Emergency department management of undifferentiated abdominal pain with hyoscine butylbromide and paracetamol: a randomised control trial

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ABSTRACT

Objective To compare the effectiveness of paracetamol, hyoscine butylbromide and the combination of paracetamol plus hyoscine butylbromide (paracetamol + hyoscine butylbromide) in the management of patients with acute undifferentiated abdominal pain attending the emergency department (ED).

Setting A large teaching hospital with an annual ED census of 120 000 adult patients.

Methods A prospective, randomised placebo controlled trial of a convenience sample of patients attending the ED. The trial compared the analgesic effect of intravenous hyoscine butylbromide, oral paracetamol and the combination of both drugs using a Visual Analogue Scale pain scoring tool. Rescue analgesia was administered when pain was inadequately controlled by trial medication.

Results 132 patients were recruited to the trial. At 30 min, all analgesic combinations produced significant similar levels of pain relief. At 60 min after administration of the trial medication, mean reductions in pain scores for patients receiving paracetamol only were significantly greater than those receiving paracetamol + hyoscine butylbromide (ANCOVA model, p=0.0180). No relationship was seen between treatment arm and the need for rescue analgesia (χ^2, p value=0.846).

Conclusion The trial data suggest that oral paracetamol is at least as effective as intravenous hyoscine butylbromide and a combination of both drugs in the management of acute undifferentiated abdominal pain presenting to the ED. Based on these results and factors such as cost and tolerability, we recommend single agent paracetamol as the agent of choice for the management of acute mild to moderate undifferentiated abdominal pain.

Trial registration number MHRA Ref: 19717/0226/001-0001; European Clinical Trials Database. EUDRAct No: 2006-005395-40.

INTRODUCTION

Acute abdominal pain is one of the principal reasons for attendance to emergency departments (ED) worldwide and accounts for between 10% and 42% of all presenting complaints.[1 2] Common causes of acute abdominal pain include appendicitis (19%), cholecystitis (3%), renal tract disease (6%), gynaecological problems (5%), small bowel obstruction (3%), perforated peptic ulcer (3%), pancreatitis (2%), diverticular disease (1.4%) and gastro-oesophageal reflux/gastritis.[3] However, 40–50% of acute abdominal presentations are classified as acute non-specific abdominal pain.[4] Acute non-specific abdominal pain is defined as abdominal pain of <7 days' duration with no diagnosis after clinical assessment and baseline investigations.[1 2] However, in the immediate acute setting, prior to baseline investigations and follow-up, these patients present with undifferentiated abdominal pain.

Ten English language clinical trials and their critical appraisal support administering analgesia to patients with acute abdominal pain, demonstrating that it is safe and does not compromise diagnostic evaluation.[5 6] The analgesic ladder promotes the use of simple analgesics, such as paracetamol, prior to the use of opiates, for patients in mild or moderate pain. A large number of medications are routinely used to manage mild to moderate abdominal pain in the ED, including paracetamol, paracetamol/codeine combinations, non-steroidal anti-inflammatory medication and antispasmodic/smooth muscle relaxants (including hyoscine butylbromide). There is a paucity of evidence relating to the most effective pain relief for patients with non-specific or undifferentiated abdominal pain in the ED setting.

Paracetamol is available as oral, rectal and injectable formulations. A large systematic review, including 40 trials,[7] examining the analgesic efficacy of a single dose of oral paracetamol compared with placebo for moderate to severe pain concludes that oral paracetamol is an effective analgesic with a low incidence of adverse effects.

Hyoscine butylbromide contains the active ingredient hyoscine-N-butylbromide and is described as an antispasmodic. Hyoscine relaxes the smooth muscle of abdominal and pelvic viscera via the intramural parasympathetic ganglia blockade. Due to hyoscine's non-selective blockade of acetylcholine receptors, hyoscine butylbromide is contraindicated in patients with myasthenia gravis, megacolon, narrow angle glaucoma, tachycardia, prostatic hypertrophy, mechanical stenoses of the gastrointestinal tract and paralytic ileus.

Two double blind, randomised, controlled trials[8 9] have been undertaken in the outpatient setting which compare the efficacy of hyoscine butylbromide with paracetamol in the management of recurrent crampy abdominal pain. There are no studies to date that are set in the ED and examine the efficacy of hyoscine butylbromide and paracetamol in patients with acute undifferentiated abdominal pain. This trial is therefore of importance as it aims to provide the first evidence base to

guide physicians in their choice of analgesia for this common presenting complaint in the ED.

MATERIALS AND METHODS

Study design

This was a prospective, single centre, double blinded, placebo controlled, randomised, controlled trial of a convenience sample of consenting eligible patients presenting to the ED with acute undifferentiated abdominal pain.

Setting

The trial ran for 12 months from July 2007 to July 2008 in the ED of the Royal London Hospital, UK. This is a large urban teaching hospital with an annual ED census of 120 000 adult patients. The study was approved by the local research ethics committee and the MHRA (MHRA Ref: 19717/0226/001-0001; EUDRAct No: 2006-005395-40). Informed consent was obtained from all patients prior to enrolment.

Participants

Figure 1 describes the recruitment process for patients. We recruited a convenience sample of patients presenting to the ED with acute, moderately severe undifferentiated abdominal pain. Patients with mild abdominal pain without a known cause or with a dipstick positive urinary tract infection were routinely referred to the walk-in centre for GP care by senior ED staff

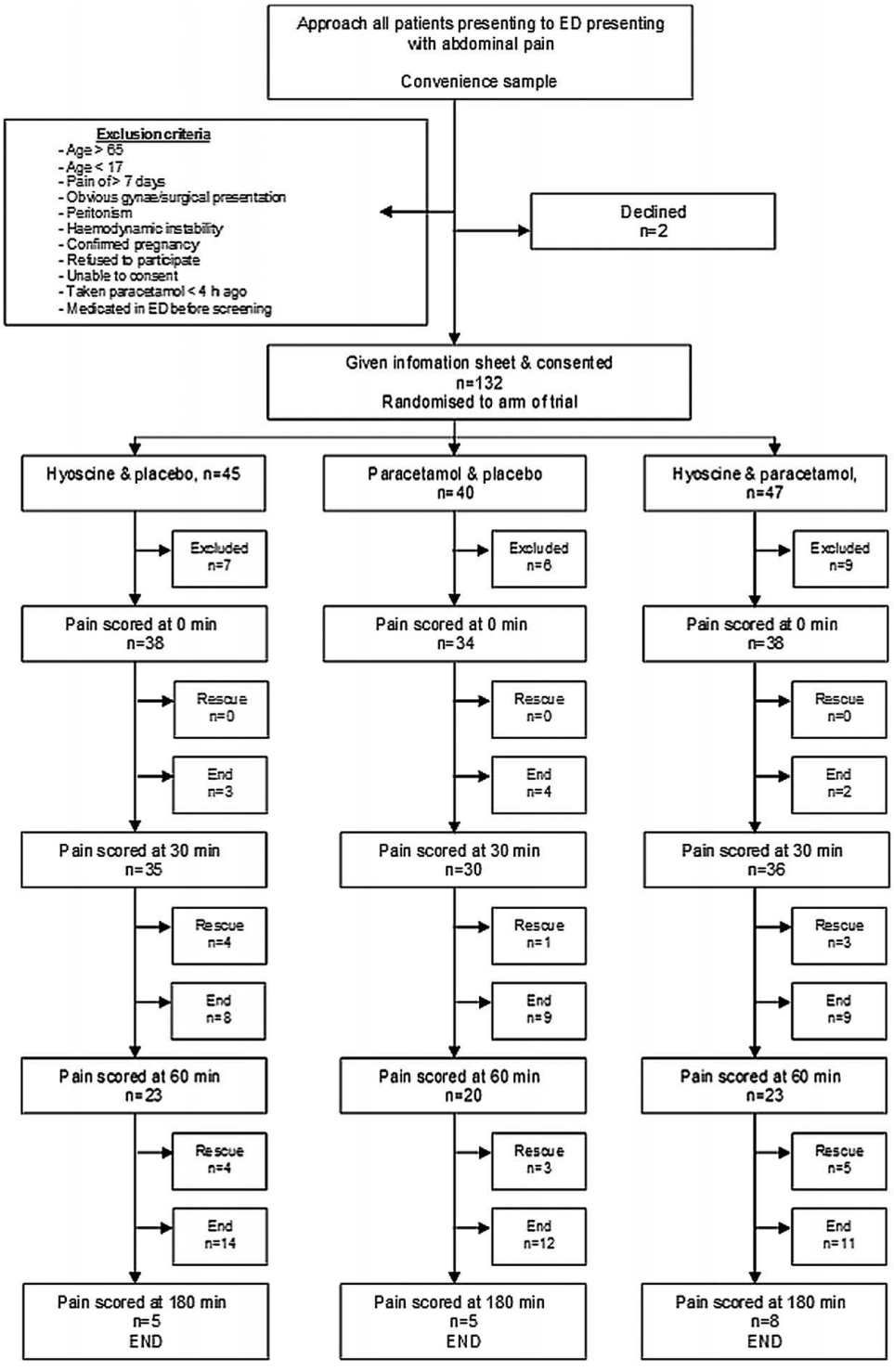


Figure 1 Consort diagram. ED, Emergency department.

member triage and were therefore not included in the study. All patients recruited to the trial were therefore deemed in need of care in the ED. Patients ineligible for inclusion in the trial only because they had a Visual Analogue Scale (VAS) pain scores >7 were offered titrated intravenous opiate analgesia and if they declined this they were then offered the chance to participate in the study. Patients were managed in the majors area of the ED and received routine clinical care: insertion of an intravenous cannula for removal of blood for investigations, fluids (at the discretion of the treating doctor) and analgesia. Regular observations were recorded on the trial data collection sheet and in the patient's ED notes. Standardised documentation, including a copy of the consent form, was inserted into the patient's notes to indicate inclusion in the trial.

Drug administration

Each patient was assigned to one of the three arms of the trial and received a 2 ml intravenous injection of hyoscine butylbromide (20 mg) and two oral tablets of 500 mg of paracetamol, 2 ml of intravenous normal saline (placebo) and two oral tablets of 500 mg of paracetamol or 2 ml of intravenous injection of hyoscine butylbromide and two oral tablets of a placebo (no active ingredient).

Prior to commencement, the arms of the trial were numbered 1–3 and a computerised randomisation programme was used to assign these trial arm codes to consecutive numbers. Sealed envelope randomisation was used and trial packages were labelled with consecutive numbers only. The packs were used in this order by members of the ED team recruiting the patients.

The patient was not informed of the medication they received. For safety reasons, the member of staff administering the medication was not blinded to the medication given but they were confined to the role of medication administration only and were not involved in any further care of the trial participant.

If a patient's pain was not adequately controlled by trial medication, 'rescue' analgesia was administered. The choice of preparation was at the discretion of the treating physician but could not contain paracetamol or hyoscine butylbromide. The timing, type and dose of rescue analgesia were recorded on the data collection sheet. All patients were followed-up by telephone at 1 and 12 weeks to assess longer term side effects and to record subsequent diagnosis.

Outcomes of interest

The primary outcome of the trial was the change in VAS score after administration of analgesia. Secondary outcomes were the need for rescue analgesia, the occurrence of side effects and complications.

Data collection

A trial specific data collection sheet was used to record four time specific pain scores (prior to administering analgesia and then at 30, 60 and 180 min intervals), routine observations, adverse reactions and any rescue analgesia administered. The 10 cm (horizontal) VAS was chosen as our tool for the assessment of subjective pain levels as this has been well validated in the ED for a variety of clinical presentations.[8 10–13] Studies have concluded that a 13 mm difference on the VAS represents the smallest measurable change in pain severity that is clinically significant.[10 11–15] Despite recent criticism,[16] this model is easy to use and requires no subjective language or reading skills, which is of great importance given the multicultural population of the trial site. In addition, familiarity and ease of use of the VAS tool required little additional staff training. Alternative functional pain scoring tools were not used as these are complex and require a level of training that was not practically available for all staff members and there is a lack of literature in the field of interest that has used functional pain scoring with which a useful comparison could be made. Objective measures of pain, including peritonism and haemodynamic instability, were incorporated into the trial selection process.

Nine months into the trial recruitment an interim analysis was performed to ensure patient safety—namely that patients entered into the trial were receiving adequate analgesia.

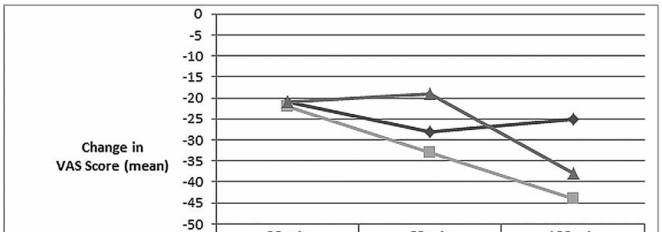
Once trial recruitment ceased, two trial investigators (GP and JRH) independently measured VAS to the nearest millimetre for all participants; any significant discrepancies were reviewed jointly.

Statistical analysis

Using a 13 mm difference on the VAS as the smallest measurable change in pain severity that is clinically important,[12 13] a power calculation suggested that 39 patients were required in each arm of the study to provide 80% power at the 0.05 significance level. Statistical analysis was based on χ^2 tests and Cochran Mantel Haenzel tests to assess the strength of the relationship between treatment and the event of interest (side effect rate, symptom rate). Where more than one time point was involved, the Mantel Haenzel test was used to control for time. A generalised linear model for a binary outcome was used to model responses against treatment and time (when appropriate). For continuous data, change from baseline VAS scores, ANCOVA method was used. The ORs and the corresponding 95% CIs were derived for binary endpoints. A conservative approach was adopted for safety data to present the worst case scenario.

RESULTS

One hundred and thirty-two patients were recruited. There were 45 patients in the hyoscine butylbromide + placebo group (male:female 1:1.4, age range 18–61 years, median age 28), 40 in the paracetamol + placebo group (male:female 1:2.3, age range 18–56 years, median age 27) and 47 in the hyoscine butylbromide + paracetamol group (male:female 1:1.2, age range 17–56 years, median age 29). Data were missing (nine patients), incomplete (seven patients) or trial violations occurred (six patients; violations included one intravenous cannula failure, two refusals of medication during administration, one code broken due to suspected drug reaction, one diagnosis during ED admission and one drug out of date) in 22 of these patients. Complete records were available for 110 patients, leaving 38 patients in the hyoscine butylbromide + placebo group (male:



	30 min	60 min	180 min
Hyoscine and placebo Baseline 61	−21	−28	−25
Paracetamol and placebo Baseline 61	−22	−33	−44
Hyoscine and paracetamol Baseline 59	−21	−19	−38

Figure 2 Mean change in pain score from pre-analgesia baseline.

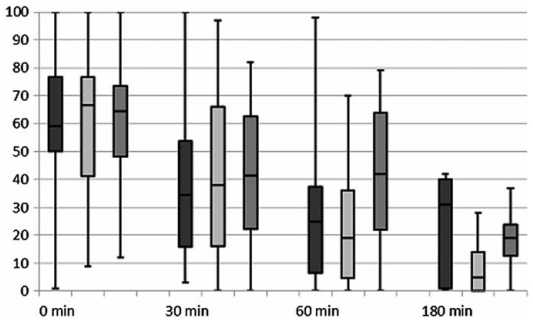


Figure 3 Grouped pain scores (dark grey, hyoscine butylbromide + placebo; light grey, paracetamol + placebo; mid-grey, hyoscine butylbromide + paracetamol).

female 1:1.4, age range 18–61 years, median age 28), 34 in the paracetamol + placebo group (male:female 1:2.3, age range 18–56 years, median age 27) and 38 in the hyoscine butylbromide + paracetamol group (male:female 1:1.2, age range 17–56 years, median age 29).

What was the effect of the trial medication on pain score?

All analgesic combinations produced a statistically and clinically significant reduction in pain scores from baseline (Figures 2 and 3).

Statistical analysis of primary outcomes

There were no statistically significant differences in pain scores (see table 1) at 30 min (all p values >0.9). At 60 min patients receiving paracetamol + placebo showed a statistically significant reduction in pain score compared with those in the paracetamol + hyoscine butylbromide treatment arm (two sided 5% level, ANCOVA model, p=0.018 (CI −32 to −3)). Those in the paracetamol + placebo treatment arm also showed a greater but non-significant reduction in pain score compared with hyoscine butylbromide + placebo (p=0.10 (CI −25 to +2)). At 180 min, only 13 patients remained in the ED and statistical analysis was not possible.

What rescue analgesia was required and what was the incidence of adverse events/complications?

Statistical analysis of the secondary outcomes (use of rescue analgesia, side effects, complications including repeat attendance at an ED) was based on the conservative assumption that all patients who were lost to follow-up or missing could have experienced side effects, complications or reattended an ED (see table 2 and 3).

No relationship was seen between treatment arms and the need for rescue analgesia (χ^2 (Fisher's exact) p value=0.846).

One hundred and ten patients were eligible for follow-up; 59% (n=65) were followed-up at 1 week and 41% (n=45) were followed-up at 12 weeks. The majority of patients lost to follow-up were non-contactable due to incomplete/inaccurate provision of contact details.

No complications were recorded during trial participation or at the 1 week and 12 week follow-up. Side effects were reported in 11 patients (10%) at the time of participation in the trial (see supplementary table 4, available online only) but no patient reported long term side effects at the 1 week or 12 week follow-up. There was no significant relationship between treatment arms and incidence of side effects after controlling for time (χ^2 (p value=0.1024)).

Findings at the 1 and 12 week follow-up

At the 1 week follow-up, 49% (n=32) of patient had ongoing symptoms and 51% (n=33) were symptom free; 34% (n=22) were undergoing further investigation. At the 12 week follow-up, 30% (n=14) had ongoing symptoms and 70% were symptom free (n=32); 20% were undergoing further investigation.

At the 1 week follow-up, 14% (n=9) of patients followed-up had a diagnosis and by 12 weeks 23% (n=15) of all patients followed-up had a diagnosis. Where a diagnosis was reached, the commonest diagnosis was gastritis (n=5). Other diagnoses included: gallstones (n=2), urinary tract infection (n=2), viral illness (n=2), polycystic ovarian disease (n=1), irritable bowel syndrome (n=1), colitis (n=1) and musculoskeletal pain (n=1).

During the entire follow-up period, nine patients reattended an ED with the same symptoms (week 1, n=7; week 12, n=2); no patient reattended an ED more than once. There was no significant relationship between treatments arms and incidence of reattendance at an ED after controlling for time (χ^2 (p value=0.7913)).

DISCUSSION

Paracetamol, hyoscine butylbromide and a combination of both demonstrated a clinically significant reduction in pain score at all time points. Specific findings of this trial were that: at 60 min, patients receiving paracetamol + placebo had a statistically significant reduction in pain score compared with those receiving paracetamol + hyoscine butylbromide.

This trial cannot provide a pharmacological explanation for this finding and, as such, to correctly interpret the meaning of statistical significance, the findings may well be due to chance. Despite this, the trial results do provide an evidence base for clinicians treating acute undifferentiated abdominal pain in the ED.

Of further use to the ED clinician, this trial validates the use of paracetamol and/or hyoscine butylbromide as analgesics capable of providing clinically significant pain reduction in acute undifferentiated abdominal pain. The mean values obtained in this study at 30, 60 and 180 min were equal to or greater than 19 mm for all combinations and prior published work has set a 13–16 mm difference in VAS pain score as the

Table 1 Statistical analysis of change in pain score

Parameter	Comparison	Difference (least squares mean)	95% CI	p Value (two sided 5% level, ANCOVA model)
30 min change	Hyoscine butylbromide + placebo vs paracetamol + placebo	0.667	−11.06 to 12.39	0.9102
	Hyoscine butylbromide + placebo vs hyoscine butylbromide + paracetamol	−0.144	−11.39 to 11.10	0.9797
	Paracetamol + placebo vs hyoscine butylbromide + paracetamol	−0.812	−12.54 to 10.91	0.8910
60 min change	Hyoscine butylbromide + placebo vs paracetamol + placebo	5.869	−8.73 to 20.47	0.4248
	Hyoscine butylbromide + placebo vs hyoscine butylbromide + paracetamol	−11.804	−25.95 to 2.34	0.1005
	Paracetamol + placebo vs hyoscine butylbromide + paracetamol	−17.674	−32.21 to −3.13	**0.0180**

Table 2 Use of rescue analgesia

Group	Yes	No	Excluded
Hyoscine butylbromide + placebo	8 (18%)	30 (67%)	7 (15%)
Paracetamol + placebo	4 (10%)	28 (70%)	8 (20%)
Hyoscine butylbromide + paracetamol	8 (17%)	30 (64%)	9 (19%)

smallest measurable change in pain severity that is clinically significant.[10–12 14] Further supporting this, the OR CIs for all group comparisons were wide, suggesting that all treatment groups were at least comparable in their efficacy in managing acute undifferentiated abdominal pain.

No relationship was seen between treatment arms and the need for rescue analgesia and no serious medication complications were experienced during the course of the trial. Ten per cent of all patients experienced some form of side effect during the trial period, of which dizziness was the most common. Other studies using hyoscine butylbromide showed similar rates (5%[8] to 17%[9]). Further analysis of the data revealed that a greater percentage of patients experienced side effects in the hyoscine butylbromide + placebo arm (18%) compared with those in the paracetamol + placebo (6%) and hyoscine butylbromide + paracetamol (5%) arms. While an increased rate of side effects in the arms using hyoscine butylbromide is not unexpected, the reason for the difference is not clear.

With regard to previously published data, there are a number of shortfalls in attempting to compare the studies mentioned in the introduction by Schafer[8] and Mueller Lissner[9] with the results from this study. Neither the complaint nor the setting is comparable. In addition, earlier studies used oral hyoscine butylbromide and paracetamol in the management of recurrent crampy abdominal pain whereas in this study, intravenous hyoscine butylbromide and oral paracetamol were used for the management of acute undifferentiated abdominal pain. Administration of intravenous medication is feasible only in the acute or inpatient setting, therefore precluding comparisons with previously published data in the outpatient setting. The objective of the 12 week data collection was to explore the link between these two conditions but follow-up was available in only a small number of cases, hence precluding meaningful analysis.

Paracetamol and hyoscine butylbromide are the most commonly used analgesic agents for the treatment of acute undifferentiated abdominal pain in the trial site ED but it is important to recognise that this combination represents only a minor proportion of the repertoire of analgesics widely used in the treatment of undifferentiated abdominal pain, including non-steroidal anti-inflammatory drugs and paracetamol—opiate combinations. The reason for this preference includes the potential for gastric irritation with non-steroidal anti-inflammatory drugs and the large numbers of patients presenting with reflux and oesophageal spasm and the published increase in opiate related side effects when paracetamol—codeine combinations are used in comparison with paracetamol alone. The inclusion of such analgesics in a similar trial design is an area for future research.

Table 3 Statistical analysis of use of rescue analgesia

Comparison	OR (95% CI)	p Value
Hyoscine butylbromide + placebo vs paracetamol + placebo	1.09 (0.91 to 1.29)	0.3411
Hyoscine butylbromide + placebo vs hyoscine butylbromide + paracetamol	1.00 (0.83 to 1.20)	0.9899
Paracetamol + placebo vs hyoscine butylbromide + paracetamol	0.92 (0.77 to 1.09)	0.3411

The limitations of this study are those that commonly affect trials run in the busy ED. On occasion, the department was too busy to approach all patients presenting with acute undifferentiated abdominal pain and it was not possible to keep an accurate record of the number of patients attending with such symptoms, regardless of their participation in the trial. The recruitment of such a convenience sample may always introduce selection bias. The double blind methodology ensured that minimal bias was introduced by the staff member involved in obtaining pain scores. A number of patients were excluded due to loss of at least part of their trial paperwork. Identification and analysis of these cases correlated this lost paper work with the changeover of junior doctors and an overhaul of the department's filing system.

Long term follow-up of patients was incomplete and the numbers meant that statistical analysis was not possible. Of those followed-up, 23% had a diagnosis by 12 weeks.

CONCLUSION

There is a dearth of evidence based literature to support the clinician in their analgesia based management of undifferentiated abdominal pain presenting to the ED. The results of this trial recommend that paracetamol alone be used in the treatment of patients presenting to the ED with mild to moderate acute undifferentiated abdominal pain. Paracetamol is a cheap universally available analgesic, and it can be administered orally, rectally or intravenously to a wide age range. Its use has been extensively studied in a variety of hospital settings and it has an excellent safety profile.[7]

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Competing interests None.

Ethics approval Ethics approval was provided by East London and City Research Ethics Committee.

Contributors TH and JRH designed the trial and submitted the trial for ethics approval and registration. JRH and TH ran the pilot study. GP and TH ran the main study. GP and JRH collated the data. GP, JRH and TH interpreted the data. GP wrote the first draft of the paper. GP, JRH and TH reviewed the paper and gave final approval for the version to be published.

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