**Name of Journal:** *World* *Journal* *of* *Gastroenterology*

**Manuscript NO:** 90141

**Manuscript Type:** OPINION REVIEW

**Nonsteroidal anti-inflammatory drugs before endoscopic ultrasound guided tissue acquisition to reduce the incidence of post procedural pancreatitis**

de Jong M *et al*. NSAIDs before EUS-TA preventing post-EUS pancreatitis

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**Author contributions:** de Jong M drafted the manuscript; van Delft F, Roozen C, van Geenen EJ, Bisseling T, Siersema P, and Bruno M edited the manuscript to the final version.

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**Received:** November 24, 2023

**Revised:** December 22, 2023

**Accepted:** January 22, 2024

**Published online:**

**Abstract**

Endoscopic ultrasound (EUS) with fine needle aspiration or fine needle biopsy is the gold standard for sampling tissue to diagnose pancreatic cancer and autoimmune pancreatitis or to analyze cyst fluid. The most common reported adverse event of fine needle aspiration and/or fine needle biopsy is acute pancreatitis, which is likely induced by the same pathophysiological mechanisms as after endoscopic retrograde cholangiopancreatography (ERCP). According to the current European Society of Gastrointestinal Endoscopy guideline, nonsteroidal anti-inflammatory drugs are administered prior to ERCP as a scientifically proven treatment to reduce post-ERCP pancreatitis incidence rate. A single suppository of diclofenac or indomethacin prior to EUS guided tissue acquisition (TA) is harmless in healthy adults. Since it is associated with low costs and, most important, may prevent a dreadsome complication, we strongly recommend the administration of 100 mg diclofenac rectally prior to EUS-TA. We will explain this recommendation in more detail in this review as well as the risk and pathophysiology of post-EUS TA pancreatitis.

**Key Words:** Pancreatitis; Endoscopic ultrasound; Tissue acquisition; Nonsteroidal anti-inflammatory drugs; Pancreatic cancer

de Jong M, van Delft F, Roozen C, van Geenen EJ, Bisseling T, Siersema P, Bruno M. Nonsteroidal anti-inflammatory drugs before endoscopic ultrasound guided tissue acquisition to reduce the incidence of post procedural pancreatitis. *World* *J* *Gastroenterol* 2024; In press

**Core Tip:** Post-endoscopic ultrasound (EUS) pancreatitis has an incidence of 1%-2%. Literature on the effectiveness of diclofenac in preventing a post-EUS-tissue acquisition (TA) pancreatitis is scarce. Based on the pathophysiological mechanism, which is nearly the same in both post-endoscopic retrograde cholangiopancreatography and post-EUS pancreatitis, diclofenac could be effective as prophylaxis of post-EUS-TA pancreatitis. There are several arguments in favor of administration, such as the cost-effective prevention of post-EUS-TA pancreatitis, which could have potentially disastrous consequences. A single suppository of diclofenac has limited side effects. In conclusion, administration of diclofenac prior to EUS-TA procedure should be strongly advised to prevent post-EUS-TA pancreatitis.

**INTRODUCTION**

Since its introduction in the early 1990s[1], endoscopic ultrasound guided tissue acquisition (EUS-TA) by fine needle aspiration (FNA) or fine needle biopsy (FNB) is the gold standard for obtaining a tissue specimen for diagnosing pancreatic cancer, with a reported sensitivity and specificity of 77% and 98%, respectively[2,3]. To confirm the diagnosis before deciding on further treatment, EUS-TA of the pancreatic lesion is often indicated[4,5]. Besides being golden standard in obtaining cytology and histology of pancreatic solid masses, EUS-FNA/FNB is also used for cyst fluid analysis[6] and evaluation of autoimmune pancreatitis[7].

A variety of needles with different diameters and needle tip designs are available. Most recent data about the efficacy of EUS-TA recommend the use of a 22-gauge FNB needle in solid masses. In case of an unfavorable position of the endoscope with a sharp angulation of the tip, the more flexible 25-gauge needle can be chosen. For aspiration of cystic fluid, the 22-gauge FNA needles are the preferred ones[8].

Multiple publications have reported the risk of developing post procedural pancreatitis after EUS-TA[9-11]. Diagnosis of pancreatitis is usually based on the revised Atlanta criteria in which two of the following three features are required for the diagnosis of acute pancreatitis: hyperlipasemia (> 3 times the upper limit of normal); acute abdominal pain; and/or signs of pancreatitis on computed tomography scan[12]. In some publications including EUS-FNA (not EUS-FNB), the reported post-EUS pancreatitis incidence was around 2%[9,10]. To date the most comprehensive approximation of the post-EUS pancreatitis rate is provided by a systematic review and meta-analysis by Tian *et al*[11]. They showed a pooled incidence of pancreatitis of 0.7%[11]. However, this meta-analysis was mainly based on publications from before 2010, and only 30 publications after 2010 were analyzed in this meta-analysis. Table 1 shows seven retrospective and/or prospective trials that were all published after the screening period of the meta-analysis[13-19]. Incidence of post-EUS-TA pancreatitis is comparable to the incidence described in the meta-analysis. Data about post-EUS pancreatitis in relation to the EUS-TA techniques are still scarce though.

The development of acute pancreatitis following a diagnostic EUS-TA may have major consequences for the patient, particularly when there is a suspicion of pancreatic cancer. Delay or even annulment of further diagnostic work-up or treatment drastically reduces the chance of cure, while the survival rate is already low in these patients[20,21].

Acute pancreatitis is also a complication reported after endoscopic retrograde cholangiopancreatography (ERCP). Rectal nonsteroidal anti-inflammatory drugs (NSAIDs) (*i.e.* diclofenac) are administered as prophylaxis to reduce the post procedural ERCP pancreatitis rate by 39%[22]. Assuming a comparable pathophysiological mechanism with the activation of the same inflammatory cascade inside the pancreas as during an ERCP, the preventive effect of diclofenac in EUS-TA could be relevant. Although the reported incidence of post-EUS-TA pancreatitis is lower compared to that after ERCP, the one-time administration of diclofenac post-EUS-TA may make it a worthwhile strategy as it has little to no side effects and is associated with limited costs while potentially avoiding a devastating complication.

Limited literature is available on the preventive value of rectal administration of diclofenac prior to an EUS-TA procedure to protect against post-EUS pancreatitis. In this review we will focus on the clinical consequence of post-EUS pancreatitis and the potential role and impact of diclofenac in its prevention.

**Pathophysiology of post-EUS pancreatitis**

Mechanical injury of the pancreas is multifactorial in origin. It can be caused by manipulation of the ampulla of Vater and pancreatic duct, possibly in combination with increased pressure and overfilling of the ductal system with contrast agents in case of ERCP or direct puncture of the pancreatic parenchyma in case of EUS-TA. In the latter, pancreatitis is most often the result of direct cell damage, while in the former also the development of tissue edema may temporarily hamper the secretion of pancreatic enzymes causing increased ductal and intraparenchymal pressure. These events induce premature activation of pancreatic enzymes causing acute intracellular injury[23]. Both prostaglandins and phospholipase A2 play a key role in the early phase of inflammation[24].

**The role of diclofenac in preventing post-EUS pancreatitis**

The use of NSAIDs, either 100 mg diclofenac or 100 mg indomethacin rectally, is recommended by the European Society of Gastrointestinal Endoscopy and the American Society of Gastrointestinal Endoscopy as prophylaxis of a post procedural pancreatitis in patients undergoing ERCP[25,26]. The most optimal timing for the administration of a rectal suppository of diclofenac or indomethacin is just prior to the ERCP[27]. NSAIDs inhibit prostaglandins, phospholipase A2, and neutrophil-endothelial interactions, which will decrease the inflammatory reaction[24]. Both diclofenac and indomethacin reach the maximum concentration between 1-2 h after administration. Both these NSAIDs are mainly bound to albumin (90% *vs* 99%, respectively)[28] and subsequently excreted *via* the hepatobiliary-fecal and kidney pathway. Two hours after administration half of the level of diclofenac has been metabolized[29], while the biological half-life of indomethacin is 5-10 h. In addition, diclofenac is very cheap ($0.19 per supp 100 mg)[30], and a single dose is harmless in healthy adults[31].

However, the use of NSAIDs has limitations. NSAIDs are contraindicated during pregnancy after a gestational age of 30 wk[32], if the glomerular filtration rate is less than 30 mL/min/1.73 m2, or in case of liver cirrhosis[33,34]. Renal blood flow will be reduced by inhibition of prostaglandins, which can lead to hepatorenal syndrome in patients with liver cirrhosis[34]. If there is a documented allergy to NSAIDs, these should obviously be avoided.

**Risk Factors for Post-EUS Pancreatitis**

Several risk factors are associated with the development of post-EUS pancreatitis. Lee *et al*[35] showed that performing more EUS-guided punctures within one procedure increases the risk of adverse events [odds ratio (OR): 1.24 (1.02-1.50)]. This also applies to performing more than 15 to-and-fro movements per punction [OR: 2.25 (1.07-4.73)]. Performing ERCP on the same day as EUS-guided TA was the greatest risk factor for post procedural pancreatitis [OR: 2.82 (1.31-6.10)]. The excess risk of doing both procedures successively on the same day rather than on separate days however was not discerned. A history of recent acute pancreatitis was also found to be a risk factor for post-EUS pancreatitis (26.6% *vs* 3.3%)[17]. Additionally, the location of the biopsy contributes to the risk of developing post procedural pancreatitis.

Pancreatitis is more common after needle biopsies taken from the uncinate process or the pancreatic head as compared to the body or tail, possibly because in some cases the needle passes a thicker layer of healthy pancreatic parenchyma[36]. Tissue sampling through normal pancreatic parenchyma or through the wall of the main pancreatic duct also increases the risk of post-EUS pancreatitis compared to passage through minimal parenchyma (9.20% *vs* 0.18%). Lastly, patients with pancreatic cancer are less likely to develop post-EUS pancreatitis compared to patients with benign pancreatic diseases, while puncture of solid lesions had a higher overall rate of pancreatitis compared to puncture of cystic lesions (60% of the pancreatitis occurred after puncture of a solid lesion)[17]. In conclusion, both patients with solid lesions and patients with cystic lesions of the pancreas are susceptible to post-EUS pancreatitis. In both cases, there is a similar risk of puncturing through normal parenchyma and/or damaging the pancreatic duct.

**FNA *vs* FNB in relation to pancreatitis**

Currently, new advances in FNB techniques and increased yield compared to FNA will gradually phase out the use of FNA needles. The advantage of FNB is that fewer needle passes are required to obtain a representative specimen[37,38]. Despite the fact that greater tissue cores are obtained, which could cause hypothetically more damage, a meta-analysis showed that adverse events between FNA and FNB were not significantly different[37]. Rapid on-site evaluation (ROSE) has been advised during an FNA procedure to increase the diagnostic adequacy and thereby reduce the number of repeat procedures[39]. To perform ROSE however, cytopathological evaluation needs to be immediately available, is time consuming, and adds to the cost of the procedure. Meta-analysis showed that FNB without ROSE has a similar diagnostic adequacy compared to FNA with ROSE[38].

**Future perspective**

The only way to answer the question whether diclofenac is useful as a prophylaxis against the development of post-EUS pancreatitis is to conduct a randomized controlled trial (RCT). Ideally, this should be a double-blind, placebo-controlled trial in which one arm receives an NSAID suppository and the other arm receives a rectal placebo prior to the EUS-TA procedure. Patients, researchers, endoscopists, and nurses should be blinded.

Conducting such an RCT has several limitations. Since the incidence of post-EUS pancreatitis is probably between 1% and 2%, many patients need to be included. Aiming to reduce the incidence of post-EUS pancreatitis by 50% from 2% to 1%, with a significance of 5%, a power of 80%, and a 10% drop-out, 2550 patients are required in each arm. Suppose this hypothetically designed trial shows that administration of diclofenac can halve the incidence of post-EUS pancreatitis, then the number needed to treat is 1/100. In other words, 100 patients must receive diclofenac to prevent one post-EUS pancreatitis case. For risk analysis, all known risk factors should be noted and registered.

Therefore, it does not seem to be practically feasible to conduct such a trial. The question is whether such proof is necessary, as the indirect evidence for the protection of post-ERCP pancreatitis is strong and the mechanism of how post-EUS-TA pancreatitis develops seems identical to post-ERCP pancreatitis. Even though post-EUS-TA pancreatitis is a relatively rare event, a cheap and relatively safe diclofenac suppository can lower the incidence and prevent a potentially dreadsome complication that may cause a serious delay in the further work-up and treatment of a patient with a pancreatic mass. Therefore, in our opinion, the associated costs of managing preventable post-EUS-TA pancreatitis are disproportionate compared to standardized prophylactic diclofenac administration prior to EUS-TA.

**CONCLUSION**

Post-EUS pancreatitis is a rare complication of EUS-FNA/FNB with an incidence of 1%-2%. Despite its low incidence, it may have a significant clinical impact as pancreatitis may run a severe disease course causing delay in further diagnostics or therapy or even worse. Diclofenac suppository is effective as prophylaxis against pancreatitis after ERCP. Literature on the effectiveness of diclofenac in preventing post-EUS-TA pancreatitis is scarce. Based on the pathophysiological mechanism, which is nearly the same in both types of pancreatitis, diclofenac could be effective as prophylaxis for post-EUS-TA pancreatitis.

Unfortunately, an RCT with unfeasible numbers of patients is the only way to answer the question whether there is a significant benefit to the administration of diclofenac. In our opinion, further attempts to investigate the use of NSAIDS in post-EUS-TA pancreatitis prevention have limited added value. There are several arguments in favor of administration, such as the cost-effective prevention of post-EUS-TA pancreatitis, which could have potentially disastrous consequences for the patient. In addition, a single suppository of diclofenac has limited side effects. In conclusion, administration of diclofenac prior to the EUS-TA procedure of a solid or cystic pancreatic lesion should be strongly advised to prevent developing post-EUS-TA pancreatitis.

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**Footnotes**

**Conflict-of-interest statement:** All the authors declare that they have no conflicts of interest.

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**Provenance and peer review:** Unsolicited article; Externally peer reviewed.

**Peer-review model:** Single blind

**Peer-review started:** November 24, 2023

**First decision:** December 15, 2023

**Article in press:**

**Specialty type:** Gastroenterology & hepatology

**Country/Territory of origin:** Netherlands

**Peer-review report’s scientific quality classification**

Grade A (Excellent): 0

Grade B (Very good): B

Grade C (Good): 0

Grade D (Fair): 0

Grade E (Poor): 0

**P-Reviewer:** Hou XH, China **S-Editor:** Chen YL **L-Editor:** Filipodia **P-Editor:**

**Table 1 Incidence of post endoscopic ultrasound tissue acquisition pancreatitis**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Ref.** | ***n*** | **Type of study** | **FNA or FNB** | **Incidence** |
| Ribeiro *et al*[17], 2018 | 712 | Prospective cohort | FNA and FNB | 16/712 (2.2%) |
| Thomsen *et al*[18], 2022 | 852 | Retrospective cohort | FNB | 20/852 (2.3%) |
| Kandel *et al*[16], 2021 | 50 | Prospective RCT | FNA and FNB | 2/50 (4.0%) |
| van Riet *et al*[19], 2019 | 608 | Prospective RCT | FNA and FNB | 2/608 (0.3%) |
| Gonzalez *et al*[14], 2022 | 105 | Retrospective cohort | FNA and FNB | 0/105 (0.0%) |
| Ishigaki *et al*[15], 2020 | 154 | Retrospective cohort | FNA and FNB | 2/154 (1.3%) |
| Chen *et al*[13], 2022 | 235 | Prospective RCT | FNA and FNB | 2/235 (0.9%) |

FNA: Fine needle aspiration; FNB: Fine needle biopsy; RCT: Randomized controlled trial.