PAINAP STUDY

Multicentre prospective audit on initial PAin management IN patients with Acute Pancreatitis: PAINAP study protocol

Study summary:

Acute pancreatitis (AP) is a common and serious inflammatory disease. The incidence of AP is 40-60 cases per 100 000 population per year. The estimated overall mortality rate is 5%, but rises to 20-50% in severe AP. Abdominal pain is the cardinal symptom in patients admitted with acute pancreatitis (AP). The approach to analgesia in current clinical practice is highly variable, largely undocumented and there is a lack of consensus from published guidelines. There is a notable dependence on opioids, increasing the risk of opioid dependence and other side effects. In addition, there is paucity of data from randomised trials comparing analgesics and evaluating their impact on short term outcomes such as severity of pancreatitis and post pancreatitis complications.

Rationale: The PAINAP Study aims to determine current analgesic practices and association between type of analgesic use and their impact on short term outcomes in patients with AP

Methods:

This is a multicenter prospective observational cohort study over a 3 month period followed by 1 month follow up.

Eligibility criteria:

Patients diagnosed with first attack of AP between 1st April 2022 to 30th June 2022

Data collection:

Data collection will be by Research Electronic Data Capture (REDCap). Each participating centre will appoint one dedicated Primary Investigator who will register their details on a secure online Programme REDCap. They will subsequently receive passwords for data input into REDCap, and access to the online case report form (CRF). No identifiable data will be uploaded to REDCap and each case will be allocated a secure and unique REDCap ID number.

Version 2. 23.02.2022. Caldecott Approval no: 9368

Background:

Abdominal pain is the cardinal symptom in almost all patients admitted with acute pancreatitis (AP).[1] It is a key to diagnosis of AP and has prognostic significance.[2] Central to the early management of AP is analgesia and fluid resuscitation, yet many guidelines remain non-committal on the topic of analgesia.[3-10] This reflects the ongoing debate about the optimal analgesic protocol for these patients, as evidence is scant. Pain is one of the most relevant dimensions of patient experience in AP. Its early and effective alleviation can improve quality of life, reduce patient anxiety, and reduce the risk of respiratory, thromboembolic and other complications. [1]

A previous systematic review which included studies published until 2012 assessing the safety and efficacy of parenteral analgesics in AP found no single favoured analgesic drug from 8 randomised control trials.[11] A further updated systematic review undertaken by our team included 12 RCT's, 542 patients and compared seven trial drugs (opiates, non-steroidal anti-inflammatories (NSAIDs), metamizole, local anaesthetic, epidural, paracetamol, and placebo) [12]. All studies and all modalities showed global improvement in pain severity (by visual analogue scales) from baseline to day 2. Epidural analgesia appears to provide the greatest improvement in pain scores within the first 24hrs, but at 48hrs was equivalent to opiates. Within the first 24hrs, NSAIDs provided equivalent pain-relief to opiates. There were several limitations to the review. The included studies were undertaken over a prolonged time span (1984-2020) during which time management of AP has evolved significantly. The included RCTs were likely to be underpowered to detect differences between arms, with the largest enrolling only 101 patients, as a result, all but 1 trial demonstrated moderate or high risk of bias. Division into opioid and non-opioid arms also combined various forms of distinct analgesic techniques and so specific-analgesic efficacy is difficult to draw from the current review. This review confirmed that opiate-based analgesia still forms the mainstay of management of pain in AP, and this is likely to continue in the absence of definitive evidence demonstrating viable non-opioid analgesic options. There are concerns about the significant side effects of opiate analgesia including ileus, slow transit and constipation, sphincter of Oddi of contraction.[13] A recent rodent study showed that opioids increased the severity of AP.[14] The over-prescription of opioids worldwide has been under increased international scrutiny highlighted by the opioid crisis in America.[15]

It is difficult to explain why there have been so few well-designed and powered clinical trials comparing analgesic protocols, for such significant symptoms in a common acute gastrointestinal

disease. The absence of such evidence explains the lack of consistent recommendations regarding analgesics for AP. In addition, there has been limited reporting of local and systemic complications after AP in relation to each analgesic class. Furthermore, none of the trials included quality of life parameters or patient reported outcome measures (PROMs), the importance of which is increasingly recognized.[16]

Evidence-based guidelines around the management of AP have not provided satisfactory guidance for addressing pain (Table 1). The 2004 UK working party, 2013 IAP/APA, and 2018 American Gastroenterological Association guidelines offered no recommendation on analgesic practices. The 2006 Japanese guidelines focused on Buprenorphine alone while their 2015 update refrained from endorsing a specific drug. National Institute of Clinical Excellence (NICE) guidelines in 2019 only offered analgesic advice in chronic pancreatitis. In 2019 the World Society for Emergency Surgery (WSES) acknowledged the paucity of RCT data, and promoted the use of current peri-operative analgesia guidelines. They did, however, advocate wider use of epidural and IV PCA. In the absence of specific guidance in AP, some recommendations have however been made for generalized abdominal pain in the emergency department setting such as supplementary Hyoscine butyl bromide for biliary colic-type pain, as well as intravenous paracetamol, metamizole and piritramide for more severe pain.

There is a significant knowledge gap and clinical need to determine optimal analgesia protocols for patients with acute pancreatitis. There is an urgent need to address this issue, and the aims of this particular study are:

1. To document current analgesic practice for patients with AP in the UK
2. To examine the relationship between different analgesics and local and systemic complications of AP.

Methods:

Study Design

Multicenter prospective observational cohort study.

Study Period and Data collection

Patients admitted with acute pancreatitis between 1st April **2022 to 30th June 2022** will be recruited.

Participants

Inclusion criteria

1. Patients aged 18 and above
2. First presentation with acute pancreatitis of any etiology

Exclusion criteria

- Recurrent acute pancreatitis
- Chronic pancreatitis
- Post ERCP pancreatitis (will have been given prophylactic NSAIDs)
- Those on regular opioids, trycyclic antodipressaants and gabapentinoids for other painful conditions, including chronic pain (for other reasons)
- Pregnancy

Data collection

This study will require the collection of patient and center demographics, Details of the exact variables to be collected (CRF) are listed in **Appendix 1.**

Statistical analysis

The proposed study is observational in methodology. We have previously undertaken multicenter observational studies in the UK and have established links with >50 hospitals specializing in management of patients with acute pancreatitis[17]. We anticipate a minimum of 20 patients recruited to the study from each hospital allowing us to recruit 1000 patients in the 3 month study period with acute pancreatitis and this will allow us to explore the primary outcomes of the study and draw conclusions.

Categorical data will be presented as frequency and percentage. Continuous data will be presented either as mean and standard deviation or as median and interquartile range depending on the distribution of the data. Student's t, Mann Whitney U, Chi-square, or Fisher's exact tests will be used as appropriate. The relationship between analgesic modalities and short term outcomes (within the 1 month follow-up period) will then be assessed using univariable analysis and any clinically relevant outcomes will be analysed using a multivariable Cox regression model using a forward stepwise entry method.

Authorship:

Each participating center will be eligible for three authorship positions and all participating authors will be acknowledged. Any publication, presentation or abstract on collected data will acknowledge all authors. Each center remains the possessor of their data, and additional reports on data collected will only be conducted with written permission.

DATA PROTECTION AND MANAGEMENT

Legal Compliance

All investigators and study site staff will comply with the requirements of the Data Protection Act 2018 and the General Data Protection Regulations (GDPR) with regards to the collection, storage, processing and disclosure of personal information and will uphold the Act's core principles.

Data extraction and de-identification process

Data will be de-identified by collaborators in the individual hospitals. The principal investigator at each site will have overall responsibility for de-identification and for ensuring the data remains confidential. All identifying factors will be removed, and patients will be allocated unique identification codes. Only de-identified data with the appropriate unique identification codes will be submitted through REDCap. No data containing any personal identifiers will be transferred. Sites will not hold personal identifiers in the study database.

Each registered center will appoint a Principal Investigator (PI) who will register their details on a secure online programme REDCap. No identifiable data will be uploaded to REDCap and each case will be allocated a unique and secure REDCap ID number. The local PI will be responsible for data collection and input from the individual centers.

Data processing for analysis

De-identified data will be stored on secure computers at an NHS site in the form of a password protected database. Data will be processed and analysed by the main research team at the Freeman Hospital. All collaborators will only have access to their own data and not access to data from other centers. Only the Chief Investigator's team will have access to the full dataset.

Long Term Data Storage

De-identified data will be stored in accordance with GDPR on a secure password-protected database and for 5 years after study findings are published in order to ensure that findings are verifiable.

Caldecott Approval

Each PI at recruiting centers has the responsibility to obtain local Caldecott/audit approval prior to data input. The study received Caldecott approval at Newcastle Hospitals NHS foundation Trust (ID 9368)

Indemnity

NHS indemnity applies to the design/ management/conduct of the study for UK recruitment centers

Steering committee

Lead CI:

Sanjay Pandanaboyana, Consultant HPB and Transplant Surgeon, Freeman Hospital, Newcastle, UK

Committee members

Manu Nayar, Consultant Gastroenterologist, Freeman Hospital, Newcastle, UK

Gabriele Capurso, San Raffaele Scientific Institute Milan, Italy

Enrique De-Madaria, Gastroenterology department, Alicante, Spain

Anita Balakrishnan, HPB Unit, Addenbrooke's Hospital, Cambridge, UK

Prof Ajith Siriwardena, HPB Unit, Manchester Royal Infirmary, Manchester, UK

Prof Asbjørn Drewes, Department of Gastroenterology, Aalborg University Hospital, Denmark

Prof John Windsor, University of Auckland, Auckland, New Zealand

References:

1. Johnson CD, Besselink MG, Carter R. Acute pancreatitis. *BMJ* 2014; **349**: g4859.
2. Goodchild G, Chouhan M, Johnson GJ. Practical guide to the management of acute pancreatitis. *Frontline Gastroenterol* 2019; **10**: 292–9.
3. Banks PA, Bollen TL, Dervenis C, *et al.* Classification of acute pancreatitis - 2012: Revision of the Atlanta classification and definitions by international consensus. *Gut* 2013; **62**: 102–11.
4. 2Phillip V, Schuster T, Hagemes F, *et al.* Time period from onset of pain to hospital admission and patients' awareness in acute pancreatitis. *Pancreas* 2013; **42**: 647–54.
5. NICE. Pancreatitis. 2019; 1–21.
6. Crockett SD, Wani S, Gardner TB, *et al.* American Gastroenterological Association Institute Guideline on Initial Management of Acute Pancreatitis. *Gastroenterology* 2018; **154**: 1096–101.
7. Yokoe M, Takada T, Mayumi T, *et al.* Japanese guidelines for the management of acute pancreatitis: Japanese Guidelines 2015. *J Hepatobiliary Pancreat Sci* 2015; **22**: 405–32.
8. Working Group IAP/APA Acute Pancreatitis Guidelines. IAP/APA evidence-based guidelines for the management of acute pancreatitis. *Pancreatology* 2013; **13**: e1-15.
9. Tenner S, Baillie J, Dewitt J, Vege SS. American college of gastroenterology guideline: Management of acute pancreatitis. *Am J Gastroenterol* 2013; **108**: 1400–15.
10. Working Party of the British Society of Gastroenterology, Association of Surgeons of Great Britain and Ireland, Pancreatic Society of Great Britain and Ireland, Association of Upper GI Surgeons of Great Britain and Ireland. UK guidelines for the management of acute pancreatitis. *Gut* 2005; **54 Suppl 3**: iii1-9.
11. Meng W, Yuan J, Zhang C et al (2013) Parenteral analgesics for pain relief in acute pancreatitis: a systematic review. Pancreatology 13:201–206.
12. Thavanesan N, White S, Lee S, Ratnayake B, Oppong KW, Nayar MK, Sharp L, Drewes AM, Capurso G, De-Madaria E, Siriwardena AK, Windsor JA, Pandanaboyana S. Analgesia in the Initial Management of Acute Pancreatitis: A Systematic Review and Meta-Analysis of Randomised Controlled Trials. World J Surg. 2022 Jan 7. doi: 10.1007/s00268-021-06420-w.
13. Farmer AD, Drewes AM, Chiarioni G et al (2019) Pathophysiology and management of opioid-induced constipation: European expert consensus statement. United Eur Gastroenterol J 7:7–20.
14. Barlass U, Dutta R, Cheema H et al (2018) Morphine worsens the severity and prevents pancreatic regeneration in mouse models of acute pancreatitis. Gut 67:719–727.
15. Volkow ND, Blanco C (2021) The changing opioid crisis: development, challenges and opportunities. Mol Psychiatry26:218–233.
16. De-Madaria E, Sánchez-Marin C, Carrillo I, *et al.* Design and validation of a patient-reported outcome measure scale in acute pancreatitis: The PAN-PROMISE study. *Gut* 2021; **70**: 139–47.
17. Pandanaboyana S, Moir J, Leeds JS, Oppong K, Kanwar A, Marzouk A. COVID PAN collaborative

group. SARS-CoV-2 infection in acute pancreatitis increases disease severity and 30-day mortality: COVID PAN collaborative study. Gut. 2021 Jun;70(6):1061-1069

Table 1 Summary of current guidelines for management of pain in acute pancreatitis

Guideline	Year	Jurisdiction	Recommendations	Reference
TPS	2020	Taiwan	- Recommend opiate use in AP	Liao 2020
WSES	2019	International	- Acknowledged paucity of EBM for analgesia and referred to available current guidance on peri-operative analgesia - Avoid NSAIDs (AKI risk) - Recommend epidural either as an alternative to or in combination with IV analgesia (especially in severe cases needing prolonged opiates) - Advocate PCA integration with all strategies - Hydromorphone (Dilaudid) recommended preferentially over Morphine/Fentanyl in non-intubated patients	Leppaniemi 2019
American Gastroenterology Association	2018	America	- No specific recommendations on pain in AP	Crockett 2018
Canadian Clinical Practice guidelines	2016	Canada	- Advise multimodal protocol of NSAIDs, opiates and Paracetamol	Greenberg 2016
JPN Guidelines	2006/2015	Japan	- Acknowledged crucial role of analgesia in AP - Recommended Buprenorphine over Procaine and Pethidine in 2006 guidelines - Refrain from recommending specific agents in 2015 update	Takeda 2006 Yokoe 2015
IAP/APA	2013	International	- No specific recommendations on pain in AP - Highlighted role of analgesia in Abdominal Compartment Syndrome	Working Group IAP/APA Acute Pancreatitis Guidelines 2013
ACG	2013	North America	- No specific recommendations on analgesia in AP	Tenner 2013
BSG/UK Working Party	2005	United Kingdom	- No specific recommendations on analgesia in AP	UK Working Party 2005

TPS – Taiwan Pancreas Society, WSES – World Society of Emergency Surgery, AGA – American Gastroenterological Association, JPN – Japan, IAP – International Association of Pancreatology, APA – American Pancreatic Association, ACG – American College of Gastroenterology, BSG – British Society of Gastroenterologists, EBM – Evidenced Based Medicine

Appendix -1
Case report Form

Recruiting center details:		**Yes**	**No**
1	In the UK		
	Overseas _____ Location		
2	Type of hospital University Hospital/ District general hospital		
3	Dedicated AP or Benign pancreas MDT		
4	Institution offers AP trials		
5	Roughly how many AP patients does the institution annually?		
	0-25		
	26-50		
	51-75		
	76-100		
	>100		

Inclusion Criteria:		**Yes**	**No***
-	Patient aged ≥ 18 years old		
-	First presentation of acute pancreatitis		

If No, how many previous admissions with AP before the current presentation: _____
**If any inclusion criteria are ticked no then the patient is not eligible for the study*.

Demographic data:

6. Age (years) at presentation

7. Sex: Female / Male

8. Date of admission:

9. Ethnicity (please tick as applicable):

	White
	Asian / Asian British
	Black, African, Caribbean / Black British
	Other ethnic group (please state):

10. Charlson comorbidity score at admission (Link on REDCAP)

11. High BMI: Yes / No (WHO classification on REDCAP)
If yes, please state: ____

12. Current smoker: Yes / No
If yes, please state pack years: ____

13. ECOG Performance status 1 / 2 / 3 / 4:

14. On regular pain medication: Yes / No : If yes then patient should be excluded from the study
If Yes, please tick as applicable

	Type of analgesia	Reason for regular analgesia
	Simple analgesics- Paracetamol / NSAIDS	
	Weak opioids- Codeine / Dihydrocodeine / Tramadol	
	Strong opioids - Morphine / Diamorphine / Oxycodone / Hydromorphone / Buprenorphine / Fentanyl / Tapentadol	
	Adjuvant analgesics - Tricyclics (Amitriptyline) / Gabapentin / SNRI (Venlafaxine,Duloxetine) / Pregabalin	
	Acupuncture	
	TENS (transcutaneous electrical nerve stimulation)	
	Other (Pls document)	

Acute Pancreatitis details and outcomes:

15. Aetiology of pancreatitis (please tick as applicable):

	Gallstones
	Alcohol
	Hypertriglyceridemia
	Others (please state):

16. Predicted severity of pancreatitis within first 24h from admission:

	Mild AP
	Moderately severe AP (Definitions on REDCAP)
	Severe AP (persistent single or multiple organ failure, > 48 hours)

System used to determine predicted severity (tick)

	Modified Glasgow
	Ransons
	CT severity score

	BISAP
	APACHE II
	Other: (please state)

17. Organ dysfunction/failure: Yes / No
If Yes (please tick as applicable)

	Systemic complications (define complications)	**Duration (days)**
	Respiratory failure	
	Renal insufficiency	
	Cardiac insufficiency	
	Hepatic insufficiency	
	Multi-organ failure (name organs)	
	Sepsis	
	Others (please state):	

18. Dialysis required: Yes / No
19. Ventilation required: Yes / No
20. Inotropes required: Yes / No

21. **Local complication**: Yes / No (Revised Atlanta Critera for complications on REDCAP)
If Yes (please tick as applicable)

	Local complication	**Day of diagnosis (after admission)**	**Duration (days)**
	Pancreatic necrosis - extent on CT (< 30%, 30-50%, >50%)		
	Walled off necrosis		
	Infected walled off necrosis		
	Acute necrotic collection		
	Infected acute necrotic collection		
	Acute pancreatic fluid collection		
	Infected pancreatic fluid collection		
	Pseudocyst		
	Portal vein / splenic vein thrombosis		
	GI Bleeding		
	Pancreatic ascites		
	Enteric fistula		
	Pleuro-peritoneal fistula		

	Pleural effusion		
	Others (please state):		

22. **Interventions** needed: Yes / No
If Yes (please tick as applicable)

	Intervention	No of days after admission	Duration (days)	Frequency	Complication
	ERCP / Endoscopic sphincterotomy		N/A		
	Percutaneous catheter drainage				
	EUS stent				
	Minimally Invasive Necrosectomy		N/A		
	Open Necrosectomy		N/A		

23. Actual severity of pancreatitis (Revised Atlanta Criteria[38]) at the time of discharge

	Mild AP
	Moderately severe AP
	Severe AP (persistent single or multiple organ failure, > 48 hours)

Feeding:

24. Patient kept NBM on admission? Yes / No
If Yes, please state the duration ___ days

25. Did patient require nutrition support? Yes / No.
If Yes, please give the details here:

	Route of feeding	Duration (days)	On which post admission day was it started?
	NG feeding		
	NJ feeding		
	Partial PN		
	Total PN		

Pain details:

26. Duration of pain prior to admission (please tick as applicable)

	< 12 hours
	12-24 hours
	> 24 hours

28. Severity of pain on admission (Visual Analogue scale): 1-10 (If available)

29. Number of days with AP pain in hospital: ___ days

30. Were there other causes of pain?
If yes, please tick as applicable

	CBD stone
	Cholangitis
	Duodenal obstruction
	Others (please state):

Analgesia details:

31. Pain relief prescribed and taken **prior to admission** for AP? Yes / No
If yes, please tick as applicable

	Type of analgesia	Frequency
	Simple analgesics: Paracetamol	
	Simple analgesics: NSAIDs	
	Weak opioids: Codeine / dihydrocodeine / tramadol (if cocodomol pls tick both Paracetamol and codeine)	
	Strong opioids: Morphine / Diamorphine / Oxycodone / Hydromorphone / Buprenorphine / Fentanyl / Tapentadol	
	Adjuvant analgesics: Tricyclics (amitriptyline) / Gabapentin / SNRI (venlafaxine, duloxetine) / antispasmodics	
	Others (please state):	

32. **1st analgesic administered** on admission (AOA)
(please tick as applicable)

	Type of analgesia	Dosage	Duration of analgesic taken	Route (oral/IV/IM)
	Simple analgesics: Paracetamol			
	Simple analgesics: NSAIDs			
	Weak opioids: Codeine / dihydrocodeine / tramadol			
	Strong opioids: Morphine / Diamorphine / Oxycodone / Hydromorphone / Buprenorphine / Fentanyl / Tapentadol			
	Adjuvant analgesics: Tricyclics (amitriptyline) / Gabapentin / SNRI (venlafaxine, duloxetine) / antispasmodics			
	Others (please state):			

33. **2nd analgesic** administered on admission (AOA)

	Type of analgesia	Dosage	Duration	Route (oral/IV/IM)
	Simple analgesics: Paracetamol			
	Simple analgesics: NSAIDs			
	Weak opioids: Codeine / dihydrocodeine / tramadol			
	Strong opioids: Morphine / Diamorphine / Oxycodone / Hydromorphone / Buprenorphine / Fentanyl / Tapentadol			
	Adjuvant analgesics: Tricyclics (amitriptyline) / Gabapentin / SNRI (venlafaxine, duloxetine) / antispasmodics			
	Others (please state):			

34. **3rd analgesic** on administered on admission (AOA)

	Type of analgesia	Dosage	Duration	Route (oral/IV/IM)
	Simple analgesics: Paracetamol			
	Simple analgesics: NSAIDs			
	Weak opioids: Codeine / dihydrocodeine / tramadol			
	Strong opioids: Morphine / Diamorphine / Oxycodone / Hydromorphone / Buprenorphine / Fentanyl / Tapentadol			
	Adjuvant analgesics: Tricyclics (amitriptyline) / Gabapentin / SNRI (venlafaxine, duloxetine) / antispasmodics			
	Others (please state):			

35. Total number of days of opioid use during hospital stay: ____ days

36. **Epidural analgesia**? Yes / No
If yes, day of admission when epidural analgesia was administered ____

37. **Acupuncture**? Yes / No
If yes, please state details including frequency and duration: ____

38. Discharge analgesia prescription (please tick as applicable)

	Type of analgesia	Duration and dosage
	Paracetamol	
	NSAIDs	
	Codeine/Dihydrocodeine/Tramadol	
	Morphine/diamorphine/oxycodone/ hydromorphone/buprenorphine/ fentanyl/tapentadol	

	Tricyclics (amitriptyline) / gabapentin/ SNRI (venlafaxine, duloxitine)/ antispasmodics	
	Others (Pls state)	

39. Did the patient develop any potential side effects from the analgesic used during the inpatient stay?

Opioids: Drowsiness/constipation/nausea, vomiting/other _____
NSAIDS: GI bleeding/Other_____
Tricyclics: constipation/drowsiness/insomnia/Other _____
Gabapentin: drowsiness/Nausea, vomiting other_____

40. Length of hospital stay: ____ days

41. HDU/ITU admission: Yes / No

42. Duration of HDU/ITU admission: ___ days

43. In hospital mortality: Yes / No
If Yes, please state the date ____

44. 30 day mortality yes/ no
If yes pls state the date

45. Readmission with pancreatitis: Yes / No
If Yes, how many days post discharge? ___ days

Readmission with a complication of pancreatitis: Yes/No

46. If readmitted, was analgesic medication on regular prescription at readmission? Yes / No
If Yes, please tick as appropriate

	Type of analgesia	Dosage	Duration
	Paracetamol/NSAIDS		
	Codeine/Dihydrocodeine/Tramadol		
	Morphine/diamorphine/oxycodone/ hydromorphone/buprenorphine/ fentanyl/tapentadol		
	Tricyclics (amitriptyline) / gabapentin/ SNRI (venlafaxine, duloxitine)/ antispasmodics		
	Others (Pls state)		