Review

Effect on diagnostic efficiency of analgesia for undifferentiated abdominal pain

S. H. Thomas[1,2,3] and W. Silen[1]

[1]Department of Surgery and [2]Division of Emergency Medicine, Harvard Medical School and [3]Department of Emergency Services, Massachusetts General Hospital, Boston, Massachusetts, USA

Correspondence to: Dr S. H. Thomas, Department of Emergency Services, Massachusetts General Hospital, Room 115 Clinics Building, Boston, Massachusetts 0-2114-2696, USA (e-mail: Thomas.Stephen@mgh.harvard.edu)

Background: The question of whether it is safe to provide analgesia for patients with undifferentiated acute abdominal pain is marked by longstanding controversy over the possible masking of physical findings. The goal of this review is to assess the pertinent studies.

Method: A Medline search was performed in April 2002, using the terms 'analgesia', 'abdominal pain', 'acute abdomen' and 'morphine'. Other articles were identified using the bibliographies of papers found through Medline. All articles reporting clinical trials of analgesia and its effects on diagnosis or physical examination were reviewed.

Results: A total of eight trials (one reported only as an abstract) were identified. Because of significant disparity in trial design, no formal analysis such as meta-analysis was performed. However, detailed review of the trials revealed a striking consistency in results. In no study was there an association between analgesia and diagnostic impairment or dangerous masking of the findings of physical examination.

Conclusion: The literature addressing early pain relief for abdominal pain is characterized by weaknesses, but there is a common theme suggesting that analgesia is safe. Pending further research, which should address some of the shortcomings of extant studies, a practice of judicious provision of analgesia appears safe, reasonable and in the best interests of patients in pain.

Paper accepted 17 August 2002

Published online 29 November 2002 in Wiley InterScience (www.bjs.co.uk). **DOI:** 10.1002/bjs.4009

Introduction and method

One criticism of modern healthcare is that patients with painful conditions frequently receive insufficient analgesia. The explanations for this are myriad, but in at least one group of patients, those with undifferentiated abdominal pain, the withholding of analgesia has theoretical foundation in a desire to avoid masking of diagnostic findings. These concerns date as far back as 1921, when Sir Zachary Cope's textbook[1] on abdominal pain cautioned against catastrophic diagnostic delays attributable to obscuration of findings at physical examination.

In fact, concerns about administration of analgesia are sufficiently deep that they have been shown to persist[2,3] despite counterarguments reported in clinical investigations[4–7], reviews[8–13], and in the most recent editions[14] of Cope's text itself. Given the importance of the issue and the fact that a literature search yielded little detailed information on the subject, this review was prepared. The goal was to summarize the relevant literature, providing an overview of each study, to create a resource for clinicians facing the common problem of timing of analgesia for patients with undiagnosed abdominal pain.

A Medline search was performed in April 2002, using the terms 'analgesia', 'abdominal pain', 'acute abdomen' and 'morphine'. Other articles were identified using the bibliographies of papers found through Medline. All articles reporting clinical trials of analgesia and its effects on diagnosis or the physical examination were reviewed. No formal statistical analyses were performed on the articles identified. The primary reason for this was the heterogeneity of the studies. Fortunately, there were sufficiently few studies that each paper could be reviewed descriptively at a level of detail limited only by the reporting methods of the study itself.

Results

Eight studies were identified as candidates for this review. These eight papers represented the only studies which could be found that assessed the effects of administration of analgesics on the physical examination, diagnostic endpoints, or both. The level of evidence of the studies can be characterized as level 1: positive results from a randomized clinical trial (RCT); or level 2: negative results from an RCT. However, attempts simply to assign each study a numerical level are fraught with difficulty. Some studies reported both 'positive' results (i.e. statistically significant *P* values between analgesia and control groups) and 'negative' results (i.e. non-significant intergroup analysis) depending on the endpoint assessed.

For the most part, the studies enrolled only adults, or in some cases, children of teenage years. One study focused on the issue of pain relief in younger paediatric patients. In all studies except one, randomization to the experimental (analgesia) group was associated with a statistically significant improvement in pain. Across most studies, the method of assessment of pain relief was the 10 cm visual analogue scale.

None of the studies identified significant side-effects of analgesia, as perceived by either patients or physicians. There were no instances raising concern about respiratory or cardiovascular ill-effects related to analgesia use.

Discussion

Clinical lore addressing evaluation and management of patients with undiagnosed abdominal pain has long included a maxim emphasizing the dangers of early analgesia. This long-held surgical tenet has recently come under increased scrutiny. Modern healthcare providers have noted that the initial concerns about clouding of physical examination findings, voiced by Sir Zachary Cope in the early twentieth century, were based on contemporary practices of intramuscular administration of up to 30 mg of morphine[15]. Such a practice arguably has limited relevance to modern-day titration of analgesia. An additional factor underpinning questioning of prohibition against analgesia is that there has not been any scientific study supporting a conclusion that reasonably dosed analgesia is dangerous. In fact, the extant literature appears to support early provision of analgesia. Furthermore, recent editions[14] of Cope's text lament the practice of analgesia denial, and a brief evidenced-based review[8] of studies addressing pain relief and the physical examination concluded that early analgesia is effective and does not cloud diagnostic findings.

There is strong indication that publication of studies of analgesia for abdominal pain has not resulted in a reversal in clinical practice. Specifically, surveys have revealed that 38–67 per cent of general surgeons in both the UK[16] and the USA[3] believe that analgesia risks masking of diagnostic findings. Another survey[17] found that 80 per cent of US emergency medicine respondents withheld opioid analgesia pending surgical assessment. Perhaps the results from the surveys of emergency physicians and surgeons indicate that the studies of analgesia for undiagnosed pain have not been read. On the other hand, perhaps the studies do not make a cast-iron case for early pain relief. To address this possibility, the remainder of this paper will consider each relevant study.

The first trial addressing the administration of opioids in abdominal pain was conducted in the UK, on a study group of 100 adults, and reported in 1986 by Zoltie and Cust[18]. This study was important in that it was the first to address the question of analgesia for undifferentiated abdominal pain in a scientific manner. The investigators used a route of medication administration (sublingual) unreported elsewhere in the abdominal pain analgesia literature. The sublingual route may or may not have been problematic, but there was a finding that control group pain relief was as high, or higher, than that of patients receiving opioid (buprenorphine). While the authors found no evidence for obscuration of physical findings, the fact that there were equal levels of pain relief in control and study groups is a serious limitation. In summarizing this study's place in the literature, it may be best characterized as an important first step towards critical evaluation of provision of analgesia to patients with abdominal pain. Because of its design limitations, however, it is doubtful whether any firm conclusions can be drawn from the study.

The next trial, also conducted in the UK, was published in 1992 by Attard *et al.*[7]. This study was characterized by an improved design, and is arguably the first work to provide good evidence supporting the practice of early pain relief. The authors assessed 100 adults admitted to the hospital for abdominal pain of less than 48 h duration. Patients were randomized to receive either intramuscular papaveretum (a mixture of opium alkaloids) or saline; the study medication was titrated to analgesic response. In contradistinction to the Zoltie and Cust series[18], study patients receiving opioid had better pain relief than those receiving placebo. In this study, there were more untoward outcome events (nine) in the placebo group than in the opioid group (two). Unfortunately, the critical endpoint of opioid-related changes in abdominal examination was not addressed adequately because the examinations conducted before and after administration of medication were performed by different physicians. It is well known that there is significant variation between

different physicians' abdominal evaluations, even when assessments are conducted simultaneously[19,20]. Therefore, the most important information yielded by this study was that early analgesia is not associated with detrimental outcomes. Of note, as all patients were admitted to hospital, the results obtained should not necessarily be generalized to outpatients.

Four years after the study by Attard *et al.*[7], Pace and Burke[6], two US emergency physicians, published the next clinical trial of analgesia for 71 adults with undifferentiated abdominal pain. This study had a slightly different focus, in that its primary endpoint was the accuracy of diagnostic lists generated before and after morphine analgesia. The examining physicians were allowed to list up to four possible diagnoses, both before and after morphine (or placebo) administration. In addition to listing differential diagnoses, examiners were asked to indicate planned disposition, for example operation, discharge home. The study had as a strength the fact that a single examiner completed the physical examination forms before and after administration of medication. There was, however, a weakness: the only physical examination variable assessed was the presence of 'peritoneal signs', as defined by the examiner. These investigators reported no between-group differences in any endpoints. Overall, the allowance for four diagnostic entities in the evaluations done before and after administration of medication could be characterized as liberal, and the evaluation of a single, subjective examination endpoint gave limited information about the link between analgesia and obscuration of physical findings. However, in providing evidence that early pain relief was not associated with detrimental effects on diagnostic accuracy, Pace and Burke added important information to the analgesia debate.

The Pace and Burke study was important, but its limited assessment of physical examination variables left room for further evaluation of this critical endpoint. Indeed, an argument can be made that the effects of opioids on the physical examination itself, while ultimately of lesser relevance than clinical outcome data, represent the most realistic endpoint for investigators. This is because untoward outcomes will occur with sufficient rarity that a large number of patients must be enrolled to identify a significant impact on morbidity associated with opioid administration. In fact, the required number of patients to assess this 'clinical' endpoint, estimated by experts[20] to be at least 1500, far exceeds the cumulative enrolment of all extant abdominal analgesia studies.

The important distinction between physical examination and clinical outcome endpoints was emphasized in 1997 by LoVecchio *et al.*[4] This paper, reporting the effects of administering either 5 or 10 mg of morphine to adult patients with acute abdominal pain, is often referenced to support early pain relief, but its results could arguably be used to support the other side of the analgesia debate. The reason for this is that both morphine groups manifested significant changes in the physical examination after administration of the study medication. Half of the patients receiving morphine, compared with only one of 16 control patients, had postmedication alterations to tenderness and localization. There was no further analysis of the examination changes or whether they represented 'improvement' or 'masking' of examination findings. As all patients had surgical evaluation and formulation of definitive plans before enrolment in the study, the finding that clinical endpoints were not altered by morphine administration is not surprising. LoVecchio *et al.*, in their paper's cogent discussion, recognized these limitations and concluded that further work was needed to answer the question of analgesia safety.

Garyfallou *et al.*[5] published an abstract, also in 1997, that outlined their study of provision of fentanyl analgesia (1·5 μg/kg) to patients (apparently adults, but not specified) with undiagnosed pain. The preliminary report described findings that early pain relief was not associated with deleterious outcomes. However, the fact that the abstract is of inherently limited scope has the result that many questions are left unanswered. For example, the doses of analgesia seemed small and pain relief achieved with fentanyl appeared to be of borderline clinical significance. Additionally, the exclusion of patients with severe pain poses questions about the ability to generalize the study to those patients for whom pain relief may be the most important. Overall, this study is interesting in its abstract form, but it cannot be reviewed comprehensively until a full-length manuscript is made available. Indeed, the impact of this study is somewhat attenuated by the fact that such a paper has not appeared in the 5 years since publication of the abstract.

In 1999, Vermeulen *et al.*[9] reported an investigation that receives relatively little attention, but which randomized more patients – 340 patients aged 16 years or older than any other study. The researchers, from a Swiss emergency department, aimed to determine whether morphine analgesia affected evaluation of adults with right lower quadrant pain. Although the study's negative results focused primarily on an endpoint, sensitivity and specificity of abdominal ultrasonography, with marginal relevance to the analgesia debate, the authors also reported no between-group difference with respect to appropriateness of operative decision making. No specific physical examination changes were assessed. In one respect,

this study has a somewhat tangential relationship to the analgesia debate. However, the negative results from this relatively large cohort add weight to the argument that provision of analgesia is not dangerous.

In another study focusing on patients with suspected appendicitis, conducted in Singapore and published in 2000, Mahadevan and Graff[21] focused on analgesia-specific effects on the abdominal examination in patients aged 12 years and older. The authors correctly noted that no previous study addressed physical examination changes in detail, and designed their study endpoints accordingly. Patients were randomized to receive either placebo or tramadol analgesia, and the study aimed to determine whether the two groups had different rates of normalization of several variables of physical examination. The authors found no adverse effects associated with analgesic administration, and there were no untoward patient outcomes. The study suffers from a few problems that limit its generalization. Most notably, the eligible population were patients with right lower quadrant pain and a clinical presentation of suspected appendicitis; this design impairs extrapolation of the results to patients with more diffuse, or differently located pain. Additionally, the use of tramadol as an analgesic limits the ability directly to compare findings from this study with those of other studies utilizing pure opioids. Despite this, the paper does an admirable job of focusing on the effect of analgesia on certain findings, and its negative results are generally supportive of arguments in favour of early pain relief.

The most recent work addressing the issue of analgesia for undifferentiated abdominal pain was reported Kim *et al.*[22]. These paediatric emergency physicians assessed the effects of morphine on the physical examination in one of the most methodologically sound of the studies reviewed here. Paediatric patients (aged 5–18 years) were randomized to receive morphine or saline, and examining paediatric emergency physicians and surgeons indicated areas of tenderness before and after administration of medication. Areas of rebound or percussion pain were also noted. The authors reported that the finding of effects of analgesia on the physical examination depended on which group of examiners, paediatric emergency physicians or surgeons, was assessed. Analgesia administration was associated with a decrease in number of areas of tenderness as evaluated by paediatric emergency physicians, but surgeons perceived no such difference in the examination. Furthermore, all morphine-group patients requiring laparotomy had persistent tenderness to palpation and percussion after analgesia. In summary, although the authors noted that their sample size was insufficient to address the question of diagnostic accuracy, the results of this study bolster the contention that early analgesia will not result in masking of abdominal findings.

Overall, the available literature is not without limitations. None of the studies reviewed has sufficient enrolment to address, with any finality, the issue of outcomes. Additionally, some[4,21,22] have found that morphine-associated changes in some examination variables do occur. The report of Kim *et al.*[22] that paediatric emergency physicians', but not surgeons', examination findings were altered by analgesia lends credence to the suggestion that analgesia be deferred until after physical examination by the surgical consultant.

In practice, experts have identified problems with an approach of deferring analgesia until a responsible surgeon can see the patient[11,18]. The issues vary with the setting. In the typical university hospital surgical service, many layers of house staff evaluate a patient before a consultant sees the patient. In community hospitals, the surgical chain of command is shorter, but evaluation by decision-making surgeons can be delayed if they are dealing with other pressing clinical matters. In either case, increasingly overburdened healthcare systems are placing growing demands on physicians and surgeons responsible for evaluation of the large number[23] of patients with undifferentiated abdominal pain. Given the contemporary emphasis on minimizing patient suffering, the frequency with which patients with such pain are seen in the emergency department, and the fact that the overall preponderance of the evidence is heavily in favour of the safety of early analgesia, a conclusion that early analgesia is safe is both humane and scientifically appropriate.

References

1 Cope Z. *The Early Diagnosis of the Acute Abdomen*. Oxford University Press: New York, 1921.
2 Thomas SH, Shackelford J, Borczuk P, Godley CD, Conn AKT. Omission of analgesia in emergency department patients with suspected appendicitis. *Acad Emerg Med* 1997; **4**: 424 (Abstract).
3 Graber MA, Ely JW, Clarke S, Kurtz S, Weir R. Informed consent and general surgeons' attitudes toward the use of pain medication in the acute abdomen. *Am J Emerg Med* 1999; **17**: 113–116.
4 LoVecchio F, Oster N, Sturmann K, Nelson LS, Flasher S. The use of analgesics in patients with acute abdominal pain. *J Emerg Med* 1997; **15**: 775–779.
5 Garyfallou GT, Grillo A, O'Connor RE, Fulda GJ, Levine BJ. A controlled trial of fentanyl analgesia in emergency department patients with abdominal pain: can

treatment obscure the diagnosis? *Acad Emerg Med* 1997; **4**: 424 (Abstract).
6 Pace S, Burke TF. Intravenous morphine for early pain relief in patients with acute abdominal pain. *Acad Emerg Med* 1996; **3**: 1086–1092.
7 Attard AR, Corlett MJ, Kidner NJ, Leslie AP, Fraser IA. Safety of early pain relief for acute abdominal pain. *BMJ* 1992; **305**: 554–556.
8 Mackway-Jones K, Harrison M. Towards evidence based emergency medicine: analgesia and assessment of abdominal pain. *J Accid Emerg Med* 2000; **17**: 128–129.
9 Vermeulen B, Morabia A, Unger PF, Goehring C, Grangier C, Skljarov I *et al*. Acute appendicitis: influence of early pain relief on the accuracy of clinical and US findings in the decision to operate – a randomized trial. *Radiology* 1999; **210**: 639–643.
10 Brewster GS, Herbert ME, Hoffman JR. Medical myth: analgesia should not be given to patients with an acute abdomen because it obscures the diagnosis. *West J Med* 2000; **172**: 209–210.
11 Paris PM. No pain, no pain. *Am J Emerg Med* 1989; **7**: 660–661.
12 Letter. Analgesia in the acute abdomen. *BMJ* 1979; **2**: 1093.
13 Yealy DM, O'Toole KS. Challenging dogma – analgesia in acute abdominal pain. *Acad Emerg Med* 1996; **3**: 1081–1082.
14 Silen W. *Cope's Early Diagnosis of the Acute Abdomen* (20th edn). Oxford University Press: New York, 2000.
15 Hughes TJ. Opiates in acute abdominal pain. *BMJ* 1979; **ii**: 1145 (Letter).
16 Tait IS, Ionescu MV, Cuschieri A. Do patients with acute abdominal pain wait unduly long for analgesia? *J R Coll Surg Edinb* 1999; **44**: 181–184.
17 Wolfe JM, Lien D, Lenkoski C, Smithline HA. Analgesic administration to patients with acute abdomens: a survey of emergency physicians. *Acad Emerg Med* 1998; **5**: 528 (Abstract).
18 Zoltie N, Cust MP. Analgesia in the acute abdomen. *Ann R Coll Surg* 1986; **68**: 209–210.
19 Graham NG, de Dombal FT, Goligher JC. Reliability of physical signs in patients with severe attacks of ulcerative colitis. *BMJ* 1971; **ii**: 746–748.
20 Lee JS, Stiell IG, Wells GA, Elder BR, Vandemheen K, Shapiro S. Adverse outcomes and opioid analgesic administration in acute abdominal pain. *Acad Emerg Med* 2000; **7**: 980–987.
21 Mahadevan M, Graff L. Prospective, randomized study of analgesic use for ED patients with right lower quadrant abdominal pain. *Am J Emerg Med* 2000; **18**: 753–756.
22 Kim MK, Strait RT, Sato TT, Hennes HM. A randomized clinical trial of analgesia in children with acute abdominal pain. *Acad Emerg Med* 2002; **9**: 281–287.
23 Stanniland JR, Ditchburn J, de Dombal FT. Clinical presentation of acute abdomen: study of 600 patients. *BMJ* 1972; **3**: 393–398.