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Endoscopic vs. Surgical Interventions for Painful Chronic Pancreatitis: What is Needed for Future Clinical Trials

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The treatment of painful chronic pancreatitis remains controversial. The available evidence from two randomized controlled trials favor surgical intervention, whereas an endotherapy-first approach is widely practiced. Chronic pancreatitis is complex disease with different genetic and environmental factors, different pain mechanisms and different treatment modalities including medical, endoscopic, and surgical. The widely practiced step-up approach remains unproven. In designing future clinical trials there are some important pre-requisites including a more comprehensive pain assessment tool, the optimization of conservative medical treatment and interventional techniques. Consideration should be given to the need of a control arm and the optimal timing of intervention. Pending better designed studies, the practical way forward is to identify subgroups of patients who clearly warrant endotherapy or surgery first, and to design the future clinical trials for the remainder.

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INTRODUCTION

Chronic pancreatitis is an enigmatic, intractable, and painful condition that results in reduced survival and considerable suffering.[1] Significant disagreement exists between surgeons and endoscopists about the best treatment of patients with pain secondary to chronic pancreatitis. This disagreement appears to derive from entrenched practice and the lack of high-quality evidence. It is not helped by contradictory guideline recommendations[2–4] and opinion,[5,6] ostensibly drawn from the same evidence base and used to justify the highly variable practice.

Although considerable progress has been made in understanding the complex basis of pain in chronic pancreatitis[1] more evidence is required to define the respective indications for and efficacy of endotherapy and surgery. Before more evidence is sought there are some important issues to be attended to. The aim of this article is to determine what is needed in designing and conducting future clinical trials.

CURRENT EVIDENCE

There are only two randomized controlled clinical trials comparing surgery and endotherapy in the treatment of pain secondary to chronic pancreatitis.

The first was published by Dite *et al.* from the Czech Republic in 2003.[7] The quality of this study of 72 patients has been criticized for the risk of selection bias (with lack of random sequence generation and allocation concealment), performance and detection bias (with the lack of blinding) and attrition bias (with incomplete outcome data).[8] The indication for intervention in this study was pain, although the nature and severity of it was not clearly stated. Patients required evidence of "obstructive" chronic pancreatitis with a dilated duct with or without pancreatic duct stones. Any previous intervention(s) excluded patients from this trial.

The second was published by Cahen *et al.* from the Netherlands in 2007 (NEJM)[9] and followed up in 2011.[10] The quality of this study of 39 patients was better with a low risk for bias.[8] The indication for intervention was for "severe recurrent pain not sufficiently relieved with non-narcotic analgesics or an opioid requirement". Obstruction of the main pancreatic duct was required with evidence of dilatation of ≥ 5 mm, a stricture, and/or stones. In this study patients were excluded if they had an inflammatory mass, defined as a pancreatic head diameter of >4 cm. This study was terminated early by the safety committee because of the highly significant difference in outcomes for pain relief.

Both trials are small, but they are consistent in strongly favouring surgical treatment over endotherapy. This has been reinforced by two meta-analyses.[8,11] Numerous benefits for surgical treatment were noted in both studies, and these included more effective and durable pain relief, higher technical success rate, fewer number of total procedures, higher quality of life, no increase in hospital stay, morbidity or mortality, no difference in pancreatic function, and no recurrent obstruction. It was also noted that almost half of those patients (47%) having endotherapy required subsequent surgery, and the delayed surgery was less effective.

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CONTRADICTORY GUIDELINE RECOMMENDATIONS

Despite this evidence for the superiority of surgery over endotherapy current guidelines do not make recommendations that consistently reflect this. For example, the German S-3 guidelines[2] state that "as the most effective long-term form of pain therapy for chronic pancreatitis, surgery should be performed" (level of evidence grade 1a, recommendation grade A, consensus). In contrast, the ESGE guidelines[3] bypass the available level 1 evidence and state that "for treating patients with uncomplicated painful chronic pancreatitis and radio-opaque stones ≥ 5 mm obstructing the main pancreatic duct, the ESGE recommends extracorporeal shock wave lithotripsy as a first step, immediately followed by endoscopic extraction of stone fragments (evidence level 1+, recommendation grade B)". These contradictions have led to confusion allowing historic practice to persist. However, there does appear to be general consensus, primarily amongst endoscopists, that some patients warrant endotherapy first whereas others warrant surgery first. But making that decision is difficult as the evidence base is wanting.

The challenge of painful chronic pancreatitis

The challenge of chronic pancreatitis is due to different etiologies, characterized by different pathophysiologies that are expected to respond differently to interventions. We know that pancreatic morphology does not reflect the severity of pain or the likely response to treatment and that there are many other factors that contribute to differences in painful chronic pancreatitis including genetic and environmental factors.[12] Further there are different mechanisms and characteristics of pain, extent of central sensitization, psychosocial consequences, co-morbidities (due to the disease and secondary to previous treatments) and the degree of exocrine and endocrine insufficiency.[1] Also important is the stage and rate of chronic pancreatitis progression.[12] It is therefore fair to say that patient subgroups exist within the spectrum of chronic pancreatitis, for which different treatments and treatment combinations might be required. And it is probable that endoscopists and surgeons treat a different spectrum of patients with chronic pancreatitis. The heterogeneity of chronic pancreatitis means that more research is required to improve the selection of patients for future trials by defining more homogenous subgroups with similar indications for intervention.

COMPLICATIONS AND COST OF INTERVENTION

Data on the morbidity and mortality of endotherapy vs. surgical treatment of painful chronic pancreatitis are not available from the randomized controlled trials, as they are not sufficiently powered for these end points. In longer term follow-up of the second trial[10] morbidity occurred in more than twice as many patients having endotherapy compared with surgery.[11] A population based study from the United States indicates that the overall inpatient mortality is lower in patients undergoing CP related surgery compared with those not having surgery (which included those having endotherapy) (6.6 vs. 8.7%, $P<0.0001$).[13] The complication rate of surgery was three times that of endotherapy (29.8 vs. 10%) in this study. Better prospective and long-term data is required to answer the question about the morbidity of surgery versus endotherapy.

The only available cost-effectiveness data, derived from the Cahen trial,[10] indicated by sensitivity analyses (varied for mortality and resource use), that surgical drainage was more cost effective for all scenarios.[14] Even though surgery is more invasive, surgeons find that patients readily trade the opportunity to lose long-term intractable pain for short-term postoperative pain. In this sense the price of efficacy is invasiveness, but the question of patient's preferences has not been systematically studied.

PRE-REQUISITES FOR FUTURE CLINICAL TRIALS

The assessment of pain is critical because pain is both the primary indication for intervention and the primary end point for trials. A significant barrier to better future clinical trials are the inadequate tools used to assess pain.[15] Most intervention studies in chronic pancreatitis have used simple uni- or bi-dimensional tools for pain assessment.[15] The AGA has recommended that pain is assessed in multiple domains to which others can be added.[16] There are no chronic pancreatitis-specific and validated pain assessment tools that capture all the important dimensions of pain. This will be required for future trials.

Another pre-requisite to future trials is the need to optimize and standardize the medical management of chronic pancreatitis. This is likely to differ within subgroups of patients, meaning that different drugs and combinations of drugs might be indicated. The classes of drugs include simple, non-steroidal and narcotic analgesics, membrane stabilizing and centrally acting drugs, antioxidants, and pancreatic enzymes. The WHO recommends a step-up approach to analgesics but this has not been formally evaluated in chronic pancreatitis. Further and within conservative treatment, protocols for EUS guided coeliac plexus neurolysis, thoracic epidural, patient controlled intravenous administration of analgesia, and spinal cord stimulation also need to be optimized and standardized. Where these techniques fit within the treatment algorithm has yet to be defined.

A third pre-requisite to clinical trials is also the need to optimize and standardize the intervention techniques. The techniques used in the two historic trials were not optimized, at least by today's standards. Contrary to usual practice, surgical resection was offered in 80% of the patients in the surgical arm of the Dite study.[7] And patients in the surgical arm of the Cahen study[9] were under-treated in regards the head of the pancreas because patients with an inflammatory mass were excluded from treatment altogether. Endotherapy did not include ESWL in the Dite study[7] and the protocol for ESWL was not optimized in the Cahen study.[9] Further repeat stenting for pain recurrence was not part of the endotherapy protocol in the Dite study.[7] Further research is required to answer a number of questions in regards to endoscopic stenting.[5] Many randomized controlled trials have been performed to determine optimal surgical treatment,[6] although these trials are still beset by problems with patient selection, timing of intervention and assessment of pain. Total pancreatectomy and auto islet transplantation is a promising surgical option that has yet to be widely adopted, and for which further evidence is required

regarding its role in relation to other surgical treatments. Before conducting any future trials it is imperative that intervention protocols and techniques are optimized and standardized through appropriately designed studies.

STEP-UP APPROACH REMAINS UNPROVEN

The step-up approach has been widely adopted, where the failure of medical treatment is followed by endotherapy, and patients are only offered surgery when this fails. One of the problems with this approach is that failure has not been soundly defined and the approach itself has not been tested in chronic pancreatitis. The Dutch Pancreatitis Study Group has argued against the "step-up approach" on the basis that opioids, the mainstay of conservative treatment, do not alter disease progression and that reliance on them delays intervention.[17] Furthermore opioids have their own problems including tolerance, hyperalgesia, dependence, adverse reactions, diminution of quality of life, and a negative impact on social functioning. The Dutch group argued on the basis of the available evidence from the randomized controlled trials that because surgery is more effective than endotherapy the latter should be relegated to second-line intervention.[17]

But an endotherapy-first approach is widely practiced and this can be traced back to the historic trials and beyond. The Dite study[7] concluded that surgery was superior to endotherapy but stated that the latter could be "offered as first line treatment, with surgery being performed in case of failure or recurrence" which contradicts the findings of the trial itself. The Cahen study[9] concluded more circumspectly that there was a need for "future studies … aimed at answering the question" about whether endotherapy could be a "valuable alternative for less extensive disease". Of note, the editorial written in response to this second trial ignored the findings and stated that endotherapy was a "reasonable treatment option on the basis of patient preference, and because it was simpler, had fewer complications, and because patients had a faster return to normal activity".[18] This systematic bias favouring endotherapy-first in the face of contrary evidence persists in the latest recommendations, where surgery is indicated for patients that "fail to respond to medical and/or endoscopic therapy".[1] The recommendations go on to state that endotherapy is still used as a first line therapy in many centers, because it is "less expensive, less invasive and more readily available", but the evidence for this is lacking.

The Dutch Pancreatitis Study Group has embarked on a trial to compare an optimized step-up approach and early surgery in relation to pain control, pancreatic function, and quality of life.[19] Patients are being recruited to this open label randomized controlled multicentre superiority trial. It is designed to recruit patients early and before narcotic dependence occurs. The interventions are well defined and the definitions for failure of conservative and endoscopic treatment are tight and appropriate. Unfortunately the assessment of pain, both at the time of recruitment and as the primary end point, is limited, as the Izbicki score covers only four aspects of pain.[15] The assessment of quality of life in this trial does not use the recently published PANQOLI, the first tool designed and validated from chronic pancreatitis.[20] Although this is the best designed trial to date, further trials will be required.

CONSIDERATIONS FOR FUTURE CLINICAL TRIALS

In addition to the introduction of an improved tool for assessing pain and quality of life in chronic pancreatitis, there are other considerations for future clinical trials. The differences in the spectrum of chronic pancreatitis in different countries must be accounted for. Future trials should account for differences in aetiology, genetic factors, environmental factors, and pain mechanisms as these will have a bearing on the response to intervention. For instance tropical pancreatitis appears to respond better to endotherapy than alcohol related pancreatitis.

The practical reality is that equipoise remains regarding endotherapy vs. surgery, despite the historic trials. As discussed, future clinical trials will need to define subgroups of patients with painful chronic pancreatitis, optimal medical treatments, morbidity and mortality of interventions, the optimal timing and protocols, and techniques for interventions.

A sham control arm has not been included in any intervention studies of chronic pancreatitis to date,[4] and this is an important consideration when the end point, such as pain, is assessed subjectively. A recent meta-analysis of randomized, sham controlled trials of surgery and invasive procedures examined effectiveness and the relative contribution of the placebo response. Sufficient data was obtained from 38 studies including 2,902 patients.[21] Reassuringly there was a positive treatment effect over sham. The non-specific placebo effect was a striking 65% for all invasive procedures, and highest when treating pain and obesity. The placebo effect for open surgery was low at 21% compared with endoscopy which was higher at 73%. This may reflect the approach taken to patient consent and the different patient expectations regarding the efficacy of endotherapy and surgery, where the latter is often considered a last resort option.

The timing of intervention is another consideration. In both historic trials patients generally had advanced chronic pancreatitis, as evidenced by narcotic dependence, frequency of exocrine insufficiency and the presence of stones and strictures.[18] The longer term outcomes of the Cahen study indicated that when surgery was delayed by failed repeated attempts at endotherapy it was less effective in relieving pain.[9] There is only one randomized controlled trial examining early surgery.[22] When compared with conservative treatment, patients having early surgery had "significantly better pain relief and better preserved endocrine/exocrine pancreatic function". Early intervention may prevent the altered neural pathways and remodeling that occurs with chronic pain. Further evidence in favor of early surgery comes from a systematic review of seven studies that showed it was associated with a reduced risk of pancreatic insufficiency and lower re-intervention rates.[23] The clinical outcome in relation to the timing of surgery has also evaluated by the Dutch Pancreatitis Study Group.[24] They found by multivariate analysis that the factors that were significantly associated with pain relief after surgery were no preoperative opioid use ($P = 0.006$), pain duration of < 3 years ($P = 0.03$) and ≤ 5 prior endoscopic procedures ($P = 0.04$).

Current recommendations indicate that the timing of surgical intervention is an important factor in clinical outcomes, and that the development of central pain (sensitization) is a concern when surgical intervention is delayed.[1] Persistence with

conservative medical and endoscopic treatment raises ethical issues if surgery is superior, as undue delay prolongs suffering and results in worse outcomes. In summary, the emerging evidence from both experimental and clinical studies suggest that surgical intervention is indicated within 3 years of pain onset, less than five prior endoscopic procedures, and before opioid dependence and central sensitization.

Towards a tailored approach to intervention and future clinical trials

There is no question that further evidence is required to guide the treatment of patients with painful chronic pancreatitis. Future clinical trials need to take into account the pre-requisites and considerations discussed above.

Before new evidence becomes available from well designed prospective clinical trials, the question is how should we treat these patients? The choice is either the "step-up approach" or a "tailored approach". The limitations of the former have been discussed, and the latter has more appeal because it is possible to identify subgroups of patients for whom an endotherapy-first or a surgery-first approach appears reasonable.

The subgroup of patients for an endotherapy-first would have had pain for <3 years, not be narcotic dependent, have a single stricture and/or limited stone load in the head or neck of the pancreas and a main pancreatic duct of <5 mm in diameter. In the absence of evidence to the contrary, it would seem reasonable to offer endotherapy with EWSL to these patients. The subgroup of patients for a surgery-first approach would have one of more of the following: an inflammatory head or tail mass (especially if there is concern about a concomitant cancer), a dilated main pancreatic ≥ 5 mm, multiple strictures and a significant stone load including possible stones in the body and tail of the pancreas. Future trials in these subgroups of patients should be used to optimize these endotherapy-first and surgery-first approaches.

Between these two subgroups of patients there is a wide gray zone where a clear case cannot be made for an endotherapy-first or surgery-first approach. It is these patients that need to be recruited to future clinical trials comparing the efficacy of endotherapy and surgery. Such clinical trials should be adequately powered to answer questions about relative effectiveness, timing of intervention, morbidity, and mortality.

CONFLICT OF INTEREST

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1. Anderson MA, Akshintala V, Albers KM *et al.* Mechanism, assessment and management of pain in chronic pancreatitis:recommendations of a multidisciplinary study group. *Pancreatology* 2016; **16**: 83–94.
2. Hoffmeister A, Mayerle J, Beglinger C *et al.* English language version of the S3-consensus guidelines on chronic pancreatitis: definition, aetiology, diagnostic examinations, medical, endoscopic and surgical management of chronic pancreatitis. *Z Gastroenterol* 2015; **53**: 1447–1495.
3. Dumonceau JM, Delhaye M, Tringali A *et al.* Endoscopic treatment of chronic pancreatitis: European Society of Gastrointestinal Endoscopy (ESGE) Clinical Guideline. *Endoscopy* 2012; **44**: 784–800.
4. Löhr M, Besselink M, Haas S *et al.* UEG Evidence-based guidelines for the diagnosis and therapy of chronic pancreatitis: Harmonising pancreatitis across Europe (HaPanEU). *United European Gastroenterol J* 2016 (in press).
5. Talukdar R, Nageshwar Reddy D. Endoscopic therapy for chronic pancreatitis. *Curr Opin Gastroenterol* 2014; **30**: 484–489.
6. Hartmann D, Friess H. Surgical approaches to chronic pancreatitis. *Gastroenterol Res Pract* 2015; **2015**: 503109.
7. Dite P, Ruzicka M, Zboril V, Novotny I. A prospective, randomised trial comparing endoscopic and surgical therapy for chronic pancreatitis. *Endoscopy* 2003; **35**: 553–558.
8. Ahmed AU, Pahlpalatz JM, Nealon WH *et al.* Endoscopic or surgical intervention for painful obstructive chronic pancreatitis. *Cochrane Database Syst Rev* 2015; **19**: CD007884.
9. Cahen DL, Gou DJ, Nio Y *et al.* Endoscopic versus surgical drainage of the pancreatic duct in chronic pancreatitis. *N Engl J Med* 2007; **356**: 676–684.
10. Cahen DL, Gouma DJ, Laramee P *et al.* Long-term outcomes of endoscopic vs surgical drainage of the pancreatic duct in patient with chronic pancreatitis. *Gastroenterology* 2011; **141**: 1690–1695.
11. Jawad ZA, Kyriakides C, Pai M *et al.* Surgery remains the best option for the management of pain in patients with chronic pancreatitis: a systemic review and meta-analysis. *Asian J Surg* 2016 (e-pub ahead of print January 6 2016); pii: S1015-9584(15)00153-0; doi: 10.1016/j.asjsur.2015.09.005.
12. Whitcomb DC, Frulloni L, Garg P *et al.* Chronic pancreatitis: an international draft consensus proposal for a new mechanistic definition. *Pancreatology* 2016; **16**: 218–224.
13. Bliss LA, Yang CJ, Eskander MF *et al.* Surgical management of chronic pancreatitis: current utilization in the United States. *HPB (Oxford)* 2015; **17**: 804–810.
14. Laramée P, Wonderling D, Cahen DL *et al.* Trial-based cost-effectiveness analysis comparing surgical and endoscopic drainage in patients with obstructive chronic pancreatitis. *BMJ Open* 2013; **3**: e003676.
15. Teo K, Johnson MH, Truter S *et al.* Pain assessment in chronic pancreatitis: a comparative review of methods. *Pancreatology* 2016; **16**: 931–939.
16. Warshaw AL, Banks PA, Fernandez-Del Castillo C. AGA technical review: treatment of pain in chronic pancreatitis. *Gastroenterology* 1998; **115**: 765–776.
17. Issa Y, van Santvoort HC, van Goor H *et al.* Surgical and endoscopic treatment of pain in chronic pancreatitis: a multidisciplinary update. *Dig Surg* 2013; **30**: 35–50.
18. Elta GH. Is there a role for the endoscopic treatment of pain from chronic pancreatitis? *N Engl J Med* 2007; **356**: 727–729.
19. Ahmed AU, Issa Y, Bruno MJ *et al.* Early surgery versus optimal current step-up practice for chronic pancreatitis (ESCAPE): design and rationale of a randomized trial. *BMC Gastroenterol* 2013; **13**: 49.
20. Wassef W, DeWitt J, McGreevy K *et al.* Pancreatitis quality of life instrument: a psychometric evaluation. *Am J Gastroenterol* 2016; **111**: 1177–1186.
21. Jonas WB, Crawford C, Colloca L *et al.* To what extent are surgery and invasive procedures effective beyond a placebo response? A systematic review with meta-analysis of randomised, sham controlled trials. *BMJ Open* 2015; **5**: e009655.
22. Nealon WH, Thompson JC. Progressive loss of pancreatic function in chronic pancreatitis is delayed by main pancreatic duct decompression. A longitudinal prospective analysis of the modified Puestow procedure. *Ann Surg* 1993; **217**: 458–466.
23. Yang CJ, Bliss LA, Schapira EF *et al.* Systematic review of early surgery for chronic pancreatitis: impact on pain, pancreatic function, and re-intervention. *J Gastrointest Surg* 2014; **18**: 1863–1869.
24. Ahmed Ali U, Nieuwenhuijs VB, van Eijck CH *et al.* Clinical outcome in relation to timing of surgery in chronic pancreatitis: a nomogram to predict pain relief. *Arch Surg* 2012; **147**: 925–932.