Aggressive fluid hydration plus non-steroidal anti-inflammatory drugs versus non-steroidal anti-inflammatory drugs alone for post-endoscopic retrograde cholangiopancreatography pancreatitis (FLUYT) a multicentre, open-label, randomised, controlled trial

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Aggressive fluid hydration plus non-steroidal anti-inflammatory drugs versus non-steroidal anti-inflammatory drugs alone for post-endoscopic retrograde cholangiopancreatography pancreatitis (FLUYT): a multicentre, open-label, randomised, controlled trial

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Summary

Background Pancreatitis is the most common complication of endoscopic retrograde cholangiopancreatography (ERCP). Prophylactic rectal administration of non-steroidal anti-inflammatory drugs (NSAIDs) is considered as standard of care to reduce the risk of post-ERCP pancreatitis. It has been suggested that aggressive hydration might further reduce this risk. Guidelines already recommend aggressive hydration in patients who are unable to receive rectal NSAIDs, although it is laborious and time consuming. We aimed to evaluate the added value of aggressive hydration in patients receiving prophylactic rectal NSAIDs.

Methods FLUYT, a multicentre, open-label, randomised, controlled trial done across 22 Dutch hospitals, included patients aged between 18 and 85 years with moderate to high risk of post-ERCP pancreatitis. Patients were randomly assigned (1:1) by a web-based module with varying block sizes to a combination of aggressive hydration and rectal NSAIDs (100 mg diclofenac or indomethacin; aggressive hydration group) or rectal NSAIDs (100 mg diclofenac or indomethacin) alone (control group). Randomisation was stratified according to treatment centre. Aggressive hydration comprised 20 mL/kg intravenous Ringer's lactate solution within 60 min from the start of ERCP, followed by 3 mL/kg per h for 8 h. The control group received normal intravenous saline with a maximum of 1·5 mL/kg per h and 3 L per 24 h. The primary endpoint was post-ERCP pancreatitis and was analysed on a modified intention-to-treat basis (including all patients who underwent randomisation and an ERCP and for whom data regarding the primary outcome were available). The trial is registered with the ISRCTN registry, ISRCTN13659155.

Findings Between June 5, 2015, and June 6, 2019, 826 patients were randomly assigned, of whom 388 in the aggressive hydration group and 425 in the control group were included in the modified intention-to-treat analysis. Post-ERCP pancreatitis occurred in 30 (8%) patients in the aggressive hydration group and in 39 (9%) patients in the control group (relative risk 0·84, 95% CI 0·53–1·33, p=0·53). There were no differences in serious adverse events, including hydration-related complications (relative risk 0·99, 95% CI 0·59–1·64; p=1·00), ERCP-related complications (0·90, 0·62–1·31; p=0·62), intensive care unit admission (0·37, 0·07–1·80; p=0·22), and 30-day mortality (0·95, 0·50–1·83; p=1·00).

Interpretation Aggressive periprocedural hydration did not reduce the incidence of post-ERCP pancreatitis in patients with moderate to high risk of developing this complication who routinely received prophylactic rectal NSAIDs. Therefore, the burden of laborious and time-consuming aggressive periprocedural hydration to further reduce the risk of post-ERCP pancreatitis is not justified.

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Introduction

In the USA alone, 169 510 endoscopic retrograde cholangiopancreatographies (ERCPs) are done annually.[1] Pancreatitis is the most common complication of ERCP, with an incidence of up to 14·7% in patients at high risk.[2] Post-ERCP pancreatitis can progress to moderate or severe pancreatitis in 4·7% of patients and is associated with an overall mortality rate of 0·7%.[2,3]

Research in context

Evidence before this study

Pancreatitis is the most common complication of endoscopic retrograde cholangiopancreatography (ERCP). Despite the use of prophylactic rectal non-steroidal anti-inflammatory drugs (NSAIDs), its prevalence remains substantial. Evidence has emerged that aggressive periprocedural hydration using Ringer's lactate solution is also effective in reducing post-ERCP pancreatitis. Therefore, we did a systemic review before trial commencement using PubMed and Embase to search for research articles published in English up to Feb 17, 2016, with the following search terms: ("cholangiopancreatography, endoscopic retrograde", "ERCP") and ("fluid therap*", "fluid administrat*", "fluid volume", "intravenous infusion", "rehydrate", or "hydrat*"). Six studies with a total of 1102 patients fulfilled the inclusion criteria: three randomised controlled trials and three retrospective studies. On the basis of this systematic review, there was evidence to suggest that periprocedural hydration affords protection against post-ERCP pancreatitis. However, the included studies did not use prophylactic rectal NSAIDs, which are now seen as the standard of care. Furthermore, the pooled sample size of the included studies was too small to detect differences in post-ERCP pancreatitis. Finally, the included studies had considerable shortcomings in methodology, reporting confounders, and various endpoint definitions.

Added value of this study

In this multicentre, randomised, controlled trial, we found that that the combination therapy with aggressive periprocedural hydration with Ringer's lactate solution and rectal NSAIDs was not superior to rectal NSAIDs alone in reducing the incidence of post-ERCP pancreatitis.

Implications of all the available evidence

In patients undergoing ERCP who already receive prophylactic rectal NSAIDs, the burden of laborious and time-consuming aggressive periprocedural hydration to further reduce the risk of post-ERCP pancreatitis is not justified. Aggressive periprocedural hydration can potentially be used in patients with contraindications for rectal NSAIDs.

Effective strategies to reduce the incidence of post-ERCP pancreatitis are periprocedural rectal non-steroidal anti-inflammatory drugs (NSAIDs) and pancreatic duct stent placement.[4–6] Rectal NSAIDs are widely regarded as the standard preventive therapy because of ease of use and negligible costs.[7–9] There is insufficient evidence, however, that a combination of rectal NSAIDs and pancreatic duct stenting is superior to either technique alone.[7,10–12] Despite these routine preventive measures, pancreatitis remains the most common complication of ERCP.[5] Evidence has emerged that aggressive periprocedural hydration with Ringer's lactate solution is also effective and safe in reducing post-ERCP pancreatitis.[13–19] Therefore, American endoscopy treatment guidelines suggest aggressive periprocedural hydration with Ringer's lactate solution when feasible to decrease the risk of post-ERCP pancreatitis,[7] and European guidelines advise aggressive periprocedural hydration in patients with a contraindication for rectal NSAIDs.[8]

A survey among American endoscopists involved in advanced endoscopy fellowships reported that 83% of the responders use intravenous fluids to prevent post-ERCP pancreatitis.[20] The strategy is rooted in the theory that early derangements of pancreatic microcirculatory perfusion correlate with acute pancreatitis severity.[21] However, the question remains whether periprocedural hydration offers protection in patients who are already receiving rectal NSAIDs. A synergistic effect of hydration and rectal NSAIDs cannot be excluded because hydration aims to preserve pancreatic microcirculation while NSAIDs suppress the inflammatory response.[21–24] Studies of aggressive periprocedural hydration as an addition to rectal NSAIDs have not provided robust conclusions.[25,26] Since aggressive hydration is laborious, time consuming, and often necessitates a prolonged hospital stay, a randomised study is needed to determine the effectiveness of such a strategy.

We aimed to compare aggressive periprocedural hydration with Ringer's lactate solution combined with rectal NSAIDs versus rectal NSAIDs alone in patients undergoing ERCP with a moderate to high risk of post-ERCP pancreatitis.

Methods

Study design and participants

FLUYT, a multicentre, open-label, randomised, controlled trial, was coordinated by the Dutch Pancreatitis Study Group. Patients were enrolled in four university medical centres and 18 large teaching hospitals in the Netherlands. The design of the trial has been published previously.[27]

Patients aged between 18 and 85 years were eligible for inclusion if they needed ERCP and they had a moderate to high risk of post-ERCP pancreatitis. We selected patients at moderate to high risk of post-ERCP pancreatitis by excluding patients with a low risk of post-ERCP pancreatitis, for which they had to fulfil at least one of the following criteria: chronic calcific pancreatitis (according to M-ANNHEIM criteria[28]), previous sphincterotomy, pancreatic head mass, or routine biliary stent exchange.[4,8] Additional exclusion criteria were active pancreatitis before ERCP and contraindications to aggressive hydration (eg, cardiac, pulmonic, or liver insufficiency, pre-existent pitting oedema, hyponatraemia, or hypernatraemia) or rectal NSAIDs (eg, renal insufficiency, allergy, active gastrointestinal bleeding, ulcer disease, and NSAID use for other indications [other than

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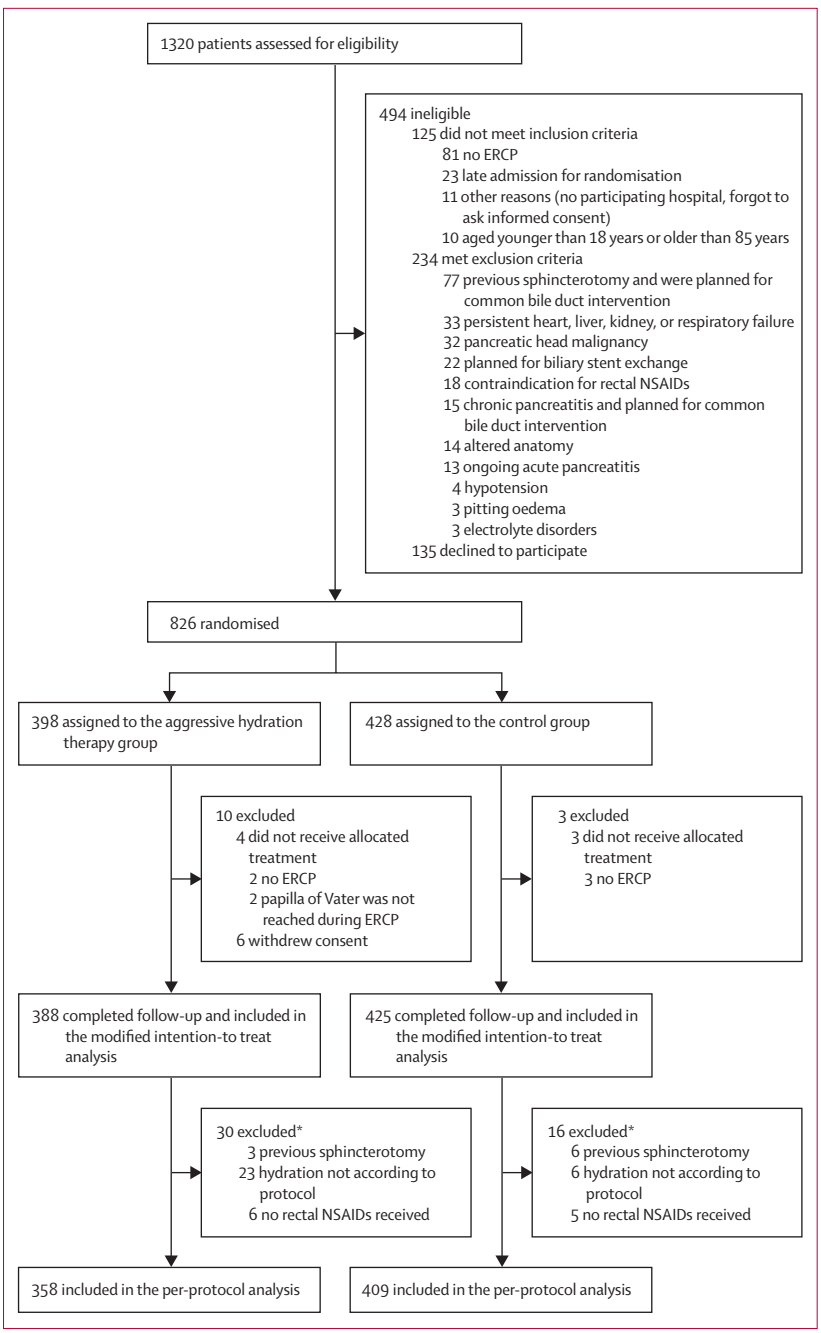

***Figure* 1: Trial profile**
ERCP=endoscopic retrograde cholangiopancreatography. NSAIDs=non-steroidal anti-inflammatory drugs.
*Some patients had more than one reason to be excluded from the per-protocol analysis.

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cardioprotective aspirin]). Full eligibility criteria are listed in the appendix (p 3).

Because medicinal products used in this study (ie, Ringer's lactate solution) were under investigation, the Central Committee on Research Involving Human Subjects carried out an extra review of the trial protocol. The boards of all participating centres gave additional permission for carrying out the study in the respective centres. This investigator-initiated study was done in accordance with the principles of the Declaration of Helsinki and Dutch law regarding research involving humans. The Medical Ethical Committee United in Nieuwegein, the Netherlands, approved the trial protocol (reference number NL52341.100.15). Written informed consent was obtained from all participants. The protocol is available online.

Randomisation and masking

Patients were randomly assigned (1:1) to either aggressive periprocedural hydration combined with rectal NSAIDs (aggressive hydration group) or rectal NSAIDs alone (control group). Patients were randomly assigned centrally by the study coordinator using a web-based computer program with concealed, permuted blocks of varying sizes (two, four, or six). Randomisation was stratified according to treatment centre. Masking of treating staff and patients was deemed impracticable because visible volume input and urine volume output greatly differed between groups. However, a masked adjudication committee evaluated all primary and secondary outcomes. Furthermore, all statisticians were masked for the prophylaxis given.

Procedures

All ERCPs were carried out by or under the direct supervision of an experienced interventional endoscopist, defined as having a lifetime exposure of more than 400 ERCPs and having done more than 50 ERCPs yearly for the past 3 years. The aggressive hydration group received 100 mg of rectal NSAIDs (diclofenac or indomethacin)[29] within 30 min before or after procedure, combined with periprocedural hydration with intravenous 20 mL/kg Ringer's lactate solution within 60 min from the start of ERCP (endoscope–mouth contact), directly followed by 3 mL/kg per h for 8 h. The control group received 100 mg of rectal NSAIDs alone (within 30 min before or after procedure) with a restricted intravenous fluid infusion with normal saline (maximum of 1·5 mL/kg per h or 3 L per 24 h).[19,27] Decisions regarding placement of pancreatic duct stents were at the discretion of the attending endoscopist. After ERCP, all patients were admitted to hospital, regardless of symptoms, for 24 h to evaluate the two criteria that constituted the primary endpoint by measuring the concentration of amylase, lipase, or both in blood and to assess the appearance of upper abdominal pain. Thereafter, or if patients developed complications beforehand, intravenous fluid administration was at the discretion of the treating clinician. A second night of hospital treatment was indicated when a patient met the two criteria of post-ERCP pancreatitis. A prolonged hospital stay due to other indications was at the discretion of the treating clinician. Patients were followed up for 180 days after randomisation and were phoned 30, 90, and 180 days after the ERCP procedure.

All data were collected prospectively using standardised digital case record forms and were verified by the study coordinator through patient chart review of all hospital contacts between randomisation and the end of follow-up. Quality of life was assessed with two generic questionnaires (EQ-5D and the Medical Outcome Study 36-Item Short Form) and the Standardised Instrument for Measuring and Valuing Health-Related Productivity Losses at 1, 3, and 6 months after randomisation.

Outcomes

The primary endpoint was post-ERCP pancreatitis according to the Cotton criteria—ie, the presence of new onset of upper abdominal pain suggestive of pancreatitis requiring extension of hospital stay for at least 2 nights; and elevation of pancreatic enzymes (amylase, lipase, or both) to more than three times the institutional upper limit of normal 24 h after ERCP.[30] Secondary endpoints were severity of post-ERCP pancreatitis according to the Cotton criteria[30] and revised Atlanta criteria,[31,32] ERCP-related complications according the Cotton criteria,[30] hydration-related complications, pancreatic insufficiency, and duration of hospital stay (appendix pp 4–7). A masked adjudication committee consisting of five endoscopists, a radiologist, and a nephrologist individually evaluated all primary and secondary outcomes. Disagreements were resolved during a consensus meeting.

Serious adverse events were defined as events that were fatal or life threatening, that resulted in clinically significant or persistent disability, that required hospital admission or a prolonged hospital stay, or that were judged by the investigator to represent a clinically significant hazard or harm to the patient that might require medical or surgical intervention. Serious adverse events were reported by treating clinicians to the study coordinator and verified by patient chart review. All events were reported to the Dutch Central Committee for Research Involving Human Subjects.

Statistical analysis

We believe that aggressive periprocedural hydration would be a useful addition to rectal NSAIDs if it has a similar relative risk reduction.[33] We assumed that a relative risk reduction of 60% would be realistic, based on the assumption that rectal NSAIDs in combination with aggressive periprocedural hydration would yield a similar relative risk reduction to rectal NSAIDs compared with placebo in previous studies.[19,34,35] This minimal clinically important difference would cause the incidence of post-ERCP pancreatitis to decrease from 8·0% in the control group to 3·2% in the aggressive hydration group, with a 4·8% absolute risk reduction. We calculated a sample size of 720 patients would be needed to detect a 60% relative reduction in post-ERCP pancreatitis in the aggressive hydration group (from 8% to 3·2%), with a power of 80% and a two-sided α level of 0·05. To allow for unexpected dropout and missing data, we increased the target sample size by 15% resulting in a final number of 826 patients (413 per group).

Patient recruitment and the association of serious adverse events with the intervention were overseen by an independent data safety monitoring board (DSMB). All events were reported to the DSMB (who were not masked) after the inclusion of 50, 150, 413, and 650 patients. An independent statistician did an interim analysis after 413 patients were included, which allowed us to include

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	Aggressive hydration group (n=388)	Control group (n=425)
Age, years	57 (44–71)	60 (49–71)
Sex		
Female	232 (60%)	250 (59%)
Male	156 (40%)	175 (41%)
Body-mass index, kg/m²*	26·7 (24–30·4)	26·9 (23·8–30·3)
Previous cholecystectomy	112 (29%)	116 (27%)
ASA class on admission		
I: healthy status	90 (23%)	103 (24%)
II: mild systemic disease	235 (61%)	255 (60%)
III: severe systemic disease	63 (16%)	67 (16%)
IV: severe systemic disease that is constant threat to life	0	0
Smoker		
Current	76/351 (22%)	95/378 (25%)
Past	79/351 (23%)	84/378 (22%)
Never	196/351 (56%)	199/378 (53%)
Alcohol abuse†	59/353 (17%)	67/369 (18%)
ERCP indication		
Common bile duct stones (or suspicion of)	307 (79%)	342 (80%)
Cholangitis	45 (12%)	46 (11%)
Metastatic cancer	6 (2%)	5 (1%)
Cholangiocarcinoma	7 (2%)	7 (2%)
Postoperative bile leak	4 (1%)	8 (2%)
Sphincter of Oddi dysfunction (or suspicion of)	5 (1%)	5 (1%)
Other	14 (4%)	12 (3%)
Complexity of ERCP[39]		
1	20 (5%)	31 (7%)
2	337 (87%)	353 (83%)
3	30 (8%)	39 (9%)
4	1 (<1%)	2 (<1%)
Common bile duct cannulation achieved	357 (92%)	395 (93%)
Pancreatic duct stent placement	23 (6%)	26 (6%)
Pancreatic duct cannulation (unintentional)	157 (40%)	158 (37%)
Pancreatic duct contrast injections (unintentional)	58 (15%)	73 (17%)
Difficult cannulation‡	113/378 (30%)	123/417 (29%)
Sphincter of Oddi dysfunction	3 (1%)	5 (1%)

Data are median (IQR) or n (%). Percentages might not sum to 100% because of rounding. ASA=American Society of Anaesthesiologists. ERCP=endoscopic retrograde cholangiopancreatography. *Assessed in 387 patients in the aggressive hydration group and 417 patients in the control group. †According to the US National Institute on Alcohol Abuse and Alcoholism (more than three drinks on any single day and more than seven drinks per week for women; more than four drinks on any single day and more than 14 drinks per week for men). ‡Difficult cannulation was defined as more than five attempts.

Table 1: **Baseline characteristics of patients in the modified intention-to-treat population**

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See Online for appendix

For the **protocol** see https://trialsjournal.biomedcentral.com/articles/10.1186/s13063-018-2583-x

an option to stop the trial early for efficacy.[36] We used a Peto approach to test for a beneficial effect (symmetrical stopping boundaries at p<0·001); there was no assessment of futility.[37,38] The access to the result of the interim analysis was limited to the study coordinator and the DSMB to minimise potential operational bias.

Baseline variables are expressed as mean with SD or median with IQR. All primary analyses were done in the modified intention-to-treat population and the per-protocol analysis population. The modified intention-to-treat analysis was based on randomly assigned patients who underwent an ERCP and for whom data regarding the primary outcome were available. For example, we excluded patients in whom the duodenum was not reached and the papilla of Vater was not manipulated during ERCP, as they cannot develop post-ERCP pancreatitis. In the modified intention-to-treat analysis, data were analysed according to the treatment to which the patient was assigned by randomisation. In the per-protocol analysis, we excluded patients who had a previous sphincterotomy, patients who did not receive rectal NSAIDs, or in case hydration was not given according to protocol. The primary endpoint was analysed using Fisher's exact test. The secondary endpoints were compared between treatment groups by the Student's *t* test, Wilcoxon rank-sum test, Pearson's χ^2 test, or Fisher's exact test, as appropriate. The amount of fluid given in the first 24 h from the start of ERCP were monitored for both groups. We compared the differences using Wilcoxon rank-sum test. Results are presented as relative risks with corresponding 95% CIs. We made no adjustments for multiple testing and did not correct for any potential bias introduced by our interim analysis because we considered the bias to be negligible. All analyses were done by an independent statistician.

We did a predefined subgroup analyses for age, sex, and pancreatic duct stent placement. Additionally, we did post-hoc analyses on risk factors for post-ERCP pancreatitis: a history of pancreatitis, difficult cannulation of the common bile duct, cannulation of the pancreatic duct, pancreatic contrast injection, and trainee involvement.[7] All subgroup analyses were evaluated for confounding and whether an interaction effect was present with aggressive periprocedural hydration in combination with rectal NSAIDs by testing for significance of a corresponding interaction term following a log binominal regression model. All statistical analyses were done with R (version 3.6.2), with significance set at a two-sided α level of 5%.

This trial is registered with the ISRCTN registry, number ISRCTN13659155.

Role of the funding source

The funders of the study had no role in study design, data collection data analysis, data interpretation, or writing of the report.

Results

Between June 5, 2015, and June 6, 2019, 1320 patients were assessed for eligibility, of whom 826 underwent randomisation (figure 1; appendix p 8). 13 patients were excluded from our intention-to-treat population: six patients withdrew informed consent before ERCP and seven patients did not undergo ERCP and therefore were unable to be assessed for the primary endpoint (appendix pp 9–10). 388 patients received aggressive periprocedural hydration and 425 patients served as controls in the modified intention-to-treat analysis. Patients had a median age of 59 years (IQR 46–71) and 482 (59%) were women. Baseline characteristics did not

	Aggressive hydration group (n=388)	Control group (n=425)	Relative risk (95% CI)	p value*
Primary outcome: post-ERCP pancreatitis	30 (8%)	39 (9%)	0·84 (0·53–1·33)	0·53
Delayed (>48 h after ERCP) post-ERCP pancreatitis	1 (<1%)	1 (<1%)	..	..
Secondary outcomes				
Post-ERCP pancreatitis severity according to Cotton criteria[30]	..	..	..	..
Mild	9 (2%)	7 (2%)	1·38 (0·52–3·66)	0·52
Moderate or severe	21 (5%)	32 (8%)	0·72 (0·42–1·23)	0·23
Post-ERCP pancreatitis severity according to revised Atlanta criteria[31,32]	..	..	..	..
Mild	27 (7%)	29 (7%)	1·00 (0·61–1·66)	0·99
Moderate or severe	3 (1%)	10 (2%)	0·33 (0·09–1·19)	0·089
Exocrine insufficiency†‡	0	2 (<1%)	0·40 (0·02–7·69)	0·25
Endocrine insufficiency§¶	4 (1%)	3 (1%)	1·70 (0·44–6·66)	0·49
Duration of hospital stay, nights	1 (1–2)	1 (1–2)	..	0·77‖

Data are n (%) or median (IQR) unless otherwise stated. Percentages might not sum to 100% because of rounding. *p values were based on Fisher's exact test. †Defined as a faecal pancreatic elastase-1 concentration of less than 200 µg/g 180 days after diagnosis of pancreatitis. ‡Assessed in 11 patients in the aggressive hydration group and in 21 patients in the control group. §Defined as a glycated haemoglobin concentration of more than 42 mmol/mol (6%) 180 days after diagnosis of pancreatitis. ¶Assessed in 14 patients in the aggressive hydration group and in 20 patients in the control group. ‖p value is based on Wilcoxon rank-sum test.

Table 2: **Primary and secondary outcomes in the modified intention-to-treat population**

differ between groups (table 1; appendix p 11). Diclofenac was the only rectal NSAID to be administered.

All ERCP characteristics were similar between the groups (appendix p 12). Suspicion of common bile duct stones was the predominant indication for ERCP (table 1). The use of pancreatic duct stents was limited and similar between both groups (table 1). The aggressive hydration group received a higher fluid volume in the first 24 h from the start of ERCP than the control group (3562 mL [IQR 3124–4101] *vs* 400 mL [0–1640], p<0·0001; appendix p 15).

A protocol violation occurred for 46 (6%) of 813 patients: nine patients had a previous sphincterotomy, 11 patients did not receive rectal NSAIDs, and hydration was not given according to the protocol in 29 patients (appendix p 10).

There were no reasons for terminating the trial after the interim analysis: post-ERCP pancreatitis occurred in 23 (11%) of the 212 patients in the control group, as compared with 16 (8%) of the 201 patients in the aggressive hydration group (p=0·40).

Post-ERCP pancreatitis occurred in 30 (8%) patients in the aggressive hydration group, as compared with 39 (9%) patients in the control group (relative risk [RR] 0·84, 95% CI 0·53–1·33; p=0·53; table 2). Two pancreatitis events had a late onset (>48 h after the ERCP procedure), one in each group. Moderate or severe post-ERCP pancreatitis based on Cotton criteria[30] was seen in 53 patients: 21 (5%) in the aggressive hydration group versus 32 (7%) in the control group (RR 0·72, 95% CI 0·42–1·23; p=0·23). Moderate or severe post-ERCP pancreatitis based on revised Atlanta criteria[31,32] was seen in 13 patients: three (1%) in the aggressive hydration group versus ten (2%) in the control group (RR 0·33, 95% CI 0·09–1·19; p=0·089). The median duration of hospital stay was 1 night (IQR 1–2; p=0·77) for both groups. Results did not change in the per-protocol analysis (appendix p 13).

No significant differences were observed between the groups with regard to hydration-related complications (RR 0·99, 95% CI 0·59–1·64; p=1·00), ERCP-related complications (0·90, 0·62–1·31; p=0·62), exocrine insufficiency (0·40, 0·02–7·69; p=0·25), endocrine insufficiency (1·70, 0·44–6·66; p=0·49), intensive care unit admission (0·37, 0·07–1·80; p=0·22), or 30-day mortality (0·95, 0·50–1·83; p=1·00; table 3; appendix pp 16–18). None of the deaths was related to aggressive hydration (appendix p 14).

In the predefined subgroup analyses for age, sex, and pancreatic duct stent placement, we observed no significant interaction term. Furthermore, no significant interaction terms were observed with respect to a history of pancreatitis, difficult cannulation of the common bile duct, cannulation of the pancreatic duct, pancreatic contrast injection, and trainee involvement (figure 2).

Discussion

This multicentre randomised study shows that the combination of aggressive periprocedural hydration with

	Aggressive hydration group (n=388)	Control group (n=425)	Relative risk (95% CI)	p value†
ERCP-related complications	16 (4%)	21 (5%)	0·90 (0·62–1·31)	0·62
Cholangitis	2 (1%)	6 (1%)	..	0·44
Bleeding	10 (3%)	12 (3%)	..	0·53
Perforation	5 (1%)	4 (1%)	..	0·49
Hydration-related complications	8 (2%)	9 (2%)	0·99 (0·59–1·64)	1·00
Pulmonary oedema	3 (1%)	5 (1%)	..	0·80
Peripheral oedema	6 (2%)	3 (1%)	..	0·22
Cardiac insufficiency	0	3 (1%)	..	0·25
Hypernatraemia	1 (<1%)	1 (<1%)	..	1·00
ICU admission after ERCP	2 (1%)	6 (1%)	0·37 (0·07–1·80)	0·22
30-day mortality	5 (1%)	6 (1%)	0·95 (0·50–1·83)	1·00
Mortality during 180-day follow-up	11 (3%)	12 (3%)	1·00 (0·45–2·25)	1·00
Cholangitis during 180-day follow-up	5 (1%)	8 (2%)	0·68 (0·23–2·08)	0·50

Data are n (%) or median (IQR). ERCP=endoscopic retrograde cholangiopancreatography. ICU=intensive care unit. *This table presents the most clinically relevant serious adverse events, intervention-related events, and events that appear in more than 1% in the study population. A complete overview of serious adverse events can be found in the appendix (pp 16–18). †p values were based on Fisher's exact test.

Table 3: **Serious adverse events***

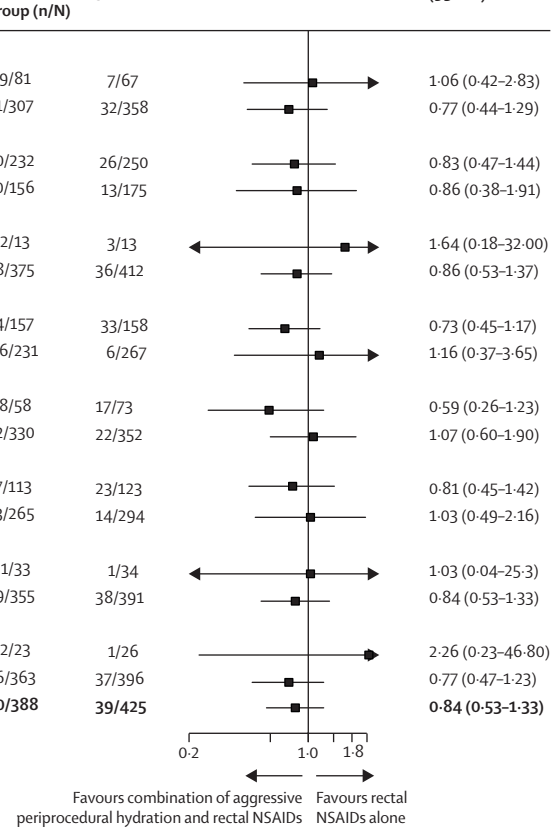

Figure 2: **Relative risk of post-ERCP pancreatitis in subgroups**
ERCP=endoscopic retrograde cholangiopancreatography. NSAIDs=non-steroidal anti-inflammatory drugs. *Difficult cannulation was defined as more than five attempts.

Ringer's lactate solution and rectal NSAIDs was not superior to rectal NSAIDs alone in reducing the incidence of post-ERCP pancreatitis in patients at moderate to high risk of developing this complication. Furthermore, combination therapy did not reduce the severity of post-ERCP pancreatitis.

ERCP is an indispensable tool to diagnose and treat pancreatobiliary tract disorders, but its inherent high risk of complications—in particular, post-ERCP pancreatitis—is concerning. The identification of patient-related and procedure-related risk factors have aided in the development of risk stratification strategies to curtail complications. Despite these measures, the incidence of post-ERCP pancreatitis remains substantial.[7] Rectal NSAIDs reduce the relative risk of developing post-ERCP pancreatitis by 60%.[5,40] The prevention of severe post-ERCP pancreatitis remains an unmet need, which is emphasised by the substantial pancreatitis incidence of 9% in our trial despite the use of rectal NSAIDs.

Aggressive periprocedural hydration has been suggested as a non-pharmacological measure to reduce the incidence of post-ERCP pancreatitis.[13,41] Aggressive hydration with Ringer's lactate solution was shown to reduce the incidence of post-ERCP pancreatitis as compared with standard hydration in patients who did not receive rectal NSAIDs in a meta-analysis (33 [6%] of 533 *vs* 65 [13%] of 514 patients; odds ratio 0·47, 95% CI 0·30–0·72; p=0·0006)[13] and a randomised study (four [3%] of 132 *vs* 15 [12%] of 129 patients; RR 0·26, 95% CI 0·08–0·76; p=0·008).[42] One large randomised study showed a reduction in the incidence of moderate to severe post-ERCP pancreatitis in patients receiving aggressive periprocedural hydration compared with standard periprocedural hydration (one [0·4%] of 255 *vs* five [2·0%] of 255 patients; p=0·04).[43] These data led to international treatment guidelines to recommend aggressive peri-procedural hydration to decrease the risk of post-ERCP pancreatitis.[7,8]

The effect of aggressive periprocedural hydration combined with rectal NSAIDs, as compared with rectal NSAIDs alone, was investigated in two smaller single-centre randomised studies with conflicting results.[25,26] In the first study, a four-armed trial that compared aggressive normal saline hydration (1 L in 2 h before ERCP and 2 L in 16 h thereafter) combined with rectal NSAIDs (n=101) and rectal NSAIDs alone (n=100), combination therapy resulted in a reduction of pancreatitis incidence from 11% to 0% (p=0·001).[25] In the second, two-arm trial, the authors found no difference in the occurrence of post-ERCP pancreatitis with aggressive periprocedural hydration with Ringer's lactate solution (a scheme similar to that used in this study) combined with rectal NSAIDs compared with rectal NSAIDs alone (one [0·9%] of 107 patients *vs* three [2·7%] of 112 patients; p=0·62).[26] Because both trials were done in an average-risk population with a low baseline risk of pancreatitis and small sample sizes, there was a substantial chance of false-positive and false-negative findings. Both trials were single-centre studies, which limits the generalisability of their results.

The current study has some limitations. First, treating staff and patients were not masked because there were major practical issues that precluded proper masking of the aggressive hydration group, such as differences in infusion volume and urine output. To address these issues, the primary outcome included objective criteria (ie, elevation of pancreatic enzymes) and was assessed by a masked adjudication committee. Second, concurrent use of rectal NSAIDs and pancreatic duct stenting is under discussion and merits further investigation. Therefore, we left pancreatic duct stent placement to the discretion of the treating endoscopist. However, few stents were used and stent use was evenly distributed between the groups.[44] Therefore, it is unlikely that pancreatic duct stent placement affected the outcomes of this trial. Third, there is no universal risk stratification system for post-ERCP pancreatitis. This potentially complicates our patient selection and sample size generation. However, the risk profile of our study population is similar to the populations of the studies that were the basis of our sample size calculation: patients with moderate to high risk who receive rectal NSAIDs.[34,35] The meta-analyses mention a post-ERCP pancreatitis incidence of 8·0% and 5·7%, which is similar to that in the control group (rectal NSAIDs alone) of our study (9%). These data are in line with those from a recent meta-analysis (mean 6·5%, range 3·2–10·1).[40]

The strengths of this study include its multicentre design and the fact that our treatment design follows international recommendations on the prevention of post-ERCP pancreatitis, which increases generalisability of the results. Inclusion of patients at moderate to high risk of post-ERCP pancreatitis led to a high pancreatitis incidence and a smaller chance of a type II error. Despite the complexity of the study and various hospital settings, the hydration protocol was closely followed in 784 (96%) of the 813 patients.

In conclusion, the combination of rectal NSAIDs and aggressive periprocedural hydration does not notably reduce the incidence of post-ERCP pancreatitis, as compared with rectal NSAIDs alone in patients with moderate to high risk of post-ERCP pancreatitis. Therefore, the burden of laborious and time-consuming hydration is not justified in patients already receiving rectal NSAIDs.

Contributors

EJMvG supervised the study. CJSW and XJNMS coordinated the trial during inclusion. RSW did the statistical analysis. CJSW checked the statistical analysis. CSW drafted the manuscript. XJNMS, EJMvG, JPHD, MJB, MGB, PF, JEvH, RCV, WK, and HCTvS co-authored the manuscript. All authors critically assessed the study design, included patients in the study, edited the manuscript, and read and approved the final manuscript. CJSW, XJNMS, and EJMvG accessed and verified the data. All authors vouch for the accuracy and completeness of the data and its analyses. The corresponding author has full access to all the data in the study and had final responsibility for the decision to submit for publication.

Declaration of interests

EJMvG reports grants from Mylan and Olympus and personal fees from MTW-Endoskopie, outside the submitted work. JPHD reports grants from Gilead, outside the submitted work. PF reports personal fees from Olympus, Cook Medical, and Ethicon Endosurgery, outside the submitted work. MJB reports personal fees from Boston Scientific, grants and personal fees from Cook Medical, and grants from Pentax Medical, 3M, InterScope, and Mylan, outside the submitted work. JEvH reports grants and personal fees from Cook Medical and personal fees from Boston Scientific and Medtronics, outside the submitted work. All other authors declare no competing interests.

Data sharing

Requests for data can be made to the corresponding author and will be discussed during a meeting of the Dutch Pancreatitis Study Group. Individual participant data that underlie the results reported in this Article, after de-identification, will be shared after approval by the Dutch Pancreatitis Study Group. Related documents, such as trial protocol and statistical analysis plan, will be available online immediately following publication without an end date to anyone who wishes to access the data.

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