3.41), papilla minor sphicnterectomy (OR = 3.82), pain during ERCP (OR = 1.95), and ampulectomy; and (3) operator factor: trainee involvement. The more risk factors present, the highest PEP incidence possibility.

High risk patient identification was an important thing to do in PEP prevention. Patient with more than one risk factors should be given detailed explanation and counseling before the procedure. Other approach such as MRSP or EUS to reduce PEP risk was prioritize to replace diagnostic ERCP procedure.

Prevention of Post-ERCP Pancreatitis (PEP)

In daily practice, there were so many treatments developed to reduce PEP in obstructive jaundice patients, from careful patients identification, pharmacological therapy, until various technique during ERCP. Unfortunately, there were no strong evidence which approach has been successful and effective to prevent PEP.

Endoscopist Prevention

This risk of pancreatitis was strongly related to endoscopist skill during ERCP. In referral center, which ERCP was done more routinely, difficulty during cannulation was commonly found and impact on the higher pancreatitis incidence. The presence of trainee was also an important factors of PEP incidence. Based on prospective study by Williams et al and Testoni et al, it can be concluded that PEP incidence was not correlate to cases number done by endoscopist in a referral center.[7]

TECHNICAL PREVENTION OF POST-ERCP PANCREATITIS

Standard Canulation

Standard biliary cannulation was using catheter with or without soft tip guidewire. Contrast then injected through catheter could be unintendedly enter pancreatic duct. A guidewire insertion to pancreatic and common bile duct could reduce the risk of contrast injection entering pancreatic duct with fluoroscopy. A systematic review study by Cheung et al from 7 RCTs showed a reduced pancreatitis risk compared to contrast injection using guidewire (RR = 0.38; 95% CI: 0.19-0.76).[7]

Pancreatic Stent as Prophylaxis

The rational use of pancreatic stent was based on the principal that mechanical trauma will cause a flow obstruction and and inflammation in pancreas. A Meta Analysis showed a reduced risk in 13.3% and NNT of 8 to prevent 1 patient develop PEP with this technique.[4] Menawhile, pancreatic stent placement has a higher risk of occlusion, migration, perforation, infection, erotion, and the need of re-endoscopy for evaluation and removal of the stent. A pancreatic duct stricture was also a possible complication. Therefore, this approach was not yet been choosen as an alternative for PEP prevention.

Pancreatic Duct Injection

Pancreatic duct injection was a multiple injection that correlate to the risk of PEP. Until now, ERCP was also done as diagnostic tool for neoplasms, such as pancreatic cyst, mainly to know any connection between cyst and biliary tract. Low osmolarity contrast was more recommended than high omsolarity. By reduce injection frequency, risk of PEP was predicted to be lower.[7]

Pancreatic Guidewire-Assisted Biliary Cannulation

Pancreatic guidewire placement was effective to ensure biliary tract access by straightening ampula and avoid pancreatic duct cannulation. This technique was mainly used in hard-cannulated patients or coincidentally recannulated pancreatic duct. Pancreatic stent placement after guidewire was recommended to reduce PEP incidence.[7]

Perendoscopic Sphincterectomy

Thermal damage caused by cauter could lead to ampula edema and obstruct pancreatic duct. Endocut was related to reduced risk of PEP by reducing edema in patients. Eventhough, bleeding risk was significantly increased. Therefore, there were still some pro and contra to done endocut.[7]

Balloon Sphincteroplasty

This technique was used to extract any stone via endoscopic sphincterectomy. The advantage was the

Oddi sphincter was preserved, especially for young patients, and also lower bleeding risk. Instead, several studies showed an increased risk of PEP in patients underwent this balloon sphincteroplasty. Yet, this technique was not concluded as a risk of PEP, exept combined with perendoscopic sphincterectomy.[7]

Needle-knife Precut

Precutting using needle knife was needed in a condition where standard cannulation was unsuccessful. This technique was strongly correlate to PEP. Meanwhile, this technique was also overcome with its less multiple cannulation possibility. Manes et al studied 151 patients with hard-cannulating after 10 minutes and compared to precut or standard cannulation with incidence was found lower in precut group (2,6% vs. 14.9%; p = 0.0008). But, a study by Cennamo et al investigate precut and standard cannulation result during hard-cannulation for 5 minutes showed no difference among two groups in PEP incidence.[7]

Oddi Sphincter Mannometry

Oddi Sphincter Mannometry was a gold standard for sphincter dysfunction examination. This sphincter dysfunction was correlate to high PEP incidence in patient. Pancreatitis risk could be reduced if pancreatic manometry was done before to know any SOD in patient, so that early pancreatic stenting could be done.

Pharmacological Prevention

Ideal pharmacological therapy was effective to reduce PEP incidence and could be administerd in short time, well-tolerated, and low side effect.

Antiinflammatory drugs was a potent inhibitor for inflammatory mediators, mainly prostaglandin and phospholipase A2 which related to acute pancreatitis. Elmunzer et al showed in a meta analysis involving 4 RCTs that NSAIDs per rectum was effective to reduce PEP incidence. Rectal indometachin before procedure or diclofenac after the procedure was effective. Oral administration of the drugs was not effective since it has a longer time to reach highest blood concentration. Besides, first-pass metabolism also reduce its bioavailability. ESGE recommended rectal diclofenac 100 mg to be administered just before the procedure.[8]

Glyceryl trinitate (GTN) was a smooth muscle relaxant thant could reduce basal pressure of Oddi sphincter, administered sublingually or as a transdermal patch. An evaluation by Kaffes et al showed that there were no significant difference between therapy and placebo groups on PEP incidence, although Moreto et al showe a significant improvement in 144 patients administered GTN. Until present, this drug administration was not recommended yet in PEP prevention.[7]

Ceftazidime was also used hypothese as its antimicrobial effect would prevent PEP development. Administration of 26 Ceftazidime 30 minutes before ERCP procedure could reduce PEP incidence in 160 patients of a trial, but this accuracy was stilll questionable.

Somatostatin and octreotide was also a potent inhibitor of pancreatic exocrine secretion that have an important rote in PEP pathogenesis. There were 2 meta analysis that investigate the role of both drugs. Andriulli et al studied 9 study in his meta analysis and showed a nonsignificant effect of Somatostatin in PEP prevention (OR = 0.73; 95% CI: 0.54-1.006). There also studies to investigate both short-term Somatostatin infusion (< 6 hours) and long-term infusfion (> 12 hours) in patients, but unfortunately it also give an insignificant result. Therefore, ESGE has not yet recommended ocreotide as PEP prevention, but further studies was developed to investigate its efficacy on > 0,5 mg dosage.[8]

Protease inhibitor was also used as assumed that acute pancreatitis was happened because of intracelullar tripsin activation, and could be precented. Several known protease inhibitor drugs was Gabexate, Ulinastatin, and Nafamostat mesylate. Several RCTs given an contradiction result. Xiong et al showed a less significant effect of PEP in 97 patients given gabexate

Agents with proven efficacy
Non steroidal anti-inflammatory drugs
Diclofenac
Agents with possible efficacy
Ceftazidime
Glyceryl trinitrate
Octreotide
Protease inhibitors
Ulinastatin
Nafamostat
Somatostatin
Agents with proven inefficacy
Allopurinol
Corticosteroids
Heparin
N-acetylcysteine
Protease inhibitor
Gabexate

Figure 3. Pharmacological regiment used to prevent post-ERCP pancreatitis (PEP)[7]

30 minutes before ERCP, while Manes et al showed a significant result in gabexate given 1 hours before or after the procedure. Meanwhile, further meta analysis showed an insignificant result of Gabexate. This was possible because of its very short half-life time (55 seconds) while there were need a continuos infusion for prevention. Differ to Gabexate, Ulinastatin has a longer half-life time (35 minutes) and could be given as bolus intravenous. Administration of Ulinastatin 150.000 Unit before ERCP was significantly reduce PEP incidence (2.9% vs. 7.4%, p = 0.041).[9]

Nafomastat showed a significant reduction in PEP if given 1 hours before ERCP and continued for the next 24 hours (p = 0.018). Yet, protease inhibitor still rarely used and have a higher cost to be given routinely in pre-ERCP patients.

Allopurinol, a xhantine oxidase inhibitor, would catalyze hypoxhantine to xhantine that its end product was free radical. This free radical would trigger capillary endothelial damage and result in acute pancreatitis. Although animal studies showed a good result, some clinical trial did not showed the same result. Administration of 600 mg Allopurinol 15 hours before ERCP and 3 hours before ERCP showed a good result (2.3% vs. 9.4%; p = 0.04), while and administration at 4 and 1 hours before ERCP showed no differences to placebo.[7]

Oral prednisone with 40 mg dose did not reduce PEP incidence in 1115 patients at a clinical trial. Heparin have a protease inhibiting effect in both plasm and tissue, but studies showed that LMWH administration before ERCP did not reduce PEP incidence (8.1% vs. 8.8%; p = 0.87).[7]

N-acetylcystein was an anti-free-radical that have an important role in pancreatitis pathogenesis. A study by Katsinelos et al and Milewski et al showed no difference of PEP incidence in patients administered N-acetylcystein compared to placebo (12.1% vs. 9.6%; p > 0.05 and 7.3% vs. 11.8%; p = NS).[7] The summary of all pharmacologic therapy in PEP prevention was shown in Table 4.

In general, prevention of PEP could be divided into 5 main area: (1) Correct patients identification; (2) Risk stratification for patients undergo ERCP; (3) Atraumatic and efficient procedure technique, 4) pancreatic stent as prophylaxis; (5) Pharmacological prevention.[11]

CONCLUSION

Pancreatitis was still a main complication of ERCP and further could reduce patient quality of life, morbidity, and mortality. Several approaches have been developed to reduce its incidence from

Table 4. Pharmacologic agents and its effect of post-ERCP pancreatitis (PEP) prevention[7]

Drug	Suggested way of action	Effective in prospective RCT
Calcium channel blockers	Sphincter spasm	No
Nitroglycerine		Conflicting data
Topical lidocaine spray		No
Antibiotics	Infection	Conflicting data, need for more trials
Ocreotide	Pancreatic secretion	Conflicting data
Somatostatin		Conflicting data
Corticosteroids	Inflammation cascade	No
Allupurinol		Conflicting data
N-acetylcysteine		No
Platelet activating factor inhibitors		No
Interleukin-10		Conflicting data
Heparin		Conflicting data
Gabexate		Conflicting data
Diclofenac (NSAIDs)		Yes in only one study, need for more trials

NSAIDs: non-steroidal anti-inflammatory drugs; RCT: randomized control trial

Table 5. Mechanism of action of several drugs for post-ERCP pancreatitis (PEP) prevention[10]

Postulated mechanism of action	Agents
Interruption of inflammatory cascade	NSAIDs, steroids, interleukin-10, allopurinol, adrenaline spray, pentoxifylline, platelet-activating factor-acetylhidrolase, semapimod, aprepitant, risperidone
Reduction of pancreatic enzyme secretion	Octreotide, somatostatin, calcitonin
Inhibition of protease activity	Gabexate mesilate, heparin, ulinastatin, nafamostat, magnesium sulphate
Reduction of sphincter of-Oddi pressure	Nitroglycerin, nifedipine, botulinum toxin, lidocaine, secretin, phosphodiesterase inhibitor type 5
Prevention of infection	Antibiotics
Anti-oxidants	Beta-carotene, N-acetylcysteine, sodium selenite
Anti-metabolites	5-fluorouracil

NSAIDs: non-steroidal anti-inflammatory drugs

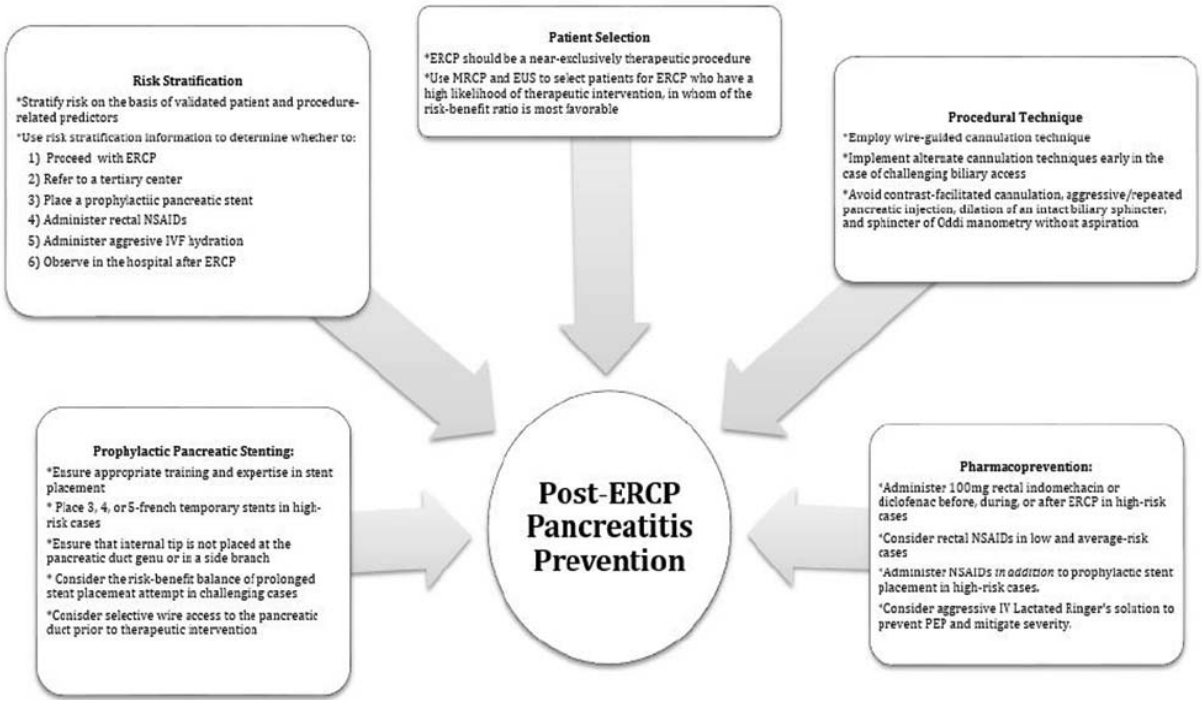

Figure 1. PEP prevention diagram[11]

patient identification, efficient procedure, until pharmacological agent prevention. Since several studies did not showed an absolute significant result, every case should be identified carefully, so that pancreatitis incidence as ERCP complication in obstructive jaundice patients could be reduced.

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