RESEARCH

Does rectal diclofenac reduce post-ERCP pancreatitis? A district general hospital experience

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ABSTRACT

Introduction There is controversy in the literature recently regarding the efficacy of rectal non-steroidal anti-inflammatory drugs (NSAID) to prevent post-ERCP pancreatitis (PEP). The aim of this study was to compare the incidence of PEP in three distinct groups of patients at the Royal United Hospital, Bath: no use of rectal diclofenac, selective use and blanket use without contraindication.

Method Readmission data, blood results, radiology reports and discharge summaries were used to identify patients with PEP from August 2010 to December 2015. The administration of rectal diclofenac postprocedure was recorded from the endoscopy reporting system.

Results 1318 endoscopic retrograde cholangiopancreatographies (ERCP) were performed by four endoscopists during the study period with 66 (5.0%) cases of pancreatitis. 445 ERCPs were performed prior to the introduction of NSAID use during which time, with an incidence of 35 (7.9%) episodes of PEP. During the selective period of NSAID use (high-risk patients) 539 ERCPs were performed and 72 (13.4%) patients received NSAIDs. 17 (3.2%) developed PEP. 334 ERCPs were performed when NSAIDs were given to all patients without contraindication. 289 (86.5%) of patients received rectal diclofenac and 13 (3.9%) developed pancreatitis. There is a statistically significant decrease in PEP comparing the groups of patients receiving NSAIDs selectively ($p=0.0009$) or routinely ($p=0.0172$) when compared with none. There is no difference between the selective and routine group ($p=0.571$).

Conclusion Our data demonstrate that the introduction of a selective or routine use of NSAIDs for PEP in a District General Hospital (DGH) significantly decreases the risk of pancreatitis (risk reduction 43.7%).

INTRODUCTION

Post-ERCP pancreatitis (PEP), a significant complication of endoscopic retrograde

cholangiopancreatography (ERCP), occurs in up to 10% of unselected case and carries a significant morbidity.¹ A number of strategies to reduce the incidence of PEP have been studied including prophylactic pancreatic stenting, preprocedural hydration and non-steroidal anti-inflammatory drugs (NSAID).² Important risk factors identified for PEP include Sphincter of Oddi dysfunction (SOD), female sex, a prior history of PEP and a variety of operator factors.³

There have been multiple studies assessing the effectiveness of NSAIDs in reducing the incidence of PEP worldwide, with the supportive evidence for its use mainly seen within high-risk patients. Sajid *et al*⁴ performed a systematic review of 13 randomised controlled trials in 2015 revealing that rectal NSAIDs significantly reduce the risk of PEP regardless of risk. Evidence for use of rectal NSAIDs in average and low-risk patients is controversial. A subgroup meta-analysis of small randomised trials performed by Yaghoobi *et al*⁵ showed a benefit in average-risk populations, which supports another meta-analysis by Sun *et al*.⁶ However, Levenick *et al*⁷ performed a single-centre randomised study which showed that rectal indomethacin is not effective in reducing the rate of pancreatitis in consecutive patients, regardless of risk. Contrary to this, a multicentre randomised controlled trial by Luo *et al*⁸ demonstrated that using rectal indomethacin in unselected patients reduced the risk of PEP. In the UK, there is little data regarding the effectiveness of rectal NSAIDs to reduce PEP after an ERCP. One small, single-centre randomised trial in 2003 by Murray *et al*⁹ provided evidence that using NSAIDs in unselected patients reduces the risk of PEP.

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The indications for ERCP, local expertise and tertiary setting can significantly affect the case mix and consequently PEP risk between institutions. The incidence of PEP rates in publications including those referenced in the European Society of Gastrointestinal Endoscopy (ESGE) guidelines is significantly higher than those experienced in the UK, suggesting that international data may not be directly applicable to the UK. Similarly, the slow adoption of the ESGE guidelines in the UK may suggest scepticism of the data and the requirement for more UK data.

The 2010 ESGE stated that routine administration of either rectal indomethacin or diclofenac before or after ERCP was recommended regardless of risk,¹⁰ partly based on a meta-analysis performed by Zheng *et al.*¹¹ The evidence points towards these particular agents being the most effective in reducing the risk of PEP. In 2014, the ESGE guidelines were amended and now suggest that rectal diclofenac or indomethacin should be used in all patients without contraindication.¹² This is also echoed in the 2017 American Society of Gastrointestinal Endoscopy guidelines, which state that it is reasonable to administer rectal NSAIDs in both high and average-risk patients.¹³

Despite guidelines advocating the use of rectal NSAIDs, uptake in the UK has been relatively poor. Sinha *et al.*¹⁴ conducted a UK-wide survey to study the practice of PEP prophylaxis. Although 79% were aware of the guidelines, only 9% used PEP for all patients. NSAID nephrotoxicity has been cited as one reason why this is the case. A survey sent to endoscopy UK practitioners performing ERCP in 2014 by Hanna *et al* revealed that only 34.6% of respondents used rectal NSAIDs.¹⁵ They cite one of the reasons for poor uptake is lack of scientific evidence for their use. The use of NSAIDs for PEP prophylaxis in the UK is growing its prevalence but is still not routine practice in all units. Previous studies have demonstrated that lack of British consensus guidelines, nephrotoxicity and conflicting evidence from published studies were the main barriers. Interestingly, this was despite good awareness of the European guidelines.

The proposed protective mechanism of NSAIDs has been studied implicating phospholipase A2 in the pathogenesis of acute pancreatitis and is demonstrated to be increased in patients with severe pancreatitis.¹⁶ In vitro, indomethacin and diclofenac are both potent inhibitors of phospholipase A2.¹⁷ Ding *et al*¹⁸ performed a meta-analysis regarding the use of rectal diclofenac and rectal indomethacin as agents for prophylaxis. This meta-analysis also compared studies looking at different routes of administration. It concluded that rectal administration was the better option, although the reasons for this are unclear. There does not appear to be a difference between using diclofenac or indomethacin in Ding's paper. This is also demonstrated in a meta-analysis conducted by Sethi *et al.*¹⁹ This meta-analysis also demonstrated that there

is no difference between administering it immediately pre or post-ERCP. These findings are also supported by a meta-analysis performed by Puig *et al.*²⁰ Contrary to this, a more recent meta-analysis performed by Hou *et al*²¹ showed that rectal diclofenac is likely to be more superior than indomethacin and post-ERCP is probably more superior to pre-ERCP. They showed a reduction in the incidence of PEP and a reduction in the severity of PEP.

Given the controversy surrounding rectal NSAIDs to reduce PEP in groups other than high risk, along with the lack of UK data, we conducted a study to see if rectal diclofenac decreased the incidence of PEP in unselected ERCP patients. The aim of this study was to see if the incidence of PEP was reduced with the use of rectal diclofenac. Rectal diclofenac was introduced in a single UK centre performing 300 procedures per year (Royal United Hospital, Bath) in two phases:

1. use of rectal diclofenac in a selective population deemed at high risk of PEP, as assessed by age, sex, common bile duct (CBD) diameter and previous pancreatitis;
2. use of rectal diclofenac in unselected, consecutive ERCP patients without contraindications for NSAIDs.

METHODS

We performed a retrospective observational study of PEP rates prior to and following the two-phase introduction of NSAIDs postprocedure. Diclofenac 100 mg suppository was administered immediately postprocedure. The sources used to collect information were the Sunquest pathology system, radiology reports (Synapse), electronic endoscopy database (Endobase) and discharge summaries (Cerner Millennium).

Endobase was used to identify all consecutive patients undergoing an ERCP at the Royal United Hospital, Bath, from August 2010 to December 2015. These were all included in the study. Demographic data, the use of rectal diclofenac post-ERCP and whether they were an inpatient or outpatient were recorded. We also recorded any deaths that occurred and other procedural complications. Data were also collected on organ dysfunction, the length of time that organ dysfunction lasted and any local complications, in order to classify the severity of PEP.

Data were collated in chronological order and split into three data sets:

1. a period where rectal diclofenac was never used from August 2010 to July 2012;
2. a period where rectal diclofenac was used in those deemed by at high risk of PEP by the endoscopist, from August 2012 to end of June 2014;
3. a period where rectal diclofenac was used in all consecutive ERCP patients if not contraindicated, from July 2014 to end of December 2015.

A diagnosis of PEP was defined as the development of symptoms of epigastric pain or vomiting with an amylase level that had risen ≥ 2 times the upper limit of

Table 1 Demographics of patients developing PEP among all patients

	PEP (n=64)	Non-PEP (n=1254)
Mean age (range)	67 (24–90)	71 (19–99)
Sex		
Female	35 (54.7%)	657 (52.4%)
Male	29 (45.3%)	597 (47.6%)
Diclofenac use	16 (25%)	344 (27.4%)

PEP, post-ERCP pancreatitis.

normal within 48 hours of the ERCP or patients with radiological imaging suggestive of acute pancreatitis.

The incidence of PEP was analysed and used Fisher's exact test to determine if there was a reduction in PEP between the three groups.

RESULTS

A total of 1318 ERCPs were performed between August 2010 and December 2015 by four endoscopists. Sixty-four (4.9%) cases of PEP were identified (tables 1 and 2).

Up to 444 patients were identified in the first group, with a mean age of 70.2 years. No rectal diclofenac was used in any of these patients. Thirty-six (8.1%) patients developed PEP.

Up to 539 patients were identified in the second group, with a mean age of 71.1 years. High-risk patients were determined by the individual endoscopists based on the risk factors of young age, female sex, non-dilated CBD, previous PEP, suspected SOD or pancreatic duct injection. Of the 16 patients who developed PEP, 5 of these had received NSAIDs compared with 11 who did not receive NSAIDs. Seventy-two (13.4%) were identified as being high risk and consequently received rectal diclofenac postprocedure. Five of these high-risk patients developed PEP (6.9%). A total of 467 were identified as low risk (and therefore did not receive rectal diclofenac). Sixty-four (13.7%) of these developed PEP. Given that this was a retrospective study, the classification of high and low-risk patients was not performed in the groups where it did not change practice. The cohort of patients pre-NSAID use was not characterised as high and low risks because there was no necessity, and similarly the third cohort

Table 3 PEP versus PEP and use of diclofenac in selective group (group 2)

	PEP (n=16)	Non-PEP (n=523)
Age (mean)	63	71
Sex		
Male	8	232
Female	8	291
Diclofenac given	5 (31.2%)	67 (12.8%)

PEP, post-ERCP pancreatitis.

all received NSAIDs removing any requirement for risk stratification.

Up to 335 patients were included in the last group, where all patients received rectal diclofenac without contraindication. A total of 288 patients received rectal diclofenac (86.0%). Twelve of the 335 patients (3.6%) developed PEP. Of the 12 who developed PEP, 11 had received NSAIDs compared with 1 who had not. The reasons for not using NSAIDs in the third group were allergy to NSAIDs, estimated glomerular filtration rate <30 (although is not the case now) or patient refusal. Unfortunately, the patient-specific reasons were not recorded.

We further analysed those patients who developed PEP compared with those who did not specifically assessing diclofenac use in the three groups (tables 3 and 4). In the blanket use group, 11 out of 12 patients who developed PEP received diclofenac.

There was a statistically significant reduction in the incidence of PEP when rectal diclofenac was used selectively compared with no rectal diclofenac being used at all ($p=0.0009$). Similarly, there was also a significant reduction in incidence when rectal diclofenac was used for all patients without contraindication compared with not using rectal diclofenac at all ($p=0.00172$). There is a no difference in using rectal diclofenac selectively or as blanket use ($p=0.571$).

DISCUSSION

Our study suggests that rectal diclofenac post-ERCP significantly reduces the incidence of PEP, when used selectively or for all patients regardless of risk. Our data support other studies that rectal diclofenac reduces the risk of PEP.

Table 2 Rates of PEP, demographics of patients and diclofenac use in each group

	Group 1 (n=444) (No NSAIDs)	Group 2 (n=539) (Selective NSAIDs)	Group 3 (n=335) (Unselected NSAIDs)
Age	70.2 (21–99)	71.1 (19–99)	70.1 (22–98)
Sex			
Female	229 (51.6%)	299 (55.4%)	164 (49.0%)
Male	215 (48.4%)	240 (44.5%)	171 (51.0%)
Diclofenac use	0 (0%)	72 (13.5%)	288 (86.2%)
Incidence of PEP	36 (8.1%)	16 (3.0%)	12 (3.6%)

NSAID, non-steroidal anti-inflammatory drugs; PEP, post-ERCP pancreatitis.

Table 4 PEP versus PEP and use of diclofenac in blanket group (group 3)

	PEP (n=12)	Non-PEP (n=323)
Age (mean)	64	70
Sex		
Male	5	166
Female	7	157
Diclofenac given	11 (91.7%)	277 (85.8%)

PEP, post-ERCP pancreatitis.

In both the selective and blanket groups, PEP developed in a statistically significant lower proportion in those who receive diclofenac. Five out of the 16 patients who developed PEP and were given diclofenac were deemed high risk. The introduction of NSAID prophylaxis was driven by awareness of the ESGE guidelines. The change in practice from groups 2 to 3 was driven by the realisation that some patients considered to be high risk were not receiving NSAIDs and adoption of the blanket policy suggested by the ESGE was felt to decrease variation in care and missing patients.

Due to this, the current practice at the Royal United Hospital, Bath, is to use rectal diclofenac in all patients unless contraindicated. In our study in the unselected group, 13.8% of patients did not receive diclofenac. The possible reasons for this are that it may have been contraindicated, refusal of the drug, they may already be taking NSAIDs or it may not have been recorded on the endoscopy report. Interestingly, only 5/16 patients in the selective group that developed PEP were deemed high risk, supporting our current policy.

Although our rates of PEP are similar to rate of PEP found in the literature,²² some studies do report slightly higher rates than in our study, for example, Cheng *et al* reported a PEP rate of 15.1%.²³ It is known that younger age is a risk factor for developing PEP. The mean age of the patients in our study was 70. Andrade-Dávila *et al*²⁴ reported an incidence of PEP of 12.6% with the mean age of the patients being 50.

Given that younger age is a risk factor for PEP, the difference seen between our data and published literature may relate to the difference in mean age and this variability makes it difficult to directly compare studies.

Another variable is the type of NSAID that is used in various studies. Multiple non-UK studies use indomethacin as the NSAID of choice when looking at its effectiveness in reducing PEP (eg, Levenick *et al*⁷ and Luo *et al*⁸). Mohammed Alizadeh *et al*²⁵ conducted a relatively small randomised study of 372 patients to assess the difference in effectiveness between rectal indomethacin, diclofenac and naproxen. This revealed that rectal indomethacin and diclofenac had a reduced incidence of PEP compared with naproxen. A meta-analysis conducted by Sajid *et al*⁴ suggested that diclofenac is more effective than indomethacin in reducing PEP.

Our data support studies where diclofenac is used in that it reduces the rate of PEP. We did not look specifically at whether it reduces the severity of PEP, which was an outcome in a randomised trial by Patil *et al*.²⁶

There are a few limitations to our study. Our study was a retrospective, observational study. There is a possibility that NSAIDs may have been given to patients but this was not recorded and we are unable to know if they were given, which means the number of patients who received diclofenac in group 2 or 3 may be under-represented. We may also have missed patients who had their ERCP performed at the Royal United Hospital, Bath, but were admitted to a different hospital postprocedure. Another significant limitation is that we did not follow patients up who may not have been readmitted or admitted to a different hospital which may mean that our incidence of pancreatitis may be underestimated.

Despite the difficulty in comparing studies and the controversy that currently exists for its use, our data do suggest that using rectal diclofenac postprocedure

Key messages

What is already known on this topic?

- ▶ There is a growing body of evidence for the use of rectal non-steroidal anti-inflammatory drugs (NSAID) to prevent post-ERCP pancreatitis (PEP). Rectal NSAIDs are recommended in the American Society of Gastrointestinal Endoscopy and the European Society of Gastrointestinal Endoscopy in all patients regardless of risk before or after the procedure. However, it is not yet a recommendation in the British Society of Gastroenterology (BSG) guidelines and there has recently been controversy in the literature regarding its efficacy in this context.

What this study adds?

- ▶ Evidence for use of rectal NSAIDs in the UK to prevent PEP is sparse. There is currently one published randomised controlled trial in the UK. This is one of the few studies that has been performed in the UK which demonstrates that use of rectal diclofenac to prevent PEP may be advantageous in a District General Hospital.

How might it impact on clinical practice in the foreseeable future?

- ▶ Use of rectal NSAIDs in all patients pre-ERCP (endoscopic retrograde cholangiopancreatography) is now the practice at Royal United Hospital, Bath. This study demonstrates that using rectal NSAIDs in a selective or routine use reduces the risk of PEP. It may help provide some clarity where there are no established BSG guidelines for this and where there is some controversy.

has some role in reducing the rate of PEP, whether for high-risk or average-risk patients.

In summary, our data suggest that postprocedural rectal diclofenac reduces the risk of PEP when used selectively or for all patients. Rectal NSAIDs are a simple and effective way to reduce the incidence of PEP in all patients.

Contributors BC provided the initial concept of this study. GS, PB and MT designed the data collection form and collected the data. GS and BC performed the analysis on the data. GS and BC wrote the paper and it was reviewed by JL and MF prior to submission.

Competing interests None declared.

Patient consent This was a retrospective analysis of data already available (ie, audit) so patient consent forms not required.

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